Dietary Lycopene and Disease Risk
Bladder Critical Findings

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Cancer: bladder	Hung RJ	Protective effects of plasma carotenoids on the risk of bladder cancer. Hung RJ, Zhang ZF, Rao JY, Pantuck A, Reuter VE, Heber D, Lu QY. J Urol. 2006 Sep;176(3):1192-7.	2006	PURPOSE: We examined the associations between plasma micronutrients and bladder cancer risk, and evaluated the combined effects of carotenoid and cigarette smoke. MATERIALS AND METHODS: We performed a case-control study in 242 patients with bladder cancer and 204 healthy controls at Memorial Sloan-Kettering Cancer Center from 1993 to 1997. Epidemiological data and blood specimens were collected on 84 cases and 173 controls. Plasma micronutrients, including lutein, zeaxanthin, beta-cryptoxanthin, lycopene, alpha-carotene, beta-carotene, retinol, alpha-tocopherol and gamma-tocopherol, were determined by high performance liquid chromatography. The logistic regression model was used to estimate the effects from carotenoid, tocopherol and retinol on the risk of bladder cancer. RESULTS: Based on quartiles of plasma micronutrient levels and continuous variables, adjusted ORs were estimated for bladder cancer after controlling for potential confounders, including patient age, sex, education and pack-years of smoking. When using plasma levels of micronutrients as continuous variables, the adjusted OR was 0.22 (95% CI 0.05 to 0.92) for alpha-carotene, 0.42 (95% CI 0.18 to 1.00) for lutein, 0.16 (95% CI 0.02 to 1.06) for zeaxanthin, 0.94 (95% CI 0.89 to 0.99) for lycopene and 0.90 (95% CI 0.81 to 1.00) for beta-cryptoxanthin. The adjusted OR for the joint effect of plasma carotenoids and tobacco smoking was 6.22 (95% CI 1.87 to 20.8) in smokers with lower lutein and 5.18 (95% CI 1.57 to 17.1) in smokers with lower zeaxanthin. CONCLUSIONS: Our results show protective effects of carotenoids on bladder cancer. They suggest that bladder cancer may be a preventable disease through nutritional intervention, especially in smokers.	CC				(-)/N ↓ risk	

Breast Cancer Critical Findings

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Cancer: breast	Potischman N	Breast cancer and dietary and plasma concentrations of carotenoids and vitamin A. Potischman N, McCulloch CE, Byers T, Nemoto T, Stubbe N, Milch R, Parker R, Rasmussen KM, Root M, Graham S, et al. Am J Clin Nutr. 1990 Nov;52(5):909-15.	1990	A case-control study of breast cancer was conducted in Buffalo. Participants completed a food frequency questionnaire and donated a fasting blood sample before definitive workup for breast masses. Dietary and plasma concentrations of carotenoids and retinol for 83 women found to have breast cancer were compared with those of 113 women found to be free of breast cancer (control subjects). There were no case-control differences in dietary estimates of vitamin A intake or in plasma alpha-carotene and lycopene. However, subjects with breast cancer had lower concentrations of plasma beta-carotene than did control subjects (P = 0.02). There was no overall association between plasma retinol and breast cancer but a positive relationship was observed between retinol and breast cancer in the subgroup with low beta-carotene values. These results suggest that low plasma beta-carotene is associated with increased risk of breast cancer. Other studies will need to determine whether low carotene oncentrations are a subtle effect of the disease or might be causally related to breast cancer.	CC				N	
Cancer: breast	Zhang S	Measurement of retinoids and carotenoids in breast adipose tissue and a comparison of concentrations in breast cancer cases and control subjects. Zhang S, Tang G, Russell RM, Mayzel KA, Stampfer MJ, Willett WC, Hunter DJ. Am J Clin Nutr. 1997 Sep;66(3):626-32.	1997	A case-control study of the associations of retinoids and specific carotenoids with breast cancer using concentrations of these nutrients in breast adipose tissue was conducted among women attending a breast clinic in the Boston area in 1989-1992. Breast adipose tissue was collected during breast biopsy. Cases (n = 46) were women whose biopsies revealed invasive or in situ breast cancer; control subjects (n = 63) were women whose biopsies revealed benign disease. We observed inverse associations between breast adipose concentrations of retinoids and carotenoids and risk of breast cancer, although not all were statistically significant. The multivariate-adjusted odds ratio comparing women above the median value of the control group for retinol with those below or equal to the median was 0.71 (95% CI: 0.26, 1.93; NS); corresponding odds ratios were 0.61 (95% CI: 0.23, 1.64; NS) for retinyl palmitate, 0.30 (95% CI: 0.11, 0.85) for beta-carotene, 0.32 (95% CI: 0.11, 0.94) for lycopene, and 0.68 (95% CI: 0.27, 1.73; NS) for lutein/zeaxanthin. There was a nonsignificant positive correlation (r = 0.23, P = 0.15) between	CC tissue				(-)	

				breast adipose tissue concentrations of retinol and dietary intake of preformed vitamin A, including supplements measured by using a food-frequency questionnaire. No correlation was found between breast adipose concentrations of carotenoids and intake of dietary carotenoids. These data suggest that higher breast adipose concentrations of retinoids and some carotenoids may be associated with decreased risk of breast cancer and that further examination of these relations is warranted.		
Cancer: breast	Dorgan JF	Relationships of serum carotenoids, retinol, alpha-tocopherol, and selenium with breast cancer risk: results from a prospective study in Columbia, Missouri (United States) Dorgan JF, Sowell A, Swanson CA, Potischman N, Miller R, Schussler N, Stephenson HE Jr. Cancer Causes Control. 1998 Jan;9(1):89-97.	1998	To evaluate relationships of serum carotenoids, alpha-tocopherol, selenium, and retinol with breast cancer prospectively, we conducted a case-control study nested in a cohort from the Breast Cancer Serum Bank in Columbia, Missouri (United States). Women free of cancer donated blood to this bank in 1977-87. During up to 9.5 years of follow-up (median = 2.7 years), 105 cases of histologically confirmed breast cancer were diagnosed. For each case, two women alive and free of cancer at the age of the case's diagnosis and matched on age and date of blood collection were selected as controls. A nonsignificant gradient of decreasing risk of breast cancer with increasing serum beta-cryptoxanthin was apparent for all women. Serum lycopene also was associated inversely with risk, and among women who donated blood at least two years before diagnosis, a significant gradient of decreasing breast cancer risk with increasing lycopene concentration was evident. A marginally significant gradient of decreasing risk with increasing serum lutein/zeaxanthin also was apparent among these women. We did not observe any evidence for protective effects of alpha- and beta-carotene, alpha-tocopherol, retinol, or selenium for breast cancer. Results of this study suggest that the carotenoids beta-cryptoxanthin, lycopene, and lutein/zeaxanthin may protect against breast cancer.	CC nested	(-)
Cancer: breast	Ito Y	A study on serum carotenoid levels in breast cancer patients of Indian women in Chennai (Madras), India. Ito Y, Gajalakshmi KC, Sasaki R, Suzuki K, Shanta V. J Epidemiol.	1999	Two-hundred and six breast cancer cases were histologically confirmed breast cancer diagnoses at the Cancer Institute in Chennai (Madras), India. One-hundred and fifty hospital controls were patients who had cancer at any site other than breast and gynecological organs, and 61 healthy controls were persons accompanying patients in the Cancer Institute. Serum levels of carotenoids such as beta-carotene, lycopene, cryptoxanthin, and zeaxanthin & lutein were determined by HPLC. Serum levels of total carotenes and total carotenoids including beta-carotene, which reflects food intake of colored vegetables and fruits and has a protective	CC serum	N?

		1999 Nov;9(5):306-14.		role for certain sites of cancer, were significantly lower among breast cancer cases and hospital controls compared to healthy controls, especially in post-menopausal women. Serum carotenoid levels appeared to change with menopausal status. Serum beta-carotene levels tended to be lower among breast cancer cases than among hospital controls in premenopausal women. Serum xanthophyll levels were significantly lower among breast cancer cases than among healthy controls in post-menopausal women, but not in premenopausal women. Serum levels of retinol and alpha-tocopherol among breast cancer cases were not significantly different from those in post-menopausal healthy controls, but were higher than those in hospital controls. Serum estrone levels were significantly higher among breast cancer cases than among healthy controls, but serum levels of estradiol and estriol were not. In conclusion, Indian women with cancer of breast or of other sites might have low intake of green-yellow vegetables rich in fiber and carotenoids such as beta-carotene and zeaxanthin & lutein.		
Cancer: breast	Simon MS	An Evaluation of Plasma Antioxidant Levels and the Risk of Breast Cancer: A Pilot Case Control Study. Simon MS, Djuric Z, Dunn B, Stephens D, Lababidi S, Heilbrun LK. Breast J. 2000 Nov;6(6):388-395.	2000	Antioxidant micronutrients found in fruits and vegetables have been shown in numerous studies to be protective against cancer. There is limited information on the relationship between blood antioxidant micronutrient levels and cancer among ethnic minorities. We conducted a pilot case-control study to evaluate the potential for accrual to a study of the association of plasma levels of beta-carotene, retinol, lycopene, alpha-tocopherol, and gamma-tocopherol with breast cancer risk among African American and Caucasian women seen at a large university medical center in Detroit. Cases included women with newly diagnosed invasive breast cancer who had not yet had any cancer-related therapy and who were age-matched to controls within 5 years. Plasma levels of micronutrients were analyzed by high-pressure liquid chromatography. Compared to the expected accrual based on cancer registry data, only 26% (11/42) of African American women with breast cancer enrolled, while 100% (16/16) of Caucasian cases enrolled. Control women were quickly accrued with only a 6% refusal rate. Among African American women, there was a weak inverse association between plasma lycopene levels and breast cancer risk, with a mean level of 0.17 &mgr;mol/L (SD = 0.18) among cases, and 0.24 &mgr; mol/L (SD = 0.18) among controls (p = 0.09). There was a weak direct association between plasma retinol levels and	CC		N

				breast cancer risk among African American women, with a mean retinol level of 2.37 &mgr;mol/L (SD = 0.73) among cases and 1.98 &mgr;mol/L (SD = 0.49) among controls (p = 0.132). The interaction effect of race and lycopene was statistically significant (p = 0.048). Among the lowest lycopene tertile, the risk of breast cancer among Caucasian women was 0.76 and the risk of breast cancer among African American women was 2.29, although these odds ratios were not statistically significant. Our recruitment efforts were largely successful among Caucasian cases and controls, and African American controls, but were unsuccessful among African American cases. The results suggest a possible relationship between plasma lycopene level and breast cancer among African American women, but these results should be confirmed by a larger, more definitive study.		
Cancer: breast	Hulten K	Carotenoids, alpha-tocopherols, and retinol in plasma and breast cancer risk in northern Sweden. Hulten K, Van Kappel AL, Winkvist A, Kaaks R, Hallmans G, Lenner P, Riboli E. Cancer Causes Control. 2001 Aug;12(6):529-37.	2001	OBJECTIVE: Using a nested case-referent design we evaluated the relationship between plasma levels of six carotenoids, alpha-tocopherol, and retinol, sampled before diagnosis, and later breast cancer risk. METHODS: In total, 201 cases and 290 referents were selected from three population-based cohorts in northern Sweden, where all subjects donated blood samples at enrolment. All blood samples were stored at -80 degrees C. Cases and referents were matched for age, age of blood sample, and sampling centre. Breast cancer cases were identified through the regional and national cancer registries. RESULTS: Plasma concentrations of carotenoids were positively intercorrelated. In analysis of three cohorts as a group none of the carotenoids was found to be significantly related to the risk of developing breast cancer. Similarly, no significant associations between breast cancer risk and plasma levels of alpha-tocopherol or retinol were found. However, in postmenopausal women from a mammography cohort with a high number of prevalent cases, lycopene was significantly associated with a decreased risk of breast cancer. A significant trend of an inverse association between lutein and breast cancer risk was seen in premenopausal women from two combined population-based cohorts with only incident cases. A non-significant reduced risk with higher plasma alpha-carotene was apparent throughout all the sub-analyses.	CC nested	(-)

				CONCLUSION: In conclusion, no significant associations were found between plasma levels of carotenoids, alpha-tocopherol or retinol and breast cancer risk in analysis of three combined cohorts. However, results from stratified analysis by cohort membership and menopausal status suggest that lycopene and other plasma-carotenoids may reduce the risk of developing breast cancer and that menopausal status has an impact on the mechanisms involved.		
Cancer: breast	Toniolo P	Serum carotenoids and breast cancer. Toniolo P, Van Kappel AL, Akhmedkhanov A, Ferrari P, Kato I, Shore RE, Riboli E. Am J Epidemiol. 2001 Jun 15;153(12):1142-7.	2001	The consumption of vegetables and fruit may protect against many types of cancer, but research evidence is not compelling for breast cancer. Carotenoids are pigments that are present in most plants and have known antioxidant properties. Blood concentrations of carotenoids have been proposed as integrated biochemical markers of vegetable, fruit, and synthetic supplements consumed. In a case-control study (270 cases, 270 controls) nested within a cohort in New York during 1985-1994, the carotenoids lutein, zeaxanthin, beta-cryptoxanthin, lycopene, alpha-carotene, and beta-carotene were measuredin archived serum samples using liquid chromatography. There was an evident increase in the risk of breast cancer for decreasing beta-carotene, lutein, alpha-carotene, and beta-cryptoxanthin. The risk of breast cancer approximately doubled among subjects with blood levels of beta-carotene at the lowest quartile, as compared with those at the highest quartile (odds ratio = 2.21; 95% confidence interval (CI): 1.29, 3.79). The risk associated with the other carotenoids was similar, varying between 2.08 (95% CI: 1.11, 3.90) for lutein and 1.68 (95% CI: 0.99, 2.86) for beta-cryptoxanthin. The odds ratio for the lower quartile of total carotenoids was 2.31 (95% CI: 1.35, 3.96). These observations offer evidence that a low intake of carotenoids, through poor diet and/or lack of vitamin supplementation, may be associated with increased risk of breast cancer and may have public health relevance for people with markedly low intakes.	CC nested	N?
Cancer: breast	Ching S	Serum levels of micronutrients, antioxidants and total antioxidant status predict risk of breast cancer in a case control study. Ching S, Ingram D,	2002	We performed a case control study to assess the association between serum micronutrient and antioxidant levels and the risk of breast cancer. Newly diagnosed breast cancer cases were recruited before any treatment and matched with controls randomly selected from the electoral roll. Blood samples were collected from 153 breast cancer cases and 151 controls. Serum samples were analyzed for retinol, alpha-tocopherol, lycopene, alpha- and beta-carotene by HPLC, and total antioxidant status by the Trolox-equivalent antioxidant assay.	CC	N?

		Hahnel R, Beilby J, Rossi E. J Nutr. 2002 Feb;132(2):303-6.		Serum albumin, bilirubin and uric acid levels were also determined. After adjustment for age at menarche, parity, dietary fat and alcohol intake, we observed the following reductions in odds ratios for breast cancer risk comparing the highest with the lowest quartiles: 0.47 [95% confidence interval (CI) 0.24, 0.91] for beta-carotene; 0.53 (CI 0.28, 1.01) for retinol; 0.50 (CI 0.26, 0.97) for bilirubin and 0.47 (CI 0.24, 0.94) for total antioxidant status. We conclude that increased serum levels of beta-carotene, retinol, bilirubin and total antioxidant status are associated with reductions in breast cancer risk.				
Cancer: breast	Sato R	Prospective study of carotenoids, tocopherols, and retinoid concentrations and the risk of breast cancer. Sato R, Helzlsouer KJ, Alberg AJ, Hoffman SC, Norkus EP, Comstock GW. Cancer Epidemiol Biomarkers Prev. 2002 May;11(5):451-7.	2002	Previous prospective studies have raised the possibility that the antioxidantproperties of carotenoids and vitamin E (alpha-tocopherol) and the role of vitamin A (retinol) in cellular differentiation may be associated with a reduced risk of subsequent breast cancer. To investigate the association between serum and plasma concentrations of retinol, retinyl palmitate, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, lycopene, total-carotenoids, alpha-tocopherol, and gamma-tocopherol with subsequent development of breast cancer, a nested case control study was conducted among female residents of Washington County, Maryland, who had donated blood for a serum bank in 1974 or 1989. Cases (n = 295) and controls (n = 295) were matched on age, race, menopausal status, and date of blood donation, and the analyses were stratified by cohort participation. Median concentrations of beta-carotene, lycopene, and total carotene were significantly lower in cases compared with controls in the 1974 cohort (13.1, 12.5, and 7.9% difference; P = 0.01, 0.04, and 0.04, respectively) and for lutein in the 1989 cohort (6.7% difference; P = 0.02). The risk of developing breast cancer in the highest fifth was approximately half of that of women in the lowest fifth for beta-carotene [odds ratio (OR) = 0.41; 95% confidence interval (CI) 0.22-0.79; P trend = 0.007], lycopene (OR = 0.55; 95% CI 0.29-1.06; P trend = 0.04), and total carotene (OR = 0.55; 95% CI 0.29-1.03; P trend = 0.02) in the 1974 cohort. There was generally a protective association for other micronutrients in both cohorts, although none reached statistical significance. The results suggest that carotenoids may protect against the development of breast cancer.	CC nested		(-)	
Cancer: breast	Sesso HD	Dietary and plasma lycopene and the risk of breast cancer.	2005	Lycopene is potentially effective in the prevention of breast cancer from laboratory and observational studies. Among 39,876 women initially free of cardiovascular disease and cancer, we first conducted a prospective cohort study of	PC	N	N	Diet lyco + food sources

		Sesso HD, Buring JE, Zhang SM, Norkus EP, Gaziano JM. Cancer Epidemiol Biomarkers Prev. 2005 May;14(5):1074-81.		dietary lycopene and its food sources. Participants completed a baseline food frequency questionnaire and provided self-reports of breast cancer risk factors. Dietary lycopene levels were divided into quintiles, and lycopene food sources were categorized. During 9.9 years of follow-up, 1,076 breast cancer cases were confirmed by medical record review. In a nested case-control study, we then identified 508 breast cancer cases and 508 controls matched by age, smoking, and follow-up time. Plasma lycopene and other carotenoids were measured. In the prospective cohort study, women with increasing quintiles of dietary lycopene had multivariate relative risks (RR) of breast cancer of 1.00 (ref), 0.95, 1.00, 1.10, and 1.00 (P, linear trend = 0.71). Women consuming <1.5, 1.5 to <4, 4 to <7, 7 to <10, and > or =10 servings/week of tomato-based products had RRs of 1.00 (ref), 1.00, 1.20, 1.18, and 1.16 (P, linear trend = 0.11). No individual lycopene food sources were associated with breast cancer. In the nested case-control study, women in increasing quartiles of plasma lycopene had multivariate RRs of breast cancer of 1.00 (ref), 0.95, 1.15, and 0.93 (P, linear trend = 0.86). The stepwise addition of individual plasma carotenoids did not impact the RRs for plasma lycopene, nor were other carotenoids associated with breast cancer. In conclusion, neither higher dietary nor plasma lycopene levels were associated with a reduced risk of breast cancer in middle-aged and older women.	~~~~~ CC nested		~~~~~ N	~~~~~ Plasma
Cancer: breast	Tamimi RM	Plasma carotenoids, retinol, and tocopherols and risk of breast cancer. Tamimi RM, Hankinson SE, Campos H, Spiegelman D, Zhang S, Colditz GA, Willett WC, Hunter DJ. Am J Epidemiol. 2005 Jan 15;161(2):153-60.	2005	The roles of carotenoids, retinol, and tocopherols in breast cancer etiology have been inconclusive. The authors prospectively assessed the relations between plasma alpha-carotene, beta-carotene, beta-cryptoxanthin, lycopene, lutein/zeaxanthin, retinol, alpha-tocopherol, and gamma-tocopherol and breast cancer risk by conducting a nested case-control study using plasma collected from women enrolled in the Nurses' Health Study. A total of 969 cases of breast cancer diagnosed after blood draw and prior to June 1, 1998, were individually matched to controls. The multivariate risk of breast cancer was 25-35% less for women with the highest quintile compared with that for women with the lowest quintile of alpha-carotene (odds ratio (OR) = 0.64, 95% confidence interval (CI): 0.47, 0.88; p(trend) = 0.01), beta-carotene (OR = 0.73, 95% CI: 0.53, 1.02; p(trend) = 0.01), lutein/zeaxanthin (OR = 0.74, 95% CI: 0.55, 1.01; p(trend) = 0.04), and total carotenoids (OR = 0.76, 95% CI: 0.55, 1.05; p(trend) = 0.05). The inverse association observed with alpha-carotene and breast cancer was greater for invasive	CC nested		N	

				cancers with nodal metastasis. The authors conclude that some carotenoids are inversely associated with breast cancer. Although the association was strongest for alpha-carotene, the high degree of collinearity among plasma carotenoids limits our ability to conclude that this association is specific to any individual carotenoid.		
Cancer: breast	Thomson CA	Plasma and dietary carotenoids are associated with reduced oxidative stress in women previously treated for breast cancer. Thomson CA, Stendell-Hollis NR, Rock CL, Cussler EC, Flatt SW, Pierce JP. Cancer Epidemiol Biomarkers Prev. 2007 Oct;16(10):2008-15.	2007	Dietary carotenoids show numerous biological activities, including antioxidant activity, induction of apoptosis, and inhibition of mammary cell proliferation. Studies examining the role of carotenoid consumption in relation to breast cancer recurrence are limited and report mixed results. We tested the hypothesis that breast cancer survivors with high dietary and plasma carotenoids would show significantly lower levels of oxidative stress than breast cancer survivors with low dietary and plasma carotenoid levels. Two hundred seven postmenopausal breast cancer survivors from the Women's Healthy Eating and Living Study volunteered for this ancillary study. Dietary data were analyzed by the Arizona Food Frequency Questionnaire and plasma carotenoids alpha-carotene, beta-carotene, lutein plus zeaxanthin, lycopene, and beta-cryptoxanthin and quantified with high-performance liquid chromatography, and immunoaffinity chromatography-monoclonal antibody-based ELISAs were used to analyze the urine samples for 8-hydroxy-2'-deoxyguanosine (8-OhdG) and 8-iso-prostaglandin-F2alpha (8-iso-PGF2alpha). The correlations between dietary and plasma carotenoids were 0.34 for beta-carotene, 0.46 for alpha-carotene, 0.39 for beta-cryptoxanthin, 0.27 for lycopene, 0.30 for lutein plus zeaxanthin, and 0.30 for total carotenoids. The 8-OHdG oxidative stress biomarker was significantly reduced at the highest quartile of total plasma carotenoid concentrations (P = 0.001) and 8-iso-PGF2alpha was moderately reduced (P = 0.088). Dietary carotenoid levels were not significantly associated with oxidative, stress indicators, although dietary lycopene and lutein/zeaxanthin were modestly associated with 8-OHdG levels (P = 0.054 and 0.088, respectively). Key findings include a significant inverse association between total plasma carotenoid concentrations and oxidative stress as measured by urinary 8-OHdG and a moderately significant inverse association with 8-iso-PGF2alpha, a protective association that was not shown for dietary carotenoid intake.	CS	(-) ↓ 8-OHdG (ox stress marker) with plasma [lyco]

Cancer: breast	Dorjgochoo T	Plasma carotenoids, tocopherols, retinol and breast cancer risk: results from the Shanghai Women Health Study (SWHS). Dorjgochoo T, Gao YT, Chow WH, Shu XO, Li H, Yang G, Cai Q, Rothman N, Cai H, Franke AA, Zheng W, Dai Q. Breast Cancer Res Treat. 2009 Sep;117(2):381-9. Epub 2008 Dec 20.	2009	Evidence from some previous studies suggests that lipophilic antioxidants, particularly carotenoids, may reduce the risk of breast cancer. We prospectively investigated the associations of plasma levels of tocopherols, retinol, carotenoids with the risk of developing breast cancer among Chinese women. We conducted a study of 365 incident breast cancer cases and 726 individually matched controls nested within a large cohort study of women aged 40-70 years at baseline. We observed no associations between breast cancer risk and any of the tocopherols, retinol, and most carotenoids. However, high levels of plasma lycopene other than trans, 5- and 7-cis or trans alpha-cryptoxanthin were inversely associated with the risk of developing breast cancer. Our results do not support an overall protective effect of lipophilic antioxidants on breast cancer risk. The few inverse associations observed for subtype of carotenoids may need to be confirmed in future studies.	CC nested	(-)
Cancer: breast	Kabat GC	Longitudinal study of serum carotenoid, retinol, and tocopherol concentrations in relation to breast cancer risk among postmenopausal women. Kabat GC, Kim M, Adams-Campbell LL, Caan BJ, Chlebowski RT, Neuhouser ML, Shikany JM, Rohan TE; WHI Investigators. Am J Clin Nutr. 2009 Jul;90(1):162-9. Epub 2009 May 27.	2009	BACKGROUND: Prospective studies have examined the association of serum and plasma carotenoids and micronutrients and breast cancer; however, to date, studies have only assessed exposure at one point in time. OBJECTIVE: This study analyzed baseline and repeated serum measurements of carotenoids, retinol, and tocopherols to assess their associations with postmenopausal breast cancer risk. ESIGN: Serum concentrations of alpha-carotene, beta-carotene, beta-cryptoxanthin, lycopene, lutein + zeaxanthin, retinol, alpha-tocopherol, and gamma-tocopherol were measured in a 6% sample of women in the Women's Health Initiative clinical trials at baseline and at years 1, 3, and 6 and in a 1% sample of women in the observational study at baseline and at year 3. The association of baseline compounds and breast cancer risk was estimated by Cox proportional hazards models. In addition, repeated measurements were analyzed as time-dependent covariates. Of 5450 women with baseline measurements, 190 incident cases of breast cancer were ascertained over a median of 8.0 y of follow-up. RESULTS: After multivariable adjustment, risk of invasive breast cancer was inversely associated with baseline serum alpha-carotene concentrations (hazard ratio for highest compared with the lowest tertile: 0.55; 95% CI: 0.34, 0.90; P = 0.02) and	PC	(+) ↑ risk

				positively associated with baseline lycopene (hazard ratio: 1.47; 95% CI: 0.98, 2.22; P = 0.06). Analysis of repeated measurements indicated that alpha-carotene and beta-carotene were inversely associated with breast cancer and that gamma-tocopherol was associated with increased risk. CONCLUSIONS: The present study, which was the first to assess repeated measurements of serum carotenoids and micronutrients in relation to breast cancer, adds to the evidence of an inverse association of specific carotenoids with breast cancer. The positive associations observed for lycopene and gamma-tocopherol require confirmation. This trial was registered at ClinicalTrials.gov as NCT00000611.		
Cancer: breast	Tamimi RM	Circulating carotenoids, mammographic density, and subsequent risk of breast cancer. Tamimi RM, Colditz GA, Hankinson SE. Cancer Res. 2009 Dec 15;69(24):9323-9. Epub	2009	Mammographic density is one of the strongest predictors of breast cancer risk. Recently, it has been suggested that reactive oxygen species may influence breast cancer risk through its influence on mammographic density. In the current study, we addressed this hypothesis and also assessed if the association between carotenoids and breast cancer risk varies by mammographic density. We conducted a nested case-control study consisting of 604 breast cancer cases and 626 controls with prospectively measured circulating carotenoid levels and mammographic density in the Nurses' Health Study. Circulating levels of alpha-carotene, beta-carotene, beta-cryptoxanthin, lycopene, and lutein/zeaxanthin were measured. We used a computer-assisted thresholding method to measure percent mammographic density. We found no evidence that circulating carotenoids are inversely associated with mammographic density. However, mammographic density significantly modified the association between total circulating carotenoids and breast cancer (P heterogeneity = 0.008). Overall, circulating total carotenoids were inversely associated with breast cancer risk (P trend = 0.01). Among women in the highest tertile of mammographic density, total carotenoids were associated with a 50% reduction in breast cancer risk (odds ratio, 0.5; 95% confidence interval, 0.3-0.8). In contrast, there was no inverse association between carotenoids and breast cancer risk among women with low mammographic density. Similarly, among women in the highest tertile of mammographic density, high levels of circulating alpha-carotene, beta-cryptoxanthin, lycopene, and lutein/zeaxanthin were associated with a significant 40% to 50% reduction in breast cancer risk (P trend < 0.05). Our results sugget that plasma levels of carotenoids may play a	CC nested	(-) in high mammo density

role in reducing breast cancer risk, particularly among women with high mammographic density.

