Research Article

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

Erin L. Van Blarigan1, Jing Ma3,4, Stacey A. Kenfield6, Meir J. Stampfer3,4,5, Howard D. Sesso3,4, Edward L. Giovannucci3,4,5, John S. Witte1,2, John W. Erdman Jr6, June M. Chan1,2, and Kathryn L. Penney3,4

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 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
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. For this analysis, we used covariate data from the baseline questionnaire to correspond with the time of blood draw.

From 1993 to 1995, 18,159 men donated blood samples. We assessed circulating α-tocopherol and 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
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 modeled according to the observed genotypes; thus, a linear least-squares model was fit to the data. We assumed an additive mode of inheritance and used the most common haplotype within the gene of interest as the reference. In addition, we examined whether the SNPs modified the associations with circulating antioxidants and risk of lethal prostate cancer. We created cross-product terms between 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
evidence of effect modification. Lastly, we examined whether any of the SNPs were associated with circulating levels of \( \alpha \)-tocopherol, \( \gamma \)-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 \( \alpha \)-tocopherol were associated with a lower risk of lethal prostate cancer (\( P \) trend: 0.02; Table 2). Men in the third quartile of plasma \( \alpha \)-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; \( P \) trend, 0.003).

Smoking status at blood draw did not seem to modify the relation between \( \alpha \)-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, 0.43; 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 \( \alpha \)-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, 0.43; 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 \( \alpha \)-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, 0.43; 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 \( \alpha \)-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, 0.43; 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 \( \alpha \)-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, 0.43; 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 \( \alpha \)-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, 0.43; 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 \( \alpha \)-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, 0.43; 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 \( \alpha \)-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, 0.43; 95% CI, 0.24–0.78; HR Q4 vs. Q1, 0.55; 95% CI, 0.32–0.96; \( P \) trend, 0.003).

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

<table>
<thead>
<tr>
<th></th>
<th>HPFS</th>
<th>PHS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>1,206</td>
<td>1,233</td>
<td>2,439</td>
</tr>
<tr>
<td>Age at diagnosis, y (mean ± SD)</td>
<td>70 ± 7</td>
<td>70 ± 7</td>
<td>70 ± 7</td>
</tr>
<tr>
<td>Smoking status at blood draw (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>50</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>Former, quit ≥ 10 y</td>
<td>38</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Former, quit &lt; 10 y</td>
<td>8</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Current</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BMI at blood draw (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td>50</td>
<td>59</td>
<td>55</td>
</tr>
<tr>
<td>25–29.9 kg/m²</td>
<td>41</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Gleason sum at diagnosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>52</td>
<td>59</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>≥8</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Clinical stage T3, %</td>
<td>2</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>PSA at diagnosis, ng/mL (median, IQR)</td>
<td>7 (5, 10)</td>
<td>7 (5, 12)</td>
<td>7 (5, 11)</td>
</tr>
<tr>
<td>( \alpha )-tocopherol, mg/L (median, IQR)</td>
<td>12.3 (9.0, 16.5)</td>
<td>11.1 (9.2, 13.7)</td>
<td>11.4 (9.1, 14.6)</td>
</tr>
<tr>
<td>( \gamma )-tocopherol, mg/L (median, IQR)</td>
<td>1.5 (0.9, 2.3)</td>
<td>1.9 (1.4, 2.5)</td>
<td>1.8 (1.2, 2.4)</td>
</tr>
<tr>
<td>Lycopene, ng/mL (median, IQR)</td>
<td>396 (291, 539)</td>
<td>313 (210, 474)</td>
<td>352 (239, 507)</td>
</tr>
<tr>
<td>Time from blood draw to diagnosis, y (median, IQR)</td>
<td>6 (3, 8)</td>
<td>13 (9, 17)</td>
<td>8 (5, 13)</td>
</tr>
<tr>
<td>Metastases or deaths due to prostate cancer, N (%)</td>
<td>84 (7)</td>
<td>139 (11)</td>
<td>223 (9)</td>
</tr>
</tbody>
</table>
of pene and risk of lethal prostate cancer. Circulating levels and diagnosis in the HPFS. There were no associations with men who were homozygous for the less common allele in rs4239605, men who had circulating tocopherol levels at or above the batch-specific median had a 3.5-fold increased risk of lethal prostate cancer compared with men who were homozygous for the less common allele in rs3746165, men who had circulating 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, 6.4; 95% CI, 1.81–22.74; P value, 0.03).}

