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Genetic Variants Reflecting Higher Vitamin E Status in Men Are Associated with Reduced Risk of Prostate Cancer[1,2]

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Abstract

Vitamin E (α-tocopherol) plays a key role in the regulation of cell growth and differentiation and has been studied as a potential chemopreventive agent for prostate cancer. The association of serum vitamin E concentrations with cancer risk may be modified by genetic variations in vitamin E–related genes. We examined whether variants in vitamin E–related genes were associated with risk of prostate cancer in a nested case-control study using 483 prostate cancer cases and 542 matched controls of European ancestry from a large U.S. multicenter trial that had available measurements of serum vitamin E concentrations and genotyping of 3 genome-wide association study meta-analysis–identified single-nucleotide polymorphisms (SNPs) associated with circulating vitamin E. ORs and 95% CIs were calculated using unconditional logistic regression adjusted for age, family history of prostate cancer, and serum total cholesterol. Findings suggest lower prostate cancer risk for men whose genotypes reflect higher vitamin E (i.e., α-tocopherol) status. An SNP (rs964184) near budding-site selection protein 13 (yeast) (*BUD13*), zinc finger protein 259 (*ZNF259*), and apolipoprotein A5 (*APOA5*) on 11q23.3 was significantly associated with prostate cancer risk (per-allele OR = 0.75; 95% CI: 0.58, 0.98; *P*-trend = 0.03). The association between rs964184 and prostate cancer risk was stronger among homozygous carriers of the minor allele (OR = 0.27; 95% CI: 0.09, 0.83). Another variant, rs11057830 in scavenger receptor class-B member 1 (*SCARB1*) on 12p24.31, approached statistical significance (OR = 0.32; 95% CI: 0.10, 1.01, *P* = 0.05; 2 minor allele copies). This study suggests that polymorphisms near *BUD13*/*ZNF259*/*APOA5*, involved in vitamin E transport and metabolism, may be associated with lower risk of prostate cancer. This trial was registered at clinicaltrials.gov as NCT00002540. J. Nutr. 144: 729–733, 2014.

Introduction

Vitamin E is a fat-soluble micronutrient consisting of 8 forms, α-, β-, γ-, and δ- tocopherols and -tocotrienols (1). Some functions of vitamin E include antioxidative and anti-inflammatory activities (2–7), inhibition of cell proliferation and angiogenesis (8), and induction of apoptosis (9). Cancer prevention studies with vitamin E have focused primarily on α-tocopherol, and, although the biologic effects of α-tocopherol have been investigated, our understanding of its role in inhibiting carcinogenesis remains incomplete.

Prostate cancer is the most common malignancy and the second leading cause of cancer-related deaths in U.S. males; however, the etiology and pathogenesis of prostate cancer remain poorly understood. The association between circulating vitamin E and risk of prostate cancer has been inconsistent in 12 prospective studies, as summarized by Key et al. (10); the majority ($n = 8$) suggest a protective association with RRs for high quantiles ranging from 0.49 to 0.85. The RRs for the remaining studies were 0.98, 1.00, 1.06, and 1.40. Furthermore, the association between vitamin E supplementation and prostate cancer risk has been inconsistent in randomized trials. Findings from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study suggest a significant 32% reduction in prostate cancer risk after 6-y trial supplementation of 50 IU/d α-tocopherol in male smokers (11, 12), which was supported by a subsequent trial examining 30 mg/d for 8 y (13). In 2 recent trials, however, α-tocopherol doses of 400 IU/d for ~6 y (3) and 400 IU on alternate days for ~8 y (14) did not prevent prostate cancer. Several studies suggest that the vitamin E–prostate cancer association may be limited to smokers (11,15–18), and recently, genetic variation in oxidative stress regulatory enzymes has been shown to modify the association of circulating α-tocopherol with aggressive prostate cancer among current smokers (16).

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The association of vitamin E with prostate cancer risk might be modified by genetic variations in vitamin E–related genes.