Cervical Cancer Critical Findings

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Cancer: cervical	Potischman N	A case-control study of nutrient status and invasive cervical cancer. II. Serologic indicators. Potischman N, Herrero R, Brinton LA, Reeves WC, Stacewicz-Sapuntzakis M, Jones CJ, Brenes MM, Tenorio F, de Britton RC, Gaitan E. Am J Epidemiol. 1991 Dec 1;134(11):1347-55.	1991	A study of 387 cases and 670 controls from four Latin American countries evaluated the hypothesis that lower serum levels of eight micronutrients were associated with a higher risk of invasive cervical cancer. The serologic analyses were restricted to a sample of subjects with stage I and II disease to minimize effects of the disease on the serologic markers. Ninety-four percent of eligible subjects donated blood samples, which were analyzed for carotenoids, retinol, and tocopherols by high-pressure liquid chromatography. Cases did not differ significantly from controls in mean serum levels of retinol, cryptoxanthin, lycopene, alpha-carotene, lutein, or alpha-tocopherol. The mean level of beta-carotene was lower and the mean level of gamma-tocopherol was higher among cases as compared with controls. After adjustment for age, study site, sexual and reproductive behavior, socioeconomic status, screening practices, detection of human papillomavirus types 16/18, cholesterol, and triglycerides, a trend of decreasing risk was associated with higher levels of beta-carotene (p for trend = 0.05), with the adjusted odds ratio decreasing to 0.72 for the highest versus the lowest quartile. beta-Carotene results were similar by stage of disease, which argues against an effect of disease progression on nutrient values. Unexpectedly, increasing risks were observed as the level of gamma-tocopherol increased (odds ratio = 2.09; p for trend = 0.03); however, levels were higher among stage II cases as compared with stage I cases, suggesting a metabolic alteration resulting from the disease process. The concordance in the strength and direction of the blood and dietary results, presented in the accompanying report (Herrero R, Potischman N, Brinton LA, et al., American Journal of Epidemiology 1991;134:1335-46), supports a role for beta-carotene or foods rich in beta-carotene in the etiology of cervical cancer. This study also indicates that simultaneous analysis using serologic and dietary nutrient indicators allows better discrimination of the association.	CC				N	

Cancer: cervical	VanEenwyk J	Dietary and serum carotenoids and cervical intraepithelial neoplasia. VanEenwyk J, Davis FG, Bowen PE. Int J Cancer. 1991 Apr 22;48(1):34-8.	1991	A case-control study examined the association between cervical intra-epithelial neoplasia (CIN) and serum and dietary alpha-carotene, beta-carotene, cryptoxanthin, lutein, and lycopene. Cases (n = 102) had biopsy confirmed CIN I, II or III. Controls matched for age, ethnic origin and clinic (n = 102) had normal Pap smears. Participants completed health history and food frequency questionnaires. Fasting venous blood samples were assayed for serum carotenoids. Multivariable conditional logistic regression analyses yielded odds ratios and 95% confidence intervals (CIs) for those in quartiles 3, 2, and 1 (lowest) compared to quartile 4 (highest) of serum lycopene of 3.5 (1.1-11.5), 4.7 (1.2-17.7) and 3.8 (1.1-12.4), respectively. Similar analyses yielded adjusted odds ratios (ORaS) and 95% CIs of 4.6 (1.1-19.7), 5.8 (1.6-21.3) and 5.4 (1.3-23.3) for dietary intake of lycopene. The findings for lycopene-rich foods (tomatoes) were consistent with this result. CIN was not associated with the lutein. Findings for alpha-carotene, beta-carotene and cryptoxanthin were ambiguous. Quartile of vitamin C intake was also inversely associated with CIN with ORaS and 95% CIs of 3.7 (0.9-14.6), 4.1 (1.0-17.2), and 6.4 (1.4-30.0) for those in quartiles 3, 2, and 1 compared to quartile 4.	CC	(-)
Cancer: cervical	Batieha AM	Serum micronutrients and the subsequent risk of cervical cancer in a population-based nested case-control study. Batieha AM, Armenian HK, Norkus EP, Morris JS, Spate VE, Comstock GW. Cancer Epidemiol Biomarkers Prev. 1993 Jul-Aug;2(4):335-9.	1993	A nested case-control study was conducted in Washington County, MD, to determine whether low serum micronutrients are related to the subsequent risk of cervical cancer. Among the 15,161 women who donated blood for future cancer research during a serum collection campaign in 1974, 18 developed invasive cervical cancer and 32 developed carcinoma in situ during the period January 1975 through May 1990. For each of these 50 cases, two matched controls were selected from the same cohort. The frozen sera of the cases and their matched controls were analyzed for a number of nutrients. The mean serum levels of total carotenoids, alpha-carotene, beta-carotene, cryptoxanthin, and lycopene were lower among cases than they were among controls. When examined by tertiles, the risk of cervical cancer was significantly higher among women in the lower tertiles of total carotenoids (odds ratio 2.7; 95% confidence limit, 1.1-6.4), alpha-carotene (odds ratio, 3.1; 95% confidence limit, 1.3-7.6), and beta-carotene (odds ratio, 3.1; 95% confidence limit, 1.2-8.1) as compared to women in the upper tertiles and the trends were statistically significant. Cryptoxanthin was significantly associated with a lower risk of cervical cancer when examined as a continuous variable. Retinol, lutein, alpha- and gamma-tocopherol, and selenium were not related to cervical cancer risk. Smoking was also strongly associated with cervical cancer. These findings are	CC nested	N

				suggestive of a protective role for total carotenoids, alpha-carotene and beta-carotene in cervical carcinogenesis and possibly for cryptoxanthin and lycopene as well.		
Cancer: cervical	Potischman N	The relations between cervical cancer and serological markers of nutritional status. Potischman N, Hoover RN, Brinton LA, Swanson CA, Herrero R, Tenorio F, de Britton RC, Gaitan E, Reeves WC. Nutr Cancer. 1994;21(3):193-201.	1994	We evaluated whether differences in serological nutrient indicators between cases and controls were likely to be due to different usual levels for cases or to altered metabolism due to disease. Blood samples obtained as part of a case-control study of invasive cervical cancer conducted in Latin America were evaluated for case-control differences and for trends with stage of disease. Serum alpha- and beta-carotene, cryptoxanthin, and alpha- and gamma-tocopherol showed no trend with extent of disease, although Stage IV cases had lower alpha- and beta-carotene values than did other cases. A slight trend of decreasing values with stage was observed for serum retinol, lycopene, and lutein. For cholesterol and triglyceride concentrations, an inverse trend was observed with stage of disease, which suggested a clinical effect of the disease on blood lipids. Adjustment for smoking, alcohol intake, or oral contraceptive use did not alter observed relations, nor was there evidence that the altered blood nutrient levels differed by histological type. These data suggest that serum values for some carotenoids from Stage I, II, and III cervical cancer are suitable for etiological studies, but spurious results may be obtained if late-stage cases are included. Evidence of trends with severity of disease for cholesterol and triglycerides, and possibly for retinol, lycopene, and lutein, suggest that special attention be given to disease effects of these nutrients in studies of cervical cancer.	CC		N?
Cancer: cervical	Palan PR	Plasma levels of beta-carotene, lycopene, canthaxanthin, retinol, and alpha- and tau-tocopherol in cervical intraepithelial neoplasia and cancer. Palan PR, Mikhail MS, Goldberg GL, Basu J, Runowicz CD, Romney SL. Clin Cancer Res. 1996 Jan;2(1):181-5.	1996	Epidemiological studies continue to identify an association of dietary antioxidant micronutrients in cancer prevention. A number of case-control and cohort studies have demonstrated a relationship between high intake of foods rich in carotenoids, tocopherols, and vitamin C with a reduced risk of certain human malignancies. The purpose of this study was to investigate the comparative plasma levels of a profile of known dietary antioxidants, namely, beta-carotene, lycopene, canthaxanthin, retinol, alpha-tocopherol, and tau-tocopherol. The target population was women with a histopathological diagnosis of cervical intraepithelial neoplasia (CIN) or cervical cancer and a control group. All women resided in the same catchment area (Bronx Borough, New York City) and were of similar inner-city socioeconomic backgrounds representing a fairly homogenous population group. A cross-sectional sample of 235 women was recruited with informed consent. Plasma nutrient levels were measured	CS		(-)

				by reverse-phase high pressure liquid chromatography under study codes. The mean plasma levels of carotenoids (beta-carotene, lycopene, and canthaxanthin), as well as alpha-tocopherol, were significantly lower in women with CIN and cervical cancer. In contrast, the mean plasma level of tau-tocopherol was higher among patients with CIN, while the mean plasma level of retinol was comparable among the groups. There were significant linear trends for all three carotenoids and quadratic trends for alpha- and tau-tocopherol with the degree of cervical histopathology. Plasma beta-carotene concentrations in cigarette smokers were significantly lower regardless of cervical pathology, whereas plasma lycopene and canthaxanthin levels were significantly lower in smokers with CIN. The findings of a decrease in all plasma antioxidant nutrient levels except tau-tocopherol in women with CIN and cancer suggest a potential role for antioxidant deficiency in the pathogenesis of CIN and carcinoma of the cervix, which requires further investigation.		
Cancer: cervical	Giuliano AR	Antioxidant nutrients: associations with persistent human papillomavirus infection. Giuliano AR, Papenfuss M, Nour M, Canfield LM, Schneider A, Hatch K. Cancer Epidemiol Biomarkers Prev. 1997 Nov;6(11):917-23.	1997	Research from the past several years has definitively shown intermediate and high risk-type human papillomavirus (HPV) infection to play a significant role in cervical carcinogenesis. Persistent compared with intermittent infection appears to confer an elevated risk, and cofactors may be necessary to allow the virus to progress to cervical cancer. We explored the association between circulating concentrations of the antioxidant nutrients (alpha- and beta-carotene, lutein, lycopene, beta-cryptoxanthin, alpha-tocopherol, gamma-tocopherol, and ascorbate) and persistent HPV infection among 123 low-income Hispanic women who were all nonsmokers and were not currently using vitamin and mineral supplements. In addition, the association between these nutrients and grade of cervical pathology, independent of HPV status, was assessed. Intermediate and high risk-type HPV infection was assessed by the Digene Hybrid Capture System at two time points, 3 months apart. At the second interview, cytology, colposcopy, and a fasting blood draw were conducted. Mean concentrations of serum and plasma antioxidant nutrients were calculated within categories of HPV status (two times HPV negative, one time HPV positive, and two times HPV positive) and colposcopy. Adjusted mean concentrations of serum beta-carotene, beta-cryptoxanthin, lutein, and alpha- and gamma-tocopherol were on average 24% ($P < 0.05$) lower among women two times HPV positive compared with either two times HPV negative or one time HPV positive. Independent of HPV status, alpha-tocopherol was significantly inversely associated with grade of cervical dysplasia (normal, 21.57 microM; cervical intraepithelial	CS		N

				neoplasia III, 17.27 microM). The results obtained in this study need to be confirmed in larger cohort studies with a longer follow-up period.		
Cancer: cervical	Goodman MT	The association of plasma micronutrients with the risk of cervical dysplasia in Hawaii. Goodman MT, Kiviat N, McDuffie K, Hankin JH, Hernandez B, Wilkens LR, Franke A, Kuypers J, Kolonel LN, Nakamura J, Ing G, Branch B, Bertram CC, Kamemoto L, Sharma S, Killeen J. Cancer Epidemiol Biomarkers Prev. 1998 Jun;7(6):537-44.	1998	Limited data from hematological studies suggest that certain nutrients, including carotenoids, tocopherols, and vitamin C, may protect against malignant change in cervical tissue. Recognizing that human papillomavirus (HPV) infection induces most neoplastic transformation of cervical tissue, the authors conducted a case-control study to examine the association of plasma micronutrient concentrations with the risk of cervical dysplasia after careful adjustment for HPV infection, using a sensitive and reliable HPV detection method. The sample included 147 multiethnic women, between 18 and 65 years of age, with biopsy-confirmed squamous intraepithelial lesions (SILs) of the cervix and 191 clinic controls identified between 1992 and 1996. Cases were identified through cytology and pathology logs in three clinics on Oahu, Hawaii. Controls were selected randomly from admission logs of the participating clinics. In-person interviews were conducted in the subjects' homes, and a fasting blood sample was drawn to measure plasma levels of lutein, lycopene, cryptoxanthin, total carotene, retinol, tocopherol, ascorbic acid, and cholesterol. The presence and type of HPV was determined in exfoliated cell samples using PCR dot blot hybridization. Mean plasma lycopene, total cryptoxanthin, and alpha-cryptoxanthin levels were lower among cases than controls. We found an inverse dose-response of alpha-cryptoxanthin, total tocopherol, and alpha-tocopherol to the odds ratios for cervical SIL after adjustment for HPV and other confounders. The odds ratio among women in the highest compared with the lowest quartile was 0.3 (95% confidence interval, 0.1-0.7) for alpha-cryptoxanthin and 0.3 (95% confidence interval, 0.1-0.8) for alpha-tocopherol. Negative trends in the odds ratios were suggested for other carotenoids and vitamin C, but these were weak, and confidence intervals were wide. Our results support existing evidence that high plasma levels of antioxidants may reduce the risk of cervical SILs independent of HPV infection. These findings are significant because diet is potentially modifiable, and nutrition education and dietary intervention might be targeted at specific high-risk groups.	CC	N
Cancer: cervical	Peng YM	Concentrations of carotenoids, tocopherols, and retinol in paired plasma and cervical	1998	Paired blood (collected after an overnight fast) and cervical tissue (cancerous, precancerous, and noncancerous) samples were obtained from 87 patients (age, 21-86 years) who had a hysterectomy or biopsy due to cervical cancer, precancer (cervical intraepithelial neoplasia I, II, and III), or	CC serum + tissue	N

		tissue of patients with cervical cancer, precancer, and noncancerous diseases. Peng YM, Peng YS, Childers JM, Hatch KD, Roe DJ, Lin Y, Lin P. Cancer Epidemiol Biomarkers Prev. 1998 Apr;7(4):347-50.		noncancerous diseases. The samples were analyzed using high-performance liquid chromatography for 10 micronutrients (lutein, zeaxanthin, beta-cryptoxanthin, lycopene, alpha-carotene, beta-carotene, cis-beta-carotene, alpha-tocopherol, gamma-tocopherol, and retinol). The results indicated that: (a) among the three patient groups, the mean plasma concentrations of all micronutrients except gamma-tocopherol were lowest in the cancer patients; however, the mean tissue concentrations of the two tocopherols and certain carotenoids were highest in the cancerous tissue; and (b) among the 10 micronutrients, only the concentrations of beta-carotene and cis-beta-carotene were lower in both the plasma and tissue of cancer and precancer patients than in those of noncancer controls. These results suggest that: (a) not all of the micronutrient concentrations in plasma reflect the micronutrient concentrations in cervical tissue; thus, in some cases, it may be necessary to measure the tissue micronutrient concentrations to define the role of the micronutrients in cervical carcinogenesis; and (b) maintaining an adequate plasma and tissue concentration of beta-carotene may be necessary for the prevention of cervical cancer and precancer.		
Cancer: cervical	Nagata C	Serum carotenoids and vitamins and risk of cervical dysplasia from a case-control study in Japan. Nagata C, Shimizu H, Yoshikawa H, Noda K, Nozawa S, Yajima A, Sekiya S, Sugimori H, Hirai Y, Kanazawa K, Sugase M, Kawana T. Br J Cancer. 1999 Dec;81(7):1234-7.	1999	The relationships between risk of cervical dysplasia and dietary and serum carotenoids and vitamins were investigated in a case-control study. Cases were 156 women who attended Papanicolaou test screening in nine institutes affiliated with Japan Study Group of Human Papillomavirus (HPV) and Cervical Cancer and had cervical dysplasia newly histologically confirmed. Age-matched controls were selected from women with normal cervical cytology attending the same clinic. Blood sample and cervical exfoliated cells were obtained for measuring serum retinol, alpha-carotene, beta-carotene, zeaxanthin/lutein, cryptoxanthin, lycopene and alpha-tocopherol and for HPV detection. Higher serum level of alpha-carotene was significantly associated with decreased risk of cervical dysplasia after controlling for HPV infection and smoking status (odds ratio (OR) = 0.16, 95% confidence interval (CI) 0.04-0.62 for the highest as compared with the lowest tertile). Decreased risk for the highest tertile of serum lycopene (OR = 0.28) was marginally significant. Decreased risks observed for the highest tertiles of beta-carotene (OR = 0.65) and zeaxanthin/lutein (OR = 0.53), were not statistically significant.	CC		(-)
Cancer: cervical	Schiff MA	Serum carotenoids and risk of cervical	2001	The objective of this research was to evaluate the association between serum carotenoids and cervical intraepithelial	CC		NR/N

		intraepithelial neoplasia in Southwestern American Indian women. Schiff MA, Patterson RE, Baumgartner RN, Masuk M, van Asselt-King L, Wheeler CM, Becker TM. Cancer Epidemiol Biomarkers Prev. 2001 Nov;10(11):1219-22.		neoplasia (CIN) among Southwestern American Indian women. Cases were American Indian women with biopsy-proven CIN II/III cervical lesions (n = 81) diagnosed between November 1994 and October 1997. Controls were American Indian women from the same clinics with normal cervical epithelium (n = 160). All of the subjects underwent interviews and laboratory evaluations. Interviews evaluated demographic information, sexual history, and cigarette smoking. Serum concentrations of alpha-carotene, beta-carotene, beta-cryptoxanthin, lycopene, and lutein/zeaxanthin were measured by high performance liquid chromatography. Cervical humanpapillomavirus infection was detected using a PCR-based test. Increasing levels of alpha-carotene, beta-cryptoxanthin, and lutein/zeaxanthin were associated with decreasing risk of CIN II/III. In addition, the highest tertiles of beta-cryptoxanthin (odds ratio = 0.39, 95% confidence interval = 0.17-0.91) and lutein/zeaxanthin (odds ratio = 0.40, 95% confidence interval = 0.17-0.95) were associated with the lowest risk of CIN. In conclusion, specially targeted intervention efforts to increase consumption of fruits and vegetables may protect Southwestern American Indian women from developing CIN.		
Cancer: cervical	Sedjo RL	Vitamin A, carotenoids, and risk of persistent oncogenic human papillomavirus infection. Sedjo RL, Roe DJ, Abrahamsen M, Harris RB, Craft N, Baldwin S, Giuliano AR. Cancer Epidemiol Biomarkers Prev. 2002 Sep;11(9):876-84.	2002	Oncogenic human papillomavirus (HPV) infection is the main etiologic factor for cervical neoplasia, although infection alone is insufficient to produce disease. Cofactors such as nutritional factors may be necessary for viral progression to neoplasia. Results from previous studies have suggested that higher dietary consumption and circulating levels of certain micronutrients may be protective against cervical neoplasia. This study evaluated the role of vitamin A and carotenoids on HPV persistence comparing women with intermittent and persistent infections. As determined by the Hybrid Capture II system, oncogenic HPV infections were assessed at baseline and at approximately 3 and 9 months postbaseline. Multivariate logistic regression analysis was used to determine the risk of persistent HPV infection associated with each tertile of dietary and circulating micronutrients. Higher levels of vegetable consumption were associated with a 54% decrease risk of HPV persistence (adjusted odds ratio, 0.46; 95% confidence interval, 0.21-0.97). Also, a 56% reduction in HPV persistence risk was observed in women with the highest plasma cis-lycopene concentrations compared with women with the lowest plasma cis-lycopene	PC	(-)

				concentrations (adjusted odds ratio, 0.44; 95% confidence interval, 0.19-1.01). These data suggest that vegetable consumption and circulating cis-lycopene may be protective against HPV persistence.		
Cancer: cervical	Goodman MT	Hawaii cohort study of serum micronutrient concentrations and clearance of incident oncogenic human papillomavirus infection of the cervix. Goodman MT, Shvetsov YB, McDuffie K, Wilkens LR, Zhu X, Franke AA, Bertram CC, Kessel B, Bernice M, Sunoo C, Ning L, Easa D, Killeen J, Kamemoto L, Hernandez BY. Cancer Res. 2007 Jun 15;67(12):5987-96. Epub 2007 Jun 6.	2007	The degree to which the resolution of human papillomavirus (HPV) infection parallels exposure to other factors, particularly those related to nutritional status, is a relatively unexplored area of research. We established a cohort of women for long-term follow-up to examine the association of serum retinol, carotenoid, and tocopherol concentrations with the clearance of incident cervical HPV infection. Interviews and biological specimens were obtained at baseline and at 4-month intervals. At each visit, a cervical cell specimen for HPV DNA analysis and cytology and a fasting blood sample to measure micronutrient levels were collected. A Cox proportional hazards model was used to study the relationship between clearance of 189 incident (type-specific) oncogenic HPV infections and the levels of 20 serum micronutrients among 122 women. Higher circulating levels of trans-zeaxanthin, total trans-lutein/zeaxanthin, cryptoxanthin (total and beta), total trans-lycopene and cis-lycopene, carotene (alpha, beta, and total), and total carotenoids were associated with a significant decrease in the clearance time of type-specific HPV infection, particularly during the early stages of infection (<or=120 days). HPV clearance time was also significantly shorter among women with the highest compared with the lowest serum levels of alpha-tocopherol and total-tocopherol, but significant trends in these associations were limited to infections lasting <or=120 days. Clearance of persistent HPV infection (lasting >120 days) was not significantly associated with circulating levels of carotenoids or tocopherols. Results from this investigation support an association of micronutrients with the rapid clearance of incident oncogenic HPV infection of the uterine cervix.	PC	(-) ↓ clearance time of HPV in early infection
Cancer: cervical	Cho H	Relationship of serum antioxidant micronutrients and sociodemographic factors to cervical neoplasia: a case-control study. Cho H, Kim MK, Lee JK, Son SK, Lee KB,	2009	BACKGROUND: Although there have been some epidemiological studies on the effects of diet and nutritional status on cervical carcinogenesis, evidence for a protective effect of antioxidant micronutrients against cervical neoplasia is insufficient. The relationship between serum antioxidant micronutrients and sociodemographic factors and the risk of cervical neoplasia was investigated in this multi-center, case-control study.	CC	(-)

		Lee JM, Lee JP, Hur SY, Kim JH. Clin Chem Lab Med. 2009;47(8):1005-12		METHODS: The study population included women with histopathological diagnosis of cervical intraepithelial neoplasia (CIN) 1 (n=147), CIN 2/3 (n=177), cervical cancer (n=160), and a control group (n=378). Epidemiological data were collected and the serum concentrations of beta-carotene, lycopene, zeaxanthin plus lutein, retinol, alpha-tocopherol, and gamma-tocopherol were measured using reverse-phase, gradient high-pressure liquid chromatography. RESULTS: Cervical cancer was found to be associated with older age, increased body mass index, and lower socioeconomic status as measured by education level and income. The mean serum concentrations of beta-carotene, lycopene, zeaxanthin plus lutein, retinol, alpha-tocopherol, and gamma-tocopherol of cervical cancer patients were significantly lower than those of control subjects. Odds ratio adjusted for age, smoking status, alcohol consumption, and human papillomavirus infection status revealed a significant gradient of decreasing risk of CIN 1, CIN 2/3, and cervical cancer with increasing serum concentrations of most antioxidant micronutrients. CONCLUSIONS: The results of this study show an inverse association between serum antioxidant micronutrient concentrations and the risk of cervical neoplasia. These results suggest that antioxidant micronutrients play a role in the prevention of cervical carcinogenesis.			
Cancer: cervical	Tong SY	Functional polymorphism in manganese superoxide dismutase and antioxidant status: their interactions on the risk of cervical intraepithelial neoplasia and cervical cancer. Tong SY, Lee JM, Song ES, Lee KB, Kim MK, Lee JK, Son SK, Lee JP, Kim JH, Kwon YI. Gynecol Oncol.	2009	OBJECTIVE: Manganese superoxide dismutase (MnSOD), the primary antioxidant enzyme in mitochondria, plays a key role in protecting cells from oxidative stress. Furthermore, the MnSOD rs4880 polymorphism is associated with enzyme activity. The authors evaluated the interaction between MnSOD genotypes and cervical carcinogenesis risk and the modulating effects of serum antioxidant nutrient status (beta-carotene, lycopene, zeaxanthin/lutein, retinol, alpha-tocopherol and gamma-tocopherol) METHODS: Cases and controls for this study were recruited between June 2006 and July 2007 (263 controls, 84 cervical intraepithelial neoplasia (CIN), 94 CIN 2/3, and 99 cases of cervical cancer). The MnSOD polymorphism at rs4880T/C was examined using SNaPshot assays. Serum antioxidant vitamin concentrations were measured by reverse-phase gradient high-pressure liquid chromatography. Odds ratios (OR) and 95% confidence intervals (95%CI) were estimated after adjusting for age, menopause, parity, oral contraceptive use, smoking and alcohol consumption RESULTS: No association was found between the MnSOD	CC		(-)	MnSOD polymorphism and Lyco interaction

		2009 Nov;115(2):272-6. Epub 2009 Aug 25		rs4880 polymorphism and cervical cancer. However, genotypes significantly modified the risk of cervical cancer in association with the serum statuses of micronutrients (P(interaction)<0.05 for beta-carotene, lycopene, zeaxanthin/lutein, alpha-tocopherol, and gamma-tocopherol). Decreased CIN1 risk in association with the MnSOD rs4880 variant genotype was also observed particularly for subjects with higher beta-carotene and gamma-tocopherol levels. Similar results were observed for lycopene and alpha-tocopherol in relation to the risk of CIN2/3. CONCLUSION: Our findings suggest that a higher antioxidant micronutrients status may decrease the risk of CIN and cervical cancer and modify the effect of the MnSOD polymorphism on disease risk.		
Cancer: cervical	Tomita LY	Diet and serum micronutrients in relation to cervical neoplasia and cancer among low-income Brazilian women. Tomita LY, Longatto Filho A, Costa MC, Andreoli MA, Villa LL, Franco EL, Cardoso MA; Brazilian Investigation into Nutrition and Cervical Cancer Prevention (BRINCA) Study Team. Int J Cancer. 2010 Feb 1;126(3):703-14	2010	Cervical cancer is a leading cancer among women in developing countries. Infection with oncogenic human papillomavirus (HPV) types has been recognized as a necessary cause of this disease. Serum carotenoids and tocopherols have also been associated with risk for cervical neoplasia, but results from previous studies were not consistent. We evaluated the association of serum total carotene and tocopherols, and dietary intakes with the risk of newly diagnosed, histologically confirmed cervical intraepithelial neoplasia (CIN) grades 1, 2, 3 and invasive cancer in a hospital-based case-control study in São Paulo, Brazil. The investigation included 453 controls and 4 groups of cases (CIN1, n = 140; CIN2, n = 126; CIN3, n = 231; invasive cancer, n =108) recruited from two major public clinics between 2003 and 2005. Increasing concentrations of serum lycopene were negatively associated with CIN1, CIN3 and cancer, with odds ratios (OR) (95% CI) for the highest compared to the lowest tertile of 0.53 (0.27-1.00, p for trend = 0.05), 0.48 (0.22-1.04, p for trend = 0.05) and 0.18 (0.06-0.52, p for trend = 0.002), respectively, after adjusting for confounding variables and HPV status. Increasing concentrations of serum alpha- and gamma-tocopherols, and higher dietary intakes of dark green and deep yellow vegetables/fruit were associated with nearly 50% decreased risk of CIN3. These results support the evidence that a healthy and balanced diet leading to provide high serum levels of antioxidants may reduce cervical neoplasia risk in low-income women.	CC		(-)

Colorectal Cancer Critical Findings

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Cancer: colorectal	Pappalardo G	Plasma (carotenoids, retinol, alpha-tocopherol) and tissue (carotenoids) levels after supplementation with beta-carotene in subjects with precancerous and cancerous lesions of sigmoid colon. Pappalardo G, Maiani G, Mobarhan S, Guadalaxara A, Azzini E, Raguzzini A, Salucci M, Serafini M, Trifero M, Illomei G, Ferro-Luzzi A. Eur J Clin Nutr. 1997 Oct;51(10):661-6.	1997	OBJECTIVES: (1) To compare tissue and plasma carotenoids status of healthy subjects and subjects with pre-cancer and cancer lesions; (2) to evaluate the effect of beta-carotene supplementation on the concentrations of other carotenoids in tissue (luteine + zeaxanthin, cryptoxanthin, lycopene, alpha-carotene) and in plasma and also retinol and alpha-tocopherol levels. DESIGN: Eighteen subjects were divided into three groups on the basis of colonoscopy and histological analytical findings: four healthy subjects (control group A); seven subjects affected by adenomatous polyps (group B with pre-cancer lesions); seven subjects suffering from colonic cancer (group C). Blood and colonic biopsy samples were taken (of colon and rectal mucosa) before and after beta-carotene supplementation in all subjects. Groups A and B received a daily dose of beta-carotene (30 mg/die) for 43 d. Group C's supplementation was terminated at the time which was performed, usually within 15 d. The tissue and plasma concentration of carotenoids, retinol and alpha-tocopherol were determined by high-performance liquid chromatography. RESULTS: The tissue concentrations of each carotenoid were similar in all the intestinal sites examined as regards groups A and B, although there was a high degree of intra individual variability within each group. Only beta-carotene made significant increases ($P < 0.001$) after supplementation. The subjects with cancer show tissue levels for each carotenoid lower than those of healthy subjects or subjects with polypous. The plasma levels of alpha-tocopherol did not change after supplementation while significant increases were noted of retinol, alpha-carotene ($P < 0.01$) and of beta-carotene ($P < 0.001$). CONCLUSIONS: The patients with colonic cancer seemed to undergo a significant reduction in their antioxidant reserves with respect to the normal subjects and or polyps. We can confirm that oral B-carotene supplementation induces also an increase in plasma alpha-carotene in all groups.	CC				(-)	weakness small study no regression analysis
Cancer: colorectal	Erhardt JG	Lycopene, beta-carotene, and colorectal adenomas.	2003	BACKGROUND: Epidemiologic studies found that high tomato intakes reduce the risk of colorectal cancers. This beneficial effect is assumed to be caused by high intakes of lycopene, a	CC				(-) ↑ risk in adenoma group if ↓	

		Erhardt JG, Meisner C, Bode JC, Bode C. Am J Clin Nutr. 2003 Dec;78(6):1219-24.		carotenoid with strong antioxidant activity that is present predominantly in tomatoes. OBJECTIVE: We assessed the relation between plasma lycopene concentrations and colorectal adenomas, the precursors formost colorectal cancers. In addition, the concentrations of 2 other antioxidants, beta-carotene and alpha-tocopherol, were measured. DESIGN: White subjects undergoing a complete colonoscopy were included in the study (73 with adenomas, 63 without any polyps, and 29 with hyperplastic polyps). A detailed dietary history and information on alcohol consumption and smoking habits were collected from all subjects. Plasma lycopene, beta-carotene, and alpha-tocopherol concentrations were measured by using HPLC. RESULTS: Patients with adenomas and control subjects without polyps did not differ significantly in body mass index; intakes of energy, fat, protein, carbohydrates, fiber, beta-carotene, and alcohol; or prevalence of smoking, but patients with adenomas were slightly older. The median plasma lycopene concentration was significantly lower in the adenoma group than in the control group (-35%; P = 0.016). The median plasma beta-carotene concentration also tended to be lower in the adenoma group (-25.5%), but the difference was not significant. In the multiple logistic regression, only smoking (odds ratio: 3.02; 95% CI: 1.46, 6.25; P = 0.003) and a plasma lycopene concentration < 70 microg/L (odds ratio: 2.31; 1.12, 4.77; P = 0.023) were risk factors for adenomatous polyps. Patients with hyperplastic polyps did not differ significantly from control subjects in any variable. CONCLUSION: Our findings support the hypothesis that lycopene contributes to the protective effect of high tomato intakes against the risk of colorectal adenomas.		plasma [lyco]
Cancer: colorectal	Ito Y	Cancer mortality and serum levels of carotenoids, retinol, and tocopherol: a population-based follow-up study of inhabitants of a rural area of Japan. Ito Y, Kurata M,	2005	A total of 3,182 subjects (1,239 males and 1,943 females) aged from 39y to 79y, were recruited from the inhabitants of a rural area in Japan who participated in health check-up programs from 1988 to 1995. During the 10.5 year follow-up, 287 deaths (175 males and 112 females) from all causes, 134 (81 males and 53 females) from cancer of all sites, 31 from lung cancer, 21 from colorectal cancer, 20 from stomach cancer, and 62 from other cancers, were identified among the cohort subjects. Fasting serum samples were taken at the time of the health check-ups, and serum levels of carotenoids, retinol and tocopherols were separately determined by HPLC. Statistical analyses were performed using Cox's proportional hazard model	PC	(-) ↓ risk with ↑ serum [lyco]

		Hioki R, Suzuki K, Ochiai J, Aoki K. Asian Pac J Cancer Prev. 2005 Jan-Mar;6(1):10-5.		after adjusting for sex, age, and other confounding factors. High serum levels of alpha- and beta- carotenes and lycopene were found to marginally significantly or significantly reduce the risk for mortality rates of cancer of all sites and of colorectal cancers. High serum levels of beta-cryptoxanthin also showed an inversely relation with the risk of mortality from lung and stomach cancers, but this was not statistically significant. High intake of green-yellow vegetables contributing to serum levels of alpha- and beta- carotenes, as well as lycopene, may reduce the risk of cancer mortality, especially from colorectal cancer, in rural Japanese.		
Cancer: colorectal	Leung EY	Vitamin antioxidants, lipid peroxidation, tumour stage, the systemic inflammatory response and survival in patients with colorectal cancer. Leung EY, Crozier JE, Talwar D, O'Reilly DS, McKee RF, Horgan PG, McMillan DC. Int J Cancer. 2008 Nov 15;123(10):2460-4.	2008	Both the tumour growth and progression and the systemic inflammatory response have the potential to increase oxidative stress. We therefore examined the relationship between lipid-soluble antioxidant vitamins, lipid peroxidation, the systemic inflammatory response and survival in patients with primary operable (n = 53) and advanced inoperable (n = 53) colorectal cancer. Compared with those patients with primary operable colorectal cancer, patients with unresectable liver disease had significantly lower median concentrations of alpha-tocopherol ($p < 0.001$), lutein ($p < 0.001$), lycopene ($p < 0.001$), alpha-carotene ($p < 0.01$) and beta-carotene ($p < 0.001$) and higher malondialdehyde concentrations. An elevated systemic inflammatory response (Glasgow prognostic score, mGPS) was associated with a greater proportion of females ($p < 0.05$) and more advanced tumour stage ($p < 0.05$), lower circulating levels of retinol ($p < 0.01$), lutein ($p < 0.01$), lycopene ($p < 0.01$) and alpha- ($p < 0.01$) and beta-carotene but not MDA ($p = 0.633$). In the liver metastases group 41 patients died of their cancer and a further 1 patient died of intercurrent disease on follow-up. On univariate survival analysis, mGPS ($p < 0.01$), retinol ($p < 0.001$), alpha-tocopherol ($p < 0.05$) and alpha-carotene ($p < 0.05$) were associated significantly with cancer-specific survival. On multivariate survival analysis of these significant variables, only mGPS ($p < 0.01$) and retinol ($p < 0.001$) were independently associated with cancer-specific survival. The results of the present study showed that the systemic inflammatory response was associated with a reduction of lipid-soluble antioxidant vitamins, whereas advanced tumour stage was associated with increased lipid peroxidation in patients with colorectal cancer. Of the antioxidant vitamins measured, only retinol was independently associated with cancer-specific survival. (c) 2008 Wiley-Liss, Inc.	CC		N ↓ lyco in inop group