### 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

<table>
<thead>
<tr>
<th>Tocopherol</th>
<th>Q1 (mg/L)</th>
<th>Q2 (mg/L)</th>
<th>Q3 (mg/L)</th>
<th>Q4 (mg/L)</th>
<th>P trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-tocopherol</td>
<td>7.8</td>
<td>10.2</td>
<td>12.6</td>
<td>18.1</td>
<td></td>
</tr>
<tr>
<td>β-tocopherol</td>
<td>0.8</td>
<td>1.5</td>
<td>2.0</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>γ-tocopherol</td>
<td>200</td>
<td>328</td>
<td>451</td>
<td>626</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Lycopene</th>
<th>Median lycopene, ng/mL</th>
<th>Events/person-years</th>
<th>Model 1 HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200</td>
<td>31/2,690</td>
<td>1.0 (ref.) 1.06 (0.65–1.72)</td>
</tr>
<tr>
<td></td>
<td>328</td>
<td>37/2,870</td>
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<td>43/2,839</td>
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<td>32/2,944</td>
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**Notes:**

- P trend calculated by modeling the quartile ordinal score (0, 1, 2, 3) as a continuous variable.
- Adjusted for age at diagnosis (continuous), circulating cholesterol (batch-specific quartiles), cohort (HPFS vs. PHS), and time between blood draw and diagnosis (continuous).
- Adjusted for above variables plus baseline BMI (<25, 25–29.9, and ≥30 kg/m²) and smoking status (never, quit ≥10 y, quit <10 y, and current).
- 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).

Published OnlineFirst April 7, 2014; DOI: 10.1158/1055-9965.EPI-13-0670

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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.

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<td>2.0</td>
<td>3.0</td>
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- Adjusted for above variables plus baseline BMI (<25, 25–29.9, and ≥30 kg/m²) and smoking status (never, quit ≥10 y, quit <10 y, and current).
- 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).

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.
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

