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Research Article

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Plasma Antioxidants, Genetic Variation in SOD2, CAT, GPX1, GPX4, and Prostate Cancer Survival

Erin L. Van Blarigan[1], Jing Ma[3,4], Stacey A. Kenfield[2], Meir J. Stampfer[3,4,5], Howard D. Sesso[3,4], Edward L. Giovannucci[3,4,5], John S. Witte[1,2], John W. Erdman Jr[6], June M. Chan[1,2], and Kathryn L. Penney[3,4]

Abstract

Background: Antioxidants may reduce risk of aggressive prostate cancer, and single-nucleotide polymorphisms (SNP) in antioxidant genes may modify this association.

Methods: We used Cox proportional hazards regression to examine circulating prediagnostic α-tocopherol, γ-tocopherol, and lycopene; SNPs in *SOD2* ($n = 5$), *CAT* ($n = 6$), *GPX1* ($n = 2$), *GPX4*, ($n = 3$); and their interactions and risk of lethal prostate cancer among 2,439 men with nonmetastatic prostate cancer in the Health Professionals Follow-up Study and Physicians' Health Study.

Results: We observed 223 events over a median follow-up of 10 years. Higher α-tocopherol levels were associated with lower risk of lethal prostate cancer [HR 3rd versus 1st quartile (Q): 0.51; 95% confidence interval (CI), 0.30–0.89; HR 4th versus 1st Q: 0.68; 95% CI, 0.41–1.13; *P* trend: 0.02]. Men homozygous for the less common allele (G) at rs3746165 in *GPX4* had a 35% lower risk of lethal prostate cancer compared with men homozygous for the more common allele (A; HR, 0.65; 95% CI, 0.43–0.99). Among men homozygous for the less common allele in rs3746165, high γ-tocopherol levels were associated with a 3.5-fold increased risk of lethal prostate cancer (95% CI, 1.27–9.72; *P* value, 0.02; interaction *P* value, 0.01).

Conclusions: Among men with nonmetastatic prostate cancer, higher circulating prediagnostic α-tocopherol may be associated with lower risk of developing lethal disease. Variants in *GPX4* may be associated with risk of lethal prostate cancer, and may modify the relation between γ-tocopherol and prostate cancer survival.

Impact: Circulating tocopherol levels and variants in GPX4 may affect prostate cancer progression. *Cancer Epidemiol Biomarkers Prev; 23(6); 1037–46. ©2014 AACR.*

Introduction

Observational studies and secondary analyses of randomized controlled trials suggest that antioxidants, including α-tocopherol, selenium, and lycopene, may reduce risk of prostate cancer, particularly aggressive disease (1–10). In contrast, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) reported that α-tocopherol supplementation was associated with an increased risk of overall prostate cancer, and there was no association between selenium supplementation and risk of prostate cancer (11). Prostate cancer is highly heterogeneous in its prognosis, however, and risk factors for aggressive disease, including advanced stage and poorly differentiated (e.g., high Gleason sum) tumors, likely differ from risk factors for total incident prostate cancer (12). In addition, several single-nucleotide polymorphisms (SNP) in antioxidant genes have been associated with prostate cancer, and these may modify the relations between circulating or dietary antioxidants and prostate cancer (13, 14). Thus, the discrepant results for antioxidants and prostate cancer may be due to a lack of focus on clinically relevant, advanced forms of the disease or the inability to account for the impact of genetic variants on antioxidant metabolism and availability.

We previously reported in the Health Professionals Follow-up Study (HPFS) that supplemental α-tocopherol was associated with a statistically nonsignificant lower risk of incident metastatic or fatal prostate cancer among current smokers and recent quitters (events = 55; HR comparing men who consumed ≥100 IU/d versus none: 0.44; 95% confidence interval, CI, 0.18–1.07; ref. 15). In addition, we reported in the Physicians Health Study (PHS) that plasma lycopene was inversely associated with risk of incident aggressive prostate cancer, defined as extraprostatic disease or Gleason sum ≥7 (OR comparing the highest versus lowest quintile: 0.56; 95% CI, 0.34–0.91; ref. 5), and the rs4880 SNP in *SOD2* modified

Authors' Affiliations: [1]Departments of Epidemiology and Biostatistics, [2]Urology, University of California, San Francisco, California; [3]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; [4]Departments of Epidemiology, and [5]Nutrition, Harvard School of Public Health, Boston, Massachusetts; and [6]Department of Food Science and Human Nutrition, University of Illinois, Urbana, Illinois

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Corresponding Author: Erin L. Van Blarigan, University of California, MC3110 UCSF, Helen Diller Cancer Research Bldg, 1450 3rd St., San Francisco, CA 94158. Phone: 415-514-4925; Fax: 415-514-4927; E-mail: erin.vanblarigan@ucsf.edu

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the association between plasma selenium and risk of aggressive prostate cancer (16). Higher levels of plasma selenium were associated with a lower risk of incident aggressive prostate cancer among men with the AA genotype. All of our previous reports examined risk of incident disease (e.g., whether levels of antioxidant nutrients in healthy men were associated with risk of being diagnosed with prostate cancer). Few studies have examined whether circulating antioxidants or germline genetic variants in antioxidant genes are associated with prostate cancer outcomes among men with nonmetastatic prostate cancer. Such analyses may identify factors that affect the growth of prostate tumors, and inform the development of clinical strategies to delay or deter disease progression. In one of the few studies conducted among men with prostate cancer to date, Watters and colleagues reported that prediagnostic circulating α-tocopherol levels were associated with a lower risk of prostate cancer death among Finnish smokers with prostate cancer (10).