Endo Cancer Critical Findings

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Cancer: endo-metrial	Jeong NH	Preoperative levels of plasma micronutrients are related to endometrial cancer risk. Jeong NH, Song ES, Lee JM, Lee KB, Kim MK, Yun YM, Lee JK, Son SK, Lee JP, Kim JH, Hur SY, Kwon YI. Acta Obstet Gynecol Scand. 2009;88(4):371-2.	2009	OBJECTIVE: To examine the relation between the plasma concentration of antioxidant micronutrients and endometrial cancer risk in Korean women. DESIGN: Hospital-based case-control study. SETTING: Seven tertiary medical institutes in Korea. POPULATION: Incidence of 28 endometrial cancer cases were identified and 140 age-matched controls selected for the same period. METHODS: Preoperative plasma concentrations of beta-carotene, lycopene, zeaxanthin plus lutein, retinol, alpha-tocopherol, and gamma-tocopherol were measured by reverse-phase, gradient high-pressure liquid chromatography. Conditional logistic regression was used to evaluate micronutrient effect after adjustment for body mass index (BMI), menopause, parity, oral contraceptive use, smoking status, and alcohol consumption status. MAIN OUTCOME MEASURES: Effect of micronutrients on endometrial cancer risk. RESULTS: The mean concentration of plasma beta-carotene (p=0.001), lycopene (p=0.008), zeaxanthin plus lutein (p=0.031), retinol (p=0.048), and gamma-tocopherol (p=0.046) were significantly lower in endometrial cancer patients than in controls. Plasma levels of beta-carotene (p for trend=0.0007) and lycopene (p for trend=0.007) were inversely associated with endometrial cancer risk across tertiles. Women in the highest tertile of plasma beta-carotene and lycopene had a 0.12-fold (95% confidence intervals (CIs) 0.03-0.48) and 0.15-fold (95% CIs 0.04-0.61) decreased risk of endometrial cancer compared to women in the lowest tertile, respectively. Other micronutrients such as zeaxanthin plus lutein (p for trend=0.142), retinol (p for trend=0.108), alpha-tocopherol (p for trend=0.322), and gamma-tocopherol (p for trend=0.087) showed no association with endometrial cancer risk. CONCLUSIONS: Plasma levels of beta-carotene and lycopene are inversely associated with the risk of endometrial cancer in Korean women.	CC				(-) ↓ risk endometrial cancer	

Gastric Cancer Critical Findings

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Cancer: gastric	Tsugane S	Cross-sectional study with multiple measurements of biological markers for assessing stomach cancer risks at the population level. Tsugane S, Tsuda M, Gey F, Watanabe S. Environ Health Perspect. 1992 Nov;98:207-10.	1992	A cross-sectional study to determine correlations between measurable biologic markers and mortality from stomach cancer was performed in various areas of Japan. Blood and urine were collected from randomly selected 40- to 49-year-old men and their spouses in four areas with different rates of mortality from stomach cancer. The samples were analyzed for levels of the micronutrients vitamins A, C, and E, beta-carotene, and lycopene in plasma and for levels of NaCl, nitrate, and N-nitrosamino acids (N-nitrosoproline, N-nitrosothioproline [NTPRO] and N-nitrosomethylthioproline [NMTPRO]) in 24-hr urine. A significant, strong correlation was found between the amount of salt excreted in urine and stomach cancer mortality in both men and women. Although the amounts of nitrate and of the three N-nitrosamino acids in 24-hr urine were not correlated with stomach cancer rates, the low excretion levels of NTPRO and NMTPRO in the lowest risk area for stomach cancer were noteworthy, regardless of the high level of nitrate excretion in the same area. This suggests a lesser degree of endogenous nitrosation in the body. No protective effect of micronutrients was observed in this correlation study; there was, however, a negative correlation between plasma lycopene level and stomach cancer mortality. Salt intake was thus confirmed to play an important role in the development of stomach cancer and is likely to be a rate-regulating factor in Japanese populations. N-Nitrosamino acids and lycopene may also be related to stomach cancer mortality.	CS				(-)	
Cancer: gastric	Nomura AM	Serum micronutrients and upper aerodigestive tract cancer. Nomura AM, Ziegler RG, Stemmermann GN, Chyou PH, Craft NE. Cancer Epidemiol Biomarkers Prev. 1997 Jun;6(6):407-12.	1997	Numerous dietary studies have found that vegetables and fruits protect against upper aerodigestive tract cancer. To evaluate the role of beta-carotene and other specific carotenoids, a nested case-control study using prediagnostic serum was conducted among 6832 American men of Japanese ancestry examined from 1971 to 1975. During a surveillance period of 20 years, the study identified 28 esophageal, 23 laryngeal, and 16 oral-pharyngeal cancer cases in this cohort. The 69 cases were matched to 138 controls. A liquid chromatography technique, designed to optimize recovery and separation of the individual carotenoids, was used to measure serum levels of lutein, zeaxanthin, beta-cryptoxanthin, lycopene, alpha-carotene, beta-carotene, retinol, retinyl palmitate, and alpha-, delta-, and gamma-tocopherol. With adjustment for cigarette smoking and alcohol intake, we found that alpha-carotene, beta-carotene, beta-cryptoxanthin, total carotenoids and gamma-tocopherol levels were significantly lower in the 69 upper aerodigestive tract cancer patients than in their controls.	CC nested				N	

				Trends in risk by tertile of serum level were significant for these five micronutrients. These significant trends persisted in cases diagnosed 10 or more years after phlebotomy for the three individual carotenoids and total carotenoid measurements. The odds ratios for the highest tertile were 0.19 (95% confidence interval, 0.05-0.75) for alpha-carotene, 0.10 (0.02-0.46) for beta-carotene, 0.25 (0.06-1.04) for beta-cryptoxanthin, and 0.22 (0.05-0.88) for total carotenoids. When the cases were separated into esophageal, laryngeal, and oral-pharyngeal cancer, both alpha-carotene and beta-carotene were consistently and strongly associated with reduced risk at each site. The findings suggest that alpha-carotene and other carotenoids, as well as beta-carotene, may be involved in the etiology of upper aerodigestive tract cancer.		
Cancer: gastric	Tsubono Y	Plasma antioxidant vitamins and carotenoids in five Japanese populations with varied mortality from gastric cancer. Tsubono Y, Tsugane S, Gey KF. Nutr Cancer. 1999;34(1):56-61.	1999	To examine the geographic associations between plasma antioxidant levels and gastric cancer risk, we conducted an ecological study in five regions of Japan representing the threefold variation in the disease mortality within the country. Subjects were 634 men aged 40-49 years sampled randomly from the five regions with 72% response rates. Plasma concentrations of five carotenoids (beta-carotene, alpha-carotene, lycopene, lutein, and zeaxanthin), alpha-tocopherol, and ascorbic acid were measured, and the mean levels were correlated with age-adjusted mortality rates from gastric cancer. beta-Carotene and alpha-tocopherol were inversely correlated with gastric cancer rates (r = -0.31 and -0.89, respectively). alpha-Carotene and lycopene showed stronger inverse correlation than did beta-carotene (r = -0.67 and -0.56, respectively), but these relations disappeared after the exclusion of one outlying region in Okinawa with the lowest mortality. In contrast, ascorbic acid revealed a negative correlation with the exclusion of this outlier (r = -0.61). Lutein and zeaxanthin were not inversely associated with risk. The results suggest that plasma levels of beta-carotene and alpha-tocopherol, and possibly alpha-carotene, lycopene, and ascorbic acid, may partly account for the regional difference in gastric cancer mortality in Japan.	Eco	N
Cancer: gastric	Nagao T	Serum antioxidant micronutrients and the risk of oral leukoplakia among Japanese. Nagao T, Ikeda N, Warnakulasuriya S, Fukano H, Yuasa H, Yano M, Miyazaki	2000	A population-based case-control study was designed for the investigation of any association between serum micronutrient levels and oral leukoplakia. Out of a total of 9536 subjects over the age of 40 years who participated in the oral mucosal screening programme in Tokoname city, 48 cases detected with oral leukoplakia (38 male:10 female) were recruited. For each case, four controls matched by age and sex were selected from the same cohort. We examined the fasting serum levels of retinol, alpha-tocopherol, zeaxanthin and lutein, cryptoxanthin, lycopene and carotenoids (alpha-carotene and beta-	CC	(-)/N risk est

		H, Ito Y. Oral Oncol. 2000 Sep;36(5):466-70.		carotene) by high-performance liquid chromatography. Among males with leukoplakia mean serum lycopene and beta-carotene levels (0.175+/-0.202, 0.357+/-0.295 micromol/l) were significantly lower than those of controls (0.257+/-0.252, 0.555+/-0.408 micromol/l) (P<0.05, P<0.005). Logistic regression analysis with leukoplakia as the dependent variable showed that high serum levels of beta-carotene were related to low risk of oral leukoplakia (odds ratio 0.160, 95% C.I.: 0.029-0.866, P<0.05). There were no significant differences in any of the serum nutrients estimated in female subjects. Our results suggest for the first time that high serum levels of beta-carotene may provide protection against oral precancer for the Japanese male.		
Cancer: gastric	Yuan JM	Prediagnostic levels of serum micronutrients in relation to risk of gastric cancer in Shanghai, China. Yuan JM, Ross RK, Gao YT, Qu YH, Chu XD, Yu MC. Cancer Epidemiol Biomarkers Prev. 2004 Nov;13(11 Pt 1):1772-80.	2004	Data on blood levels of specific carotenoids and vitamins in relation to gastric cancer are scarce. Little is known about the relationship between prediagnostic serum levels of carotenoids other than beta-carotene and risk of gastric cancer especially in non-Western populations. Prediagnostic serum concentrations of alpha-carotene, beta-carotene, beta-cryptoxanthin, lycopene, lutein/zeaxanthin, retinol, alpha-tocopherol, gamma-tocopherol, and vitamin C were determined on 191 cases and 570 matched controls within a cohort of 18,244 middle-aged or older men in Shanghai, China, with a follow-up of 12 years. High serum levels of alpha-carotene, beta-carotene, and lycopene were significantly associated with reduced risk of developing gastric cancer (all Ps for trend </= 0.05); the odds ratios (95% confidence intervals) for the highest versus the lowest quartile of alpha-carotene, beta-carotene, and lycopene were 0.38 (0.13-1.11), 0.54 (0.32-0.89), and 0.55 (0.30-1.00), respectively. Increased serum level of vitamin C was significantly associated with reduced risk of gastric cancer among men who neither smoked cigarettes over lifetime nor consumed >/=3 drinks of alcohol per day; the odds ratios (95% confidence intervals) for the second, third, and fourth quartile categories were 0.69 (0.28-1.70), 0.36 (0.14-0.94), and 0.39 (0.15-0.98), respectively, compared with the lowest quartile of vitamin C (P for trend = 0.02). There were no statistically significant relationships of serum levels of beta-cryptoxanthin, lutein/zeaxanthin, retinol, alpha-tocopherol, and gamma-tocopherol with gastric cancer risk. The present study implicates that dietary carotenes, lycopene, and vitamin C are potential chemopreventive agents for gastric cancer in humans.	CC nested	(-) modest ↓ risk with ↑ serum [lyco]
Cancer: gastric	Persson C	Plasma levels of carotenoids, retinol and tocopherol and	2008	Fruits and vegetables have been suggested to confer protection against diseases such as cancer through the effects of antioxidants, often represented by carotenoids. We investigated the impact of carotenoids, retinol and tocopherol	CC nested	N

the risk of gastric cancer in Japan: a nested case-control study. Persson C, Sasazuki S, Inoue M, Kurahashi N, Iwasaki M, Miura T, Ye W, Tsugane S; JPHC Study Group. Carcinogenesis. 2008 May;29(5):1042-8. Epub 2008 Mar 13.	on gastric cancer development in a large nested case-control study among Japanese with known Helicobacter pylori infection status. A total of 36 745 subjects aged 40-69 in the Japan Public Health Center-based Prospective Study who responded to the baseline questionnaire and provided blood samples in 1990-1995 were followed until 2004. Plasma levels of carotenoids in 511 gastric cancer cases and 511 matched controls were measured by high-performance liquid chromatography. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were estimated using conditional logistic regression models. Plasma level of beta-carotene was inversely associated with the risk of gastric cancer (compared with the lowest quartile: OR = 0.63, 95% CI = 0.31-0.75; OR = 0.48, 95% CI = 0.31-0.75 and OR = 0.46, 95% CI = 0.28-0.75, for quartile 2, 3 and 4, respectively, P(trend) < 0.01). Inverse associations were evident in men for alpha-carotene (P(trend) = 0.04) and beta-carotene (P(trend) < 0.01), but not in women, who had relatively higher plasma levels compared with men. We found no statistically significant association between plasma levels of lutein/zeaxanthin, lycopene, retinol, alpha- or gamma-tocopherol and gastric cancer risk. Our findings suggest that those who have very low plasma levels of alpha-carotene and beta-carotene are at a higher risk of gastric cancer. Collaborators (100): Sobue T, Hanaoka T, Ogata J, Baba S, Mannami T, Okayama A, Kokubo Y, Miyakawa K, Saito F, Koizumi A, Sano Y, Hashimoto I, Ikuta T, Miyajima Y, Suzuki N, Nagasawa S, Furusugi Y, Nagai N, Sanada H, Hatayama Y, Kobayashi F, Uchino H, Shirai Y, Kondo T, Sasaki R, Watanabe Y, Miyagawa Y, Kobayashi Y, Kishimoto Y, Takara E, Fukuyama T, Kinjo M, Irei M, Sakiyama H, Imoto K, Yazawa H, Seo T, Seiko A, Ito F, Shoji F, Murata A, Minato K, Motegi K, Fujieda T, Matsui K, Abe T, Katagiri M, Suzuki M, Doi M, Terao A, Ishikawa Y, Tagami T, Sueta H, Doi H, Urata M, Okamoto N, Ide F, Sakiyama H, Onga N, Takaesu H, Uehara M, Horii F, Asano I, Yamaguchi H, Aoki K, Maruyama S, Ichii M, Takano M, Tsubono Y, Suzuki K, Honda Y, Yamagishi K, Sakurai S, Kabuto M, Yamaguchi M, Matsumura Y, Sasaki S, Watanabe S, Akabane M, Kadowaki T, Noda M, Kawaguchi Y, Takashima Y, Nakamura K, Matsushima S, Natsukawa S, Shimizu H, Sugimura H, Tominaga S, Iso H, Iida M, Ajiki W, Ioka A, Sato S, Maruyama E, Konishi M, Okada K, Saito I, Yasuda N, Kono S.

Head and Neck Cancer Critical Findings

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -

Cancer: head and neck	Djuric Z	Levels of fat-soluble micronutrients and 2,6-cyclolycopene-1,5-diol in head and neck cancer patients. Djuric Z, Ronis DL, Fowler KE, Ren J, Duffy SA. Int J Vitam Nutr Res. 2007 Nov;77(6):382-8	2007	Smoking negatively affects serum carotenoid levels, and it is a negative prognostic factor for head and neck cancer. In this study, micronutrient levels were examined in 60 smoking and non-smoking head and neck cancer patients. The goal was to determine if oxidation of the carotenoid lycopene would occur to a greater extent in smokers. Subjects were drawn from a prospective cohort study and matched on seven demographic factors. Serum levels of alpha-carotene, zeaxanthin, and 2,6-cyclolycopene-1,5-diol A, an oxidation product of lycopene, were all lower in smokers versus non-smokers (18%, 22%, and 8%, respectively) while beta-carotene, beta-cryptoxanthin, and lutein were about the same in the two groups. Levels of lycopene, gamma-tocopherol, and alpha-tocopherol were higher in smokers, and notably serum alpha-tocopherol was 48% higher in smokers. The majority of vitamin E intake was from supplements. The higher levels of alpha-tocopherol in smokers were interesting in that higher alpha-tocopherol levels have been associated with higher mortality in head and neck cancer. Although this was a pilot investigation, there was no evidence that 2,6-cyclolycopene-1,5-diol A formation was appreciably affected by smoking status, but alpha-tocopherol levels were higher in smokers.	CS nested	↓ in smokers	Lower in smokers Smokers vs non-smokers
Cancer: head and neck	Hughes KJ	Plasma Carotenoids and Biomarkers of Oxidative Stress in Patients with prior Head and Neck Cancer. Hughes KJ, Mayne ST, Blumberg JB, Ribaya-Mercado JD, Johnson EJ, Cartmel B. Biomark Insights. 2009 Mar 23;4:17-26.	2009	Diets high in fruits and vegetables are generally believed protective against several chronic diseases. One suggested mechanism is a reduction in oxidative stress. The carotenoids, nutrients found in colored fruits and vegetables, possess antioxidant properties in vitro, but their role in humans is less well documented. The aim of this cross-sectional study was to explore the relationships between the most abundant plasma carotenoids (alpha-carotene, beta-carotene, lycopene, lutein, zeaxanthin and beta-cryptoxanthin), as well as grouped carotenoids (total xanthophylls, carotenes and carotenoids), and urinary excretion of the F(2)-isoprostanes (F(2)-IsoPs), stable and specific biomarkers of oxidative damage to lipids. Two F(2)-IsoP measures were utilized: total F(2)-IsoPs and 8-iso-PGF(2alpha). The study population (N = 52) was drawn from a study among patients curatively treated for early-stage head and neck cancer. Unadjusted linear regression analyses revealed significant inverse associations between plasma lutein, total xanthophylls and both F(2)-IsoP measures at baseline. After control for potential confounders, all individual and grouped xanthophylls remained inversely associated with the F(2)-IsoP measures, but none of these associations achieved significance. The carotenes were not inversely associated with total F(2)-IsoPs or 8-iso-PGF(2a) concentrations. The finding of consistent inverse associations between individual and grouped xanthophylls, but not individual and grouped carotenes, and F(2)-IsoPs is intriguing and warrants further investigation.	CS	N Ox stress markers: F(2)-isoP and 8-iso-PGF(2alpha)	

Cancer: head and neck	Sakhi AK	Postradiotherapy plasma lutein, alpha-carotene, and beta-carotene are positively associated with survival in patients with head and neck squamous cell carcinoma. Sakhi AK, Bøhn SK, Smeland S, Thoresen M, Smedshaug GB, Tausjø J, Svilaas A, Karlsen A, Russnes KM, Svilaas T, Blomhoff R. Nutr Cancer. 2010;62(3):322-8	2010	The aim of our study was to compare plasma carotenoids (i.e., biomarkers of fruits and vegetables intake) and tocopherols in 29 head and neck squamous cell carcinoma (HNSCC) patients with 51 healthy controls and to explore the possibility whether these plasma antioxidants could be related to outcome among patients. The patients' blood samples were taken at the end of radiotherapy. We observed that plasma lutein, zeaxanthin, alpha-carotene, beta-carotene, lycopene, and total carotenoids were significantly lower in HNSCC patients than controls. Among the patients, 18 died and 11 were still alive during median follow-up of 55 mo for survivors. We found a significant positive association between postradiotherapy plasma carotenoids (lutein, alpha-carotene, and beta-carotene) and progression-free survival in these patients. This study indicates that increasing postradiotherapy plasma carotenoid concentration may reduce risk of premature death or recurrence of tumor in HNSCC patients. Increasing plasma carotenoid concentration should be done by increasing intake of carotenoid-rich fruits and vegetables, as other studies have shown either no or negative effects due to use of carotenoid supplements.	CC			N		Survival

Lung Cancer Critical Findings

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Cancer: lung	Comstock GW	The risk of developing lung cancer associated with antioxidants in the blood: ascorbic acid, carotenoids, alpha-tocopherol, selenium, and total peroxyl radical absorbing capacity. Comstock GW, Alberg AJ, Huang HY, Wu K, Burke AE, Hoffman SC, Norkus EP, Gross M, Cutler RG, Morris JS, Spate VL, Helzlsouer KJ.	1997	Lung cancer cases diagnosed during the period 1975 through 1993 and matched controls were identified in the rosters of Washington County, Maryland residents who had donated blood for a serum bank in 1974 or 1989. Plasma from participants in the 1989 project was assayed for ascorbic acid; serum or plasma was assayed for participants in either project for alpha- and beta-carotene, cryptoxanthin, lutein/zeaxanthin, lycopene, alpha-tocopherol, selenium, and peroxyl radical absorption capacity. Among the total group of 258 cases and 515 controls, serum/plasma concentrations were significantly lower among cases than controls for cryptoxanthin, beta-carotene, and lutein/zeaxanthin with case-control differences of -25.5, -17.1, and -10.1%, respectively. Modest nonsignificant case-control differences in a protective direction were noted for alpha-carotene and ascorbic acid. There were only trivial differences for lycopene, alpha-tocopherol, selenium, and peroxyl radical absorption capacity. Findings are reported for males and females and for persons who had never smoked cigarettes, former smokers, and current smokers at baseline. These results and those from previous studies	CC nested				N	

		Cancer Epidemiol Biomarkers Prev. 1997 Nov;6(11):907-16.		suggest that beta-carotene is a marker for some protective factor(s) against lung cancer; that cryptoxanthin, alpha-carotene, and ascorbic acid need to be investigated further as potentially protective factors or associates of a protective factor; and that lycopene, alpha-tocopherol, selenium, and peroxyl radical absorption capacity are unlikely to be associated with lung cancer risk. Until specific preventive factors are identified, the best protection against lung cancer is still the avoidance of airborne carcinogens, especially tobacco smoke; second best is the consumption of a diet rich in fruits and vegetables.		
Cancer: lung	Yuan JM	Prediagnostic levels of serum beta-cryptoxanthin and retinol predict smoking-related lung cancer risk in Shanghai, China. Yuan JM, Ross RK, Chu XD, Gao YT, Yu MC. Cancer Epidemiol Biomarkers Prev. 2001 Jul;10(7):767-73.	2001	Higher blood levels of beta-carotene have been found to be associated with reduced risk of lung cancer, but large intervention trials have failed to demonstrate reduced lung cancer incidence after prolonged high-dose beta-carotene supplementation. Data on blood levels of specific carotenoids other than beta-carotene in relation to lung cancer are scarce. Little is known about the relationship between prediagnostic serum levels of carotenoids, retinol, and tocopherols, and risk of lung cancer especially in non-Western populations. Between January 1986 and September 1989, 18,244 men ages 45-64 years participated in a prospective study of diet and cancer in Shanghai, China. Information on tobacco smoking and other lifestyle factors was obtained through in-person interviews. A serum sample was collected from each study participant at baseline. During the first 12 years of follow-up, 209 lung cancer cases, excluding those diagnosed within 2 years of enrollment, were identified. For each cancer case, three cancer-free control subjects were randomly selected from the cohort and matched to the index case by age (within 2 years), month and year of blood sample collection, and neighborhood of residence. Serum concentrations of retinol, alpha- and gamma-tocopherols, and specific carotenoids including alpha-carotene, beta-carotene, beta-cryptoxanthin, lycopene, and lutein/zeaxanthin were determined on the 209 cases and 622 matched controls by high-performance liquid chromatography methods. A high prediagnostic serum level of beta-cryptoxanthin was significantly associated with reduced risk of lung cancer; relative to the lowest quartile, the smoking-adjusted relative risks (95% confidence intervals) for the 2nd, 3rd, and 4th quartile categories were 0.72 (0.41-1.26), 0.42 (0.21-0.84), and 0.45 (0.22-0.92), respectively (P for trend = 0.02). Increased serum levels of other specific carotenoids including alpha-carotene, beta-carotene, lycopene, and lutein/zeaxanthinwere related to reduced risk of lung cancer although the inverse associations were no longer statistically significant after adjustment for smoking. A statistically significant 37% reduction in risk of lung cancer was noted in smokers with above versus below median level of total carotenoids. Serum retinol levels showed a threshold effect on lung cancer risk. Compared with the lowest quartile (<40 microg/dl), the smoking-adjusted relative risk (95% confidence interval) was 0.60	CC nested	N

				(0.39-0.92) for men in the 2nd-4th quartiles of retinol values combined; no additional decrease in risk was observed between individuals from the 2nd to 4th quartiles. There were no associations between prediagnostic serum levels of alpha- and gamma- tocopherols and lung cancer (all Ps for trend > or =0.4). The present data indicate that higher prediagnostic serum levels of total carotenoids and beta-cryptoxanthin were associated with lower smoking-related lung cancer risk in middle-aged and older men in Shanghai, China. Low level of serum retinol (with a threshold effect) is associated with increased lung cancer risk in this oriental population.		
Cancer: lung	Ito Y	Serum carotenoids and mortality from lung cancer: a case-control study nested in the Japan Collaborative Cohort (JACC) study. Ito Y, Wakai K, Suzuki K, Tamakoshi A, Seki N, Ando M, Nishino Y, Kondo T, Watanabe Y, Ozasa K, Ohno Y; JACC Study Group. Cancer Sci. 2003 Jan;94(1):57-63.	2003	To investigate whether high serum levels of carotenoids, tocopherols, and folic acid decrease risk of lung cancer in Japanese, we conducted a case-control study nested in the Japan Collaborative Cohort (JACC) Study. A total of 39,140 subjects provided serum samples at baseline between 1988 and 1990. We identified 147 cases (113 males and 34 females) of death from lung cancer during an 8-year follow-up. Of the subjects who survived to the end of this follow-up, 311 controls (237 males and 74 females) were selected, matched to each case of lung cancer death for gender, age and participating institution. We measured serum levels of antioxidants in cases of lung cancer death and controls. Odds ratios (ORs) for lung cancer death were estimated using conditional logistic models. The risk of lung cancer death for the highest quartile of serum alpha-carotene, beta-carotene, lycopene, beta-cryptoxanthin, and canthaxanthin was significantly or marginally significantly lower than for the lowest quartile: the ORs, adjusted for smoking and other covariates, were 0.35 (95% confidence interval (CI), 0.14-0.88), 0.21 (0.08-0.58), 0.46 (0.21-1.04), 0.44 (0.17-1.16) and 0.37 (0.15-0.91), respectively. The ORs for the highest serum levels of zeaxanthin/lutein and folic acid tended to be low, but the differences were not statistically significant. Serum total cholesterol was also inversely related to risk of lung cancer death: the OR for the highest vs. the lowest quartile was 0.39 (95% CI, 0.19-0.79). Higher serum levels of carotenoids such as alpha- and beta-carotenes may play a role in preventing death from lung cancer among Japanese.	CC nested		N
Cancer: lung	Comstock GW	The risk of developing lung cancer associated with antioxidants in the blood: ascorbic acids, carotenoids, alpha-tocopherol, selenium, and total peroxyl radical absorbing capacity.	2008	Lung cancer cases diagnosed during the period 1975 through 1993 and matched controls were identified in the rosters of Washington County, Maryland residents who had donated blood for a serum bank in 1974 or 1989. Plasma from participants in the 1989 project was assayed for ascorbic acid; serum or plasma was assayed for participants in either project for alpha- and beta-carotene, cryptoxanthin, lutein/zeaxanthin, lycopene, alpha-tocopherol, selenium, and peroxyl radical absorption capacity. Among the total group of 258 cases and 515 controls, serum/plasma concentrations were significantly lower among cases than controls for cryptoxanthin, beta-carotene, and lutein/zeaxanthin with case-control	CC		N

		Comstock GW, Alberg AJ, Huang HY, Wu K, Burke AE, Hoffman SC, Norkus EP, Gross M, Cutler RG, Morris JS, Spate VL, Helzlsouer KJ. Am J Epidemiol. 2008 Oct 1;168(7):831-40.		differences of -25.5, -17.1, and -10.1%, respectively. Modest nonsignificant case-control differences in a protective direction were noted for alpha-carotene and ascorbic acid. There were only trivial differences for lycopene, alpha-tocopherol, selenium, and peroxyl radical absorption capacity. Findings are reported for males and females and for persons who had never smoked cigarettes, former smokers, and current smokers at baseline. These results and those from previous studies suggest that beta-carotene is a marker for some protective factor(s) against lung cancer; that cryptoxanthin, alpha-carotene, and ascorbic acid need to be investigated further as potentially protective factors or associates of a protective factor; and that lycopene, alpha-tocopherol, selenium, and peroxyl radical absorption capacity are unlikely to be associated with lung cancer risk. Until specific preventive factors are identified, the best protection against lung cancer is still the avoidance of airborne carcinogens, especially tobacco smoke; second best is the consumption of a diet rich in fruits and vegetables.			
Cancer: lung	Klarod K	Serum antioxidant levels and nutritional status in early and advanced stage lung cancer patients. Klarod K, Hongsprabhas P, Khampitak T, Wirasorn K, Kiertiburanakul S, Tangrassameeprasert R, Daduang J, Yongvanit P, Boonsiri P. Nutrition. 2011 Apr 27. [Epub ahead of print]	2011	OBJECTIVE: Malnutrition frequently occurs in lung cancer patients. We aimed to determine nutritional status and antioxidant and mineral levels in Thai patients with lung cancer. METHODS: A prospective study with matched case-control was conducted. Nutritional status was assessed by body mass index (BMI) and subjective global assessment (SGA). Eastern Cooperative Oncology Group (ECOG) performance status was used to assess the performance. The serum antioxidant and mineral levels were determined. RESULTS: Forty-nine patients with a mean age of 58.8 (range, 35-82) who were first diagnosed with lung cancer were enrolled. They were compared with 60 healthy controls, and levels of retinol, α-tocopherol, β-carotene, lycopene, β-cryptoxanthin, selenium, and zinc were lower ($P < 0.05$). However, peroxidase activity was higher ($P = 0.002$) in patients. Selenium levels were higher in early stage compared to advanced stage patients ($P = 0.041$). Overweight patients had higher selenium levels (0.04 mg/L) than normal BMI patients ($\beta = 0.04$, $P = 0.035$). Patients with SGA class C had lower selenium levels (0.03 mg/L) than those with class A ($\beta = -0.03$, $P = 0.035$). The poorer ECOG performance patients had significantly lower β-carotene ($\beta = -0.192$, $P = 0.003$) and selenium ($\beta = -0.031$, $P = 0.011$) levels compared with those with good ECOG performance status. CONCLUSIONS: Significantly lower levels of antioxidants and selenium were found in lung cancer patients compared to healthy controls. Levels of some antioxidants and minerals differed among categories of BMI, SGA categories, or ECOG performance status. These findings may be helpful for further studies, such as the effect of nutritional supplementation on clinical outcomes.	CC		(-)	Low lyco in cases

Ovarian Cancer Critical Findings

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Cancer: ovarian	Jeong NH	Plasma carotenoids, retinol and tocopherol levels and the risk of ovarian cancer. Jeong NH, Song ES, Lee JM, Lee KB, Kim MK, Cheon JE, Lee JK, Son SK, Lee JP, Kim JH, Hur SY, Kwon YI. Acta Obstet Gynecol Scand. 2009;88(4):457-62.	2009	OBJECTIVE: We investigated the relation between plasma carotenoids, retinol and tocopherol levels and ovarian cancer risk in Korean women. DESIGN: Hospital-based case-control study. SETTING: Six tertiary medical institutes in Korea. POPULATION: Forty-five epithelial ovarian cancers and 135 age-matched controls. METHODS: Preoperative plasma concentrations of beta-carotene, lycopene, zeaxanthin plus lutein, retinol, alpha-tocopherol, and gamma-tocopherol were measured by reverse-phase, gradient high-pressure liquid chromatography. MAIN OUTCOME MEASURES: Odds ratios (OR) and 95% confidence intervals (95%CI) were estimated by tertiles to evaluate the effect of micronutrients on endometrial cancer risk after adjustment for body mass (BMI) index, menopause, parity, oral contraceptive use, smoking status, and alcohol consumption status. RESULTS: Women in the highest tertile for beta-carotene had 0.12-times the risk of ovarian cancer of in the lowest tertile (OR 0.12; 95%CI 0.04-0.36). Women with the highest tertiles of lycopene (OR 0.09; 95%CI 0.03-0.32), zeaxanthin/lutein (OR 0.21; 95%CI 0.09-0.52), retinol (OR 0.45; 95%CI 0.21-0.98), alpha-tocopherol (OR 0.23; 95%CI 0.10-0.53) and gamma-tocopherol (OR 0.28; 95%CI 0.11-0.70) had lower risk of ovarian cancer than women in the lowest tertiles. Results were consistent across strata of socio-epidemiologic factors. CONCLUSIONS: Micronutrients, specifically ss-carotene, lycopene, zeaxanthin, lutein, retinol, alpha-tocopherol, and gamma-tocopherol, may play a role in reducing the risk of ovarian cancer.	CC				(-)	
Cancer: ovarian	Helzlsouer KJ	Prospective study of serum micronutrients and	1996	BACKGROUND: Antioxidant micronutrients, such as alpha-tocopherol (vitamin E), the carotenoids, and selenium, may protect against the	CC nested				N	

ovarian cancer.