Genetic variants in genes involved in vitamin E transport or metabolism may be important determinants of potential beneficial effects of vitamin E supplementation on prostate cancer risk (19). In our previous genome-wide association studies (GWASs)[6], we identified regions of the genome that influence vitamin E biochemical status, providing a framework for investigation of this membrane-integrated micronutrient that is important in complex chronic diseases, such as prostate cancer (20,21). To our knowledge, no studies on the association between these GWAS-identified vitamin E–associated single-nucleotide polymorphisms (SNPs) (i.e., rs964184, rs2108622, and rs11057830) and development of prostate cancer have been published. The purpose of this study is to examine whether variants in vitamin E–related genes are associated with risk of prostate cancer.

Materials and Methods

Study participants. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was a multicenter, randomized controlled trial of ~155,000 men and women conducted in the United States to test the efficacy of screening for prostate, lung, colorectal, and ovarian cancers (22). Enrollment occurred from November 1993 through June 2001. Screening was performed at 10 centers located across the United States, including the following: *1*) Birmingham, Alabama; *2*) Denver, Colorado; *3*) Detroit, Michigan; *4*) Honolulu, Hawaii; *5*) Marshfield, Wisconsin; *6*) Minneapolis, Minnesota; *7*) Pittsburgh, Pennsylvania; *8*) Salt Lake City, Utah; *9*) St. Louis, Missouri; and *10*) Washington, DC. Men in the screening arm received both serum prostate-specific antigen (PSA) and digital rectal examination at study entry and then annually for 3 y and continued to receive PSA screening for years 4 and 5. Men with a positive screening result (PSA > 4 μg/L or digital rectal examination suspicious for prostate cancer) were referred to their medical care providers for prostate cancer diagnostic evaluation. All men were followed from their initial cancer screening to the occurrence of prostate cancer, loss to follow-up, or death, whichever came first. Clinical and pathologic records, related to diagnostic follow-up of prostate cancer, were obtained by certified tumor registrars at each screening center using a standardized protocol. Aggressive cancers were defined as Gleason score $\geq$ 7 or stage III or IV of the tumor-node-metastasis staging system, as defined by the American Joint Committee on Cancer, at the time of diagnosis because of our interest in the more clinically significant but less common aggressive forms of prostate cancer. Participants from a previous nested case-control study on prostate cancer consisting of Caucasian men, aged 55–74 y, with no previous history of prostate cancer before random assignment were included in the present study if they were from the screened arm of the study trial and had serum α-tocopherol concentration measured in provided blood samples (n = 1536 individuals) (23). For our present analytic cohort, genotype data on vitamin E–related polymorphisms were available for 483 cases and 542 controls (n = 1025; 97% of those with baseline serum). The institutional review boards of the U.S. National Cancer Institute and the 10 study centers approved the trial, and all participants provided written informed consent.

Phenotypic measurements and genotype data. Nonfasting baseline blood specimens collected at the clinical centers were processed and frozen within 2 h of blood draw and stored at −70°C. Serum concentrations of α-tocopherol were determined using reversed-phase HPLC with UV detection (24). The estimated CV for α-tocopherol concentrations was 5.8%. Total serum cholesterol was measured enzymatically by a standard procedure at 37°C on a Hitachi 912 autoanalyzer. Genotyping for SNPs was conducted previously using the TaqMan assay (Applied Biosystems) at the National Cancer Institute Core Genotyping Facility, NIH. The SNPs include rs964184 near budding-site selection protein 13 (yeast) (*BUD13*), zinc finger protein 259 (*ZNF259*), and apolipoprotein A5 (*APOA5*) on 11q23.3, rs2108622 in cytochrome p450, family 4, subfamily F, polypeptide 2 on 19pter-p13.11, and rs11057830 in scavenger receptor class B member 1 (*SCARB1*) 12p24.31, which were found to be associated with higher circulating vitamin E concentrations at the genome-wide significance level in our previous GWAS meta-analysis (19). The overall completion rate was between 92% and 99%. Details for each TaqMan assay may be found at http://variantgps.nci.nih.gov.