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype frequencies</th>
<th>Codominant modela</th>
<th>Additive modela</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths/metastases n (%)</td>
<td>All other cases n (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>SOD2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>–rs4880b</td>
<td>58 (28)</td>
<td>507 (24)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>–CT</td>
<td>104 (50)</td>
<td>1,031 (50)</td>
<td>0.89 (0.65–1.23)</td>
</tr>
<tr>
<td>–CC</td>
<td>45 (22)</td>
<td>539 (26)</td>
<td>0.79 (0.53–1.16)</td>
</tr>
<tr>
<td>–rs7855c</td>
<td>192 (92)</td>
<td>1,886 (90)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>–CT</td>
<td>16 (8)</td>
<td>209 (10)</td>
<td>0.70 (0.42–1.17)</td>
</tr>
<tr>
<td>–CC</td>
<td>0 (0)</td>
<td>5 (0)</td>
<td>0.70 (0.42–1.17)</td>
</tr>
<tr>
<td>–rs2842980</td>
<td>127 (62)</td>
<td>1,310 (63)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>–AA</td>
<td>68 (33)</td>
<td>660 (32)</td>
<td>1.02 (0.76–1.37)</td>
</tr>
<tr>
<td>–TT</td>
<td>11 (5)</td>
<td>98 (5)</td>
<td>1.18 (0.64–2.19)</td>
</tr>
<tr>
<td>–rs5746151c</td>
<td>182 (90)</td>
<td>1,830 (88)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>–GG</td>
<td>20 (10)</td>
<td>247 (12)</td>
<td>0.76 (0.48–1.21)</td>
</tr>
<tr>
<td>–AA</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.76 (0.48–1.21)</td>
</tr>
<tr>
<td>–rs6917589</td>
<td>103 (53)</td>
<td>1,255 (61)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>–AA</td>
<td>80 (41)</td>
<td>693 (34)</td>
<td>1.37 (1.02–1.83)</td>
</tr>
<tr>
<td>–GG</td>
<td>11 (6)</td>
<td>109 (5)</td>
<td>1.17 (0.63–2.19)</td>
</tr>
<tr>
<td>CAT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>–rs511895</td>
<td>81 (40)</td>
<td>728 (35)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>–CT</td>
<td>90 (45)</td>
<td>997 (48)</td>
<td>0.82 (0.61–1.11)</td>
</tr>
<tr>
<td>–TT</td>
<td>31 (15)</td>
<td>333 (16)</td>
<td>0.82 (0.54–1.24)</td>
</tr>
<tr>
<td>–rs769217</td>
<td>126 (61)</td>
<td>1,263 (60)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>–CC</td>
<td>68 (33)</td>
<td>733 (35)</td>
<td>0.97 (0.72–1.31)</td>
</tr>
<tr>
<td>–CT</td>
<td>14 (7)</td>
<td>94 (5)</td>
<td>1.43 (0.82–2.48)</td>
</tr>
<tr>
<td>–TT</td>
<td>119 (59)</td>
<td>1,222 (59)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>–CC</td>
<td>76 (37)</td>
<td>727 (35)</td>
<td>1.10 (0.83–1.47)</td>
</tr>
<tr>
<td>–TT</td>
<td>8 (4)</td>
<td>117 (6)</td>
<td>0.66 (0.32–1.35)</td>
</tr>
<tr>
<td>–rs2076556c</td>
<td>155 (75)</td>
<td>1,566 (76)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>–AA</td>
<td>49 (24)</td>
<td>469 (23)</td>
<td>1.08 (0.79–1.48)</td>
</tr>
<tr>
<td>–AG</td>
<td>2 (1)</td>
<td>25 (1)</td>
<td>1.08 (0.88–1.32)</td>
</tr>
<tr>
<td>–GG</td>
<td>87 (44)</td>
<td>940 (46)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>–AC</td>
<td>88 (44)</td>
<td>882 (43)</td>
<td>1.11 (0.82–1.49)</td>
</tr>
<tr>
<td>–CC</td>
<td>24 (12)</td>
<td>229 (11)</td>
<td>1.13 (0.72–1.78)</td>
</tr>
<tr>
<td>–rs11032703c</td>
<td>164 (80)</td>
<td>1,615 (78)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>–CC</td>
<td>36 (18)</td>
<td>415 (20)</td>
<td>0.88 (0.63–1.24)</td>
</tr>
<tr>
<td>–TT</td>
<td>5 (2)</td>
<td>35 (2)</td>
<td>0.88 (0.63–1.24)</td>
</tr>
<tr>
<td>GPX1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>–rs3448</td>
<td>115 (56)</td>
<td>1,178 (57)</td>
<td>1.0 (ref.)</td>
</tr>
</tbody>
</table>

(Continued on the following page)
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 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)

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

aAdjusted for age at diagnosis (years).

bC = alanine (A) and T = valine (V).

The heterozygous and homozygous less common allele categories were combined when <5% of the study population was homozygous for the less common allele.

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

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

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

bInteraction 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).
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 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...
between serum measurements 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–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.

**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:** J.L. Penney

**Acknowledgments**

The authors thank the participants and staff of the HPFS and PHS and the following state cancer registries for their invaluable contributions to this project: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WV. In addition, this study was approved by the Connecticut Department of Public Health (DPH) Human Investigations Committee. Certain data used in this study, report, publication, etc. were obtained from the DPH. They also thank the Prostate Cancer Foundation for their contribution to the original efforts to collect data from men with prostate cancer in the HPFS.

**Grant Support**

The HPFS is supported by CA16552 from the NIH. The PHS is supported by CA097193, CA43944, CA40360, HL26490, and HL34595 from the NIH. This work was also supported by NIH grants [CA141298 to M.J. Stampfer], CA12355 (to J.S. Witte and E.L. Van Blarigan), CA133891 (to E.L. Giovannucci), and CA106947 (to J.M. Chan) and the Prostate Cancer Foundation (to S.A. Kenfield and K.L. Penney). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received October 10, 2013; revised February 21, 2014; accepted March 6, 2014; published OnlineFirst April 7, 2014.
Van Blarigan et al.

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


Cancer Epidemiol Biomarkers Prev 2014;23:1037-1046. Published OnlineFirst April 7, 2014.

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