Helzlsouer KJ, Alberg AJ, Norkus EP, Morris JS, Hoffman SC, Comstock GW.

J Natl Cancer Inst. 1996 Jan 3;88(1):32-7.

development of cancer by preventing free radical damage at the cellular level.

PURPOSE: A nested case--control study was conducted among donors to a serum bank to examine the association between levels of serum micronutrients and/or cholesterol and the development of ovarian cancer.

METHODS: In 1974, sera were collected from 20,305 residents of Washington County, MD, over a 4-month period and stored at -70 °C. Serum micronutrient concentrations of women who developed ovarian cancer (case subjects, n = 35) were compared with those of women who remained free of cancer and who were matched to case subjects on age and menopausal status (control subjects, n = 67). Serum levels of retinol (vitamin A), alpha- and beta-carotene, lycopene, and alpha- and gamma- tocopherol were measured using high-performance liquid chromatography. Serum selenium (Se) was measured by neutron activation analysis. Cholesterol was measured by enzymatic assay. The data were categorized into thirds and conditional logistic regression analyses were performed to determine the association between prediagnostic serum cholesterol and micronutrient levels and the development of ovarian cancer; matched odds ratios (ORs) were determined from these regression analyses. P values for trend and for interaction were calculated with the use of two-sided likelihood ratio tests. RESULTS: Higher serum alpha-tocopherol levels were associated with an increased risk of ovarian cancer (P for trend = .04); however, this association diminished after adjustment for cholesterol. Women with higher serum cholesterol levels had an increased risk of ovarian cancer compared with women in the lowest third of cholesterol levels (OR = 3.2; 95% confidence interval = 0.9-11.3). The association between serum cholesterol levels and the risk of ovarian cancer was examined, stratifying by micronutrient level. The general pattern observed was an increased risk of ovarian cancer associated with cholesterol levels greater than 200 mg/dL, regardless of the micronutrient level. Serum selenium was associated with a decreased risk of ovarian cancer only among case participants diagnosed 4 or more years after blood collections (P for trend = .02). Concentrations of carotenoids and retinol were not associated with the development of ovarian cancer. CONCLUSIONS: Se may have a protective role against the development of ovarian cancer. Higher serum cholesterol levels were associated with an increased risk of developing ovarian cancer, which persisted regardless of serum micronutrient level.

IMPLICATIONS: Given the small size of this study and the inconsistency of results among the few prospective studies of ovarian cancer conducted

to test these associations, replications of these findings are highly desirable.

Pancreatic Cancer Critical Findings

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Cancer: pancreatic	Burney PG	Serologic precursors of cancer: serum micronutrients and the subsequent risk of pancreatic cancer. Burney PG, Comstock GW, Morris JS. Am J Clin Nutr. 1989 May;49(5):895-900.	1989	In a nested case-control study the stored, frozen sera from 22 cases of cancer of the pancreas and 44 matched control subjects were assayed for retinol, retinol-binding protein, total carotenoids, beta-carotene, lycopene, vitamin E (alpha-tocopherol), and selenium. Prediagnostic serum levels of lycopene and Se were lower among cases than among matched control subjects. These differences remained after adjustment was made for possible confounding by smoking, educational level, and the other measured serum levels. Low levels of serum vitamin E appeared to have a protective effect but a chance association between vitamin E and cancer of the pancreas could not reasonably be excluded. The association between cancer of the pancreas and serum Se was significant when the data were analyzed as a whole but its effect was seen principally in men.	CC nested				(-)	

Prostate Cancer Critical Findings

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Cancer: prostate	Hsing AW	Serologic precursors of cancer. Retinol, carotenoids, and tocopherol and risk of prostate cancer. Hsing AW, Comstock GW, Abbey H, Polk BF. J Natl Cancer Inst.	1990	We investigated the associations of serum retinol, the carotenoids beta-carotene and lycopene, and tocopherol (vitamin E) with the risk of prostate cancer in a nested case-control study. For the study, serum obtained in 1974 from 25,802 persons in Washington County, MD, was used. Serum levels of the nutrients in 103 men who developed prostate cancer during the subsequent 13 years were compared with levels in 103 control subjects matched for age and race. Although no significant associations were observed with beta-carotene, lycopene, or tocopherol, the data suggested an inverse relationship between serum retinol and risk of prostate cancer. We analyzed data on the distribution of serum retinol by quartiles, using the lowest	CC nested				N	

		1990 Jun 6;82(11):941-6.		quartile as the reference value. Odds ratios were 0.67, 0.39, and 0.40 for the second, third, and highest quartiles, respectively.				
Cancer: prostate	Nomura AM	Serum micronutrients and prostate cancer in Japanese Americans in Hawaii. Nomura AM, Stemmermann GN, Lee J, Craft NE. Cancer Epidemiol Biomarkers Prev. 1997 Jul;6(7):487-91.	1997	Numerous dietary studies and several serum micronutrient studies have produced equivocal results on the relation of vitamins A and E to prostate cancer risk. To evaluate this association further, we conducted a nested case-control study in a cohort of 6860 Japanese-American men examined from 1971 to 1975. At the time of examination, a single blood specimen was obtained, and the serum was frozen. After a surveillance period of more than 20 years, 142 tissue-confirmed incident cases of prostate cancer were identified. Their stored sera and those of 142 matched controls were measured by high-performance liquid chromatography for the following: total carotenoids, lutein, zeaxanthin, beta-cryptoxanthin, lycopene, alpha-carotene, beta-carotene, total retinoids, retinol, total tocopherols, alpha-tocopherol, delta-tocopherol, and gamma-tocopherol. Odds ratios for prostate cancer, based on quartiles of serum micronutrient levels, were determined using conditional logistic regression analysis. The odds ratio for the highest quartiles were 1.8 (95% confidence interval, 0.9-3.9) for beta-cryptoxanthin, 1.6 (0.8-3.5) for beta-carotene, 0.8 (0.4-1.5) for retinol, and 0.7 (0.3-1.5) for gamma-tocopherol, but none of the differences was statistically significant. For the other micronutrients, the results were also unremarkable. The findings of this study indicate that none of the micronutrients is strongly associated with prostate cancer risk.	CC nested		N	
Cancer: prostate	Gann PH	Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. Gann PH, Ma J, Giovannucci E, Willett W, Sacks FM, Hennekens CH, Stampfer MJ. Cancer Res. 1999 Mar 15;59(6):1225-30.	1999	Dietary consumption of the carotenoid lycopene (mostly from tomato products) has been associated with a lower risk of prostate cancer. Evidence relating other carotenoids, tocopherols, and retinol to prostate cancer risk has been equivocal. This prospective study was designed to examine the relationship between plasma concentrations of several major antioxidants and risk of prostate cancer. We conducted a nested case-control study using plasma samples obtained in 1982 from healthy men enrolled in the Physicians' Health Study, a randomized, placebo-controlled trial of aspirin and beta-carotene. Subjects included 578 men who developed prostate cancer within 13 years of follow-up and 1294 age- and smoking status-matched controls. We quantified the five major plasma carotenoid peaks (alpha- and beta-carotene, beta-cryptoxanthin, lutein, and lycopene) plus alpha- and gamma-tocopherol and retinol using high-performance liquid chromatography. Results for plasma beta-carotene are reported separately. Odds ratios (ORs), 95% confidence intervals (CIs), and Ps for trend were calculated for each quintile of plasma antioxidant using logistic regression models that allowed for adjustment of potential confounders and estimation of effect modification by assignment to either active beta-carotene or	CC nested		(-)/N	Pbo=(-) b-caro=(N)

				placebo in the trial. Lycopene was the only antioxidant found at significantly lower mean levels in cases than in matched controls (P = 0.04 for all cases). The ORs for all prostate cancers declined slightly with increasing quintile of plasma lycopene (5th quintile OR = 0.75, 95% CI = 0.54-1.06; P, trend = 0.12); there was a stronger inverse association for aggressive prostate cancers (5th quintile OR = 0.56, 95% CI = 0.34-0.91; P, trend = 0.05). In the placebo group, plasma lycopene was very strongly related to lower prostate cancer risk (5th quintile OR = 0.40; P, trend = 0.006 for aggressive cancer), whereas there was no evidence for a trend among those assigned to beta-carotene supplements. However, in the beta-carotene group, prostate cancer risk was reduced in each lycopene quintile relative to men with low lycopene and placebo. The only other notable association was a reduced risk of aggressive cancer with higher alpha-tocopherol levels that was not statistically significant. None of the associations for lycopene were confounded by age, smoking, body mass index, exercise, alcohol, multivitamin use, or plasma total cholesterol level. These results concur with a recent prospective dietary analysis, which identified lycopene as the carotenoid with the clearest inverse relation to the development of prostate cancer. The inverse association was particularly apparent for aggressive cancer and for men not consuming beta-carotene supplements. For men with low lycopene, beta-carotene supplements were associated with risk reductions comparable to those observed with high lycopene. These data provide further evidence that increased consumption of tomato products and other lycopene-containing foods might reduce the occurrence or progression of prostate cancer.		
Cancer: prostate	Rao AV	Serum and tissue lycopene and biomarkers of oxidation in prostate cancer patients: a case-control study. Rao AV, Fleshner N, Agarwal S. Nutr Cancer. 1999;33(2):159-64	1999	Dietary intake of tomatoes and tomato products containing lycopene, an antioxidant carotenoid, has been shown in recent studies to reduce the risk of cancer. This study was conducted to investigate the serum and prostate tissue lycopene and other major carotenoid concentrations in cancer patients and their controls. Serum lipid and protein oxidation was also measured. Twelve prostate cancer patients and 12 age-matched subjects were used in the study. Significantly lower serum and tissue lycopene levels (44%, p = 0.04; 78%, p = 0.050, respectively) were observed in the cancer patients than in their controls. Serum and tissue beta-carotene and other major carotenoids did not differ between the two groups (p = 0.395 and p = 0.280, respectively). Although there was no difference (p = 0.760) in serum lipid peroxidation between cancer patients and their controls (7.09 +/- 0.74 and 6.81 +/- 0.56 mumol/l, respectively), serum protein thiol levels were significantly lower among the cancer patients (p = 0.026). This study demonstrates that the status of lycopene but not other carotenoids in prostate cancer patients is different from controls. The role of dietary lycopene in	CC	(-)

				preventing oxidative damage of biomolecules and thereby reducing the risk of prostate cancer needs to be evaluated in future studies.		
Cancer: prostate	Lu QY	Inverse associations between plasma lycopene and other carotenoids and prostate cancer. Lu QY, Hung JC, Heber D, Go VL, Reuter VE, Cordon-Cardo C, Scher HI, Marshall JR, Zhang ZF. Cancer Epidemiol Biomarkers Prev. 2001 Jul;10(7):749-56.	2001	Although dietary intake of tomatoes and tomato products containing lycopene has been reported to reduce the risk of prostate cancer, few studies have been done on the relationship between plasma lycopene and other carotenoids and prostate cancer. This case-control study was conducted to investigate the effects of plasma lycopene, other carotenoids, and retinol, as well as alpha- and gamma-tocopherols on the risk of prostate cancer. The study included 65 patients with prostate cancer and 132 cancer-free controls; all of them were interviewed using a standard epidemiological questionnaire at the Memorial Sloan-Kettering Cancer Center from 1993 to 1997. Plasma levels of carotenoids, retinol, and tocopherols were measured by high performance liquid chromatography. An unconditional logistic regression model was used in bivariate and multivariate analyses using Statistical Analysis System (SAS). After adjusting for age, race, years of education, daily caloric intake, pack-years of smoking, alcohol consumption, and family history of prostate cancer, significantly inverse associations with prostate cancer were observed with plasma concentrations of the following carotenoids: lycopene [odds ratio (OR), 0.17; 95% confidence interval (CI), 0.04-0.78; P for trend, 0.0052] and zeaxanthin (OR, 0.22; 95% CI, 0.06-0.83; P for trend, 0.0028) when comparing highest with lowest quartiles. Borderline associations were found for lutein (OR, 0.30; 95% CI, 0.09-1.03; P for trend, 0.0064) and beta-cryptoxanthin (OR, 0.31; 95% CI, 0.08-1.24; P for trend, 0.0666). No obvious associations were found for alpha- and beta-carotenes, retinol, and alpha- and gamma-tocopherols. Our study confirmed the inverse associations between lycopene, other carotenoids such as zeaxanthin, lutein, and beta-cryptoxanthin, and prostate cancer. This study provides justification for further research on the associations between lycopene and other antioxidants and the risk of prostate cancer.	CC nested	(-)
Cancer: prostate	Vogt TM	Serum lycopene, other serum carotenoids, and risk of prostate cancer in US Blacks and Whites. Vogt TM, Mayne ST, Graubard BI, Swanson CA, Sowell AL,	2002	Epidemiologic studies investigating the relation between individual carotenoids and risk of prostate cancer have produced inconsistent results. To further explore these associations and to search for reasons prostate cancer incidence is over 50% higher in US Blacks than Whites, the authors analyzed the serum levels of individual carotenoids in 209 cases and 228 controls in a US multicenter, population-based case-control study (1986-1989) that included comparable numbers of Black men and White men aged 40-79 years. Lycopene was inversely associated with prostate cancer risk (comparing highest with lowest quartiles, odds ratio (OR) = 0.65, 95% confidence interval (CI): 0.36,	CC	(-)/N

		Schoenberg JB, Swanson GM, Greenberg RS, Hoover RN, Hayes RB, Ziegler RG. Am J Epidemiol. 2002 Jun 1;155(11):1023-32.		1.15; test for trend, p = 0.09), particularly for aggressive disease (comparing extreme quartiles, OR = 0.37, 95% CI: 0.15, 0.94; test for trend, p = 0.04). Other carotenoids were positively associated with risk. For all carotenoids, patterns were similar for Blacks and Whites. However, in both the controls and the Third National Health and Nutrition Examination Survey, serum lycopene concentrations were significantly lower in Blacks than in Whites, raising the possibility that differences in lycopene exposure may contribute to the racial disparity in incidence. In conclusion, the results, though not statistically significant, suggest that serum lycopene is inversely related to prostate cancer risk in US Blacks and Whites.		
Cancer: prostate	Huang HY	Prospective study of antioxidant micronutrients in the blood and the risk of developing prostate cancer. Huang HY, Alberg AJ, Norkus EP, Hoffman SC, Comstock GW, Helzlsouer KJ. Am J Epidemiol. 2003 Feb 15;157(4):335-44.	2003	Antioxidant micronutrients may have hemopreventive effects. The authors examined the associations between prediagnostic blood levels of micronutrients and prostate cancer risk in two nested case-control studies of 9,804 and 10,456 male residents of Washington County, Maryland, who donated blood in 1974 (CLUE I) and 1989 (CLUE II), respectively. Until 1996, 182 men for whom adequate serum remained for assays in the CLUE I cohort and 142 men in the CLUE II cohort developed prostate cancer. Each case was matched with two controls by age, gender, race, and date of blood donation. In both cohorts, cases and controls had similar concentrations of alpha-carotene, beta-carotene, total carotene, beta-cryptoxanthin, lutein, lycopene, retinol, and ascorbic acid; serum alpha-tocopherol was weakly associated with prostate cancer risk. Higher retinyl palmitate concentrations were associated with a lower risk in CLUE I but not CLUE II. In CLUE I, cases had lower concentrations of gamma-tocopherol than did controls (p = 0.02), but no dose-response trend was observed. A strong inverse association between gamma-tocopherol and prostate cancer risk was observed in CLUE II. Findings do not replicate previous reports of a protective association between lycopene and prostate cancer, but they suggest potential chemopreventive effects of gamma-tocopherol on prostate cancer.	CC nested		N
Cancer: prostate	Wu K	Plasma and dietary carotenoids, and the risk of prostate cancer: a nested case-control study. Wu K, Erdman JW Jr, Schwartz SJ, Platz EA, Leitzmann M, Clinton SK, DeGroff V, Willett	2004	The association between plasma carotenoids and prostate cancer risk was investigated in a case-control study nested within the prospective Health Professionals Follow-up Study. We matched 450 incident prostate cancer cases diagnosed from 1993-1998 to 450 controls by age, time, month, and year of blood donation. Modest inverse, but not statistically significant, associations were observed among plasma alpha-carotene, beta-carotene, and lycopene concentrations, and overall risk of prostate cancer diagnosis [odds ratio (highest versus lowest quintile; OR), alpha-carotene: OR, 0.67 [95% confidence interval (CI), -0.40-1.09]; beta-carotene: OR, 0.78 (95% CI, 0.48-1.25); lycopene: OR, 0.66 (95% CI, 0.38-1.13)]. The inverse association	CC nested		N (-) >65y, w/o FH

		WC, Giovannucci E. Cancer Epidemiol Biomarkers Prev. 2004 Feb;13(2):260-9.		between plasma lycopene concentrations and prostate cancer risk was limited to participants who were 65 years or older (OR, 0.47; 95% CI, 0.23-0.98) and without a family history of prostate cancer (OR, 0.48; 95% CI, 0.26-0.89). Combining, older age and a negative family history provided similar results (OR, 0.43; 95% CI, 0.18-1.02). Inverse associations between beta-carotene and prostate cancer risk were also found among younger participants (<65 years of age; OR, 0.36; 95% CI, 0.14-0.91; P(trend) = 0.03). Combining dietary intake and plasma data confirmed our results. We found a statistically significant inverse association between higher plasma lycopene concentrations and lower risk of prostate cancer, which was restricted to older participants and those without a family history of prostate cancer. This observation suggests that tomato products may exhibit more potent protection against sporadic prostate cancer rather than those with a stronger familial or hereditary component. In addition, our findings also suggest that among younger men, diets rich in beta-carotene may also play a protective role in prostate carcinogenesis.		
Cancer: prostate	Chang S	Relationship between plasma carotenoids and prostate cancer. Chang S, Erdman JW Jr, Clinton SK, Vadiveloo M, Strom SS, Yamamura Y, Duphorne CM, Spitz MR, Amos CI, Contois JH, Gu X, Babaian RJ, Scardino PT, Hursting SD. Nutr Cancer. 2005;53(2):127-34.	2005	Carotenoids, particularly lycopene, are thought to decrease prostate cancer risk, but the relationship between plasma carotenoid concentrations and risk in various populations has not been well characterized. Comparing 118 non-Hispanic Caucasian men mainly from southeast Texas with nonmetastatic prostate cancer with 52 healthy men from the same area, we conducted a case-control analysis evaluating associations between risk and plasma levels of total carotenoids, beta-cryptoxanthin, alpha- and trans-beta-carotene, lutein and zeaxanthin, total lycopenes, trans-lycopene, total cis-lycopenes, and cis-lycopene isoforms 1, 2, 3, and 5. Risk for men with high plasma levels of alpha-carotene, trans-beta-carotene, beta-cryptoxanthin, and lutein and zeaxanthin was less than half that for those with lower levels. In contrast, we observed no significant associations for total lycopenes, all-trans-lycopene, and cis-lycopene isomer peaks 2, 3, and 5, although high levels of cis-lycopene isomer peak 1 were inversely associated with risk. Analysis of men with aggressive disease (Gleason scores of > or =7, n = 88) vs. less aggressive cases (Gleason scores of <7, n = 30) failed to reveal significant associations between carotenoid levels and the risk of diagnosis with aggressive disease. These findings suggest that, in these men, higher circulating levels of alpha-cryptoxanthin, alpha-carotene, trans-beta-carotene, and lutein and zeaxanthin may contribute to lower prostate cancer risk but not to disease progression.	CC	N/(-) only ↓ risk with cis-lyco isomer 1

Cancer: prostate	Key TJ	Plasma carotenoids, retinol, and tocopherols and the risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition study. Key TJ, Appleby PN, Allen NE, Travis RC, Roddam AW, Jenab M, Egevad L, Tjanneland A, Riboli E., et al. Am J Clin Nutr. 2007 Sep;86(3):672-81.	2007	BACKGROUND: Previous studies suggest that high plasma concentrations of carotenoids, retinol, or tocopherols may reduce the risk of prostate cancer. OBJECTIVE: We aimed to examine the associations between plasma concentrations of 7 carotenoids, retinol, alpha-tocopherol, and gamma-tocopherol and prostate cancer risk. DESIGN: A total of 137,001 men in 8 European countries participated. After a mean of 6 y, 966 incident cases of prostate cancer with plasma were available. A total of 1064 control subjects were selected and were matched for study center, age, and date of recruitment. The relative risk of prostate cancer was estimated by conditional logistic regression, which was adjusted for smoking status, alcohol intake, body mass index, marital status, physical activity, and education level. RESULTS: Overall, none of the micronutrients examined were significantly associated with prostate cancer risk. For lycopene and the sum of carotenoids, there was evidence of heterogeneity between the associations with risks of localized and advanced disease. These carotenoids were not associated with the risk of localized disease but were inversely associated with the risk of advanced disease. The risk of advanced disease for men in the highest fifth of plasma concentrations compared with men in the lowest fifth was 0.40 (95% CI: 0.19, 0.88) for lycopene and 0.35 (95% CI: 0.17, 0.78) for the sum of carotenoids. CONCLUSIONS: We observed no associations between plasma concentrations of carotenoids, retinol, or tocopherols and overall prostate cancer risk. The inverse associations of lycopene and the sum of carotenoids with the risk of advanced disease may involve a protective effect, an association of dietary choice with delayed detection of prostate cancer, reverse causality, or other factors. Additional authors: Johnsen NF, Overvad K, Linseisen J, Rohrmann S, Boeing H, Pischon T, Psaltopoulou T, Trichopoulou A, Trichopoulos D, Palli D, Vineis P, Tumino R, Berrino F, Kiemeney L, Bueno-de-Mesquita HB, Quiras JR, Gonzalez CA, Martinez C, Larranaga N, Chirlaque MD, Ardanaz E, Stattin P, Hallmans G, Khaw KT, Bingham S, Slimani N, Ferrari P, Rinaldi S	CC		(-) ↓ risk
Cancer: prostate	Peters U	Serum lycopene, other carotenoids, and prostate cancer risk: a nested case-control study in the prostate, lung,	2007	BACKGROUND: Reports from several studies have suggested that carotenoids, and in particular lycopene, could be prostate cancer-preventive agents. This has stimulated extensive laboratory and clinical research, as well as much commercial and public enthusiasm. However, the epidemiologic evidence remains inconclusive.	CC		N

		colorectal, and ovarian cancer screening trial. Peters U, Leitzmann MF, Chatterjee N, Wang Y, Albanes D, Gelmann EP, Friesen MD, Riboli E, Hayes RB. Cancer Epidemiol Biomarkers Prev. 2007 May;16(5):962-8.		MATERIALS AND METHODS: We investigated the association between prediagnostic serum carotenoids (lycopene, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, and zeaxanthin) and risk of prostate cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, a multicenter study designed to examine methods of early detection and risk factors for cancer. The study included 692 incident prostate cancer cases, diagnosed 1 to 8 years after study entry, including 270 aggressive cases, with regional or distant stage (n = 90) or Gleason score >or=7 (n = 235), and 844 randomly selected, matched controls. As study participants were selected from those who were assigned to annual standardized screening for prostate cancer, results are unlikely to be biased by differential screening, a circumstance that is difficult to attain under non-trial conditions. RESULTS: No association was observed between serum lycopene and total prostate cancer [odds ratios (OR), 1.14; 95% confidence intervals (95% CI), 0.82-1.58 for highest versus lowest quintile; P for trend, 0.28] or aggressive prostate cancer (OR, 0.99; 95% CI, 0.62-1.57 for highest versus lowest quintile; P for trend, 0.433). beta-Carotene was associated with an ncreased risk of aggressive prostate cancer (OR, 1.67; 95% CI, 1.03-2.72 for highest versus lowest quintile; P for trend, 0.13); in particular, regional or distant stage disease (OR, 3.16; 95% CI, 1.37-7.31 for highest versus lowest quintile; P for trend, 0.02); other carotenoids were not associated with risk. CONCLUSION: In this large prospective study, high serum beta-carotene concentrations were associated with increased risk for aggressive, clinically relevant prostate cancer. Lycopene and other carotenoids were unrelated to prostate cancer. Consistent with other recent publications, these results suggest that lycopene or tomato-based regimens will not be effective for prostate cancer prevention.		
Cancer: prostate	Zhang J	Plasma carotenoids and prostate cancer: a population-based case-control study in Arkansas. Zhang J, Dhakal I, Stone A, Ning B, Greene G, Lang NP, Kadlubar FF.	2007	Carotenoids possess antioxidant properties and thus may protect against prostate cancer. Epidemiological studies of dietary carotenoids and this malignancy were inconsistent, partially due to dietary assessment error. In this study, we aimed to investigate the relation between plasma concentrations of carotenoids and the risk of prostate cancer in a population-based case-control study in Arkansas. Cases (n = 193) were men with prostate cancer diagnosed in 3 major hospitals, and controls (n = 197) were matched to cases by age, race, and county of residence. After adjustment for confounders, plasma levels of lycopene, utein/zeaxanthin, and beta-cryptoxanthin were inversely associated with prostate cancer risk. Subjects in the highest quartile of plasma lycopene (513.7 microg/l) had a 55% lower risk	CC	(-) ↓ risk

		Nutr Cancer. 2007;59(1):46-53.		of prostate cancer than those in the lowest quartile (140.5 microg/l; P trend = 0.042). No apparent association was observed for plasma alpha-carotene and beta-carotene. Further adjustment for the other 4 carotenoids did not materially alter the risk estimates for plasma lycopene, lutein/zeaxanthin, and beta-cryptoxanthin but appeared to result in an elevated risk with high levels of plasma alpha-carotene and beta-carotene. The results of all analyses did not vary substantially by age, race, and smoking status. This study added to the emerging evidence that high circulating levels of lycopene, lutein/zeaxanthin, and beta-cryptoxanthin are associated with a low risk of prostate cancer.		
Cancer: prostate	Mikhak B	Manganese superoxide dismutase (MnSOD) gene polymorphism, interactions with carotenoid levels and prostate cancer risk. Mikhak B, Hunter DJ, Spiegelman D, Platz EA, Wu K, Erdman JW Jr, Giovannucci E. Carcinogenesis. 2008 Dec;29(12):2335-40. Epub 2008 Sep 10. Gene.	2008	BACKGROUND: The manganese superoxide dismutase (MnSOD) gene encodes an antioxidant enzyme (SOD2) that may protect cells from oxidative damage. The MnSOD allele with Val as amino acid 16 encodes a protein that has 30-40% lower activity compared with the MnSOD Ala variant, hence possibly increasing susceptibility to oxidative stress. On the other hand, some epidemiologic studies suggest that the Ala allele is associated with a higher risk of cancer, including prostate cancer. METHODS: We conducted a nested case-control study in the Health Professionals Follow-up Study with 612 incident prostate cancer cases and 612 matched controls to investigate the role of the MnSOD gene Ala16Val polymorphism and its joint association with plasma carotenoid concentrations in relation to risk of total prostate cancer and aggressive prostate cancer (advanced stage or Gleason sum > or =7). RESULTS: The allele frequencies in the controls were 49.8% for Ala and 50.2% for Val. No association was found between the MnSOD genotype and risk of total and aggressive prostate cancer. Furthermore, no statistically significant interaction was observed between the MnSOD genotype and any of the plasma carotenoids in relation to risk of total and aggressive prostate cancer. In analyses in which we combined data from plasma and dietary carotenoids and created a quintile score to reflect long-term carotenoid status, a 3-fold [95% confidence interval: 1.37-7.02] increased risk of aggressive prostate cancer was observed among men with the Ala/Ala genotype in the presence of low long-term lycopene status (P-value, test for interaction = 0.02) as compared with men with the Ala/Val+Val/Val genotypes with low long-term lycopene status. CONCLUSION: In this cohort of mainly white men, the MnSOD gene Ala16Val polymorphism was not associated with total or aggressive prostate cancer risk. However, men with the MnSOD Ala/Ala genotype who had low long-term lycopene status had a higher risk of aggressive prostate cancer compared with	CC	(-) ↓ long term lyco status ↑ PC risk IF have Ala/Ala genotype

				individuals with the other genotypes. These results are consistent with findings from earlier studies that reported when antioxidant status is low, the MnSOD Ala/Ala genotype may be associated with an increased risk of aggressive prostate cancer.		
Cancer: prostate	Karppi J	Serum lycopene and the risk of cancer: the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) study. Karppi J, Kurl S, Nurmi T, Rissanen TH, Pukkala E, Nyyssanen K. Ann Epidemiol. 2009 Jul;19(7):512-8. Epub 2009 May 13.	2009	PURPOSE: Lycopene is thought to decrease the risk of cancers, although previous epidemiologic studies have produced inconsistent results. The aim of the present study was to evaluate the protective effect of lycopene against the risk of cancer. METHODS: The study population consisted of 997 middle-aged Finnish men in the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) cohort. During the mean follow-up time of 12.6 years, a total of 141 cancer cases appeared, of which 55 were prostate cancers. The association between the serum concentrations of lycopene and the risk of cancer was studied using the Cox proportional hazard models. RESULTS: An inverse association was observed between serum lycopene and overall cancer incidence. The adjusted risk ratio (RR) in the highest tertile of serum lycopene was 0.55 (95% confidence interval [CI], 0.34-0.89; p=0.015) compared with the lowest serum lycopene group. No association was observed between the lycopene concentrations and a prostate cancer risk. RR for other cancers was 0.43 (95% CI, 0.23-0.79; p=0.007). CONCLUSIONS: These findings suggest that in middle-aged men, the higher circulating concentrations of lycopene may contribute to the lower risk of cancer, with the exception of prostate cancer.	PC	(-)/N (-) ↓ risk overall cancer ~~~~~~ N prostate cancer
Cancer: prostate	Lee KM	Nitric oxide synthase gene polymorphisms and prostate cancer risk. Lee KM, Kang D, Park SK, Berndt SI, Reding D, Chatterjee N, Chanock S, Huang WY, Hayes RB. Carcinogenesis. 2009 Apr;30(4):621-5. Epub 2009 Jan 23.	2009	Nitric oxide (NO) induces cytotoxicity and angiogenesis, and may play a role in prostate carcinogenesis, potentially modulated by environmental exposures. We evaluated the association of prostate cancer with genetic polymorphisms in two genes related to intracellular NO: NOS2A [inducible nitric oxide synthase (NOS); -2892T>C, Ex16 + 14C>T (S608L), IVS16 + 88T>G and IVS20 + 524G>A] and NOS3 [endothelial NOS; IVS1-762C>T, Ex7-43C>T (D258D), IVS7-26A>G, Ex8-63G>T (E298D) and IVS15-62G>T]. Prostate cancer cases (n = 1320) from the screening arm of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial were frequency matched to controls (n = 1842), by age, race, time since initial screening and year of blood draw. An antioxidant score [range 3-12; low (3-7) versus high (8-12)] was created by summing the quartile levels of vitamin E, beta-carotene and lycopene, which were coded from 1 to 4, respectively. The global tests for all eight single-nucleotide polymorphisms (SNPs) (excluding NOS2A-2892T>C, with low minor allele frequency) were statistically significant for prostate cancer (P = 0.005), especially for	CC	(-) ↑ [lyco] modified effect of NOS2A IVS16 SNP

				aggressive cancer (stage III-IV or Gleason score > or = 7) (P = 0.01). The NOS2A IVS16 + 88 GT/TT was associated with increased prostate cancer risk (odds ratio = 1.24, 95% confidence interval = 1.00-1.54), whereas the IVS20 + 524 AG/GG was associated with decreased risk (0.77, 0.66-0.90). The NOS3 IVS7-26GG was associated with increased prostate cancer risk (1.33, 1.07-1.64). All these SNPs showed significant associations with aggressive cancer and not for non-aggressive cancer. In the evaluation of effect modification, the effect of the NOS2A IVS16 + 88 GT/TT on aggressive cancer was stronger among subjects with higher antioxidant intake (1.61, 1.18-2.19; P(interaction) = 0.01). Our results suggest that NOS gene polymorphisms are genetic susceptibility factors for aggressive prostate cancer.			
Cancer: prostate	Beilby J	Serum levels of folate, lycopene, β-carotene, retinol and vitamin E and prostate cancer risk. Beilby J, Ambrosini GL, Rossi E, de Klerk NH, Musk AW. Eur J Clin Nutr. 2010 Oct;64(10):1235-8. Epub 2010 Aug 4	2010	Previous studies relating increased serum levels of folate and fat-soluble vitamins to prostate cancer risk have variously shown null associations or to either decrease or increase the risk of developing prostate cancer. Prospective studies of serum folate levels have been reported to show a null association and increased serum levels to either decrease or increase the risk of subsequently developing prostate cancer. Similarly, serum β-carotene and lycopene levels have either been reported to be inversely correlated or not associated with prostate cancer risk. Using a prospective nested case-control study design, which minimized the possibility of disease effects on serum-vitamin concentrations, we report null associations for serum concentrations of folate, lycopene, β-carotene, vitamin A and vitamin E, and subsequent development of prostate cancer.	PC CC nested		N	
Cancer: prostate	Venkitaraman R	Serum micronutrient and antioxidant levels at baseline and the natural history of men with localised prostate cancer on active surveillance. Venkitaraman R, Thomas K, Grace P, Dearnaley DP, Horwich A, Huddart RA, Parker CC. Tumour Biol. 2010	2010	The aim of this study was to determine whether serum concentrations of micronutrients, antioxidants and vitamins predict rate of disease progression in untreated, localised prostate cancer. Patients with localised prostatic adenocarcinoma on a prospective study of active surveillance underwent monitoring with serial PSA levels and repeat prostate biopsies. Disease progression was defined as either adverse histology on repeat biopsy (primary Gleason grade >or=4 or >50% positive cores of total) or radical treatment for PSA velocity >1 ng ml(-1) year(-1). Time to disease progression was analysed with respect to baseline levels of alpha-tocopherol, gamma-tocopherol, alpha-carotene and beta-carotene, lycopene, retinol and selenium. One hundred four patients were evaluable, with a median follow-up of 2.5 years. Thirty-eight patients experienced disease progression, 13 biochemical and 25 histologic progression. Median time to disease progression was 2.62 years. No significant association was seen between time to disease progression and baseline serum levels of alpha-	PC		N	PSA Biopsies