Thus, we conducted a survival analysis to examine whether prediagnostic circulating α-tocopherol, γ-tocopherol, or lycopene levels were associated with lower risk of lethal prostate cancer among men initially diagnosed with nonmetastatic prostate cancer in the HPFS and the PHS. In addition, we examined whether SNPs in *SOD2*, catalase (*CAT*), *GPX1*, or *GPX4* were associated with risk of progression to lethal prostate cancer, and whether these SNPs modified associations between the circulating antioxidants and risk of lethal prostate cancer. *SOD2* was chosen based on the previous reports (14, 16, 17), and *CAT*, *GPX1*, and *GPX4* were included because they reduce hydrogen peroxide, a byproduct of superoxide dismutase (SOD) reactions, to water. We hypothesized that higher circulating α-tocopherol and lycopene would be associated with lower risk of lethal prostate cancer, and that the rs4880 SNP in *SOD2* would modify these relations such that the inverse associations would be strongest among men with the AA genotype in rs4880.

Materials and Methods

Study populations

The HPFS is a prospective cohort initiated in 1986 among 51,529 male health professionals of 40 to 75 years of age. At baseline, the men completed a questionnaire on medical diagnoses, medication use, physical activity, weight, height, and smoking. These data have been updated every 2 years. Participants also completed a food frequency questionnaire at baseline and every 4 years thereafter. From 1993 to 1995, 18,159 men donated blood samples. For this analysis, we used covariate data from the 1994 questionnaire to correspond with the time of blood draw.

The PHS was a randomized controlled trial of aspirin and β-carotene supplementation initiated in 1982 among 22,071 male physicians. The interventions were stopped in 1988 (aspirin) and 2003 (β-carotene), and the men have been followed via annual questionnaires on health behaviors and biannual postcards to ascertain disease endpoints. Blood was collected in August 1982 to December 1984 from 14,916 men before randomization. Covariate data were obtained from the baseline questionnaire to correspond with the time of blood draw.

In the HPFS and PHS, participants were mailed a blood collection kit, and EDTA-preserved samples were received and processed within 24 hours of blood draw, and stored in liquid nitrogen freezers. The genotyping and plasma assessments were originally conducted in nested case–control studies of prostate cancer incidence in the HPFS and PHS, as previously described (5, 16, 18, 19). Incident prostate cancer cases and controls were selected using a risk-set sampling design at three time points in the HPFS (1996, 1998, and 2000). In the PHS, incident cases (diagnosed up to 2005) and controls were selected using a risk-set sampling design and additionally matched on age at baseline and smoking status (never, former, and current). Prostate cancer cases, and controls who were subsequently diagnosed with prostate cancer during follow-up, were eligible for this analysis.

Prostate cancer follow-up

In the HPFS and PHS, men were asked if they have been diagnosed with prostate cancer every 2 years, and over 90% of surviving participants responded in each questionnaire cycle. After a report of prostate cancer, we request permission to obtain their medical records to verify the diagnosis and abstract clinical information such as prostate-specific antigen (PSA) levels, Gleason sum, and clinical stage. In addition, prostate cancer–specific questionnaires were mailed to participants with prostate cancer to obtain information on their disease course, including events of metastases.

Our main outcome was lethal prostate cancer, defined as distant organ metastases or death due to prostate cancer. Deaths were ascertained via mail, telephone, and review of the National Death Index; follow-up for mortality is at least 98% complete (20). The cause of death and presence of metastases were verified via medical records and death certificates.

Circulating antioxidant nutrient assessments

We assessed circulating α-tocopherol, γ-tocopherol, and lycopene in this study because these nutrients have been previously associated with risk of aggressive prostate cancer (1, 5, 10, 21–23). Blood levels of selenium were not available in the HPFS, and therefore we were unable to examine this nutrient. The methods to assess lycopene in the HPFS (24), and lycopene and tocopherols in PHS (5), have been previously described. In HPFS, α- and γ-tocopherol were quantified from approximately 200 μL or serum with tocol (Matreya) used as an internal standard. Ethanol was used to precipitate serum proteins and hexane was used to extract tocopherols. Hexane extracts were dried in a Speedvac concentrator (Savant model AES 1010) and stored in a −80°C until analysis (~1–2 days). The mobile phase was acetonitrile:methanol:chloroform, 47:47:6. The laboratory participates in the National Institute of Standards

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and Technology (NIST) micronutrient proficiency testing program and values for tocopherols are within approximately 8% of the medium. The mean coefficient of variations for all nutrients in HPFS and PHS examined was 12% or less.