Statistical methods. Descriptive statistics were calculated for the characteristics of prostate cancer cases and controls. The genotype frequencies between the 2 groups were compared using χ^2 or Fisher's exact tests. There were no significant deviations from Hardy-Weinberg equilibrium observed (P > 0.05). Unconditional logistic regression models, adjusted for established risk factors of prostate cancer (age and family history of prostate cancer) and serum concentrations of total cholesterol, were used to estimate ORs and 95% CIs for the association of each vitamin E–related SNP with overall prostate cancer risk assuming an additive mode of inheritance. We adjusted for total cholesterol because it is well established that vitamin E concentrations are affected by circulating lipids; inclusion of cholesterol in the models slightly attenuated results, albeit not significantly. Additional covariates considered included BMI, smoking status (never, former, or current smoker), and history of diabetes. None of the additional covariates markedly changed the results (<10% change in OR) and therefore were not included in the final parsimonious regression models. Sensitivity analyses were conducted for aggressive and non-aggressive disease, in which aggressive disease was defined as Gleason score $\geq$ 7 or tumor stage III or IV (25). The P value for trend was generated by entering the three-level ordinal variable coded as the number of minor alleles (zero, 1, or 2) as a single term in the model (i.e., 1 df). To more closely examine the results of the tests for trend, we also report the ORs by genotype. Because of the smaller number of cases with 2 copies of the minor allele, those with 1 or 2 copies were combined. In addition, a polygenic score was used to examine the combined genetic effect of the 3 SNPs. Potential effect modification by smoking status (ever vs. never) and serum α-tocopherol concentrations (above vs. below median cut point based on the distribution among controls) was examined using stratified analyses and by additionally including an interaction term in the same regression model that included the SNP and potential effect modifier. All statistical

TABLE 1 Characteristics of prostate cancer cases and controls, PLCO Cancer Screening Trial[1]

Characteristic	Cases (n = 483)	Controls (n = 542)
Age at study entry, *y*	64.6 ± 4.9	64.4 ± 4.9
Family history of prostate cancer, *n (%)*	51 (10.8)	23 (4.3)
History of diabetes, *n (%)*	27 (5.6)	48 (8.9)
Smoking status, *n (%)*		
Never smoker	208 (43.0)	201 (37.1)
Former smoker	243 (50.3)	292 (53.9)
Current smoker	32 (6.6)	49 (9.0)
BMI, *kg/m²*	27.3 ± 3.5	27.4 ± 3.9
Serum total cholesterol, *mmol/L*	6.1 ± 1.9	6.1 ± 1.9
Serum α-tocopherol,[2] *mg/L*	19.0 ± 9.7	19.1 ± 9.5
Tumor stage, *n* (%)		
I/II	468 (97.1)	—
III/IV	14 (2.9)	—
Gleason score on biopsy, *n* (%)		
2–6	315 (65.5)	—
7	141 (29.2)	—
8–10	26 (5.3)	—

[1] Means ± SDs are reported unless indicated otherwise. PLCO, Prostate, Lung, Colorectal, and Ovarian.
[2] To convert serum tocopherol values from mg/L to μmol/L, multiply by 2.322.

[6] Abbreviations used: *APOA5*, apolipoprotein A5; *BUD13*, budding-site selection protein 13 (yeast); GWAS, genome-wide association study; PLCO, Prostate, Lung, Colorectal, and Ovarian; *SCARB1*, scavenger receptor class-B member 1; SNP, single-nucleotide polymorphism; *ZNF259*, zinc finger protein 259.