		Apr;31(2):97-102. Epub 2010 Feb 16		tocopherol (p = 0.86), gamma-tocopherol (p = 0.84), alpha-carotenoid (p = 0.66), beta-carotene (p = 0.65), lycopene (p = 0.0.15), retinol (p = 0.76) or selenium (p = 0.76). No significant association was seen between serum levels of the micronutrients, antioxidants or vitamins and either adverse histology on repeat biopsy or PSA velocity. Our data do not support the hypothesis that high serum concentrations of micronutrients, antioxidants and vitamins prevent disease progression in men with localised prostate cancer.			
Cancer: prostate	Zhang J	Polymorphisms in inflammatory genes, plasma antioxidants, and prostate cancer risk. Zhang J, Dhakal IB, Lang NP, Kadlubar FF. Cancer Causes Control. 2010 Sep;21(9):1437-44. Epub 2010 Apr 30	2010	BACKGROUND: Presence of xenotropic murine leukemia virus-related virus and chronic inflammation in prostate tumor suggests that inflammation plays a role in prostate cancer etiology. This study investigated whether variants in inflammatory genes act alone or interact with plasma antioxidants to influence prostate cancer risk in a population-based case-control study in Central Arkansas. METHODS: Cases (n = 193) were men, aged 40-80, diagnosed with prostate cancer in three major hospitals in 1998-2003, and controls (n = 197) were matched to cases by age, race, and county of residence. RESULTS: After adjustment for confounders, olymorphisms in COX-2 (rs689466) and IL-8 (rs4073) were not significantly associated with prostate cancer risk. However, apparent interactions were observed between these genetic variants and plasma antioxidants on the risk of this malignancy. The protective effect of the mutant allele of the COX-2 polymorphism was more pronounced among subjects with high plasma levels of beta-cryptoxanthin, lycopene, beta-carotene, or selenium (>or=median) [e.g., OR (95% CI): 0.37 (0.15, 0.86) (AG/GG vs. AA) for beta-cryptoxanthin]. Conversely, the promoting effect of the variant allele of the IL-8 polymorphism was more remarkable in subjects with low plasma levels of Lutein/zeaxanthin, beta-cryptoxanthin, and beta-carotene (<median) [e.g., OR (95% CI): 2.44 (1.08, 5.75) (AT/TT vs. AA) for beta-carotene]. CONCLUSIONS: We found that sequence variants in inflammatory genes interact with plasma antioxidants to modulate prostate cancer risk.	CC	(-) COX-2 gene ~~~~~ N IL-8 gene	
Cancer: prostate	Beydoun HA	Associations of serum vitamin A and carotenoid	2011	Associations of serum vitamin A and carotenoid levels with markers of prostate cancer detection were evaluated among 3,927 US men, 40-85 years of age, who participated in the 2001-	CS	(+)	PSA

		levels with markers of prostate cancer detection among US men. Beydoun HA, Shroff MR, Mohan R, Beydoun MA. Cancer Causes Control. 2011 Jul 29. [Epub ahead of print]		2006 National Health and Nutrition Examination Surveys. Five recommended definitions of prostate cancer detection were adopted using total and free prostate-specific antigen (tPSA and fPSA) laboratory measurements. Men were identified as high risk based on alternative cutoffs, namely tPSA > 10 ng/ml, tPSA > 4 ng/ml, tPSA > 2.5 ng/ml, %fPSA < 25%, and %fPSA < 15%. %fPSA was defined as (fPSA÷tPSA)× 100%. Serum levels of vitamin A (retinol and retinyl esters) and carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein + zeaxanthin, lycopene) were defined as quartiles and examined as risk/protective factors for PSA biomarkers. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using binary logistic models. After adjustment for known demographic, socioeconomic, and lifestyle confounders, high serum levels of retinyl esters (tPSA > 10 ng/ml: Q4 vs. Q1 → OR = 0.38, 95% CI: 0.14-1.00) and α-carotene (%fPSA < 15%: Q4 vs. Q1 → OR = 0.49, 95% CI: 0.32-0.76) were associated with a lower odds, whereas high serum level of lycopene (tPSA > 2.5 ng/ml: Q4 vs. Q1 → OR = 1.49, 95% CI: 1.01-2.14) was associated with a greater odds of prostate cancer detection. Apart from the three significant associations observed, no other exposure-outcome association was significant. Monitoring specific antioxidant levels may be helpful in the early detection of prostate cancer.		
Cancer: prostate	Kristal AR	Serum lycopene concentration and prostate cancer risk: results from the Prostate Cancer Prevention Trial. Kristal AR, Till C, Platz EA, Song X, King IB, Neuhouser ML, Ambrosone CB, Thompson IM. Cancer Epidemiol Biomarkers Prev. 2011 Apr;20(4):638-46. Epub 2011 Feb 18.	2011	BACKGROUND: Lycopene has been promoted for prostate cancer prevention, despite the inconsistency of scientific evidence. METHODS: This nested case-control study examined whether serum lycopene was associated with prostate cancer risk among participants in the Prostate Cancer Prevention Trial, a placebo-controlled trial of finasteride for prostate cancer prevention. Presence or absence of cancer was determined by prostate biopsy, recommended during the trial due to elevated prostate specific antigen (PSA) level or abnormal digital rectal examination (DRE) and offered to all men at the trial end. There were 1,683 cases (461 Gleason score ≥ 7, 125 Gleason score ≥ 8) and 1,751 controls. RESULTS:There were no associations of lycopene with prostate cancer risk. The odds ratios for a linear increase in lycopene (per 10 μg/dL) were 0.99 (95% CI: 0.94-1.04), 1.01 (0.94-1.08), and 1.02 (0.90-1.15) for Gleason 2 to 6, 7 to 10, and 8 to 10, respectively. In the placebo arm, a 10 μg/dL increase in lycopene was associated with a 7% (95% CI: 14-0) reduced risk of cancer diagnosed following an elevated PSA or abnormal DRE, which are cancers that best match those detected in screened populations. However, a 10 μg/dL increase in lycopene was also associated with an 8% (95% CI: 1-16) increased risk of cancer diagnosed without a biopsy prompt, which are cancers generally not	CC nested		N

detected. These findings were similar for low- and high-grade cancer.

CONCLUSION: This study does not support a role for lycopene in prostate cancer prevention.

IMPACT: Scientists and the public should understand that early studies supporting an association of dietary lycopene with reduced prostate cancer risk have not been replicated in studies using serum biomarkers of lycopene intake. Recommendations of professional societies to the public should be modified to reflect the likelihood that increasing lycopene intake will not affect prostate cancer risk.

Prostate Cancer Critical Findings

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Cancer: prostate	Key TJ	A case-control study of diet and prostate cancer. Key TJ, Silcocks PB, Davey GK, Appleby PN, Bishop DT. Br J Cancer. 1997;76(5):678-87.	1997	We interviewed 328 men diagnosed with prostate cancer before the age of 75 years and 328 age-matched population controls. The principal hypotheses were that risk would increase with a high intake of total or saturated fat and would decrease with a high intake of carotene (beta-carotene equivalents) or lycopene. We also examined the associations of other nutrients and foods with risk. There was no evidence for an association between fat intake and risk, although the average fat intake was high and the range of fat intakes was narrow (medians of lower and upper thirds of percentage of energy	CC				N	

				from fat among controls were 34.3% and 42.9% respectively). Risk was lower in subjects with higher carotene intake: odds ratios 0.65 (95% CI 0.45-0.94) and 0.76 (0.53-1.10) in the middle and upper thirds of carotene intake respectively (P for trend = 0.150). Lycopene was not associated with risk. Among 13 other nutrients examined, the odds ratios in the top third of intake were below 0.8 for: potassium, 0.74 (0.51-1.09; P for trend = 0.054); zinc, 0.73 (0.49-1.08; P for trend = 0.126); iodine, 0.75 (0.51-1.11; P for trend = 0.077); vitamin B6 food only, 0.77 (0.53-1.12; P for trend = 0.077); and vitamin B6 including supplements, 0.70 (0.48-1.03; P for trend = 0.029). Among 18 foods examined, statistically significant associations were observed for: garlic as food, > or = 2/week vs never, 0.56 (0.33-0.93); garlic including supplements, > or = 2/week vs never, 0.60 (0.37-0.96); baked beans, > or = 2/week vs < 1/month, 0.57 (0.34-0.95); and garden peas, > or = 5/week vs < or = 3/month, 0.35 (0.13-0.91). This study does not support the hypothesis that fat increases risk and is quivocal in relation to carotene. The possible relationships of vitamin B6, garlic, beans and peas with risk for prostate cancer should be further investigated.		
Cancer: prostate	Meyer F	Dietary energy and nutrients in relation to preclinical prostate	1997	Previous studies of diet and prostate cancer have focused on advanced disease and have suggested a positive association with saturated fat intake. We	CC		N

		cancer. Meyer F, Bairati I, Fradet Y, Moore L. Nutr Cancer. 1997;29(2):120-6.		report a study assessing the relationship between diet and preclinical prostate cancer. A total of 215 men with preclinical prostate cancer and 593 controls with no evidence of cancer articipated in a case-control study conducted in Quebec City betweenOctober 1990 and May 1993. The study population comprised two groups: men treated surgically for benign prostatic hypertrophy and participants in a prostate cancer screening program. Trained nutritionists interviewed the participants on their usual diet using a diet history questionnaire. Odds ratios for prostate cancer associated with quartiles of dietary intake and P values for trend were estimated by logistic regression while controlling for age, education, group, and family history of prostate cancer. A positive association was observed between total energy intake and preclinical prostate cancer (p = 0.004). The odds ratios for prostate cancer increased with each quartile of energy intake: 1.00, 1.77, 1.90, and 2.67. After adjustment for energy, nutrients were not associated with prostate cancer. This study provides some evidence that total energy intake is related to preclinical prostate cancer and suggests that diet could be involved earlier than thought in the occurrence of prostate cancer.		
Cancer: prostate	Hayes RB	Dietary factors and risks for	1999	Prostate cancer is the most common malignancy in men in	CC	N

prostate cancer among blacks and whites in the United States.

Hayes RB, Ziegler RG, Gridley G, Swanson C, Greenberg RS, Swanson GM, Schoenberg JB, Silverman DT, Brown LM, Pottern LM, Liff J, Schwartz AG, Fraumeni JF Jr, Hoover RN.

Cancer Epidemiol Biomarkers Prev. 1999 Jan;8(1):25-34.

the United States, with substantially higher rates among American blacks than whites. We carried out a population-based case-control study in three geographic areas of the United States to evaluate the reasons for the racial disparity in incidence rates. A total of 932 men (449 black men and 483 white men) who had been newly diagnosed with pathologically confirmed prostate cancer and 1201 controls (543 black men and 658 white men) were interviewed in person to elicit information on potential risk factors. This report evaluates the impact of dietary factors, particularly the consumption of animal products and animal fat, on the risk of prostate cancer among blacks and whites in the United States. ncreased consumption (grams/day) of foods high in animal fat was linked to prostate cancer (independent of intake of other calories) among American blacks [by quartile of intake, odds ratio (OR) = 1.0 (referent), 1.5, 2.1, and 2.0; Ptrend = 0.007], but not among American whites [by quartile of intake, OR = 1.0 (referent), 1.6, 1.5, and 1.1; Ptrend = 0.90]. However, risks for advanced prostate cancer were higher with greater intake of foods high in animal fat among blacks [by quartile of intake, OR = 1.0 (referent), 2.2, 4.2, and 3.1; Ptrend = 0.006] and whites [by quartile of intake, OR = 1.0 (referent), 2.2, 2.6, and 2.4; Ptrend = 0.02]. Increased intake of animal fat as a proportion of total caloric intake also showed

				positive but weaker associations with advanced prostate cancer among blacks (Ptrend = 0.13) and whites (Ptrend = 0.08). No clear associations were found with vitamin A, calcium, or specific lycopene-rich foods. The study linked greater consumption of fat from animal sources to increased risk for prostate cancer among American blacks and to advanced prostate cancer among American blacks and whites. A reduction of fat from animal sources in the diet could lead to decreased incidence and mortality rates for prostate cancer, particularly among American blacks.		
Cancer: prostate	Vogt TM	Dietary factors and risks for prostate cancer among blacks and whites in the United States. Vogt TM, Mayne ST, Graubard BI, Swanson CA, Sowell AL, Schoenberg JB, Swanson GM, Greenberg RS, Hoover RN, Hayes RB, Ziegler RG. Cancer Epidemiol Biomarkers Prev. 1999 Jan;8(1):25-34.	1999	Prostate cancer is the most common malignancy in men in the United States, with substantially higher rates among American blacks than whites. We carried out a population-based case-control study in three geographic areas of the United States to evaluate the reasons for the racial disparity in incidence rates. A total of 932 men (449 black men and 483 white men) who had been newly diagnosed with pathologically confirmed prostate cancer and 1201 controls (543 black men and 658 white men) were interviewed in person to elicit information on potential risk factors. This report evaluates the impact of dietary factors, particularly the consumption of animal products and animal fat, on the risk of prostate cancer among blacks and whites in the	CC	N

United States. Increased consumption (grams/day) of foods high in animal fat was linked to prostate cancer (independent of intake of other calories) among American blacks [by quartile of intake, odds ratio (OR) = 1.0 (referent), 1.5, 2.1, and 2.0; Ptrend = 0.007], but not among American whites [by quartile of intake, OR = 1.0 (referent), 1.6, 1.5, and 1.1; Ptrend = 0.90]. However, risks for advanced prostate cancer were higher with greater intake of foods high in animal fat among blacks [by quartile of intake, OR = 1.0 (referent), 2.2, 4.2, and 3.1; Ptrend = 0.006] and whites [by quartile of intake, OR = 1.0 (referent), 2.2, 2.6, and 2.4; Ptrend = 0.02]. Increased intake of animal fat as a proportion of total caloric intake also showed positive but weaker associations with advanced prostate cancer among blacks (Ptrend = 0.13) and whites (Ptrend = 0.08). No clear associations were found with vitamin A, calcium, or specific lycopene-rich foods. The study linked greater consumption of fat from animal sources to increased risk for prostate cancer among American blacks and to advanced prostate cancer among American blacks and whites. A reduction of fat from animal sources in the diet could lead to decreased incidence and mortality rates for prostate cancer, particularly among American blacks.

Cancer: prostate	Norrish AE	Prostate cancer and dietary carotenoids. Norrish AE, Jackson RT, Sharpe SJ, Skeaff CM. Am J Epidemiol. 2000 Jan 15;151(2):119-23.	2000	This population-based case-control study investigated associations between prostatecancer risk and dietary intake of the carotenoids beta-carotene and lycopene and their major plant food sources, including carrots, green leafy vegetables, and tomato-based foods. The study was carried out in Auckland, New Zealand, during 1996-1997 and recruited 317 prostate cancer cases and 480 controls. The authors found that dietary intake of beta-carotene and its main vegetable sources was largely unassociated with prostate cancer risk, whereas intake of lycopene and tomato-based foods was weakly associated with a reduced risk. These results suggest that in contrast to the findings regarding many types of cancers, vegetables rich in beta-carotene are not protective against prostate cancer. However, lycopene from tomato-based foods was found to be associated with a small reduction in risk.	CC	(-)		(-)
Cancer: prostate	Giovannucci E	A prospective study of tomato products, lycopene, and prostate cancer risk. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. J Natl Cancer	2002	BACKGROUND: Some data, including our findings from the Health Professionals Follow-Up Study (HPFS) from 1986 through January 31, 1992, suggest that frequent intake of tomato products or lycopene, a carotenoid from tomatoes, is associated with reduced risk of prostate cancer. Overall, however, the data are inconclusive. We evaluated additional data from the HPFS to determine if the association would persist. METHODS: We	PC	(-)	(-)	(-)

Inst. 2002 Mar 6;94(5):391-8.

ascertained prostate cancer cases from 1986 through January 31, 1998, among 47 365 HPFS participants who completed dietary questionnaires in 1986, 1990, and 1994. We used pooled logistic regression to compute multivariate relative risks (RR) and 95% confidence intervals (CIs). All statistical tests were two-sided. RESULTS: From 1986 through January 31, 1998, 2481 men in the study developed prostate cancer. Results for the period from 1992 through 1998 confirmed our previous findings---that frequent tomato or lycopene intake was associated with a reduced risk of prostate cancer. Similarly, for the entire period of 1986 through 1998, using the cumulative average of the three dietary questionnaires, lycopene intake was associated with reduced risk of prostate cancer (RR for high versus low quintiles = 0.84; 95% CI = 0.73 to 0.96; P(trend) =.003); intake of tomato sauce, the primary source of bioavailable lycopene, was associated with an even greater reduction in prostate cancer risk (RR for 2+ servings/week versus <1 serving/month = 0.77; 95% CI = 0.66 to 0.90; P(trend)<.001), especially for extraprostatic cancers (RR = 0.65; 95% CI = 0.42 to 0.99). These associations persisted in analyses controlling for fruit and vegetable consumption and for olive oil use (a marker for editerranean diet) and were observed separately in men of Southern European or other Caucasian ancestry. CONCLUSION: Frequent consumption of tomato

				products is associated with a lower risk of prostate cancer. The magnitude of the association was moderate enough that it could be missed in a small study or one with substantial errors in measurement or based on a single dietary assessment.		
Cancer: prostate	Schuurman AG	A prospective cohort study on intake of retinol, vitamins C and E, and carotenoids and prostate cancer risk (Netherlands). Schuurman AG, Goldbohm RA, Brants HA, van den Brandt PA. Cancer Causes Control. 2002 Aug;13(6):573-82.	2003	OBJECTIVES: The roles of retinol, vitamins C and E, and carotenoids as risk factors for prostate carcinoma are still questionable. We evaluated these in the Netherlands Cohort Study. METHODS: The cohort study consisted of 58,279 men ages 55-69 years at baseline in 1986. After 6.3 years of follow-up, 642 incident prostate carcinoma cases were available for analysis. Intakes of retinol, vitamins C and E, and several carotenoids were measured by means of a 150-item semi-quantitative food-frequency questionnaire. RESULTS: In multivariate analyses a positive association with prostate cancer risk was observed for intake of beta- cryptoxanthin. Rate ratios (RRs) in increasing quintiles were 1.00 (ref), 0.94, 1.01, 1.16, 1.41; p-trend < 0.01. For intake of retinol, vitamins C and E and other carotenoids (alpha-carotene, beta-carotene, lycopene, and lutein/zeaxanthin) no effect on overall prostate cancer risk was found. RRs for vitamin supplement use were decreased, but not significantly. Among nondrinkers,	PC		N

				nonsignificant inverse associations were observed for intake of retinol, alpha-carotene, and beta-carotene (RRs, highest vs lowest quintile, were 0.23, 0.60, and 0.76, respectively). Among drinkers, beta-cryptoxanthin was positively associated (RR highest vs lowest quintile = 1.40). CONCLUSIONS: These data show a positive association between beta-cryptoxanthin and prostate cancer risk. Our study also shows inverse associations for retinol, alpha-carotene, and beta-carotene among nondrinkers; this suggests an interaction between vitamins and alcohol consumption, which needs confirmation. Lycopene was not associated with prostate cancer.			
Cancer: prostate	Jian L	Do dietary lycopene and other carotenoids protect against prostate cancer? Jian L, Du CJ, Lee AH, Binns CW. Int J Cancer. 2005 Mar 1;113(6):1010-4.	2005	To determine whether dietary intake of lycopene and other carotenoids has an etiological association with prostate cancer, a case-control study was conducted in Hangzhou, southeast China during 2001-2002. The cases were 130 incident patients with histologically confirmed adenocarcinoma of the prostate. The controls were 274 hospital inpatients without prostate cancer or any other malignant diseases. Information on usual food consumption, including vegetables and fruits, was collected by face-to-face interviews using a structured food frequency questionnaire. The risks of prostate cancer for the intake of carotenoids and selected vegetables and fruits rich in carotenoids were assessed using multivariate	CC	(-) ↓ risk prostate cancer	(-) ↓ risk prostate cancer

				logistic regression, adjusting for age, locality, education, income, body mass index, marital status, number of children, family history of prostate cancer, tea drinking, total fat and caloric intake. The prostate cancer risk declined with increasing consumption of lycopene, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein and zeaxanthin. Intake of tomatoes, pumpkin, spinach, watermelon and citrus fruits were also inversely associated with the prostate cancer risk. The adjusted odds ratios for the highest versus the lowest quartiles of intake were 0.18 (95% CI: 0.08-0.41) for lycopene, 0.43 (95% CI: 0.21-0.85) for alpha-carotene, 0.34 (95% CI: 0.17-0.69) for beta-carotene, 0.15 (95% CI: 0.06-0.34) for beta-cryptoxanthin and 0.02 (and zeaxanthin. The corresponding dose-response relationships were also significant, suggesting that vegetables and fruits rich in lycopene and other carotenoids may be protective against prostate cancer.		
Cancer: prostate	Goodman M	Lycopene intake and prostate cancer risk: effect modification by plasma antioxidants and the XRCC1 genotype. Goodman M, Bostick RM,	2006	Lycopene has been associated with reduced prostate cancer risk, although the results of epidemiological studies have varied. We hypothesize that an effect of lycopene may be modified by XRCC1 genotype and other antioxidants. We used a food-frequency questionnaire to assess lycopene intake in a case-control study of prostate cancer in North Carolina. Plasma	CC		(-) ↓ risk if have XRCC1 genotype and ↑ lyco intake

		Ward KC, Terry PD, van Gils CH, Taylor JA, Mandel JS. Nutr Cancer. 2006;55(1):13-		alpha-tocopherol and beta-carotene levels were measured using high-performance liquid chromatography. XRCC1 genotypes were detected using polymerase chain reaction-restriction fragment length polymorphism. The final dataset included 77 cases and 174 controls with complete questionnaires, genotyping, and plasma analyses. Among men with the Arg/Arg genotype at codon 399, odds ratios (ORs) for prostate cancer risk associated with medium (732-1,529 microg/day) and high (>1,529 microg/day) lycopene intake were 0.59 (95% confidence interval = 0.23-1.50) and 0.21 (0.06-0.71), respectively (P(trend) < 0.01). Similar analyses for persons with Arg/Gln or Gln/Gln genotypes produced null results. Above-median (1,048 microg/day) lycopene intake combined with above-median levels of alpha-tocopherol and beta-carotene was associated with an OR of 0.11 (0.02-0.65) among men with the Arg/Arg genotype but not those with at least one Gln allele (P(interaction) = 0.01). Although limited by small sample size, these findings indicate that the association between lycopene and prostate cancer is complex and may be modified by other antioxidants and by XRCC1 genotype.		
Cancer: prostate	Jian L	Tea and lycopene protect against prostate cancer.	2007	Prostate cancer is the most common male cancer in developed countries and is increasing in the developing world. Its long latency and	CC	(-) ↓ risk and

Jian L, Lee AH, Binns CW. Asia Pac J Clin Nutr. 2007;16 Suppl 1:453-7.	geographical variation suggest the possibility of prevention or postponement of onset by dietary modification. To investigate the possible joint effect of lycopene and green tea on prostate cancer risk, a case-control study was conducted in Hangzhou, China, with 130 prostate cancer patients and 274 hospital controls. Information on tea and dietary intakes, and possible confounders was collected using a structured questionnaire. The risk of prostate cancer for the intake of tea and lycopene and their joint effect were assessed using multivariate logistic regression models. Prostate cancer risk was reduced with increased consumption of green tea. The protective effect of green tea was significant (odds ratio 0.14, 95% CI: 0.06-0.35) for the highest quartile relative to the lowest after adjusting for total vegetables and fruits intakes and other potential confounding factors. Intakes of vegetables and fruits rich in lycopene were also inversely associated with prostate cancer risk (odds ratio 0.18, 95% CI 0.08-0.39). Interaction analysis showed that the protective effect from tea and lycopene consumption was synergistic ($p<0.01$). This study suggests that habitual drinking tea and intakes of vegetables and fruits rich in lycopene could lead to a reduced risk of prostate cancer in Chinese men. Together they have a stronger preventive effect than either component taken separately. This is the first epidemiological study to	with green tea ↓↓ risk

				investigate the joint effect between tea drinking and lycopene intake.		
Cancer: prostate	Pourmand G	The risk factors of prostate cancer: a multicentric case-control study in Iran. Pourmand G, Salem S, Mehrsai A, Lotfi M, Amirzargar MA, Mazdak H, Roshani A, Kheirollahi A, Kalantar E, Baradaran N, Saboury B, Allameh F, Karami A, Ahmadi H, Jahani Y. Asian Pac J Cancer Prev. 2007 Jul-Sep;8(3):422-8.	2007	Prostate cancer (PC), in Iran, is the third most frequently diagnosed visceral cancer among men and the seventh most common underlying cause of cancer mortality. We evaluated the relation between speculated factors and PC risk using data from a multicentric case-control study conducted in Iran from 2005 to 2007 on 130 cases of incident, clinicopathologically confirmed PC, and 75 controls admitted to the same network of hospitals without any malignant disease. Odds ratios (OR) and corresponding 95% confidence intervals (CIs) were estimated using conditional logistic regression models. The risk of PC was increased with aging (OR: 5.35, 95% CI: 2.17-13.19; P<0.0001), and with the number of sexual intercourse >or=2 times/week (OR: 3.14, 95% CI: 1.2-8.2; P=0.02). One unit elevation in serum estradiol and testosterone concentration was related to increase (OR: 1.04, 95% CI: 1.01-1.06; P=0.006) and decrease (OR: 0.79; 95% CI: 0.64-0.96; P=0.02) of PC risk, respectively. Cases were less likely to have a history of diabetes (OR: 0.34, 95% CI: 0.12-0.98; P=0.04). Increasing in dietary consumption of lycopene and fat was associated with declined (OR: 0.45, 95% CI: 0.09-2.12) and increased (OR: 2.38, 95% CI: 0.29-19.4) PC development,	CC		N

				respectively. Other factors including educational level, marriage status, dietary meat consumption, vasectomy and smoking have not been shown to affect PC risk in the Iranian population. Our study adds further information on the potential risk factors of PC and is the first epidemiologic report from Iran. However, justification of these results requires more well-designed studies with a larger number of participants.		
Cancer: prostate	Kristal AR	Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. Kristal AR, Arnold KB, Schenk JM, Neuhouser ML, Goodman P, Penson DF, Thompson IM. Am J Epidemiol. 2008 Apr 15;167(8):925-34. Epub 2008 Feb 7.	2008	This study examined dietary risk factors for incident benign prostatic hyperplasia (BPH) in 4,770 Prostate Cancer Prevention Trial (1994-2003) placebo-arm participants who were free of BPH at baseline. BPH was assessed over 7 years and was defined as medical or surgical treatment or repeated elevation (>14) on the International Prostate Symptom Score questionnaire. Diet, alcohol, and supplement use were assessed by use of a food frequency questionnaire. There were 876 incident BPH cases (33.6/1,000 person-years). The hazard ratios for the contrasts of the highest to lowest quintiles increased 31% for total fat and 27% for polyunsaturated fat and decreased 15% for protein (all p(trend) < 0.05). The risk was significantly lower in high consumers of alcoholic beverages (0 vs. > or =2/day: hazard ratio (HR) = 0.67) and vegetables (<1 vs. > or =4/day: HR = 0.68) and higher in daily (vs. <1/week) consumers of red meat (HR = 1.38). There were no	PC	N BPH

				associations of supplemental antioxidants with risk, and there was weak evidence for associations of lycopene, zinc, and supplemental vitamin D with reduced risk. A diet low in fat and red meat and high in protein and vegetables, as well as regular alcohol consumption, may reduce the risk of symptomatic BPH.		
Cancer: prostate	Kristal AR	Diet, supplement use, and prostate cancer risk: results from the prostate cancer prevention trial. Kristal AR, Arnold KB, Neuhouser ML, Goodman P, Platz EA, Albanes D, Thompson IM. Am J Epidemiol. 2010 Sep 1;172(5):566-77. Epub 2010 Aug 6.	2010	The authors examined nutritional risk factors for prostate cancer among 9,559 participants in the Prostate Cancer Prevention Trial (United States and Canada, 1994-2003). The presence or absence of cancer was determined by prostate biopsy, which was recommended during the trial because of an elevated prostate-specific antigen level or an abnormal digital rectal examination and was offered to all men at the trial's end. Nutrient intake was assessed using a food frequency questionnaire and a structured supplement-use questionnaire. Cancer was detected in 1,703 men; 127 cancers were high-grade (Gleason score 8-10). There were no associations of any nutrient or supplement with prostate cancer risk overall. Risk of high-grade cancer was associated with high intake of polyunsaturated fats (quartile 4 vs. quartile 1: odds ratio = 2.41, 95% confidence interval (CI): 1.33, 4.38). Dietary calcium was positively associated with low-grade cancer but inversely associated with high-grade cancer (for quartile 4 vs. quartile 1, odds ratios were 1.27 (95% CI:	PC	N Diet N Suppl