SNPs, DNA, and genotyping

The antioxidant defense system includes SODs, CAT, and glutathione peroxidases (GPX). SOD enzymes catalyze the conversion of superoxide radicals into oxygen and hydrogen peroxide, and CAT and GPXs reduce hydrogen peroxide to water. In HPFS and PHS, SNPs that capture common variation (>5%) at a linkage disequilibrium $r^2 > 0.8$ within *SOD2*, *CAT*, *GPX1*, and *GPX4* as well as 5-kb upstream and downstream of the genes were selected using the HapMap database and the Tagger Pairwise program. DNA was extracted from whole blood and genotyping was done with Sequenom iPLEX matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry technology. All SNPs had >91% genotype success rates. The SNPs included in this analysis were rs4880, rs7855, rs2842980, rs5746151, and rs6917589 in *SOD2*; rs511895, rs769217, rs1001179, rs2076556, rs11032700, and rs11032703 in *CAT*; rs3448 and rs1800668 in *GPX1*; rs2074452, rs3746165, and rs4239605 in *GPX4*.

Inclusion/exclusion criteria

Of the 4,533 men who donated blood in the HPFS and PHS and were subsequently diagnosed with prostate cancer, 2,958 men (65%) had data on at least one of the nutrients or SNPs of interest. We excluded men who had metastatic disease at diagnosis or were missing clinical stage ($n = 375$) and non-Caucasian men to limit the potential for population stratification ($n = 144$), leaving 2,439 men for analysis.

Statistical analysis

We used Cox proportional hazards regression to examine circulating α-tocopherol, γ-tocopherol, and lycopene in relation to risk of lethal prostate cancer. In HPFS, person-time was contributed from date of diagnosis until date of lethal prostate cancer, death from another cause, or end of follow-up (January 31, 2010), whichever occurred first. In PHS, person-time was contributed from date of diagnosis until date of lethal prostate cancer, death from another cause, or end of follow-up (October 2, 2008 or date of the last available questionnaire if returned after October 2, 2008), whichever occurred first. We also conducted sensitivity analyses examining the plasma nutrients and SNPs in relation to prostate cancer–specific mortality (vs. the combined endpoint of distant metastases and prostate cancer death). For these sensitivity analyses, person-time was contributed from prostate cancer diagnosis until death or end of follow-up.

We categorized the antioxidants into batch-specific quartiles (e.g., within each batch, we categorized all study participants into quartiles and assigned each man a value of 0, 1, 2, or 3 corresponding to his quartile of the circulating nutrient of interest) and modeled the resulting ordinal variable using indicator variables. To test for evidence of a linear trend, we modeled the quartile score as a continuous term (0, 1, 2, and 3). Model 1 was adjusted for age at diagnosis (continuous), circulating cholesterol (batch-specific quartiles), cohort (HPFS and PHS), and time from blood draw to diagnosis (continuous). Blood cholesterol was included because tocopherols and lycopene are transported in the blood via lipoproteins (25). Model 2 was additionally adjusted for body mass index (BMI; <25, 25–29.9, and ≥30 kg/m^2) and smoking status (never, quit ≥10 years, quit <10 years, and current). To examine whether the relations between prediagnostic circulating antioxidants and lethal prostate cancer were independent of known clinical prognostic factors, we examined a model adjusting for PSA levels at diagnosis (tertiles plus an indicator for missing), Gleason sum (<7, 7, >7, missing), and clinical T stage (T1/T2 vs. T3). On the basis of the results of the α-tocopherol β-carotene trial among male Finnish smokers (4, 10), we performed a sensitivity analysis to examine whether smoking status at the time of blood draw modified the association between α-tocopherol and risk of lethal prostate cancer by including a cross-product term between α-tocopherol levels (continuous) and dichotomized smoking status (never or quit ≥10 years vs. quit <10 years or current), and using a Wald test to examine whether there was evidence of an interaction. Too few men were current smokers at the time of blood draw (4%) to examine this category separately from recent quitters. In addition, due to the difference in length of time from blood draw to diagnosis in the HPFS and PHS, we performed a sensitivity analysis stratified by cohort.

Using Pearson goodness-of-fit test, one SNP, rs554518 in *CAT*, violated Hardy–Weinberg equilibrium (*P* value: 0.03); therefore, we excluded this SNP from further analyses. We used Cox proportional hazards regression to examine the relations between genetic variants in *SOD2*, *CAT*, *GPX1*, and *GPX4* and time to lethal prostate cancer, adjusting for age at diagnosis. Person-time was defined as stated above. SNPs were analyzed under additive and codominant genetic models. If the rare homozygous genotype was present in <5% of the study population, we analyzed the SNP using a dominant genetic model. In addition, we used SAS PROC HAPLOTYPE to generate haplotype scores conditional on the observed genotypes; haplotypes with a frequency of <0.05 were combined. We modeled the haplotype probabilities as continuous covariates in Cox proportional hazards models adjusting for age at diagnosis. We assumed an additive mode of inheritance and used the most common haplotype within the gene of interest as the reference (26).