TABLE 2 Per-allele associations between 3 SNPs identified in GWASs and risk of prostate cancer by tumor aggressiveness, PLCO Cancer Screening Trial[1]

SNP	Gene	Chromosome	Minor allele	MAF	Tumor type	OR (95% CI)[2]	*P*-trend[3]
rs964184	*BUD13/ZNF259/APOA5*	11	G	0.15	Any	0.75 (0.58, 0.98)	0.03
					Non-aggressive	0.77 (0.57, 1.04)	0.09
					Aggressive	0.74 (0.51, 1.08)	0.12
rs2108622	*CYP4F2*	19	T	0.21	Any	1.02 (0.83, 1.26)	0.83
					Non-aggressive	1.07 (0.85, 1.35)	0.54
					Aggressive	0.93 (0.69, 1.25)	0.64
rs11057830	*SCARB1*	12	A	0.15	Any	0.92 (0.71, 1.20)	0.56
					Non-aggressive	0.92 (0.68, 1.24)	0.60
					Aggressive	0.92 (0.64, 1.33)	0.67

[1] SNPs identified in previous GWAS meta-analysis to be associated with higher circulating α-tocopherol amounts. Models adjusted for age, family history of prostate cancer, and serum total cholesterol. *APOA5*, apolipoprotein A5; *BUD13*, budding-site selection protein 13 (yeast); *CYP4F2*, cytochrome p450, family 4, subfamily F, polypeptide 2; GWAS, genome-wide association study; MAF, minor allele frequency; PLCO, Prostate, Lung, Colorectal, and Ovarian; *SCARB1*, scavenger receptor class-B member 1; SNP, single-nucleotide polymorphism; *ZNF259*, zinc finger protein 259.
[2] OR per copy of minor allele.
[3] The *P*-trend values summarize the linear relation across the increasing number of minor alleles (1 df).

analyses were conducted with SAS version 9.3 (SAS Institute). Two-sided *P* values < 0.05 were considered significant.

Results

Among the 1025 men in this study sample, the mean age at study entry was 64.8 y. A total of 116 (8%) men, 76 cases and 40 controls, reported having a family history of prostate cancer (**Table 1**). Cases were also less likely to have a history of diabetes or to be current smokers. The mean serum α-tocopherol concentration was 19 mg/L (44.1 μmol/L). Mean concentrations did not vary significantly between cases and controls.

The associations (per-allele ORs) between each of the 3 vitamin E–related SNPs (rs964184, rs2108622, and rs11057830) and prostate cancer risk are summarized in **Table 2**. The strongest association was observed for rs964184, located at 11q23.3 (per-allele OR = 0.75; 95% CI: 0.58, 0.98; *P*-trend = 0.03). We found no strong evidence that associations between the 3 SNPs and prostate cancer differed according to disease status, with risks for aggressive cancer being similar to those for non-aggressive cancer (Table 2). The results did not change after further excluding 4 cases with stage III disease, which may represent non-lethal, local invasion.

Genotype associations for each SNP are reported in **Table 3**. Minor allele carriers [i.e., men with 1 or 2 copies of the variant (G) allele] of rs964184 had lower risks of prostate cancer compared with men with the more common genotype (CC) (OR = 0.79; 95% CI: 0.59, 1.05). This finding was marginally not statistically significant (*P* = 0.06). However, homozygous carriers of the G allele of rs964184 had a substantially reduced risk of prostate cancer compared with homozygous carriers of the common C allele (OR = 0.27; 95% CI: 0.09, 0.83). For rs11057830, on 12q24.31, a marginally significant association was observed; men who carried 2 copies of the variant allele (AA) had a lower risk of prostate cancer compared with men with the wild type (GG) (OR = 0.32; 95% CI: 0.10, 1.01; *P* = 0.05). Although the associations between rs2108622 genotypes and prostate cancer risk were in the same direction as the other vitamin E–related SNPs, no significant association was observed (TT vs. CC; OR = 0.75; 95% CI: 0.44, 1.29). The analysis of a combined genetic effect of the 3 SNPs as a score suggested a decreased risk for men with 2 or more copies of minor alleles, with an ORs of 0.25 among men with 4 or more copies; however, results should be interpreted with caution given the small number of men who had 4 or more copies of minor alleles across the 3 SNPs (*n* = 10).