				1.02, 1.57) and 0.43 (95% CI: 0.21, 0.89), respectively). Neither dietary nor supplemental intakes of nutrients often suggested for prostate cancer prevention, including lycopene, long-chain n-3 fatty acids, vitamin D, vitamin E, and selenium, were significantly associated with cancer risk. High intake of n-6 fatty acids, through their effects on inflammation and oxidative stress, may increase prostate cancer risk.		
Cancer: prostate	Agalliu I	Oxidative balance score and risk of prostate cancer: results from a case-cohort study. Agalliu I, Kirsh VA, Kreiger N, Soskolne CL, Rohan TE. Cancer Epidemiol. 2011 Aug;35(4):353-61. Epub 2010 Dec 9	2011	BACKGROUND: Prostate cancer is a disease with a complex etiology. Oxidative stress has been implicated in its pathogenesis; however, few prospective studies have investigated the association between an oxidative stress/balance score and risk of prostate cancer. METHODS: We investigated associations between an oxidative balance score, calculated as the summation of individual scores obtained from five pro-oxidative and eight anti-oxidative exposures, as well as each individual constituent of the score and risks of prostate cancer overall, and by clinical characteristics, in a case-cohort study (661 cases and 1864 subcohort) nested within the Canadian Study of Diet, Lifestyle, and Health cohort. Men in the lowest quintiles of each pro-oxidant exposure received a score of four (the highest score), while those in the highest quintile received a score of zero (the lowest score). In contrast, scoring for all anti-oxidants was	CC nested		(-)

				performed in the opposite way. Total oxidative balance score was calculated by summating all individual scores of pro- and anti-oxidative variables, with higher values indicating a higher antioxidant status. RESULTS: The average oxidative balance score was similar between prostate cancer cases and men in the subcohort: 25.2 and 25.3, respectively. There was no association between oxidative balance score and overall risk of prostate cancer with hazard ratios (HRs) of 1.00, 1.02, 1.03, 0.97 and 1.01 for increasing quintiles of the score (p-trend=0.71). There were also no associations for non-advanced or advanced disease, or when analysis was restricted to incident cases that arose after two years of follow-up (n=508). In general constituents of the score were not associated with prostate cancer, except for red meat intake (HR=1.44; 95%CI 1.06-1.95 comparing Q5 vs. Q1) and lycopene (HRs of 0.7-0.8 for increasing quintiles). CONCLUSION: Our findings do not support an association between oxidative balance score and risks of overall prostate cancer or advanced disease.				
Cancer: prostate	Shahar S	Roles of diet, lifetime physical activity and oxidative DNA damage in the occurrence of	2011	BACKGROUND: There is a paucity of information on risk factors of prostate cancer, especially those related to dietary and lifestyle among Asian populations. OBJECTIVE: This study aimed to	CC	(-)	(-)	(-)

prostate cancer among men in Klang Valley, Malaysia. Shahar S, Shafurah S, Hasan Shaari NS, Rajikan R, Rajab NF, Golkhalkhali B, Zainuddin ZM. Asian Pac J Cancer Prev. 2011;12(3):605-11	determine the relationship between dietary intake (macronutrients, fruits, vegetables and lycopene), lifetime physical activity and oxidative DNA damage with prostate cancer. DESIGN: A case control study was carried out among 105 subjects (case n=35, control n=70), matched for age and ethnicity. Data on sociodemographic, medical, dietary intake, consumption of lycopene rich food and lifetime physical activity were obtained through an interview based questionnaire. Anthropometric measurements including weight, height and waist hip circumferences were also carried out on subjects. A total of 3 mL fasting venous blood was drawn to assess lymphocyte oxidative DNA damage using the alkaline comet assay. RESULTS: Cases had a significantly higher intake of fat (27.7 ± 5.5%) as compared to controls (25.1 ± 5.9%) ($p < 0.05$). Mean intakes of fruits and vegetables (3.11 ± 1.01 servings/d)($p < 0.05$), fruits (1.23 ± 0.59 servings/d) ($p<0.05$) and vegetables (1.97 ± 0.94 servings/d) were higher in controls than cases (2.53 ± 1.01, 0.91 ∓ 0.69, 1.62 ± 0.82 servings/d). A total of 71% of cases did not met the recommendation of a minimum of three servings of fruits and vegetables daily, as compared to 34% of controls ($p < 0.05$) (adjusted OR 6.52 (95% CI 2.3-17.8)) ($p < 0.05$). Estimated lycopene intake among cases

(2,339 ∓ 1,312 mcg/d) were lower than controls (3881 ∓ 3120 mcg/d) ($p< 0.01$). Estimated lycopene intake of less than 2,498 mcg/day (50th percentile) increased risk of prostate cancer by double [Adjusted OR 2.5 (95%CI 0.99-6.31)]. Intake of tomatoes, watermelon, guava, pomelo, papaya, mango, oranges, dragon fruit, carrot, tomato sauce and barbeque sauce were higher in controls compared to cases. Intake of tomato sauce of more than 2.24 g/d (25th percentile), papaya more than 22.7 g/d (50th percentile) and oranges more than 19.1g/h (50th percentile) reduced prostate cancer risk by 7.4 (Adjusted OR 7.4 (95% CI 1.17-46.8)), 2.7 (adjusted OR 2.75 (95% CI 1.03-7.39)) and 2.6 times (adjusted OR = 2.6 (95% CI=1.01-6.67)), respectively ($p < 0.05$ for all parameters). No oxidative damage was observed among subjects. Past history of not engaging with any physical activities at the age of 45 to 54 years old increased risk of prostate cancer by pproximately three folds (Adjusted OR 2.9(95% CI = 0.8-10.8)) ($p < 0.05$). In conclusion, low fat diet, high intake of fruits, vegetables and lycopene rich foods and being physical active at middle age were found to be protective. Thus, it is essential for Malaysian men to consume adequate fruits and vegetables, reduce fat intake and engage in physical activity in order to reduce prostate cancer risk.

Renal Cancer Critical Findings

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Cancer: renal	Bosetti C	Micronutrients and the risk of renal cell cancer: a case-control study from Italy. Bosetti C, Scotti L, Maso LD, Talamini R, Montella M, Negri E, Ramazzotti V, Franceschi S, La Vecchia C. Int J Cancer. 2007 Feb 15;120(4):892-6.	2007	The role of various micronutrients on the risk of renal cell cancer (RCC) was examined in a multicentric case-control study from Italy, in which information on dietary habits were collected using a validated food-frequency questionnaire. Cases were 767 patients (494 men and 273 women) with incident, histologically confirmed RCC; controls were 1,534 subjects (988 men and 546 women) admitted to the same hospitals as cases for a wide spectrum of acute, nonneoplastic conditions. After allowing for energy and other major covariates, a significant inverse association was found for vitamin E (odds ratio, OR, for the highest quintile of intake versus the lowest one 0.56, 95% confidence interval, CI 0.41-0.75), and vitamin C (OR = 0.72, 95% CI = 0.54-0.96), although the trend in risk for vitamin C was of borderline significance. No significant trend of decreasing risk was found for other micronutrients analyzed, although for most of them the risk estimates were below unity for intakes above the lowest. The ORs for the upper quintile of intake when compared with the lowest one were 0.80 (95% confidence interval, CI = 0.59-1.08) for retinol, 0.82 (95% CI = 0.61-1.10) for alpha-carotene, 0.90 (95% CI = 0.68-1.20) for	CC				N	

				beta-carotene, 0.94 (95% CI = 0.73-1.21) for beta-criptoxanthin, 0.85 (95% CI = 0.63-1.14) for lutein/zeaxanthin, 0.76 (95% CI = 0.57-1.01) for vitamin D, 0.75 (95% CI = 0.55-1.01) for thiamine, 0.88 (95% CI = 0.66-1.19) for riboflavin, 0.85 for vitamin B6 (95% CI = 0.64-1.13), 0.85 (95% CI = 0.64-1.12) for folate and 0.80 (95% CI = 0.60-1.07) for niacin. No meaningful associations emerged for lycopene (OR = 1.11). The present findings support a possible beneficial effect of vitamin E and C on RCC.		
Cancer: renal	Hu J	Dietary vitamin C, E, and carotenoid intake and risk of renal cell carcinoma. Hu J, La Vecchia C, Negri E, DesMeules M, Mery L; Canadian Cancer Registries Epidemiology Research Group. Cancer Causes Control. 2009 Oct;20(8):1451-8. Epub 2009 Jun 17	2009	OBJECT: The study examines the association between dietary intake of vitamin C, E, and carotenoids and the risk of renal cell carcinoma (RCC). METHODS: Between 1994 and 1997 in 8 Canadian provinces, mailed questionnaires were completed by 1,138 incident, histologically confirmed cases of RCC and 5,039 population controls, including information on socio-economic status, lifestyle habits and diet. A 69-item food frequency questionnaire provided data on eating habits 2 years before data collection. Odds ratios (OR) and 95% confidence intervals (CI) were computed using unconditional logistic regression. RESULTS: Dietary intake of beta-carotene and lutein/zeaxanthin was inversely associated with the risk of RCC. The ORs for the highest versus the lowest quartile were 0.74 (95% CI, 0.59-0.92) and 0.77 (95% CI, 0.62-0.95), respectively. The significant inverse association with	CC		N

				beta-carotene and lutein/zeaxanthin was more pronounced in women, and in overweight or obese subjects. The relation of lutein/zeaxanthin to RCC was stronger in ever smokers. No clear association was observed with vitamin C and E, beta-cryptozanthin, and lycopene. CONCLUSION: The findings provide evidence that a diet rich in beta-carotene and lutein/zeaxanthin may play a role in RCC prevention.		
Cancer: renal	Lee JE	Intakes of fruit, vegetables, and carotenoids and renal cell cancer risk: a pooled analysis of 13 prospective studies. Lee JE, Mannisto S, Spiegelman D, Hunter DJ, Bernstein L, van den Brandt PA, Buring JE, Cho E, English DR, Flood A, Freudenheim JL, Giles GG, Giovannucci E, Hakansson N, Horn-Ross PL, Jacobs EJ, Leitzmann MF, Marshall JR, McCullough ML, Miller AB, Rohan TE, Ross JA, Schatzkin A, Schouten LJ, Virtamo J, Wolk A, Zhang SM, Smith-Warner SA.	2009	Fruit and vegetable consumption has been hypothesized to reduce the risk of renal cell cancer. We conducted a pooled analysis of 13 prospective studies, including 1,478 incident cases of renal cell cancer (709 women and 769 men) among 530,469 women and 244,483 men followed for up to 7 to 20 years. Participants completed a validated food-frequency questionnaire at baseline. Using the primary data from each study, the study-specific relative risks (RR) were calculated using the Cox proportional hazards model and then pooled using a random effects model. We found that fruit and vegetable consumption was associated with a reduced risk of renal cell cancer. Compared with <200 g/d of fruit and vegetable intake, the pooled multivariate RR for >or=600 g/d was 0.68 [95% confidence interval (95% CI) = 0.54-0.87; P for between-studies heterogeneity = 0.86; P for trend = 0.001]. Compared with <100 g/d, the pooled multivariate RRs (95% CI) for >or=400 g/d	PC pooled		N

		Cancer Epidemiol Biomarkers Prev. 2009 Jun;18(6):1730-9.		were 0.79 (0.63-0.99; P for trend = 0.03) for total fruit and 0.72 (0.48-1.08; P for trend = 0.07) for total vegetables. For specific carotenoids, the pooled multivariate RRs (95% CIs) comparing the highest and lowest quintiles were 0.87 (0.73-1.03) for alpha-carotene, 0.82 (0.69-0.98) for beta-carotene, 0.86 (0.73-1.01) for beta-cryptoxanthin, 0.82 (0.64-1.06) for lutein/zeaxanthin, and 1.13 (0.95-1.34) for lycopene. In conclusion, increasing fruit and vegetable consumption is associated with decreasing risk of renal cell cancer; carotenoids present in fruit and vegetables may partly contribute to this protection.			
Cancer: uterine	Terry KL	Lycopene and other carotenoid intake in relation to risk of uterine leiomyomata. Terry KL, Missmer SA, Hankinson SE, Willett WC, De Vivo I. Am J Obstet Gynecol. 2008 Jan;198(1):37.e1-8. Epub 2007 Nov 5.	2008	OBJECTIVE: Carotenoids have antioxidant properties and have been associated with reduced risks of some cancers. We hypothesized that carotenoid intake may reduce the risk of diagnosed uterine leiomyoma (UL). STUDY DESIGN: We evaluated the associations between dietary carotenoids and risk of diagnosed UL in 82,512 premenopausal women aged 26-46 years in 1991 in the Nurses' Health Study II over 10 years of follow-up. Diet was assessed every 4 years with a validated food frequency questionnaire, and incidence of UL was assessed biennially by questionnaire. RESULTS: Total lycopene intake was not associated with diagnosed UL risk. Intake of beta-carotene was associated with slightly increased risks of diagnosed UL; this association was restricted to current smokers (for highest vs lowest	PC		N

				quintile, relative risk = 1.36, 95% confidence interval 1.05 to 1.76; P(trend) = .003). CONCLUSION: Overall, our findings do not suggest that carotenoids reduce the risk of diagnosed UL. Among current smokers, high intake of beta-carotene may slightly increase risk of diagnosed UL.		
Cancer: Mortality	Agudo A	Fruit and vegetable intakes, dietary antioxidant nutrients, and total mortality in Spanish adults: findings from the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain). Agudo A, Cabrera L, Amiano P, Ardanaz E, Barricarte A, Berenguer T, Chirlaque MD, Dorronsoro M, Jakszyn P, Larranaga N, Martinez C, Navarro C, Quiras JR, Sanchez MJ, Tormo MJ, Gonzalez CA. Demark-Wahnefried W.	2008	BACKGROUND: Epidemiologic data suggest that persons with diets rich in fruit and vegetables are at a lower risk of several chronic diseases and mortality than are persons with diets poor in fruit and vegetables. Often, this effect is attributed to antioxidant micronutrients found in plant foods. OBJECTIVE: We aimed to assess the relation of mortality to the consumption of fruit, vegetables, and other plant foods and to the dietary intake of vitamin C, vitamin E, and carotenoids. DESIGN: The study was a prospective study in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition. During 6.5 y of follow-up, 562 deaths occurred in 41 358 subjects aged 30-69 y. Proportional hazards regression analysis was used to assess the relation between dietary factors and total mortality. RESULTS: After adjustment for age, sex, and several potential confounders, the hazard ratio for the highest versus the lowest quartile of consumption was 0.79 (95% CI: 0.62, 1.00; P for trend = 0.029) for fresh fruit, 0.72 (0.56, 0.91; P for trend = 0.006) for root vegetables, and 0.77 (0.60, 0.98; P for trend = 0.015) for fruiting vegetables (ie, vegetables that contain the "fruit" part of the plant, the seeds). The corresponding figures for antioxidant nutrients were	PC	(-) ↓ mortality

		Curr Urol Rep. 2008 May; 9(3):217-25.		0.74 (0.58, 0.94; P for trend = 0.009) for vitamin C, 0.68 (0.53, 0.87; P for trend = 0.006) for provitamin A carotenoids, and 0.65 (0.51, 0.84; P for trend 0.001) for lycopene. The effect of vitamin C and provitamin A disappeared after adjustment for total antioxidant capacity in plant foods. CONCLUSIONS: A high intake of fresh fruit, root vegetables, and fruiting vegetables is associated with reduced mortality, probably as a result of their high content of vitamin C, provitamin A carotenoids, and lycopene. Antioxidant capacity could partly explain the effect of ascorbic acid and provitamin A but not the association with lycopene.						
Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Cancer Risk Reviews	Peto R	Can dietary beta-carotene materially reduce human cancer rates? Peto R, Doll R, Buckley JD, Sporn MB. Nature. 1981 Mar 19;290(5803):201-8.	1981	Human cancer risks are inversely correlated with (a) blood retinol and (b) dietary beta-carotene. Although retinol in the blood might well be truly protective, this would be of little immediate value without discovery of the important external determinants of blood retinol which	Review					

				(in developed countries) do not include dietary retinol or beta-carotene. If dietary beta-carotene is truly protective--which could be tested by controlled trials--there are a number of theoretical mechanisms whereby it might act, some of which do not directly involve its 'provitamin A' activity.		
Cancer Risk Reviews	Weisburger JH	Mechanisms of action of antioxidants as exemplified in vegetables, tomatoes and tea. Weisburger JH. Food Chem Toxicol. 1999 Sep-Oct;37(9-10):943-8.	1999	Most chronic diseases, including coronary heart disease and many types of cancer depend on the in vivo conversion of cellular macromolecules or of carcinogens to specific reactive, oxidized forms. For that reason, health promoting nutrition involves the daily intake of five to 10 vegetables and fruits, fruit juices, red wine and tea that are rich sources of micronutrients with antioxidant properties, including the antioxidant vitamins C, E and beta-carotene. Tomatoes contain	Review	(-) ↓ pre and neoplastic cell growth ↓ active oxygen and peroxy compnds

lycopene, a stable, active antioxidant. Many vegetables contain quercetin and related polyphenolic compounds. Tea is a source of epigallocatechin gallate, in green tea, and theaflavin and the associated thearubigins, in black tea. Red wine contains resveratrol. The diverse antioxidants in foods, red wine and tea provide the necessary antioxidant resources for the body to control oxidation reactions in the body with possible adverse consequences. For example, the oxidation of low density lipoprotein (LDL) cholesterol yields a product that damages the vascular system. Thus, a lower intake of saturated fats to decrease the levels of LDL cholesterol, together with an adequate intake of antioxidants, is the optimal approach to lower heart disease risk. Cancer of the stomach involves the consumption of salted, pickled foods yielding direct-

acting carcinogens, and their formation is inhibited by vitamins C and E. Cancer in the colon, breast, prostate and pancreas may be caused by a new class of carcinogens, the heterocyclic amines, formed during the broiling or frying of creatinine-containing foods, including fish and meats. Their formation and action can be inhibited by antioxidants such as those in soy, tea, vitamin C and also by the synthetic antioxidants BHA or BHT. The growth, cell proliferation and development of abnormal preneoplastic and neoplastic cells also involves oxidation reactions, including the formation of active oxygen or peroxy compounds. Such reactions can be inhibited by antioxidants, such as those in tea, tomatoes or vegetables. Even ageing and longevity in good health would be favoured by the availability of adequate amounts of varied

				antioxidants. Prevention of the formation and of action of reactive products by antioxidants as present in fruits, vegetables, tomatoes, red wine and tea is of great public health importance in decreasing the risk of major diseases. Prevention is the optimal approach to disease control, and also as an effective route to lower costs of medical care.	
Cancer Risk Reviews	Agarwal S	Tomato lycopene and its role in human health and chronic diseases. Agarwal S, Rao AV. CMAJ. 2000 Sep 19;163(6):739-44.	2000	Lycopene is a carotenoid that is present in tomatoes, processed tomato products and other fruits. It is one of the most potent antioxidants among dietary carotenoids. Dietary intake of tomatoes and tomato products containing lycopene has been shown to be associated with a decreased risk of chronic diseases, such as cancer and cardiovascular disease. Serum and tissue lycopene levels have been found to be inversely related to the incidence of several types of cancer,	Review

				including breast cancer and prostate cancer. Although the antioxidant properties of lycopene are thought to be primarily responsible for its beneficial effects, evidence is accumulating to suggest that other mechanisms may also be involved. In this article we outline the possible mechanisms of action of lycopene and review the current understanding of its role in human health and disease prevention	
Cancer Risk Reviews	Montesano R	Environmental causes of human cancers. Montesano R, Hall J. Eur J Cancer. 2001 Oct;37 Suppl 8:S67-87.	2001	Epidemiological studies have clearly shown a causal association between tobacco exposure and various human cancers, hepatitis B and C infection and hepatocellular carcinoma, human papilloma viruses and cervical cancer, and the occupational origin of certain human cancers is well established. The identification of the environmental causes of human cancers has been a long and difficult	Review

				process. Much remains to be understood about the role of specific components of the diet and the interaction of different risk factors in the aetiology of human cancers. Withstanding the progress made on the understanding of the cancer process and their potential impact in the therapy of cancer, primary prevention remains, in developed and developing countries, the most effective measure to reduce cancer mortality.	
Cancer Risk Reviews	Cohen LA.	A review of animal model studies of tomato carotenoids, lycopene, and cancer chemopreventio n. Cohen LA. Exp Biol Med (Maywood). 2002 Nov;227(10):864-8.	200 2	There are relatively few reports on the cancer chemopreventive effects of lycopene or tomato carotenoids in animal models. The majority, but not all, of these studies indicate a protective effect. Inhibitory effects were reported in two studies using aberrant crypt foci, an intermediate lesion leading to colon cancer, as an end point and in two mammary tumor	Review

studies, one using the dimethylbenz(a)anthracene model, and the other the spontaneous mouse model. Inhibitory effects were also reported in mouse lung and rat hepatocarcinoma and bladder cancer models. However, a report from the author's laboratory found no effect in the N-nitrosomethylurea-induced mammary tumor model when crystalline lycopene or a lycopene-rich tomato carotenoid oleoresin was administered in the diet. Unfortunately, because of differences in routes of administration (gavage, intraperitoneal injection, intra-rectal instillation, drinking water, and diet supplementation), species and strain differences, form of lycopene (pure crystalline, beadlet, mixed carotenoid suspension), varying diets (grain-based, casein based) and dose ranges (0.5-500 ppm), no two studies are comparable. It is clear that the majority of ingested

lycopene is excreted in the feces and that 1000-fold more lycopene is absorbed and stored in the liver than accumulates in other target organs. Nonetheless, physiologically significant (nanogram) levels of lycopene are assimilated by key organs such as breast, prostate, lung, and colon, and there is a rough dose-response relationship between lycopene intake and blood levels. Pure lycopene was absorbed less efficiently than the lycopene-rich tomato carotenoid oleoresin and blood levels of lycopene in rats fed a grain-based diet were consistently lower than those in rats fed lycopene in a casein-based diet. The latter suggests that the matrix in which lycopene is incorporated is an important determinant of lycopene uptake. A number of issues remain to be resolved before any definitive conclusions can be drawn concerning

				the anticancer effects of lycopene. These include the following: the optimal dose and form of lycopene, interactions among lycopene and other carotenoids and fat soluble vitamins such as vitamin E and D, the role of dietary fat in regulating lycopene uptake and disposition, organ and tissue specificity, and the problem of extrapolation from rodent models to human populations.					
Cancer Risk Reviews	Etminan M	The role of tomato products and lycopene in the prevention of prostate cancer: a metaanalysis of observational studies. Etminan M, Takkouche B, Caamano-Isorna F. Cancer Epidemiol Biomarkers Prev. 2004;13(3):340–345.	2004	PURPOSE: To determine whether intake of tomato products reduces the risk of prostate cancer using a meta-analysis. METHODS: We systematically searched MEDLINE and EMBASE and contacted authors to identify potential studies. Log relative risks (RRs) were weighed by the inverse of their variances to obtain a pooled estimate with its 95% confidence interval (CI). Logistic regression and Poisson regression analyses were used	Meta-Analysis Specific to prostate cancer	(-) High intake >200g	(-)	N	N/(-)

to determine the effect produced by a daily intake of one serving of tomato product. RESULTS: Eleven case-control studies and 10 cohort studies or nested case-control studies presented data on the use of tomato, tomato products, or lycopene and met our inclusion criteria. Compared with nonfrequent users of tomato products (1st quartile of intake), the RR of prostate cancer among consumers of high amounts of raw tomato (5th quintile of intake) was 0.89 (95% CI 0.80-1.00). For high intake of cooked tomato products, this RR was 0.81 (95% CI 0.71-0.92). The RR of prostate cancer related to an intake of one serving/day of raw tomato (200 g) was 0.97 (95% CI 0.85-1.10) for the case-control studies and 0.78 (95% CI 0.66-0.92) for cohort studies. CONCLUSIONS: Our results show that tomato products may play a role in the prevention of prostate cancer. However, this effect

				is modest and restricted to high amounts of tomato intake. Further research is needed to determine the type and quantity of tomato products with respect to their role in preventing prostate cancer.	
Cancer Risk Reviews	Aggarwal BB	Molecular targets of dietary agents for prevention and therapy of cancer. Aggarwal BB, Shishodia S. Biochem Pharmacol. 2006 May 14;71(10):1397-421. Epub 2006 Feb 23.	2006	While fruits and vegetables are recommended for prevention of cancer and other diseases, their active ingredients (at the molecular level) and their mechanisms of action less well understood. Extensive research during the last half century has identified various molecular targets that can potentially be used not only for the prevention of cancer but also for treatment. However, lack of success with targeted monotherapy resulting from bypass mechanisms has forced researchers to employ either combination therapy or agents that interfere with multiple cell-signaling pathways. In this review, we present evidence	Review

that numerous agents identified from fruits and vegetables can interfere with several cell-signaling pathways. The agents include curcumin (turmeric), resveratrol (red grapes, peanuts and berries), genistein (soybean), diallyl sulfide (allium), S-allyl cysteine (allium), allicin (garlic), lycopene (tomato), capsaicin (red chilli), diosgenin (fenugreek), 6-gingerol (ginger), ellagic acid (pomegranate), ursolic acid (apple, pears, prunes), silymarin (milk thistle), anethol (anise, camphor, and fennel), catechins (green tea), eugenol (cloves), indole-3-carbinol (cruciferous vegetables), limonene (citrus fruits), beta carotene (carrots), and dietary fiber. For instance, the cell-signaling pathways inhibited by curcumin alone include NF-kappaB, AP-1, STAT3, Akt, Bcl-2, Bcl-X(L), caspases, PARP, IKK, EGFR, HER2, JNK, MAPK, COX2, and 5-LOX. The active principle

				identified in fruit and vegetables and the molecular targets modulated may be the basis for how these dietary agents not only prevent but also treat cancer and other diseases. This work reaffirms what Hippocrates said 25 centuries ago, let food be thy medicine and medicine be thy food.	
Cancer Risk Reviews	Divisi D	Diet and cancer. Divisi D, Di Tommaso S, Salvemini S, Garramone M, Crisci R. Acta Biomed. 2006 Aug;77(2):118-23.	2006	The aim of our study is to evaluate the relationship between diet and cancer development. It has been estimated that 30-40% of all kinds of cancer can be prevented with a healthy lifestyle and dietary measures. A low use of fibres, the intake of red meat and an imbalance of Omega-3 and Omega-6 fats may contribute to increase the risk of cancer. On the other hand, the assumption of lots of fruit and vegetables may lower the risk of cancer. Protective elements in a cancer-preventive diet include selenium, folic acid, vitamin B12, vitamin D, chlorophyll and	Review

				antioxidants such as carotenoids (alpha-carotene, beta-carotene, lycopene, lutein, cryptoxanthin). Ascorbic acid has limited benefits if taken orally, but it effective through intravenous injection. A supplementary use of oral digestive enzymes and probiotics is also an anticancer dietary measure. A diet drawn up according to the proposed guidelines could decrease the incidence of breast, colon-rectal, prostate and bronchogenic cancer.			
Cancer Risk Reviews	Kavanaugh CJ	The U.S. Food and Drug Administration's evidence-based review for qualified health claims: tomatoes, lycopene, and cancer. Kavanaugh CJ, Trumbo PR, Ellwood KC. J Natl Cancer Inst. 2007 Jul 18;99(14):1059. J Natl Cancer	2007	Several studies have reported an inverse association between tomato and/or lycopene intake and the risk of some types of cancer. In 2004, the U.S. Food and Drug Administration (FDA) received two petitions for qualified health claims regarding tomatoes, lycopene, and the risk reduction for some forms of cancer. Health claims that	Review	N/(-) ↓ cancer risk		N ↓ cancer risk

Inst. 2007 Jul 18;99(14):1060-2.

characterize the relationship between a food or food component and a disease or health-related condition require premarket approval by FDA to be included on the labels of conventional foods and dietary supplements. Here we describe FDA's review of the scientific data for tomato and/or lycopene intake with respect to risk reduction for certain forms of cancer. The FDA found no credible evidence to support an association between lycopene intake and a reduced risk of prostate, lung, colorectal, gastric, breast, ovarian, endometrial, or pancreatic cancer. The FDA also found no credible evidence for an association between tomato consumption and a reduced risk of lung, colorectal, breast, cervical, or endometrial cancer. The FDA found very limited evidence to support an association between tomato consumption and reduced risks of prostate, ovarian,

				gastric, and pancreatic cancers.		
Cancer Risk Reviews	Gallicchio L	Carotenoids and the risk of developing lung cancer: a systematic review. Gallicchio L, Boyd K, Matanoski G, Tao XG, Chen L, Lam TK, Shiels M, Hammond E, Robinson KA, Caulfield LE, Herman JG, Guallar E, Alberg AJ. Am J Clin Nutr. 2008 Aug;88(2):372-83.	2008	BACKGROUND: Carotenoids are thought to have anti-cancer properties, but findings from population-based research have been inconsistent. OBJECTIVE: We aimed to conduct a systematic review of the associations between carotenoids and lung cancer. DESIGN: We searched electronic databases for articles published through September 2007. Six randomized clinical trials examining the efficacy of beta-carotene supplements and 25 prospective observational studies assessing the associations between carotenoids and lung cancer were analyzed by using random-effects meta-analysis. RESULTS: The pooled relative risk (RR) for the studies comparing beta-carotene supplements with placebo was 1.10	Review 6 RCT 25 PC	(-)

(95% confidence limits: 0.89, 1.36; P = 0.39). Among the observational studies that adjusted for smoking, the pooled RRs comparing highest and lowest categories of total carotenoid intake and of total carotenoid serum concentrations were 0.79 (0.71, 0.87; P < 0.001) and 0.70 (0.44, 1.11; P = 0.14), respectively. For beta-carotene, highest compared with lowest pooled RRs were 0.92 (0.83, 1.01; P = 0.09) for dietary intake and 0.84 (0.66, 1.07; P = 0.15) for serum concentrations. For other carotenoids, the RRs comparing highest and lowest categories of intake ranged from 0.80 for beta-cryptoxanthin to 0.89 for alpha-carotene and lutein-zeaxanthin; for serum concentrations, the RRs ranged from 0.71 for lycopene to 0.95 for lutein-zeaxanthin. CONCLUSIONS: beta-Carotene supplementation is not associated with a decrease in the risk of developing lung cancer. Findings from

				prospective cohort studies suggest inverse associations between carotenoids and lung cancer; however, the decreases in risk are generally small and not statistically significant. These inverse associations may be the result of carotenoid measurements' function as a marker of a healthier lifestyle (higher fruit and vegetable consumption) or of residual confounding by smoking.	
Cancer Risk Reviews	Khan N	Cancer chemopreventio n through dietary antioxidants: progress and promise. Khan N, Afaq F, Mukhtar H. Antioxid Redox Signal. 2008 Mar;10(3):475-510. Review	200 8	It is estimated that nearly one-third of all cancer deaths in the United States could be prevented through appropriate dietary modification. Various dietary antioxidants have shown considerable promise as effective agents for cancer prevention by reducing oxidative stress which has been implicated in the development of many diseases, including cancer. Therefore, for reducing the incidence of cancer,	Review

modifications in dietary habits, especially by increasing consumption of fruits and vegetables rich in antioxidants, are increasingly advocated. Accumulating research evidence suggests that many dietary factors may be used alone or in combination with traditional chemotherapeutic agents to prevent the occurrence of cancer, their metastatic spread, or even to treat cancer. The reduced cancer risk and lack of toxicity associated with high intake of fruits and vegetables suggest that specific concentrations of antioxidant agents from these dietary sources may produce cancer chemopreventive effects without causing significant levels of toxicity. This review presents an extensive analysis of the key findings from studies on the effects of dietary antioxidants such as tea polyphenols, curcumin, genistein, resveratrol, lycopene,

				pomegranate, and lupeol against cancers of the skin, prostate, breast, lung, and liver. This research is also leading to the identification of novel cancer drug targets.			
Cancer Risk Reviews	Liu C	Nutrition and gastric cancer risk: an update. Liu C, Russell RM. Nutr Rev. 2008 May;66(5):237-49.	2008	Data from epidemiologic, experimental, and animal studies indicate that diet plays an important role in the etiology of gastric cancer. High intake of fresh fruits and vegetables, lycopene and lycopene-containing food products, and potentially vitamin C and selenium may reduce the risk for gastric cancer. Data also suggest that high intake of nitrosamines, processed meat products, salt and salted foods, and overweight and obesity are associated with increased risk for gastric cancer. However, current data provide little support for an association of beta-carotene, vitamin E, and alcohol consumption with	Review		N

				risk for gastric cancer.			
Cancer Risk Reviews	Mein JR	Biological activity of lycopene metabolites: implications for cancer prevention. Mein JR, Lian F, Wang XD. Nutr Rev. 2008 Dec;66(12):667-83.	2008	While early studies focused on the potential roles in health and disease of provitamin A carotenoids, such as beta-carotene, research over the past decade has provided a framework for our understanding of the functions of non-provitamin A carotenoids such as lycopene, especially in regards to its association with a reduced risk of a number of chronic diseases, including cancer. Recent data suggests that lycopene metabolites may possess specific biological activities on several important cellular signaling pathways and molecular targets. Carotenoid metabolites may have more important biological roles than their parent compounds in human health and disease. This notion has been reinforced by the observation of both beneficial and detrimental effects of	Review		(-) lyco meta-bolites may↓ risk prostate cancer

				carotenoid metabolites in cancer prevention.		
Cancer Risk Reviews	Seren S	Potential role of lycopene in the treatment of hepatitis C and prevention of hepatocellular carcinoma. Seren S, Mutchnick M, Hutchinson D, Harmanci O, Bayraktar Y, Mutchnick S, Sahin K, Kucuk O. Nutr Cancer. 2008;60(6):729-35.	2008	Hepatitis C virus (HCV) infection and hepatocellular carcinoma (HCC) are growing health problems around the world. Oxidative stress plays a significant role in the initiation and progression of hepatocellular damage and possibly in the development of HCC in HCV infected patients. In vitro, animal and clinical studies suggest that lycopene, a nonprovitamin A carotenoid and a potent antioxidant, may attenuate the liver injury and possibly prevent the development of HCC. In this article, we discuss the relationship between HCV infection and oxidative stress and review the potential role of lycopene in the treatment of HCV and prevention of HCC.	(-) ↓ liver injury	

Cancer Risk Reviews	van Breemen RB	Multitargeted therapy of cancer by lycopene. van Breemen RB, Pajkovic N. Cancer Lett. 2008 Oct 8;269(2):339-51. Epub 2008 Jun 27.	2008	Lycopene (psi,psi-carotene) is the most abundant carotenoid in tomatoes and is the red pigment of not only tomatoes but also rosehips, watermelon, papaya, pink grapefruit, and guava. Unlike beta-carotene, lycopene lacks a beta-ionone ring and therefore has no pro-vitamin A activity. However, the 11 conjugated and two non-conjugated double bonds in lycopene make it highly reactive towards oxygen and free radicals, and this anti-oxidant activity probably contributes to its efficacy as a chemoprevention agent. The reactivity of lycopene also explains why it isomerizes rapidly in blood and tissues from the biosynthetic all-trans form to a mixture of cis-isomers. Prospective and retrospective epidemiological studies indicating an inverse relationship between lycopene intake and prostate cancer risk have been supported by in vitro and in vivo experiments showing	Review		N as a chemoprotective agent, needs further study

that oral lycopene is bioavailable, accumulates in prostate tissue and is localized to the nucleus of prostate epithelial cells. In addition to antioxidant activity, in vitro experiments indicate other mechanisms of chemoprevention by lycopene including induction of apoptosis and antiproliferation in cancer cells, anti-metastatic activity, and the upregulation of the antioxidant response element leading to the synthesis of cytoprotective enzymes. Lycopene is a substrate for carotene-9',10'-monooxygenase (CMO2) and can be converted to apo-10'-carotenal. Although Phase I and II studies have been published that establish the safety of lycopene supplementation, carefully designed and adequately powered clinical studies of lycopene are still needed to confirm its efficacy as a chemoprevention agent.