In addition, we examined whether the SNPs modified the relations between the circulating antioxidants and risk of lethal prostate cancer. We created cross-product terms between the genetic variants assuming an additive genetic model and the plasma nutrient levels dichotomized at the batch-specific median, and used a Wald test to test for

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Table 1. Characteristics of 2,439 men initially diagnosed with nonmetastatic prostate cancer in the HPFS and the PHS

	HPFS	PHS	Total
Number of participants	1,206	1,233	2,439
Date of diagnosis (median, IQR)	1999 (1997, 2002)	1995 (1991, 1999)	1998 (1994, 2001)
Age at diagnosis, y (mean ± SD)	70 ± 7	70 ± 7	70 ± 7
Smoking status at blood draw (%)			
Never	50	48	49
Former, quit ≥10 y	38	36	37
Former, quit <10 y	8	11	10
Current	3	4	4
Missing	1	0	0
BMI at blood draw (%)			
<25 kg/m^2	50	59	55
25–29.9 kg/m^2	41	39	40
≥30 kg/m^2	8	3	5
Gleason sum at diagnosis (%)			
<7	52	59	56
7	35	23	29
≥8	11	11	11
Missing	2	7	5
Clinical stage T3, %	2	6	4
PSA at diagnosis, ng/mL (median, IQR)	7 (5, 10)	7 (5, 12)	7 (5, 11)
α-tocopherol, mg/L (median, IQR)	12.3 (9.0, 16.5)	11.1 (9.2, 13.7)	11.4 (9.1, 14.6)
γ-tocopherol, mg/L (median, IQR)	1.5 (0.9, 2.3)	1.9 (1.4, 2.5)	1.8 (1.2, 2.4)
Lycopene, ng/mL (median, IQR)	396 (291, 539)	313 (210, 474)	352 (239, 507)
Time from blood draw to diagnosis, y (median, IQR)	6 (3, 8)	13 (9, 17)	8 (5, 13)
Metastases or deaths due to prostate cancer, *N* (%)	84 (7)	139 (11)	223 (9)

evidence of effect modification. Lastly, we examined whether any of the SNPs were associated with circulating levels of α-tocopherol, γ-tocopherol, or lycopene under an additive genetic model using multivariate linear regression adjusting for age at diagnosis and circulating cholesterol. The circulating nutrient levels were log-transformed to improve normality for the linear regression models.

The Institutional Review Boards of the Harvard School of Public Health and University of California, San Francisco approved this study. All analyses were performed using SAS version 9.2 and *P* values were two-sided.

Results

We observed 223 events of lethal prostate cancer (84 in the HPFS and 139 in the PHS) during a median follow-up of 10 years (9 years in the HPFS and 12 years in the PHS) among 2,439 men initially diagnosed with nonmetastatic prostate cancer. Characteristics of our study population are described in Table 1. Overall, the men from HPFS and PHS were similar, with a mean age at diagnosis of 70 years, PSA at diagnosis of 7 ng/mL, over 90% diagnosed with clinical T stage T2 or less, and over 50% had Gleason sum of 2 to 6. The median time from blood draw to diagnosis was 8 years [interquartile range (IQR): 5, 13], 6 years in the HPFS, and 13 years in the PHS. In addition, the distribution of the genetic variants was similar between the HPFS and PHS cohorts (Supplementary Table S1); therefore, the main analyses were conducted in the combined study population.

Higher circulating prediagnostic levels of α-tocopherol were associated with a lower risk of lethal prostate cancer (*P* trend: 0.02; Table 2). Men in the third quartile of plasma α-tocopherol had a 49% lower risk of lethal prostate cancer compared with men in the first quartile (HR, 0.51; 95% CI, 0.30–0.89), and men in the fourth quartile had a statistically nonsignificant 32% lower risk of lethal prostate cancer compared with men in the first quartile (HR, 0.68; 95% CI, 0.41–1.13). The relation was unchanged when adjusting for clinical T stage, Gleason sum, and PSA at diagnosis, and became stronger when examining risk of prostate cancer–specific mortality (HR Q3 vs. Q1, 0.43; 95% CI, 0.24–0.78; HR Q4 vs. Q1, 0.55; 95% CI, 0.32–0.96; *P* trend, 0.003). Smoking status at blood draw did not seem to modify the relation between α-tocopherol and risk of lethal prostate cancer, but we had limited power to examine this interaction due to few current smokers or recent quitters in our study population. Furthermore, the inverse relation was apparent in both cohorts, although stronger and more consistent in the HPFS (HR Q3 vs. Q1, 0.45; 95% CI,

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Table 2. Circulating tocopherols and lycopene before diagnosis and risk of lethal prostate cancer among men initially diagnosed with nonmetastatic prostate cancer in the HPFS and PHS