A significant interaction was observed for rs11057830 (*P*-interaction = 0.02), with the strongest association observed for men with baseline serum α-tocopherol below median concentration values (per-allele OR = 0.71; 95% CI: 0.50, 1.01) (**Table 4**). There was no effect modification by serum concentrations of α-tocopherol or smoking status for rs964184 and rs2108622, partly because of the small sample sizes. The per-allele association for rs964184 appeared to be stronger among men whose circulating vitamin E concentrations were below the median value at

TABLE 3 Association between vitamin E–related SNP genotypes and prostate cancer, PLCO Cancer Screening Trial[1]

Genotype	OR	95% CI	*P*-global[2]
rs964184 (*BUD13/ZNF259/APOA5*)			0.05
CC (*n* = 745)	1.00 (reference)	—	
CG (*n* = 242)	0.85	0.63, 1.15	
GG (*n* = 21)	0.27	0.09, 0.83	
CG/GG vs. CC	0.79	0.59, 1.05	
rs2108622 (*CYP4F2*)			0.16
CC (*n* = 561)	1.00 (reference)	—	
CT (*n* = 380)	1.21	0.92, 1.58	
TT (*n* = 62)	0.75	0.44, 1.29	
CT/TT vs. CC	1.13	0.87, 1.46	
rs11057830 (*SCARB1*)			0.13
GG (*n* = 747)	1.00 (reference)	—	
AG (*n* = 244)	1.07	0.79, 1.44	
AA (*n* = 17)	0.32	0.10, 1.01	
AG/AA vs. GG	0.99	0.74, 1.33	
Combined SNP score			0.36
<2 copies of minor alleles (*n* = 707)	1.00 (reference)	—	
2 copies of minor alleles (*n* = 212)	0.79	(0.58, 1.08)	
3 copies of minor alleles (*n* = 53)	0.83	(0.49, 1.40)	
≥4 copies of minor alleles (*n* = 10)	0.25	(0.05, 1.36)	

[1] Models adjusted for age, family history of prostate cancer, and serum total cholesterol. *APOA5*, apolipoprotein A5; *BUD13*, budding-site selection protein 13 (yeast); *CYP4F2*, cytochrome p450, family 4, subfamily F, polypeptide 2; PLCO, Prostate, Lung, Colorectal, and Ovarian; *SCARB1*, scavenger receptor class-B member 1; SNP, single-nucleotide polymorphism; *ZNF259*, zinc finger protein 259.
[2] The *P*-global values summarize the overall association of each SNP on the risk of prostate cancer (2 df).

TABLE 4 Association between SNPs and prostate cancer risk stratified by selected factors, PLCO Cancer Screening Trial[1]

	rs964184 (460 cases/514 controls)		rs2108622 (453 cases/515 controls)		rs11057830 (457 cases/515 controls)		Combined SNP score (455 cases/527 controls)	
	OR (95% CI)	*P*-interaction	OR (95% CI)	*P*-interaction	OR (95% CI)	*P*-interaction	OR (95% CI)	*P*-interaction
Smoking status		0.60		0.24		0.54		0.61
Never smoker	0.69 (0.45, 1.07)		0.92 (0.67, 1.28)		1.03 (0.68, 1.56)		0.88 (0.69, 1.11)	
Former smoker	0.85 (0.59, 1.21)		1.04 (0.78, 1.38)		0.87 (0.60, 1.26)		0.95 (0.78, 1.14)	
Current smoker	0.54 (0.21, 1.38)		1.71 (0.75, 3.87)		0.74 (0.35, 2.52)		0.97 (0.58, 1.63)	
Serum α-tocopherol		0.27		0.11		0.02		0.40
Less than median concentration	0.66 (0.46, 0.95)		1.19 (0.90, 1.56)		0.71 (0.50, 1.01)		0.88 (0.73, 1.06)	
More than median concentration	0.90 (0.61, 1.34)		0.83 (0.60, 1.15)		1.29 (0.86, 1.94)		0.98 (0.79, 1.23)	