Cancer Risk Reviews	Coyle YM	Lifestyle, genes, and cancer. Coyle YM. Methods Mol Biol. 2009;472:25-56.	2009	It is estimated that almost 1.5 million people in the USA are diagnosed with cancer every year. However, due to the substantial effect of modifiable lifestyle factors on the most prevalent cancers, it has been estimated that 50% of cancer is preventable. Physical activity, weight loss, and a reduction in alcohol use can strongly be recommended for the reduction of breast cancer risk. Similarly, weight loss, physical activity, and cessation of tobacco use are important behavior changes to reduce colorectal cancer risk, along with the potential benefit for the reduction of red meat consumption and the increase in folic acid intake. Smoking cessation is still the most important prevention intervention for reducing lung cancer risk, but recent evidence indicates that increasing physical activity may also be an important prevention intervention for this disease. The	Review		N However, might ↓ risk by ↓ free radical production= ↓ gene mutatioins= ↓ cancer risk

potential benefit of lifestyle change to reduce prostate cancer risk is growing, with recent evidence indicating the importance of a diet rich in tomato-based foods and weight loss. Also, in the cancers for which there are established lifestyle risk factors, such as physical inactivity for breast cancer and obesity for colorectal cancer, there is emerging information on the role that genetics plays in interacting with these factors, as well as the interaction of combinations of lifestyle factors. Integration of genetic information into lifestyle factors can help to clarify the causal relationships between lifestyle and genetic factors and assist in better identifying cancer risk, ultimately leading to better-informed choices about effective methods to enhance health and prevent cancer.

Cancer Risk Reviews	Musa-Veloso K	Influence of observational study design on the interpretation of cancer risk reduction by carotenoids. Musa-Veloso K, Card JW, Wong AW, Cooper DA. Nutr Rev. 2009 Sep;67(9):527-45.	2009	Recently published literature has been reviewed to determine whether lycopene, beta-carotene, alpha-carotene, and beta-cryptoxanthin are associated with reductions in cancer risk and whether study findings differ by study design. A total of 57 publications meeting pre-defined inclusion and exclusion criteria were identified, with the majority (55) being observational studies. None of the intervention studies supported a significant reduction in cancer risk with carotenoid (beta-carotene) supplementation. The majority of observational studies did not support significant reductions in cancer risk with increased carotenoid dietary intakes/circulating levels. A larger percentage of case-control studies supported significant associations between increased dietary intakes/circulating levels of carotenoids relative to prospective (cohort	Review

				and nested case-control) studies. Compared to prospective studies, case-control studies cannot be used to establish temporality and may be more susceptible to selection and recall biases. Thus, diet-disease relationships suggested by case-control studies should ideally be confirmed by additional evidence from prospective studies.	
Cancer Risk Reviews	Svennevig K	Re: "Long-term use of beta-carotene, retinol, lycopene, and lutein supplements and lung cancer risk: results from the VITamins and Lifestyle (VITAL) Study". Svennevig K. Am J Epidemiol. 2009 Aug 1;170(3):401-2. Epub 2009 Jul 15.	2009	In their recent article, Satia et al. (1) used data from the VITamins And Lifestyle (VITAL) Study to draw some conclusions about an association between intake of dietary supplements and lung cancer risk. A previous VITAL Study publication concluded that multivitamin use does not increase lung cancer risk (2). The current study focused on long-term use of individual supplements at high doses. The participants using individual lutein supplements were categorized as	Letter to editor

				noncancer cases (n = 1,606) and lung cancer cases (n = 20). Relatively infrequent lutein supplement use by lung cancer cases made it impossible to divide the group with regard to dosage or duration of use. Satia et al. concluded that long-term use of high doses of individual β-carotene, retinol, and lutein supplements may be harmful in terms of lung cancer risk.	
Cancer Risk Reviews	Giovannucci E	Commentary: Serum lycopene and prostate cancer progression: a re-consideration of findings from the prostate cancer prevention trial. Giovannucci E. Cancer Causes Control. 2011 Jul;22(7):1055-9. Epub 2011 May 15.	2011	A recent analysis in the Prostate Cancer Prevention Trial (PCPT) appeared to show no association between serum lycopene and prostate cancer risk, but the unique study design of the PCPT and the complexity of prostate cancer epidemiology suggest an alternative interpretation of the reported findings.	Commentary
Cancer Risk Reviews	Key TJ	Fruit and vegetables and cancer risk. Key TJ.	2011	The possibility that fruit and vegetables may help to reduce the risk of cancer has been studied for	Review

Br J Cancer. 2011 Jan 4;104(1):6-11. Epub 2010 Nov 30.

over 30 years, but no protective effects have been firmly established. For cancers of the upper gastrointestinal tract, epidemiological studies have generally observed that people with a relatively high intake of fruit and vegetables have a moderately reduced risk, but these observations must be interpreted cautiously because of potential confounding by smoking and alcohol. For lung cancer, recent large prospective analyses with detailed adjustment for smoking have not shown a convincing association between fruit and vegetable intake and reduced risk. For other common cancers, including colorectal, breast and prostate cancer, epidemiological studies suggest little or no association between total fruit and vegetable consumption and risk. It is still possible that there are benefits to be identified: there could be benefits in

populations with low average intakes of fruit and vegetables, such that those eating moderate amounts have a lower cancer risk than those eating very low amounts, and there could also be effects of particular nutrients in certain fruits and vegetables, as fruit and vegetables have very varied composition. Nutritional principles indicate that healthy diets should include at least moderate amounts of fruit and vegetables, but the available data suggest that general increases in fruit and vegetable intake would not have much effect on cancer rates, at least in well-nourished populations. Current advice in relation to diet and cancer should include the recommendation to consume adequate amounts of fruit and vegetables, but should put most emphasis on the well-established adverse effects of obesity and high alcohol intakes. Portion of above that has

"tomato/lycopene" mention. Prostate cancer: The aetiology of prostate cancer is not well understood. Risk is increased in men with relatively high plasma concentrations of insulin-like growth factor-I, and levels of this growth factor can be affected by diet, but more research on this pathway is needed (Roddam et al, 2008). In relation to fruit and vegetables, recent large prospective studies suggest that there is little or no association between total fruit and vegetable intake and prostate cancer risk (Kirsh et al, 2007). There has been much interest in the possibility that fruits and vegetables, such as tomatoes, which are rich in the carotenoid lycopene might reduce the risk for prostate cancer, but overall the data do not support this hypothesis (Kavanaugh et al, 2007). Studies of soyabeans and prostate cancer have suggested that this vegetable may

				help to reduce risk, but the results are not conclusive (Hwang et al, 2009).	
Cancer Risk Reviews	Niclis C	Dietary Habits and Prostate Cancer Prevention: A Review of Observational Studies by Focusing on South America. Niclis C, Díaz MD, Eynard AR, Román MD, Vecchia CL. Nutr Cancer. 2011 Dec 2. [Epub ahead of print]	2011	There exist several works considering the association between diet and prostate cancer (PC) risk, but the issue is largely unsettled. This article systematically reviews the epidemiological studies on diet and risk of PC focusing on those carried out in countries of South America. There is some suggestion that dairy products, red meat, processed meat, a-linolenic fatty acids, as well as dietary patterns characterized by higher intakes of red and processed meat, eggs, and grains may play some role in the development of PC. There is no clear association with the intake of vegetables and fruits, lycopene, fats, and different types of fatty acids. The evidence on diet and PC is therefore inconclusive in general and specifically in South America. Particular	Review

				attention must be paid to the study of cancer risk in some countries of South America because of the singularly risky dietary pattern consumed by its population				
Cancer Risk Reviews	Giovannucci E	Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. Giovannucci E. J Natl Cancer Inst. 1999 Feb 17;91(4):317-31.	1999	The epidemiologic literature in the English language regarding intake of tomatoes and tomato-based products and blood lycopene (a compound derived predominantly from tomatoes) level in relation to the risk of various cancers was reviewed. Among 72 studies identified, 57 reported inverse associations between tomato intake or blood lycopene level and the risk of cancer at a defined anatomic site; 35 of these inverse associations were statistically significant. No study indicated that higher tomato consumption or blood lycopene level statistically significantly increased the risk of cancer at any of the investigated sites. About half of the relative risks for	Review	N/(-) ↓ cancer risk by ↑ fruit/vegetable intake	N/(-) ↓ cancer risk by ↑ fruit/vegetable intake	N/(-) ↓ cancer risk by having ↑ blood [lyco]

comparisons of high with low intakes or levels for tomatoes or lycopene were approximately 0.6 or lower. The evidence for a benefit was strongest for cancers of the prostate, lung, and stomach. Data were also suggestive of a benefit for cancers of the pancreas, colon and rectum, esophagus, oral cavity, breast, and cervix. Because the data are from observational studies, a cause-effect relationship cannot be established definitively. However, the consistency of the results across numerous studies in diverse populations, for case-control and rospective studies, and for dietary-based and blood-based investigations argues against bias or confounding as the explanation for these findings. Lycopene may account for or contribute to these benefits, but this possibility is not yet proven and requires further study. Numerous other potentially beneficial

				compounds are present in tomatoes, and, conceivably, complex interactions among multiple components may contribute to the anticancer properties of tomatoes. The consistently lower risk of cancer for a variety of anatomic sites that is associated with higher consumption of tomatoes and tomato-based products adds further support for current dietary recommendations to increase fruit and vegetable consumption.	
Cancer Risk Reviews (renal cell)	Lee JE	Intakes of fruit, vegetables, and carotenoids and renal cell cancer risk: a pooled analysis of 13 prospective studies. Lee JE, Männistö S, Spiegelman D, Hunter DJ, Bernstein L, van den Brandt PA, Buring JE, Cho E, English DR, Flood A, Freudenheim JL, Giles GG, Giovannucci E, Håkansson N, Horn-Ross PL,	2009	Fruit and vegetable consumption has been hypothesized to reduce the risk of renal cell cancer. We conducted a pooled analysis of 13 prospective studies, including 1,478 incident cases of renal cell cancer (709 women and 769 men) among 530,469 women and 244,483 men followed for up to 7 to 20 years. Participants completed a validated food-frequency	Review

Jacobs EJ, Leitzmann MF, Marshall JR, McCullough ML, Miller AB, Rohan TE, Ross JA, Schatzkin A, Schouten LJ, Virtamo J, Wolk A, Zhang SM, Smith-Warner SA.

Cancer Epidemiol Biomarkers Prev. 2009 Jun;18(6):1730-9.

questionnaire at baseline. Using the primary data from each study, the study-specific relative risks (RR) were calculated using the Cox proportional hazards model and then pooled using a random effects model. We found that fruit and vegetable consumption was associated with a reduced risk of renal cell cancer. Compared with <200 g/d of fruit and vegetable intake, the pooled multivariate RR for >or=600 g/d was 0.68 [95% confidence interval (95% CI) = 0.54-0.87; P for between-studies heterogeneity = 0.86; P for trend = 0.001]. Compared with <100 g/d, the pooled multivariate RRs (95% CI) for >or=400 g/d were 0.79 (0.63-0.99; P for trend = 0.03) for total fruit and 0.72 (0.48-1.08; P for trend = 0.07) for total vegetables. For specific carotenoids, the pooled multivariate RRs (95% CIs) comparing the highest and lowest

				quintiles were 0.87 (0.73-1.03) for alpha-carotene, 0.82 (0.69-0.98) for beta-carotene, 0.86 (0.73-1.01) for beta-cryptoxanthin, 0.82 (0.64-1.06) for lutein/zeaxanthin, and 1.13 (0.95-1.34) for lycopene. In conclusion, increasing fruit and vegetable consumption is associated with decreasing risk of renal cell cancer; carotenoids present in fruit and vegetables may partly contribute to this protection.	
Cancer Risk Reviews (prostate)	Rackley JD	Complementary and alternative medicine for advanced prostate cancer. Rackley JD, Clark PE, Hall MC. Urol Clin North Am. 2006 May;33(2):237-46, viii.	2006	Complimentary and alternative medicines (CAM) have increased drastically in popularity in the past decade. These are largely in the form of nutritional supplements. Despite a wealth of information sources on the subject, the fundamental problem with CAM herapies is a dearth of evidence-based medicine. Advanced prostate cancer has significant long-term morbidity, and there is a growing interest	Review

				in alternative and complimentary forms of therapy that will improve the outcomes of patients who have recurrent or advanced prostate cancer while obviating the need for more toxic forms of therapy. In this article we summarize the use of some of the more common CAM nutritional supplements and review the scientific data that are available to support their use.			
Cancer Risk Reviews (prostate)	Giovannucci E	Does prostate-specific antigen screening influence the results of studies of tomatoes, lycopene, and prostate cancer risk? Giovannucci E. J Natl Cancer Inst. 2007 Jul 18;99(14):1060-2. Epub 2007 Jul 10.	2007	In this issue of the Journal, Kavanaugh et al. (1) describe how the U. S. Food and Drug Administration (FDA) evaluated the scientific evidence for proposed qualified health claims for tomatoes and lycopene with respect to the risks of prostate cancer and other types of cancers. After the authors qualitatively reviewed the studies, they concluded that there was "a very low level of comfort that a relationship exists between the consumption of tomatoes and/or	Editorial		N

tomato sauce and prostate cancer risk." This conclusion is disappointing given that some initial studies of tomato product intake or circulating lycopene levels suggested an association with a reduced risk of prostate cancer, providing some hope for prostate cancer prevention (2–6). However, a number of recent studies, including some (7–9) too recent to be included in the review by Kavanaugh et al. (1), have not supported this association or have been equivocal. Should we now conclude that tomatoes or lycopene are unlikely to have any role in prostate carcinogenesis? Before we do, we should consider a potentially complicating factor, which is that most of the recent studies have been conducted in populations in which most prostate cancers are identified through prostate-specific antigen (PSA)

				screening. In interpreting the evidence for a risk factor in relation to prostate cancer risk, two major considerations are how PSA screening influences the diagnosis and epidemiology of prostate cancer and when during prostate carcinogenesis that risk factor is operative.	
Cancer Risk Reviews (skin)	Dinkova-Kostova AT	Phytochemicals as protectors against ultraviolet radiation: versatility of effects and mechanisms. Dinkova-Kostova AT. Planta Med. 2008 Oct;74(13):1548-59. Epub 2008 Aug 11.	2008	Ultraviolet (UV) radiation is one of the most abundant carcinogens in our environment, and the development of non-melanoma skin cancers, the most common type of human malignancy worldwide, represents one of the major consequences of excessive exposure. Because of growing concerns that the level of UV radiation is increasing as a result of depletion of the stratospheric ozone and climate change, the development of strategies for protection of the skin is an urgent need. Many phytochemicals that	Review

belong to various families of secondary metabolites, such as alkaloids (caffeine, sanguinarine), flavonoids [(-)-epigallocatechin 3-gallate, genistein, silibinin], carotenoids (beta-carotene, lycopene), and isothiocyanates (sulforaphane), offer exciting platforms for the development of such protective strategies. These phytochemicals have been consumed by humans for many centuries as part of plant-rich diets and are presumed to be of low toxicity, an essential requirement for a chemoprotective agent. Mechanistically, they affect multiple signalling pathways and protect against UV radiation-inflicted damage by their ability to act as direct and indirect antioxidants, as well as anti-inflammatory and immunomodulatory agents. Such "pluripotent character" is a critical prerequisite for an agent that is designed to

				counteract the multiple damaging effects of UV radiation. Especially attractive are inducers of the Keap1/Nrf2/ARE pathway, which controls the gene expression of proteins whose activation leads to enhanced protection against oxidants and electrophiles. Such protection is comprehensive, long-lasting, and unlikely to cause pro-oxidant effects or interfere with the synthesis of vitamin D.		
Cancer Risk Reviews (liver)	Glauert HP	Dietary antioxidants in the prevention of hepatocarcinogenesis: a review. Glauert HP, Calfee-Mason K, Stemm DN, Tharappel JC, Spear BT. Mol Nutr Food Res. 2010 Jul;54(7):875-96. Review.	2010	In this review, the role of dietary antioxidants in the prevention of hepatocarcinogenesis is examined. Both human and animal models are discussed. Vitamin C, vitamin E, and selenium are antioxidants that are essential in the human diet. A number of non-essential chemicals also contain antioxidant activity and are consumed in the human diet, mainly as plants or as supplements,	Review	N

				including beta-carotene, ellagic acid, curcumin, lycopene, coenzyme Q(10), epigallocatechin gallate, N-acetyl cysteine, and resveratrol. Although some human and animal studies show protection against carcinogenesis with the consumption of higher amounts of antioxidants, many studies show no effect or an enhancement of carcinogenesis. Because of the conflicting results from these studies, it is difficult to make dietary recommendations as to whether consuming higher amounts of specific antioxidants will decrease the risk of developing hepatocellular carcinoma.			
Cancer Risk Reviews (lung)	Gallicchio L	Carotenoids and the risk of developing lung cancer: a systematic review. Gallicchio L, Boyd K, Matanoski G, Tao XG, Chen L, Lam TK, Shiels M,	2008	BACKGROUND: Carotenoids are thought to have anti-cancer properties, but findings from population-based research have been inconsistent. OBJECTIVE: We aimed to conduct a systematic review of	Meta-Analysis		N

Hammond E, Robinson KA, Caulfield LE, Herman JG, Guallar E, Alberg AJ.

Am J Clin Nutr. 2008 Aug;88(2):372-83. Review.

the associations between carotenoids and lung cancer. DESIGN: We searched electronic databases for articles published through September 2007. Six randomized clinical trials examining the efficacy of beta-carotene supplements and 25 prospective observational studies assessing the associations between carotenoids and lung cancer were analyzed by using random-effects meta-analysis. RESULTS: The pooled relative risk (RR) for the studies comparing beta-carotene supplements with placebo was 1.10 (95% confidence limits: 0.89, 1.36; P = 0.39). Among the observational studies that adjusted for smoking, the pooled RRs comparing highest and lowest categories of total carotenoid intake and of total carotenoid serum concentrations were 0.79 (0.71, 0.87; P < 0.001) and 0.70 (0.44, 1.11; P = 0.14),

respectively. For beta-carotene, highest compared with lowest pooled RRs were 0.92 (0.83, 1.01; P = 0.09) for dietary intake and 0.84 (0.66, 1.07; P = 0.15) for serum concentrations. For other carotenoids, the RRs comparing highest and lowest categories of intake ranged from 0.80 for beta-cryptoxanthin to 0.89 for alpha-carotene and lutein-zeaxanthin; for serum concentrations, the RRs ranged from 0.71 for lycopene to 0.95 for lutein-zeaxanthin. CONCLUSIONS: beta-Carotene supplementation is not associated with a decrease in the risk of developing lung cancer. Findings from prospective cohort studies suggest inverse associations between carotenoids and lung cancer; however, the decreases in risk are generally small and not statistically significant. These inverse associations may be the result of carotenoid measurements' function as a marker

				of a healthier lifestyle (higher fruit and vegetable consumption) or of residual confounding by smoking.	
Cancer Risk Reviews (panc)	Nitsche C	Environmental risk factors for chronic pancreatitis and pancreatic cancer. Nitsche C, Simon P, Weiss FU, Fluhr G, Weber E, Gärtner S, Behn CO, Kraft M, Ringel J, Aghdassi A, Mayerle J, Lerch MM. Dig Dis. 2011;29(2):235-42. Epub 2011 Jul 5.	2011	Chronic pancreatitis has long been thought to be mainly associated with immoderate alcohol consumption. The observation that only ~10% of heavy drinkers develop chronic pancreatitis not only suggests that other environmental factors, such as tobacco smoke, are potent additional risk factors, but also that the genetic component of pancreatitis is more common than previously presumed. Either disease-causing or protective traits have been indentified for mutations in different trypsinogen genes, the gene for the trypsin inhibitor SPINK1, chymotrypsinogen C, and the cystic fibrosis transmembane conductance regulator (CFTR). Other factors that	Review

have been proposed to contribute to pancreatitis are obesity, diets high in animal protein and fat, as well as antioxidant deficiencies. For the development of pancreatic cancer, preexisting chronic pancreatitis, more prominently hereditary pancreatitis, is a risk factor. The data on environmental risk factors for pancreatic cancer are, with the notable exception of tobacco smoke, either sparse, unconfirmed or controversial. Obesity appears to increase the risk of pancreatic cancer in the West but not in Japan. Diets high in processed or red meat, diets low in fruits and vegetables, phytochemicals such as lycopene and flavonols, have been proposed and refuted as risk or protective factors in different trials. The best established and single most important risk factor for cancer as well as pancreatitis and the

				one to clearly avoid is tobacco smoke.		
Cancer Risk Reviews (prostate)	Gerster H	The potential role of lycopene for human health. Gerster H. J Am Coll Nutr. 1997 Apr;16(2):109-26.	1997	Lycopene is one of the major carotenoids in Western diets and is found almost exclusively in tomatoes and tomato products. It accounts for about 50% of carotenoids in human serum. Among the common dietary carotenoids lycopene has the highest singlet oxygen quenching capacity in vitro. Other outstanding features are its high concentration in testes, adrenal gland and prostate. In contrast to other carotenoids its serum values are not regularly reduced by smoking or alcohol consumption but by increasing age. Remarkable inverse relationships between lycopene intake or serum values and risk have been observed in particular for cancers of the prostate, pancreas and to a certain extent of the stomach. In some of the studies lycopene was the only carotenoid	Review		(-) ↓ cancer risk by having ↑ blood [lyco]

				associated with risk reduction. Its role in cancer risk reduction still needs to be clarified. Patients with HIV infection, inflammatory diseases and hyperlipidemia with and without lipid lowering treatment may have depleted lycopene serum concentrations. Before embarking on large-scale human trials the distribution of lycopene and its biological functions need to be further evaluated.	
Cancer Risk Reviews (prostate)	Hadley CW	Tomatoes, lycopene, and prostate cancer: progress and promise. Hadley CW, Miller EC, Schwartz SJ, Clinton SK. Exp Biol Med (Maywood). 2002 Nov;227(10):869-80.	2002	Prostate cancer has emerged as a major public health problem in nations that have an affluent culture with an aging population. The search for etiologic risk factors and an emphasis on the development of chemopreventive agents has gained momentum over the last decade. Among the landmark epidemiologic findings during this period has been the association between the consumption of tomato products and a lower risk of	Review

prostate cancer. The traditional reductionist scientific approach has led many investigators to propose that lycopene, a carotenoid consumed largely from tomato products, may be the component responsible for lowering the risk of prostate cancer. Thus, many laboratory and clinical studies are now underway with the goal of assessing the ability of pure lycopene to serve as a chemopreventive agent for prostate and other malignancies. The focus on lycopene should continue, and an improved understanding of lycopene absorption, distribution, role in antioxidant reactions, and metabolism is critical in the quest to elucidate mechanisms whereby this compound could possibly reduce prostate cancer risk. In contrast to the pharmacologic approach with pure lycopene, many nutritional scientists

				direct their attention upon the diverse array of tomato products as a complex mixture of biologically active phytochemicals that together may have anti-prostate cancer benefits beyond those of any single constituent. These contrasting approaches will continue to be explored in clinical, laboratory and epidemiologic studies in the near future, providing hope that the next generation will benefit from this knowledge and experience a lower risk of prostate cancer.	
Cancer Risk Reviews (prostate)	Oh WK	Complementary and alternative therapies in prostate cancer. Oh WK, Small EJ. Semin Oncol 2002; 29: 575–584.	2002	Complementary and alternative therapies are used with increasing frequency in men with prostate cancer. However, little is known about the efficacy of such therapies for this cancer. While epidemiological data support the association between intake of certain micronutrients with development of prostate cancer, there exist limited	Review

prospective data that support the chemopreventative or therapeutic value of such nutritional agents in prostate cancer. To date, one of the most studied treatments has been PC-SPES, a combination of eight herbal therapies with activity against prostate cancer. Studies in cell lines of human prostate cancer demonstrate significant dose-dependent decreases in cellular viability after exposure to extracts of this agent. Clinical studies suggested that PC-SPES could reduce prostate specific antigen levels in patients with either androgen-dependent or androgen-independent prostate cancer. Toxicity was mild, although there was a low risk of thromboembolic events with such treatment. Manufacture of PC-SPES was recently halted, after revelations that the herbal combination was contaminated with warfarin, which led to a recall by the manufacturer.

				Subsequent analyses also revealed the presence of diethylstilbestrol (DES) and indomethicin in some lots of PC-SPES. Available data regarding other alternative therapies are reviewed as well. Semin Oncol 29:575-584.	
Cancer Risk Reviews (prostate)	Campbell JK	Tomato phytochemicals and prostate cancer risk. Campbell JK, Canene-Adams K, Lindshield BL, Boileau TW, Clinton SK, Erdman JW Jr. J Nutr. 2004 Dec;134(12 Suppl):3486S-3492S.	2004	Mounting evidence over the past decade suggests that the consumption of fresh and processed tomato products is associated with reduced risk of prostate cancer. The emerging hypothesis is that lycopene, the primary red carotenoid in tomatoes, may be the principle phytochemical responsible for this reduction in risk. A number of potential mechanisms by which lycopene may act have emerged, including serving as an important in vivo antioxidant, enhancing cell-to-cell communication via increasing gap junctions between cells, and modulating cell-	Review

cycle progression. Although the effect of lycopene is biologically relevant, the tomato is also an excellent source of nutrients, including folate, vitamin C, and various other carotenoids and phytochemicals, such as polyphenols, which also may be associated with lower cancer risk. Tomatoes also contain significant quantities of potassium, as well as some vitamin A and vitamin E. Our laboratory has been interested in identifying specific components or combination of components in tomatoes that are responsible for reducing prostate cancer risk. We carried out cell culture trials to evaluate the effects of tomato carotenoids and tomato polyphenols on growth of prostate cancer cells. We also evaluated the ability of freeze-dried whole-tomato powder or lycopene alone to reduce growth of prostate tumors in rats. This paper reviews the

				epidemiological evidence, evaluating the relationship between prostate cancer risk and tomato consumption, and presents experimental data from this and other laboratories that support the hypothesis that whole tomato and its phytochemical components reduce the risk of prostate cancer.	
Cancer Risk Reviews (prostate)	Bemis DL	Clinical trials of natural products as chemopreventive agents for prostate cancer. Bemis DL, Katz AE, Buttyan R. Expert Opin Investig Drugs. 2006 Oct;15(10):1191-200.	2006	Epidemiological research on prostate cancer risk in men throughout the world has identified significant correlations between dietary habits and prostate cancer occurrence. These studies served as a catalyst for exploration into the potential of dietary substances to act as chemopreventive agents against this disease, and include green tea catechins, lycopene, soy isoflavones, pomegranate phenolics, selenium, vitamins E and D, curcumin and resveratrol. Before these agents (in the dietary or purified	Review

				forms) can be recommended as useful chemopreventive strategies for patients, their activity must be confirmed in rigorously designed clinical trials. This review discusses the preclinical and clinical data available for these dietary agents and describes relevant clinical trials currently being conducted.			
Cancer Risk Reviews (prostate)	Bemis DL	The use of herbal and over-the-counter dietary supplements for the prevention of prostate cancer. Bemis DL, Capodice JL, Costello JE, Vorys GC, Katz AE, Buttyan R. Curr Urol Rep. 2006 May;7(3):166-74.	2006	Having a high probability of experiencing prostate cancer during their lifetime, men are increasingly seeking protection against this disease with the use of over-the-counter dietary supplements containing herbs, vitamins, or plant-derived biochemical agents. The use of these agents for prostate cancer prevention is driven by epidemiology supporting the idea that regional diets and consumption of specific dietary components (certain herbs, vitamins, isoflavones, and polyphenols)	Review		N

				are associated with a lower risk for prostate cancer, in conjunction with basic research that is defining molecules within food substances that kill or suppress growth of cultured human prostate cancer cells. Moreover, there is a sense that these dietary agents lack side effects, although this assumption often is faulty. Unfortunately, at this time, there is insufficient clinical evidence to support the widespread use of these dietary supplements for chemoprevention of prostate cancer, although ongoing clinical trials of the most promising vitamins and minerals are approaching conclusion.				
Cancer Risk Reviews (prostate)	Ellinger S	Tomatoes, tomato products and lycopene in the prevention and treatment of prostate cancer: do we have the evidence from intervention studies? Ellinger S, Ellinger	2006	PURPOSE OF REVIEW: Lycopene-rich foods such as fresh tomatoes and tomato products are discussed as potential effectors in the prevention and therapy of prostate cancer. This review provides an overview on the efficacy of	Review	(-) ↓ DNA strand breaks in mononuclear leukocyte		N

J, Stehle P.