	Batch-specific quartiles				
	Q1	Q2	Q3	Q4	*P* trend[a]
α-tocopherol					
Median α-tocopherol, mg/L	7.8	10.2	12.6	18.1	
Events/person-years	36/2,752	44/2,810	21/2,895	29/2,761	
Model 1 HR (95% CI)[b]	1.0 (ref.)	1.16 (0.74–1.81)	0.52 (0.30–0.89)	0.67 (0.40–1.13)	0.02
Model 2 HR (95% CI)[c]	1.0 (ref.)	1.16 (0.74–1.81)	0.51 (0.30–0.89)	0.68 (0.41–1.13)	0.02
Model 3 HR (95% CI)[d]	1.0 (ref.)	1.08 (0.69–1.70)	0.50 (0.29–0.88)	0.68 (0.40–1.14)	0.02
γ-tocopherol					
Median γ-tocopherol, mg/L	0.8	1.5	2.0	3.0	
Events/person-years	25/2,664	32/2,812	43/2,839	30/2,878	
Model 1 HR (95% CI)[b]	1.0 (ref.)	1.25 (0.74–2.11)	1.75 (1.07–2.88)	1.15 (0.67–1.98)	0.37
Model 2 HR (95% CI)[c]	1.0 (ref.)	1.26 (0.74–2.12)	1.74 (1.06–2.87)	1.09 (0.63–1.88)	0.49
Model 3 HR (95% CI)[c]	1.0 (ref.)	1.24 (0.73–2.10)	1.53 (0.93–2.52)	0.99 (0.56–1.72)	0.84
Lycopene					
Median lycopene, ng/mL	200	328	451	626	
Events/person-years	31/2,690	37/2,870	32/2,847	32/2,944	
Model 1 HR (95% CI)[b]	1.0 (ref.)	1.07 (0.66–1.73)	0.98 (0.60–1.62)	1.00 (0.60–1.66)	0.91
Model 2 HR (95% CI)[c]	1.0 (ref.)	1.06 (0.65–1.71)	0.99 (0.60–1.63)	1.01 (0.61–1.69)	0.97
Model 3 HR (95% CI)[c]	1.0 (ref.)	1.17 (0.72–1.91)	1.23 (0.74–2.05)	1.21 (0.72–2.03)	0.46

[a]*P* trend calculated by modeling the quartile ordinal score (0, 1, 2, 3) as a continuous variable.

[b]Adjusted for age at diagnosis (continuous), circulating cholesterol (batch-specific quartiles), cohort (HPFS vs. PHS), and time between blood draw and diagnosis (continuous).

[c]Adjusted for above variables plus baseline BMI (<25, 25–29.9, and ≥30 kg/m^2) and smoking status (never, quit 10+ y, quit <10 y, and current).

[d]Adjusted for above variables plus Gleason sum (2–6, 7, 8–10, missing), PSA at diagnosis (tertiles and an indicator for missing), and clinical T stage (T1/T2 vs. T3).

0.21–0.99; HR Q4 vs. Q1, 0.47; 95% CI, 0.22–1.00; *P* trend, 0.02) compared with the PHS (HR Q3 vs. Q1, 0.57; 95% CI, 0.27–1.23; HR Q4 vs. Q1, 0.85; 95% CI, 0.43–1.70; *P* trend, 0.23), possibly due to the shorter time between blood draw and diagnosis in the HPFS. There were no associations between prediagnostic circulating γ-tocopherol or lycopene and risk of lethal prostate cancer. Circulating levels of α-tocopherol and γ-tocopherol were not correlated in our study population (r = −0.04; *P* value, 0.12), and the results were similar when mutually adjusting α-tocopherol and γ-tocopherol (HR Q3 vs. Q1, 0.53; 95% CI, 0.31–0.92; HR Q4 vs. Q1, 0.74; 95% CI, 0.44–1.25; *P* trend, 0.05).

Men who were homozygous for the less common G allele in rs3746165, a SNP in *GPX4*, had a 35% decreased risk of lethal prostate cancer compared with men who were homozygous for the more common A allele (HR, 0.65; 95% CI, 0.43–0.99; Table 3). In addition, men who were heterozygous at the rs6917589 SNP in *SOD2* had a 37% increased risk of lethal prostate cancer compared with men homozygous for the more common A allele (HR, 1.37; 95% CI, 1.02–1.83); however, there was no increased risk among men homozygous for the less common G allele (HR, 1.17; 95% CI, 0.63–2.19) nor was there statistically significant evidence of a linear trend in the additive model (HR, 1.22; 95% CI, 0.97–1.52; *P* value, 0.09). In addition, two haplotypes, one in GPX4 and one in CAT, were associated with risk of lethal prostate cancer (Supplementary Table S2). Given the number of tests conducted, these results may be due to chance and should be interpreted cautiously.

In addition, two SNPs in *GPX4*, including rs3746165, seemed to modify the relation between circulating γ-tocopherol and lethal prostate cancer (Table 4). Among men who were homozygous for the less common allele in rs3746165, men who had circulating γ-tocopherol levels at or above the batch-specific median had a 3.5-fold higher risk of lethal prostate cancer compared with men below the median (HR, 3.52; 95% CI, 1.27–9.72; *P* value, 0.02). There was no association between circulating γ-tocopherol and risk of lethal prostate cancer among men who were heterozygous or homozygous for the more common allele (*P* interaction: 0.01). Similarly, among men who were homozygous for the less common allele in rs4239605, men who had circulating γ-tocopherol levels at or above the batch-specific median had a 6.4-fold increased risk of lethal prostate cancer (HR, 6.35; 95% CI, 1.78–22.74;

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Table 3. SNPs in *SOD2*, *CAT*, *GPX1*, and *GPX4* and risk of lethal prostate cancer among men initially diagnosed with nonmetastatic prostate cancer in the PHS and the HPFS

