Plasma/Serum Lycopene and Disease Risk
Prostate Cancer Critial 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 Jun 6;82(11):941-6.	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 quartile as the reference value. Odds ratios were 0.67, 0.39, and 0.40 for the second, third, and highest quartiles, respectively.	CC nested				N	
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	CC nested				N	

				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.						
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 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,	CC nested				(-)/N	Pbo=(-) b-caro=(N)

				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,	CC				(-)	

				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 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	CC nested				(-)	

				lycopene and other antioxidants and the risk of prostate cancer.						
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, Schoenberg JB, Swanson GM, Greenberg RS, Hoover RN, Hayes RB, Ziegler RG. Am J Epidemiol. 2002 Jun 1;155(11):1023-32.	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, 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.	CC				(-)/N	
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	Antioxidant micronutrients may have chemopreventive 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-	CC nested				N	

		2003 Feb 15;157(4):335-44.		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.						
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 WC, Giovannucci E. Cancer Epidemiol Biomarkers Prev. 2004 Feb;13(2):260-9.	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 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	CC nested				N (-) >65y, w/o FH	

				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	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	CC				(-) ↓ risk	

		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.		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						
Cancer: prostate	Peters U	Serum lycopene, other carotenoids, and prostate cancer risk: a nested case-control study in the prostate, lung, colorectal, and ovarian cancer	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. MATERIALS AND METHODS: We investigated the association between prediagnostic serum carotenoids (lycopene, alpha-	CC				N	

		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.		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,	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	CC				(-) ↓ risk	

		Greene G, Lang NP, Kadlubar FF. Nutr Cancer. 2007;59(1):46-53.		cases by age, race, and county of residence. After adjustment for confounders, plasma levels of lycopene, lutein/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 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	CC				(-) ↓ long term lyco status ↑ PC risk IF have Ala/Ala genotype	

				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 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 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.	CC				(-) ↑ [lyco] modified effect of NOS2A IVS16 SNP	
Cancer: prostate	Beilby J	Serum levels of folate, lycopene, β-carotene, retinol and vitamin E and prostate cancer	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	PC CC nested				N	

		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		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.						
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 Apr;31(2):97-102. Epub 2010 Feb 16	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-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.	PC				N	PSA Biopsies

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, polymorphisms 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 levels with markers of prostate cancer detection among US men. Beydoun HA, Shroff MR, Mohan R, Beydoun MA. Cancer Causes Control. 2011 Jul	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 2001-2006 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 (a-carotene, β-carotene, β-cryptoxanthin,	CS				(+)	PSA

		29. [Epub ahead of print]		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 a-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	CC nested				N	

				cancers generally not 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.						