Curr Opin Clin Nutr Metab Care. 2006 Nov;9(6):722-7.

supplementation with tomatoes, tomato products and lycopene on appropriate surrogate endpoint biomarkers such as DNA damage and metabolites of the insulin-like growth factor pathway in healthy individuals and prostate cancer patients.
RECENT FINDINGS: Intervention studies show that the daily consumption of one serving of tomatoes or tomato products, but not supplementation with lycopene alone, increases the resistance of mononuclear leukocytes against DNA strand breaks induced by reactive oxygen species in healthy volunteers. Data from clinical trials with prostate cancer patients are scarce and contradictory. There is a paucity of reliable data on DNA damage in prostate tissue.
SUMMARY: Increasing evidence suggests that a single serving of tomatoes or tomato products ingested daily may contribute to protect from DNA

				damage. As DNA damage seems to be involved in the pathogenesis of prostate cancer, the regular ingestion of tomatoes or tomato products might prevent the disease. Further well-designed studies are necessary to establish the role of tomatoes and tomato products in the prevention and therapy of prostate cancer.			
Cancer Risk Reviews (prostate)	Theobald S	[Nutrition and prostate cancer--what is the scientific evidence?] Theobald S. Med Monatsschr Pharm. 2006 Oct;29(10):371-7.	2006	Prostate cancer is the most frequently occurring form of cancer in German men with an incidence of 49.000 in the year 2002. Epidemiological studies indicate diet and physical activity may play major roles in both incidence and progression of the disease. Obesity may increase both primary risk and biochemical (increase in prostate specific antigen) or clinical recurrence. Among individual food groups/nutrients a high consumption of total fat, saturated fats, meat, dairy, and calcium are	Review	(-) ↓ risk	(-) ↓ risk

related to an increased risk. Tomato products, soy, lycopene, selenium, marine omega-3-fatty acids and vitamin E in smokers may inversely be associated with prostate cancer. Interventional studies with supplemental tomato products and selenium also showed a delay in disease progression. Evidence from experimental studies and clinical experience suggest that application of selenium during chemotherapy and/or radiotherapy may decrease therapy related toxicities and increases the effect of the standard therapy on cancer cells. For expert patients it is essential to participate in decisions concerning their standard as well as complementary therapy by developing individual self-help concepts. These often include both changing dietary habits and taking dietary supplements. Physicians should consider these

				needs when they counsel cancer patients.		
Cancer Risk Reviews (prostate)	Coates PM	Evidence-based reviews in support of health policy decisions. Coates PM. J Natl Cancer Inst. 2007 Jul 18;99(14):1059. Epub 2007 Jul 10.	2007	In this issue of the Journal, Kavanaugh et al. (2) describe the approach that the U. S. Food and Drug Administration (FDA) has used to incorporate evidence-based review principles into the challenging area of evaluating qualified claims for health benefits of foods and food components that are marketed as dietary supplements (2). The particular topic of this paper was qualified health claims for tomatoes and for lycopene, a constituent of tomatoes that is marketed as a dietary supplement, in reducing the risk of some forms of cancer, including prostate cancer. FDA's systematic review of the relevant literature followed the rules that are crucial to evidence-based review and, as such, exemplifies the transparency and neutrality of an evidence-based review approach in	Editorial	N

				evaluating the strength of the available evidence in an area where the expectation of risk reduction sometimes results in a biased interpretation of the evidence. However, there are several issues that must be taken into account when considering the processes that FDA was obliged to use to meet its needs.	
Cancer Risk Reviews (prostate)	Fleshner N	Prostate cancer prevention: past, present, and future. Fleshner N, Zlotta AR. Cancer. 2007 Nov 1;110(9):1889-99.	2007	Prostate cancer is the most common male malignancy and the second or third leading cause of cancer death among men in the West. The descriptive epidemiology of prostate cancer suggests that it is a preventable disease. Prevention has the theoretical advantage of not only saving lives, but also reduce the morbidity of radical prostate cancer therapy. This article reviews the past, present, and future of prostate cancer prevention. In particular, the evidence and scientific data of a variety of prevention strategies are	Review

reviewed. Strategies reviewed include dietary fat reduction and supplementation with vitamins D and E, and selenium. Dietary intake of soy, green tea, and tomato-rich products (lycopene) are also reviewed. Data regarding pharmacological intervention with cyclo-oxygenease inhibitors, antiestrogens, and in particular 5-alpha reductase inhibitors are reviewed. The results of the Prostate Cancer Prevention Trial including the controversy surrounding higher-grade cancers among men randomized to finasteride are also summarized. Finally, a variety of trial designs as well as a roster of current phase 2 trials are presented. Probably no cancer is being investigated more thoroughly in the context of prevention as prostate cancer in 2007. Definitive answers to pivotal phase 3 trials will be available in the coming 2 to 7 years.

Cancer Risk Reviews (prostate)	Lindshield BL	Lycopenoids: are lycopene metabolites bioactive? Lindshield BL, Canene-Adams K, Erdman JW Jr. Arch Biochem Biophys. 2007 Feb 15;458(2):136-40. Epub 2006 Oct 4.	2007	In vitro lycopene is the most potent antioxidant among carotenoids. While antioxidant function may be relevant to health, we hypothesize that metabolites of lycopene may be bioactive and responsible for the beneficial effects of tomato product consumption. We term these metabolites "lycopenoids," which we believe may be produced from carotenoid monooxygenase (CMO) II, paralleling the production of retinoids from beta-carotene by CMO I. We present evidence suggesting that tomato carotenoid metabolites may be responsible for the reduced risk of prostate cancer seen in men consuming high levels of tomato products. Finally, we identify gaps in knowledge in this evolving area of carotenoid research.	Review	(-) ↓ risk		(-) ↓ risk
Cancer Risk Reviews (prostate)	Syed DN	Chemopreventio n of prostate cancer through dietary agents:	2007	Prostate cancer (CaP) is second only to lung cancer as the cause of	Review		

progress and promise.

Syed DN, Khan N, Afaq F, Mukhtar H.

Cancer Epidemiol Biomarkers Prev. 2007 Nov;16(11):2193-203.

cancer-related deaths in American men and is responsible for over 29,000 deaths per year. One promising approach to reduce the incidence of CaP is through chemoprevention, which has been recognized as a plausible and cost-effective approach to reduce cancer morbidity and mortality by inhibiting precancerous events before the occurrence of clinical disease. Indeed, CaP is an ideal candidate disease for chemoprevention because it is typically diagnosed in the elderly population with a relatively slower rate of growth and progression, and therefore, even a modest delay in the development of cancer, achieved through pharmacologic or nutritional intervention, could result in substantial reduction in the incidence of clinically detectable disease. In this review, we have summarized the

				recent investigations and mechanistic studies on CaP chemoprevention using dietary agents, such as selenium, vitamins D and E, lycopene, phytoestrogens, flavonoids, and green tea polyphenols. Well-designed trials are required to delineate the potential clinical usefulness of these agents through issues, such as determining the optimal period and route of administration, systemic bioavailability, optimal dosing and toxicity of the agent, and single or combinatorial approach. It is hoped that, combining the knowledge based on agents with targets, effective approaches for CaP chemoprevention can be established.			
Cancer Risk Reviews (prostate)	Von Low EC	Review. Facts and fiction of phytotherapy for prostate cancer: a critical assessment of preclinical and clinical data.	2007	The objective of this work was to substantially review all preclinical and clinical data on phytochemicals, such as genistein, lycopene, curcumin,	Review		N

Von Low EC, Perabo FG, Siener R, Muller SC.

In Vivo. 2007 Mar-Apr;21(2):189-204.

epigallocatechin-gallate, and resveratrol, in terms of their effects as a potential treatment of prostate cancer. It is known, that prostate cancer patients increasingly use complementary and alternative medicines in the hope of preventing or curing cancer. The preclinical data for the phytochemicals presented in this review show a remarkable efficacy against prostate cancer cells in vitro, with molecular targets ranging from cell cycle regulation to induction of apoptosis. In addition, well-conducted animal experiments support the belief that these substances might have a clinical activity on human cancer. However, it is impossible to make definite statements or conclusions on the clinical efficacy in cancer patients because of the great variability and differences of the study designs, small patient numbers, short treatment duration and lack of a standardised drug

				formulation. Although some results from these clinical studies seem encouraging, reliable or long-term data on tumor recurrence, disease progression and survival are unknown. At present, there is no convincing clinical proof or evidence that the cited phythochemicals might be used in an attempt to cure cancer of the prostate.			
Cancer Risk Reviews (prostate)	Dahan K	Lycopene in the prevention of prostate cancer. Dahan K, Fennal M, Kumar NB. J Soc Integr Oncol. 2008 Winter;6(1):29-36.	2008	Based on the evidence from epidemiologic, animal, and in vitro data and human clinical trials, it is evident that lycopene, a non-provitamin A carotenoid, is a promising agent for prostate cancer chemoprevention. It is also clear that the form of lycopene used (purified versus food sources), dose of lycopene and concomitant use with other carotenoids and antioxidants, duration of exposure, specific target populations, and stage of disease	Review		(-) ↓ risk prostate cancer

				appear to play a major role in determining agonistic or antagonistic effects. Based on our review, there is enough evidence to warrant use of lycopene in phase I and II clinical trials to examine its safety and efficacy as a potential chemopreventive agent for prostate cancer. The objective of this article is to review this evidence from epidemiologic, animal, in vitro, and clinical trials and provide the need and rationale to examine further the role of lycopene for prostate cancer prevention.			
Cancer Risk Reviews (prostate)	Magri V	Activity of Serenoa repens, lycopene and selenium on prostatic disease: evidences and hypotheses. Magri V, Trinchieri A, Perletti G, Marras E. Arch Ital Urol Androl. 2008 Jun;80(2):65-78.	2008	An increasing number of preclinical data, epidemiological evidences and clinical trials point to a potential role of natural compounds like herbal extracts, carotenoids and specific metals in the prevention and/or treatment of different prostate conditions, like hyperplasia, inflammation, cancer. The present	Review		(-) ↓ inflammation

				article reviews some of the major and most recent findings on the therapeutic properties of three of the most widely used compounds, i.e. Serenoa repens, lycopene and selenium. Although the mechanism of action of these compounds ought to be further characterized by focused investigation, it appears that a common feature of these agents may be a dual activity on proliferative disorders as well as on inflammatory conditions at the level of the prostate gland.			
Cancer Risk Reviews (prostate)	Van Patten CL	Diet and dietary supplement intervention trials for the prevention of prostate cancer recurrence: a review of the randomized controlled trial evidence. Van Patten CL, de Boer JG, Tomlinson Guns ES. J Urol. 2008 Dec;180(6):2314-	2008	PURPOSE: We review the effect of diet and dietary supplement interventions on prostate cancer progression, recurrence and survival. MATERIALS AND METHODS: A literature search was conducted in MEDLINE, EMBASE and CINAHL to identify diet and dietary supplement intervention studies in men with prostate cancer using	Review		N

21; discussion 2721-2. Epub 2008 Oct 18. Review

prostate specific antigen or prostate specific antigen doubling time as a surrogate serum biomarker of prostate cancer recurrence and/or survival.
RESULTS: Of the 32 studies identified 9 (28%) were randomized controlled trials and the focus of this review. In these studies men had confirmed prostate cancer and elevated or increasing prostate specific antigen. Only 1 trial included men with metastatic disease. When body mass index was reported, men were overweight or obese. A significant decrease in prostate specific antigen was observed in some studies using a low fat vegan diet, soy beverage or lycopene supplement. While not often reported as an end point, a significant increase in prostate specific antigen doubling time was observed in a study on lycopene supplementation. In only 1 randomized controlled trial in

				men undergoing orchiectomy was a survival end point of fewer deaths with lycopene supplementation reported. CONCLUSIONS: A limited number of randomized controlled trials were identified in which diet and dietary supplement interventions appeared to slow disease progression in men with prostate cancer, although results vary. Studies were limited by reliance on the surrogate biomarker prostate specific antigen, sample size and study duration. Well designed trials are warranted to expand knowledge, replicate findings and further assess the impact of diet and dietary supplement interventions on recurrence and treatment associated morbidities.			
Cancer Risk Reviews (prostate)	Wigle DT	Role of hormonal and other factors in human prostate cancer. Wigle DT, Turner MC, Gomes J,	2008	American men have a lifetime risk of about 18% for prostate cancer diagnosis. Large international variations in prostate	Review	(-) protective role	(-) protective role

Parent ME.

J Toxicol Environ Health B Crit Rev. 2008 Mar;11(3-4):242-59.

cancer risks and increased risks among migrants from low- to high-risk countries indicate important roles for environmental factors. Major known risk factors include age, family history, and country/ethnicity. Type 2 diabetes appears to reduce risk, while high birth weight and adult height are linked to increased risk of aggressive prostate cancer. Limited evidence supports an association with a history of sexually transmitted infections. A previous meta-analysis of eight cohort studies indicated no associations with plasma androgen, estrogen, or sex hormone binding globulin (SHBG) levels. However, there were dose-response relationships with baseline plasma testosterone levels in two studies that adjusted for other serum hormones and obesity. Finasteride (a drug that blocks testosterone activation) reduced

prostate cancer risk by 25%. Low-frequency genes linked to familial prostate cancer only explain a small fraction of all cases. Sporadic cases were linked to relatively common polymorphisms of genes involved in (1) androgen synthesis, activation, inactivation and excretion, (2) hormone and vitamin D receptors, (3) carcinogen metabolism, and (4) DNA repair. Epidemiologic evidence supports protective roles for dietary selenium, vitamin E, pulses, tomatoes/lycopene, and soy foods, and high plasma 1,25-dihydroxyvitamin D levels. There is inadequate evidence that vegetables, fruit, carotenoids, and vitamins A and C reduce risk and that animal fat, alpha-linoleic acid, meat, coffee, and tea increase risk. Two major cohort studies found dose-response relationships with dietary calcium intake. Total dietary energy intake may enhance risk. Limited

				evidence supports a protective role for physical activity and elevated risk for farmers and other men with occupational pesticide exposure, particularly to organochlorine compounds and phenoxy herbicides. There is inadequate evidence for a relationship with alcohol or smoking. Most known or suspected external risk factors may act through hormonal mechanisms, but our review found little supporting evidence, and substantial further research is needed.				
Cancer Risk Reviews (prostate)	Chan R	Prostate cancer and vegetable consumption. Chan R, Lok K, Woo J. Mol Nutr Food Res. 2009 Feb;53(2):201-16.	2009	Epidemiological studies have shown marked variations in prostate cancer incidence and mortality across different geographic regions, leading to the rising interest in the role of nutrition in prostate cancer risk. There is also a large body of evidence that a diverse diet, rich in vegetables, can reduce the risk of prostate cancer. In this review, the role of various kinds of vegetables and	Review	(-) ↓ risk		(-) ↓ risk

their bioactive compounds associated with prostate cancer risk, and the underlying mechanisms of these associations are summarized. There is accumulating evidence to support the consumption of lycopene, in particular tomato and tomato-based products, as protective factors against prostate cancer. Evidence on the protective role of beta-carotene was inconsistent from cohort and case-control studies. Evidence on the effect of pulses or soy consumption on prostate cancer risk was limited but suggestive of decreased risk with increased pulses or soy consumption. However, the role of vitamin C, vitamin E, allium vegetables, and cruciferous vegetables on prostate cancer risk remains to be determined due to limited evidence. Although the impact on prostate cancer risk differs among various vegetables and their constituent nutrients, the overall benefits of plant

				based diet on cancer prevention and other diet-related diseases should be promoted.			
Cancer Risk Reviews (prostate)	Colli JL	Chemopreventio n of prostate cancer: what can be recommended to patients? Colli JL, Amling CL. Curr Urol Rep. 2009 May;10(3):165-71.	200 9	Prostate cancer is third to lung and colon cancer as the cause of cancer-related deaths in American men. It is estimated that there will have been more than 28,000 deaths and 186,000 new cases in 2008 that will impose a significant burden on national health care costs. Chemoprevention aims to reduce both incidence and mortality through the use of agents to prevent, reverse, or delay the carcinogenic process. This study provides clinicians with information on some chemoprevention agents that have been considered to reduce prostate cancer risks, including 5-alpha-reductase inhibitors; statins (a class of compounds used to reduce cholesterol); NSAIDs; selenium; vitamins E and D; lycopene; allium vegetables (garlic,	Review		(-) ↓ risk

				scallions, onions, chives, and leeks); soy/isoflavones; and green tea polyphenols. The evidence to support prostate cancer risk reduction benefits for each chemoprevention agent based on a review of the literature is provided.			
Cancer Risk Reviews (prostate)	Ellinger S	[Tomatoes and lycopene in prevention and therapy--is there an evidence for prostate diseases?] Ellinger S, Ellinger J, MÃller SC, Stehle P. Aktuelle Urol. 2009 Jan;40(1):37-43. Epub 2009 Jan 28.	2009	Tomatoes are discussed to have an important role in the prevention of and therapy for prostate cancer (PCA). Whether or not they are also useful in the primary and secondary prevention of benign prostate hyperplasia (BPH) is not clear. This review summarises the results of original contributions with a focus on interventional studies. Whereas epidemiological studies on BPH prevention provide no evidence for a preventive potential of tomatoes and tomato products, the majority of interventional trials points to an increased DNA resistance against	Review	N/(-) may be protective	N/(-) may be protective

				oxidative-induced damage. Even though their effect on a surrogate marker of the IGF pathway cannot be evaluated so far due to insufficient data, the consumption of tomatoes and tomato products may probably protect from PCA--at least when considering low-grade PCA. Thus, regular consumption of these foods can be recommended for the prevention of PCA. Tomato products might also be useful in the therapy for BPH and PCA. The intake of isolated lycopene does not protect from the development of PCA. However, in the doses achieved by consumption of tomato products, lycopene ingestion might also be effective in PCA therapy.				
Cancer Risk Reviews (prostate)	Haseen F	Is there a benefit from lycopene supplementation in men with prostate cancer? A systematic review.	2009	Lycopene has a chemopreventive effect against prostate cancer but its role in prostate cancer progression is unknown; many patients increase their intake of	Review		(-)	PSA (6/8) studies

Haseen F, Cantwell MM, O'Sullivan JM, Murray LJ.

Prostate Cancer Prostatic Dis. 2009;12(4):325-32. Epub 2009 Sep 1. Review

lycopene, although there are no evidence-based guidelines to suggest an effect. Our objective was to conduct a systematic review of literature to evaluate the association between lycopene intake and prostate cancer progression. MEDLINE, EMBASE CINAHL Plus, Web of Science, AMED and CENTRAL databases were systematically searched using terms for lycopene and prostate cancer progression to identify studies published before January 2009. Eight intervention studies were identified (five with no control group; one with an unmatched control group; and two randomized controlled trials (RCTs)). An inverse association was observed between lycopene intake and PSA levels in six studies. The rates of progression measured by bone scan in one RCT were lower in the intervention group. Lycopene resulted in lowering cancer-related symptoms (pain, urinary tract

				symptoms), and severe toxicity or intolerance was not evident. However, the evidence available to date is insufficient to draw a firm conclusion with respect to lycopene supplementation in prostate cancer patients and larger RCTs are required in broader patient groups.			
Cancer Risk Reviews (prostate)	Itsiopoulos C	Can the Mediterranean diet prevent prostate cancer? Itsiopoulos C, Hodge A, Kaimakamis M. Mol Nutr Food Res. 2009 Feb;53(2):227-39.	2009	Prostate cancer is the second most common cancer in men worldwide. Despite the global importance of this cancer, until recently little was known about risk factors apart from the well-established factors: age, family history and country of birth. The large worldwide variation in prostate cancer risk and increased risk in migrants moving from low to high risk countries provides strong support for modifiable environmental factors. We have based our review on the findings of a systematic review undertaken by an expert panel on behalf of the World	Review		(-) ↓ risk

Cancer Research Fund and the American Institute for Cancer Research, and new data since then, linking identified foods and nutrients with prostate cancer. Evidence indicates that foods containing lycopene, as well as selenium and foods containing it, probably protect against prostate cancer, and excess consumption of foods or supplements containing calcium are a probable cause of this cancer. The expert panel also concluded that it is unlikely that beta-carotene (whether from foods or supplements) has a substantial effect on the risk of this cancer. A recent review on environmental factors in human prostate cancer also found that there were protective effects of vitamin E, pulses, soy foods and high plasma 1,25-dihydroxyvitamin D levels. The Mediterranean diet is abundant in foods that may protect

				against prostate cancer and is associated with longevity and reduced cardiovascular and cancer mortality. Compared with many Western countries Greece has lower prostate cancer mortality and Greek migrant men in Australia have retained their low risk for prostate cancer. Consumption of a traditional Mediterranean diet, rich in bioactive nutrients, may confer protection to Greek migrant men, and this dietary pattern offers a palatable alternative for prevention of this disease.	
Cancer Risk Reviews (prostate)	Ma RW	A systematic review of the effect of diet in prostate cancer prevention and treatment. Ma RW, Chapman K. Hum Nutr Diet. 2009 Jun;22(3):187-99; quiz 200-2. Epub 2009 Apr 1.	2009	Dietary therapy has been proposed as a cost effective and noninvasive means of reducing the risk of prostate cancer (PC) and its progression. There is a large volume of published studies describing the role of diet in the prevention and treatment of PC. This article systematically reviews the data for dietary-based	Review

				therapy in the prevention of PC, as well as in the management of patients with PC, aiming to provide clarity surrounding the role of diet in preventing and treating PC. Although conclusive evidence is limited, the current data are indicative that a diet low in fat, high in vegetables and fruits, and avoiding high energy intake, excessive meat, excessive dairy products and calcium intake, is possibly effective in preventing PC. However, caution must be taken to ensure that members of the public do not take excessive amounts of dietary supplements because there may be adverse affects associated with their over consumption. The dietary recommendations for patients diagnosed with PC are similar to those aiming to reduce their risk of PC	
Cancer Risk	Ilic D	Lycopene for the prevention of prostate cancer.	2011	BACKGROUND: Prostate cancer is a common cause of	Review

Reviews (prostate)	Ilic D, Forbes KM, Hassed C. Cochrane Database Syst Rev. 2011 Nov 9;11:CD008007.	death in developed countries, yet the benefits of screening for prostate cancer still remain controversial. A prostate-specific antigen (PSA) test result greater than 4 ng/mL (nanograms/millilitre) has commonly been used as the cut-off level for seeking further tests to diagnose the presence (or absence) of prostate cancer. An increase in PSA levels may not necessarily be associated with an increased risk of prostate cancer, as PSA levels may also be increased in men with benign prostatic hyperplasia and prostatitis. Despite the uncertainty of the net benefit of early detection and treatment, safe and effective methods to prevent prostate cancer are of value. Consumers, seeking greater involvement in their healthcare, are increasingly turning to lifestyle modification and complementary and alternative medicines (CAMs) to maintain their health and prevent

disease. Lycopene is a member of the carotenoid family, which is found abundantly in tomatoes, tomato-based products, strawberries, and watermelon. It has been hypothesised that lycopene is a strong antioxidant, which may lower the risk of cancer (including prostate cancer) in people who have diets rich in lycopene.
OBJECTIVES: To determine whether lycopene reduces the incidence of prostate cancer and prostate cancer-specific mortality. Secondary objectives include changes in PSA levels, prostate symptoms and the nature of adverse events associated with lycopene use.
SEARCH STRATEGY: Electronic searches were conducted across MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) databases. No language or other limitations were imposed.
SELECTION CRITERIA: Randomised

				controlled trials (RCTs) that investigated the use of lycopene for the prevention of prostate cancer were eligible for inclusion in this review. DATA COLLECTION AND ANALYSIS: A search of electronic databases, performed in August 2011, identified 64 citations. All articles were selected for full-text review. From these citations, three studies were identified as meeting the inclusion criteria. Handsearching did not provide any additional studies.			
Cancer Risk Reviews (prostate)	Lippi G	Tomatoes, lycopene-containing foods and cancer risk. Lippi G, Targher G. Br J Cancer. 2011 Mar 29;104(7):1234-5. Epub 2011 Feb 22.	2011	EXCERPT: We read with interest the recent review article by Key (2011), who concluded that the published results from the epidemiological studies suggest little or no association between the total intake of fruit and vegetables and the risk of common cancers, including colorectal, breast and prostate cancer. Although the association between food intake and cancer is	RCT		(-)

still under intense debate, we believe that there is a growing body of clinical evidence suggesting that certain types of food, for example, those rich in lycopene such as tomatoes, might have beneficial effects on the development of certain cancers, especially prostate cancer.
First and foremost, the most recent expert report issued by the World Cancer Research Fund, together with the American Institute for Cancer Research, has reviewed the strength of the evidence that causally correlates food intake to the risk of several forms of cancer. Basically, it has been concluded that a higher consumption of several plant foods might protect against cancers of various sites. In particular, foods rich in folate may protect against pancreatic cancer, those rich in carotenoids against cancers of the mouth, pharynx,

				larynx and lung cancer, those rich in β-carotene or vitamin C against oesophageal cancer, and those rich in lycopene against prostate cancer (World Cancer Research Fund/American Institute for Cancer Research, 2007).			
Cancer Risk Reviews (prostate)	Van Patten CL	Diet and dietary supplement intervention trials for the prevention of prostate cancer recurrence: a review of the randomized controlled trial evidence. Van Patten CL, de Boer JG, Tomlinson Guns ES. J Urol. 2008 Dec;180(6):2314-21; discussion 2721-2. Epub 2008 Oct 18.	2008	PURPOSE: We review the effect of diet and dietary supplement interventions on prostate cancer progression, recurrence and survival. MATERIALS AND METHODS: A literature search was conducted in MEDLINE, EMBASE and CINAHL to identify diet and dietary supplement intervention studies in men with prostate cancer using prostate specific antigen or prostate specific antigen doubling time as a surrogate serum biomarker of prostate cancer recurrence and/or survival. RESULTS: Of the 32 studies identified 9 (28%) were randomized	Review	(-) ↓ PSA ↑ PSA doubling time	(-) ↓ PSA ↑ PSA doubling time

controlled trials and the focus of this review. In these studies men had confirmed prostate cancer and elevated or increasing prostate specific antigen. Only 1 trial included men with metastatic disease. When body mass index was reported, men were overweight or obese. A significant decrease in prostate specific antigen was observed in some studies using a low fat vegan diet, soy beverage or lycopene supplement. While not often reported as an endpoint, a significant increase in prostate specific antigen doubling time was observed in a study on lycopene supplementation. In only 1 randomized controlled trial in men undergoing orchiectomy was a survival end point of fewer deaths with lycopene supplementation reported. CONCLUSIONS: A limited number of randomized controlled trials were identified in which diet and dietary

				supplement interventions appeared to slow disease progression in men with prostate cancer, although results vary.Studies were limited by reliance on the surrogate biomarker prostate specific antigen, sample size and study duration. Well designed trials are warranted to expand knowledge, replicate findings and further assess the impact of diet and dietary supplement interventions on recurrence and treatment associated morbidities.	
Cancer Risk Reviews (skin)	Wright TI	Chemopreventio n of nonmelanoma skin cancer. Wright TI, Spencer JM, Flowers FP. J Am Acad Dermatol. 2006 Jun;54(6):933-46; quiz 947-50.	200 6	Skin cancer is the most common cancer in human beings. The increased incidence of skin cancer has brought much attention to the process by which these tumors develop and how they can be revented. Efforts have been made to educate the public about the importance of protecting skin from excessive ultraviolet light. Despite this	Review

work, the incidence of skin cancer continues to increase. Available compounds may be useful in the chemoprevention of skin cancer. Chemoprevention is defined as oral or topical use of dietary or pharmacologic agents to inhibit or reverse the development of cancer. Potential agents included are the retinoids; difluoromethylornithine; T4 endonuclease V; polyphenolic antioxidants, such as (-)-epigallocatechin gallate, found in green tea and grape seed extract; silymarin; isoflavone genestein; nonsteroidal anti-inflammatory drugs; curcumin; lycopene; vitamin E; beta-carotene; and selenium. Many of these agents are available over the counter as topical or oral preparations. LEARNING OBJECTIVE: At the conclusion of this activity, participants should be familiar with the chemopreventive agents and their efficacy, as well as

				any significant side effects associated with them.		
Cancer: breast	Hu F	Carotenoids and breast cancer risk: a meta-analysis and meta-regression. Hu F, Wang Yi B, Zhang W, Liang J, Lin C, Li D, Wang F, Pang D, Zhao Y. Breast Cancer Res Treat. 2011 Sep 7. [Epub ahead of print]	2011	The purpose of this article is to comprehensively summarize the associations between carotenoids and breast cancer and quantitatively estimate their dose-response relationships. We searched PubMed, Embase, and Cochrane databases (from January 1982 to 1 May 2011) and the references of the relevant articles in English with sufficient information to estimate relative risk or odds ratio and the 95% confidence intervals, and comparable categories of carotenoids. Two reviewers independently extracted data using a standardized form; with any discrepancy adjudicated by the third reviewer. 33 studies met the inclusion criteria. Comparing the highest with the lowest intake: dietary a-carotene	Meta-Analysis	N

intake significantly reduced the breast cancer risk by 9.0% (pooled RR = 0.91; 95% CI: 0.85-0.98; P = 0.01), dietary β-carotene intake reduced the risk by 6.0% (pooled RR = 0.94; 95% CI: 0.88-1.00; P = 0.05); total β-carotene intake reduced the risk by 5.0% (pooled RR = 0.95; 95% CI: 0.90-1.01; P = 0.08) when data from cohort studies were pooled. Significant dose-response relationships were observed in both the higher intake of dietary and total β-carotene with reduced breast cancer risk when data from cohort studies (P (trend) < 0.01, P (trend) = 0.03) and case-control studies (P (trend) < 0.01, P (trend) < 0.01) were pooled, respectively. Dietary α-carotene intake could reduce the breast cancer risk. The relationships between dietary and total β-carotene intake and breast cancer need to be confirmed. No significant association between dietary intake of β-cryptoxanthin,

			lutein/+zeaxanthin, and lycopene and breast cancer was observed.	
Ilic D	Continuation of: Lycopene for the prevention of prostate cancer.	2011	MAIN RESULTS: Three RCTs, with a total of 154 participants were included in this review. None of the studies reported data on prostate cancer mortality. All of the included studies differed with respect to design, participants included and allocation of lycopene. This clinical heterogeneity limits the value on the pooled estimated of the meta-analyses. The methodological quality of two of the three included studies was assessed as posing a 'high' risk of bias. Meta-analysis indicated no statistical difference in PSA levels between men randomised to receive lycopene and the comparison group (MD (mean difference) -0.34, 95% CI (confidence interval) -2.01, 1.32). Only one study reported incidence of prostate cancer (10% in the lycopene	Review

group versus 30% in control group). The level of lycopene was also not statistically different in men randomised to receive lycopene and the comparison group (MD 0.39 µg/mL (micrograms/millilitre), 95% CI -0.19, 0.98). No other meta-analyses were possible since other outcomes assessed only had one study contributing data.
AUTHORS' CONCLUSIONS: Given that only three RCTs were included in this systematic review, and the high risk of bias in two of the three studies, there is insufficient evidence to either support, or refute, the use of lycopene for the prevention of prostate cancer. Similarly, there is no robust evidence from RCTs to identify the impact of lycopene consumption upon the incidence of prostate cancer, prostate symptoms, PSA levels or adverse events.