	Genotype frequencies		Codominant model[a]	Additive model[a]	
SNP	Deaths/metastases *n* (%)	All other cases *n* (%)	HR (95% CI)	HR (95% CI)	*P* value
SOD2					
–rs4880[b]				0.89 (0.73–1.08)	0.23
—TT	58 (28)	507 (24)	1.0 (ref.)		
—CT	104 (50)	1,031 (50)	0.89 (0.65–1.23)		
—CC	45 (22)	539 (26)	0.79 (0.53–1.16)		
–rs7855[c]				0.70 (0.42–1.17)	0.17
—TT	192 (92)	1,886 (90)	1.0 (ref.)		
—CT	16 (8)	209 (10)	0.70 (0.42–1.17)		
—CC	0 (0)	5 (0)			
–rs2842980				1.05 (0.83–1.33)	0.67
—AA	127 (62)	1,310 (63)	1.0 (ref.)		
—AT	68 (33)	660 (32)	1.02 (0.76–1.37)		
—TT	11 (5)	98 (5)	1.18 (0.64–2.19)		
–rs5746151[c]				0.76 (0.48–1.21)	0.25
—GG	182 (90)	1,830 (88)	1.0 (ref.)		
—AG	20 (10)	247 (12)	0.76 (0.48–1.21)		
—AA	0 (0)	8 (0)			
–rs6917589				1.22 (0.97–1.52)	0.09
—AA	103 (53)	1,255 (61)	1.0 (ref.)		
—AG	80 (41)	693 (34)	1.37 (1.02–1.83)		
—GG	11 (6)	109 (5)	1.17 (0.63–2.19)		
CAT					
–rs511895				0.88 (0.72–1.08)	0.23
—CC	81 (40)	728 (35)	1.0 (ref.)		
—CT	90 (45)	997 (48)	0.82 (0.61–1.11)		
—TT	31 (15)	333 (16)	0.82 (0.54–1.24)		
–rs769217				1.08 (0.86–1.36)	0.52
—CC	126 (61)	1,263 (60)	1.0 (ref.)		
—CT	68 (33)	733 (35)	0.97 (0.72–1.31)		
—TT	14 (7)	94 (5)	1.43 (0.82–2.48)		
–rs1001179				0.97 (0.77–1.21)	0.76
—CC	119 (59)	1,222 (59)	1.0 (ref.)		
—CT	76 (37)	727 (35)	1.10 (0.83–1.47)		
—TT	8 (4)	117 (6)	0.66 (0.32–1.35)		
–rs2076556[c]				1.08 (0.79–1.48)	0.64
—AA	155 (75)	1,566 (76)	1.0 (ref.)		
—AG	49 (24)	469 (23)	1.08 (0.79–1.48)		
—GG	2 (1)	25 (1)			
–rs11032700				1.08 (0.88–1.32)	0.48
—AA	87 (44)	940 (46)	1.0 (ref.)		
—AC	88 (44)	882 (43)	1.11 (0.82–1.49)		
—CC	24 (12)	229 (11)	1.13 (0.72–1.78)		
–rs11032703[c]				0.88 (0.63–1.24)	0.47
—CC	164 (80)	1,615 (78)	1.0 (ref.)		
—CT	36 (18)	415 (20)	0.88 (0.63–1.24)		
—TT	5 (2)	35 (2)			
GPX1					
–rs3448				1.10 (0.89–1.37)	0.39
—GG	115 (56)	1,178 (57)	1.0 (ref.)		

(Continued on the following page)

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Table 3. SNPs in *SOD2*, *CAT*, *GPX1*, and *GPX4* and risk of lethal prostate cancer among men initially diagnosed with nonmetastatic prostate cancer in the PHS and the HPFS (Cont'd)

	Genotype frequencies		Codominant model[a]	Additive model[a]	
SNP	Deaths/metastases *n* (%)	All other cases *n* (%)	HR (95% CI)	HR (95% CI)	*P* value
—GA	76 (37)	748 (36)	1.08 (0.81–1.44)		
—AA	15 (7)	126 (6)	1.26 (0.74–2.16)		
–rs1800668				0.97 (0.79–1.19)	0.74
—CC	90 (45)	933 (45)	1.0 (ref.)		
—CT	89 (44)	893 (43)	0.98 (0.73–1.31)		
—TT	23 (11)	244 (12)	0.92 (0.58–1.46)		
GPX4					
–rs2074452				1.06 (0.85–1.31)	0.63
—CC	105 (52)	1,169 (57)	1.0 (ref.)		
—CT	86 (43)	759 (37)	1.22 (0.92–1.63)		
—TT	11 (5)	140 (7)	0.83 (0.45–1.54)		
–rs3746165				0.83 (0.68–1.01)	0.06
—AA	56 (28)	549 (27)	1.0 (ref.)		
—AG	110 (55)	990 (49)	1.06 (0.77–1.46)		
—GG	35 (17)	501 (25)	0.65 (0.43–0.99)		
–rs4239605				0.85 (0.69–1.05)	0.14
—AA	52 (30)	498 (26)	1.0 (ref.)		
—AG	93 (53)	1,006 (52)	0.92 (0.65–1.29)		
—GG	31 (18)	443 (23)	0.71 (0.45–1.10)		

[a]Adjusted for age at diagnosis (years).
[b]C = alanine (A) and T = valine (V).
[c]The heterozygous and homozygous less common allele categories were combined when <5% of the study population was homozygous for the less common allele.