[1] Models adjusted for age, family history of prostate cancer, and serum total cholesterol. PLCO, Prostate, Lung, Colorectal, and Ovarian; SNP, single-nucleotide polymorphism.

study baseline (per-allele OR = 0.66; 95% CI: 0.46, 0.95) and among current smokers (per-allele OR = 0.54; 95% CI: 0.21, 1.38). However, findings from stratified analyses should be interpreted with caution because of the limited statistical power for interaction assessments.

Discussion

The present study examined whether genetic variants identified in our previous GWAS meta-analysis of circulating vitamin E modified risk of prostate cancer. Specifically, we examined the association between rs964181, rs2108622, and rs11057830 and prostate cancer risk in a case-control study nested within the PLCO Cancer Screening Trial. We found that a higher vitamin E variant in a SNP near the *BUD13/ZNF259/APOA5* region (rs964184) was associated with a decreased risk of prostate cancer as well as a suggested protective association for homozygous carriers of the higher vitamin E allele (A) of rs11057830 in *SCARB1*. The cancer-risk associations for these SNPs were directionally consistent with their relation to circulating vitamin E (α-tocopherol) (20,21) (i.e., SNPs were associated with higher concentrations of serum α-tocopherol, an antioxidant, assuming an additive model in previous GWAS studies).

The mechanisms involved in the potential benefits of vitamin E in cancer may function at multiple levels. For example, its antioxidant properties may protect against oxidative damage or inhibit free radical–mediated lipid peroxidation within lipid-rich regions of the cell. Alternatively, vitamin E may modify the signal transduction cascade of proinflammatory cytokines through inhibition of NF-$\kappa\beta$ activation (26). Recent studies suggest that polymorphisms in specific genes involved in vitamin E transport, metabolism, and molecular action may also be important determinants for the protective effects of vitamin E supplementation (16,19,27,28). In the present study, men who carried 2 copies of the minor allele for rs964184 had lower risks of prostate cancer when compared with men with the wild-type genotype. These results suggest that the *BUD13/ZNF259/APOA5* variant allele may be associated with a reduction in prostate cancer risk.

However, to our knowledge, no previous study has examined the association between these GWAS-identified vitamin E–associated genetic variants and prostate cancer risk. An association of serum α-tocopherol and an effect modification by polymorphisms in oxidative stress regulatory enzymes has been reported in relation to aggressive prostate cancer risk among current smokers (16). Cigarette smokers with genetic variation in myeloperoxidase (GA or AA genotypes; genotypes downregulating oxidative stress), who had high serum α-tocopherol concentrations, had a reduced risk (OR = 0.34; 95% CI: 0.15, 0.80) (16).

Strengths of the present study include the prospective design of the PLCO Cancer Screening Trial in which blood samples were collected years before the development of prostate cancer and that the analyses were adjusted for established risk factors of prostate cancer, including age and family history of prostate cancer. A potential limitation is that our study was based on older men of European ancestry and may not be generalizable to younger and ethnically diverse populations. Furthermore, the men in this analysis came from a highly screened population with PSA-detected prostate cancer that may not be representative of all prostate cancers. Because of the limited statistical power to detect associations among smokers, larger-scale studies of these and other genetic variants yet to be identified that may influence α-tocopherol concentrations may help reliably determine their association with prostate cancer risk among current smokers.

In summary, we found that an SNP near the *BUD13/ZNF250/APOA5* region was associated with lower prostate cancer risk among men of European ancestry. The association for a second SNP, rs11057830 in *SCARB1*, was restricted to men who had low serum α-tocopherol concentrations at study baseline. These findings support the hypothesis that the variant allele may enhance antioxidant enzyme activity or other functions; however, more research is needed to substantiate this finding.

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