P trend, 0.005). There was no association between circulating γ-tocopherol and risk of lethal prostate cancer among men who were heterozygous or homozygous for the more common allele (*P* interaction: 0.003). All other interactions were evaluated and are not shown; only interactions with $P < 0.05$ are summarized in Table 4.

Table 4. Circulating γ-tocopherol before diagnosis and risk of lethal prostate cancer by two SNPs in *GPX4* among men initially diagnosed with nonmetastatic prostate cancer in the HPFS and PHS

SNP alleles	Events/person-years	Below batch-specific median HR (95% CI)[a]	Batch-specific median or higher HR (95% CI)[a]	*P* value	Interaction *P* value[b]
rs3746165					0.01
AA	30/2,731	1.0 (ref.)	0.86 (0.41–1.81)	0.69	
AG	63/4,850	1.0 (ref.)	1.07 (0.64–1.79)	0.80	
GG	21/2,624	1.0 (ref.)	3.52 (1.27–9.72)	0.02	
rs4239605					0.003
AA	28/2,793	1.0 (ref.)	0.66 (0.30–1.46)	0.31	
AG	45/4,666	1.0 (ref.)	1.12 (0.61–2.04)	0.71	
GG	20/2,032	1.0 (ref.)	6.35 (1.78–22.74)	0.005	

[a]Adjusted for age at diagnosis (continuous), cohort (HPFS vs. PHS), circulating cholesterol levels (batch-specific quartiles), and time between blood draw and diagnosis (continuous).
[b]Interaction *P* value calculated by adding a cross-product term between the dichotomized γ-tocopherol levels (at or above batch-specific median vs. below) and genotype (additive model) in a model that included the genotype, dichotomized γ-tocopherol levels, circulating cholesterol (batch-specific quartiles), cohort (HPFS vs. PHS), and time between blood draw and diagnosis (continuous).

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Lastly, three SNPs, rs511895 and rs1001179 in *CAT* and rs3746165 in *GPX4*, were associated with circulating levels of α-tocopherol (rs511895 β, −0.04; SE, 0.02; *P* value, 0.02; rs1001179 β, −0.04; SE, 0.02; *P* value, 0.03; and rs3746165 β, −0.03; SE, 0.02; *P* value, 0.04). We examined the relation between rs3746165 and risk of lethal prostate cancer adjusting for circulating α-tocopherol levels to examine if the relation between this SNP and lethal prostate cancer may be mediated through α-tocopherol levels. In that model, the estimates for the relation between both the SNP and α-tocopherol levels and risk of lethal prostate cancer were essentially unchanged, although no longer statistically significant (rs3746165 AA/AG (ref.) vs. GG HR: 0.65; 95% CI, 0.40–1.04; *P* value, 0.07; α-tocopherol HR Q3 vs. Q1: 0.57; 95% CI, 0.32–1.00; HR Q4 vs. Q1: 0.65; 95% CI, 0.37–1.14; *P* trend: 0.02). The lack of statistical significance may be due to the correlation between the SNP and plasma α-tocopherol levels (27). None of the SNPs were associated with circulating levels of γ-tocopherol or lycopene.

Discussion

In this prospective survival analysis among men initially diagnosed with nonmetastatic prostate cancer, we observed an inverse association between circulating α-tocopherol before diagnosis and risk of lethal prostate cancer. Circulating γ-tocopherol and lycopene were not associated with progression to lethal prostate cancer. In addition, one SNP (rs3746165) in *GPX4* was associated with risk of lethal prostate cancer, and this SNP and another in the same gene seemed to modify the relation between circulating γ-tocopherol and risk of lethal prostate cancer.

α-tocopherol has been extensively studied in relation to incident prostate cancer, with inconsistent results. Secondary analyses of the α-tocopherol β-carotene trial indicated that male smokers randomized to 50 mg/d of α-tocopherol for a median of 6 years had a 32% lower risk of prostate cancer (95% CI, −47% to −12%) and a 41% lower risk of dying from prostate cancer (95% CI, −65% to −1%) compared with placebo (4). A prospective analysis among the 1,891 men diagnosed with prostate cancer during the trial reported that men in the highest quintile of serum α-tocopherol at baseline had lower risk of prostate cancer–specific death compared with men in the lowest quintile (10). Several, although not all (1, 15, 28, 29), prospective cohort studies have also reported an inverse association between dietary or circulating vitamin E and risk of aggressive prostate cancer (22, 23), particularly among smokers. In contrast, SELECT reported an increased risk of prostate cancer among men assigned to 400 IU/d of α-tocopherol (11); however, the study population in SELECT was replete with vitamin E at baseline and there were too few advanced prostate cancers to examine this outcome.

Our results are consistent with those from the α-tocopherol β-carotene trial of Finnish male smokers, and suggest that higher circulating levels of α-tocopherol before diagnosis may be associated with a lower risk of progression to lethal prostate cancer (10). Further, only 14% of the men in our study population were current smokers or had quit smoking within 10 years of blood donation, and thus the beneficial effects of α-tocopherol may not be restricted to smokers. Our observations are consistent with two potential scenarios. First, higher α-tocopherol levels may predispose healthy men to develop a form of prostate cancer that has less potential for progression. Second, if the α-tocopherol levels assessed in our study are correlated with levels after diagnosis, it is possible that higher α-tocopherol levels after diagnosis of nonmetastatic prostate cancer may deter or delay progression of the disease. A second assessment of α-tocopherol levels obtained after diagnosis of nonmetastatic prostate cancer is needed to differentiate these two potential scenarios, and would be of interest in future studies.

In this survival analysis among men diagnosed with nonmetastatic prostate cancer, we did not observe an association between prediagnostic circulating levels of lycopene and risk of lethal prostate cancer. We previously reported in a nested case–control study in the PHS that men in the fifth quintile of plasma lycopene had a 44% lower risk of incident aggressive prostate cancer, defined as extraprostatic disease or Gleason sum ≥7 tumors (n = 259), compared with men in the lowest quintile (5). Together, these data suggest that lycopene may act early in the disease process, affecting the initiation of aggressive prostate cancer rather than its progression. Additional studies with long follow-up and multiple assessments of circulating lycopene would be of interest to identify the time window during which lycopene may act in the natural history of aggressive prostate cancer.

One SNP in *GPX4*, rs3746165, was associated with risk of lethal prostate cancer, and modified the relation between circulating γ-tocopherol and risk of lethal prostate cancer. This SNP is located 2-kb upstream of the gene, and has not been previously reported to be associated with risk of prostate cancer or prostate cancer survival; thus, the results observed might be due to chance. Another SNP in *GPX4* (rs2074452) was associated with prostate cancer–specific mortality in a study with 81 events and a median follow-up of 9 years, but this SNP was not associated with lethal prostate cancer in our population (30). In addition, we did not observe an association between rs4880, a SNP in *SOD2*, and risk of lethal prostate cancer. rs4880 has been associated with risk of prostate cancer in multiple study populations (14), including risk of aggressive disease among men initially diagnosed with nonmetastatic prostate cancer (31). Overall, studies on germline genetic variants and prostate cancer survival are limited, and studies in larger populations are needed.

This study had several limitations. First, we had only one assessment of the circulating antioxidant nutrients taken at a median of 8 years before diagnosis. Among 144 men in the HPFS, two measures of plasma lycopene assessed 3 to 4 years apart had a Spearman correlation of 0.58 (24). In a different cohort of 166 men, the correlation

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between serum measures taken 15 years apart was 0.35 for lycopene, 0.61 for α-tocopherol, and 0.48 for γ-tocopherol (32). Thus, although not free from nondifferential misclassification, the quartile ranking of plasma levels assessed in this study is likely a fair representation of the quartile ranking at the time of diagnosis, particularly for α-tocopherol. Second, we performed many statistical tests, and the statistically significant results that we observed could be due to chance. However, as one of the first studies to examine genetic variants in antioxidants SNPs and risk of lethal prostate cancer, we took an exploratory approach and did not adjust for multiple testing. Independent studies are necessary to replicate the suggestive findings reported here. Third, we examined the combined endpoint of distant metastases or death due to prostate cancer because essentially all fatal cases of prostate cancer are preceded by metastases to distant organs. However, it is possible that the role of antioxidants may differ for metastasis and prostate cancer death; we observed that the relation between plasma α-tocopherol and prostate cancer–specific mortality was stronger than its relation with the combined endpoint that included metastases. Fourth, we combined data from two prospective U.S. cohorts to examine the rare outcome of lethal prostate cancer. The time between blood draw and diagnosis of prostate cancer was shorter in the HPFS compared with the PHS, and thus the degree of measurement error for the plasma nutrient levels may differ between the cohorts. We included an indicator variable for cohort in all of our models examining plasma nutrient levels, and analyses stratified by cohort showed that the relation between plasma α-tocopherol and risk of lethal prostate cancer was inverse in both populations. Lastly, we restricted our study population to Caucasians to reduce the potential for population stratification; our results may not be generalizable to populations with other racial, and therefore genotype, distributions.

In conclusion, among men initially diagnosed with nonmetastatic prostate cancer, higher circulating levels of α-tocopherol before diagnosis may be associated with a lower risk of developing lethal disease. In addition, genetic variants in *GPX4* may be associated with risk of lethal prostate cancer, and may modify the relation between circulating γ-tocopherol and risk of lethal prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The author(s) assume(s) full responsibility for analyses and interpretation of these data.

Authors' Contributions

Conception and design: J. Ma, S.A. Kenfield, J.S. Witte, J.M. Chan, K.L. Penney
Development of methodology: E.L. Giovannucci, J.W. Erdman Jr
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E.L. Van Blarigan, J. Ma, M.J. Stampfer, H.D. Sesso, J.M. Chan, K.L. Penney
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E.L. Van Blarigan, S.A. Kenfield, M.J. Stampfer, E.L. Giovannucci, J.S. Witte, J.M. Chan, K.L. Penney
Writing, review, and/or revision of the manuscript: E.L. Van Blarigan, J. Ma, S.A. Kenfield, M.J. Stampfer, H.D. Sesso, E.L. Giovannucci, J.S. Witte, J.W. Erdman Jr., J.M. Chan, K.L. Penney
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Ma, S.A. Kenfield, H.D. Sesso
Study supervision: K.L. Penney

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