A 28-Year Prospective Analysis of Serum Vitamin E, Vitamin E-Related Genetic Variation and Risk of Prostate Cancer

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Abstract

Objective: Investigate the relationship between serum α-tocopherol concentration and long-term risk of prostate cancer, and evaluate the interaction with vitamin E–related genetic variants and their polygenic risk score (PRS).

Methods: We conducted a biochemical analysis of 29 102 male Finnish smokers in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Serum α-tocopherol was measured at baseline using high-performance liquid chromatography, and 2 724 prostate cancer cases were identified during 28 years of follow-up. Cox proportional hazards models examined whether serum α-tocopherol concentrations were associated with prostate cancer risk. Among 8 383 participants, three SNPs related to vitamin E status (rs964184, rs2108622, and rs11057830) were examined to determine whether they modified the relationship between serum α-tocopherol concentrations and prostate cancer risk, both individually and as a PRS using logistic regression models.

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Results: No association was observed between serum α-tocopherol and prostate cancer risk (fifth quintile (Q5) versus Q1 hazard ratio (HR)=0.87, 95% confidence interval (95% CI) 0.75, 1.02; p-trend=0.57). Though no interactions were seen by population characteristics, high α-tocopherol concentration was associated with reduced prostate cancer risk among the trial α-tocopherol supplementation group (Q5 quintile versus Q1 HR=0.79, 95% CI 0.64, 0.99). Finally, no associated interaction between the three SNPs or their PRS and prostate cancer risk was observed.

Conclusion: Although there was a weak inverse association between α-tocopherol concentration and prostate cancer risk over nearly three decades, our findings suggest that men receiving the trial α-tocopherol supplementation who had higher baseline serum α-tocopherol concentration experienced reduced prostate cancer risk. Vitamin E–related genotypes did not modify the serum α-tocopherol-prostate cancer risk association.

Introduction

Prostate cancer is one of the most frequently diagnosed malignancies among men globally.[1] Though prostate cancer does not account for a large proportion of cancer mortality, treatment-related morbidities (e.g., sexual dysfunction, urinary incontinence, and depression) are common and adversely affect quality of life.[2,3] Common risk factors for prostate cancer include family history, age, diet, and genetic susceptibility.[4,5] Due to the high prevalence of prostate cancer and relatively few known risk factors, identifying preventable lifestyle and related factors to reduce risk is an important public health priority.

The role of vitamin E in health and disease prevention has been examined in laboratory experiments, observational studies, and controlled trials.[6,7] Vitamin E is a lipid-soluble antioxidant suggested to protect against membrane and tissue oxidative injury, thereby reducing risk of chronic diseases, including cancer and cardiovascular disease.[6,8,9] Studies have also suggested that vitamin E can affect carcinogenesis through interaction with other nutrients (e.g., carotenoids).[10] The predominant form of vitamin E in humans is α-tocopherol, which previous studies have suggested inhibits cancer development.[8,11] Epidemiological studies have investigated serum α-tocopherol in relation to prostate cancer risk, where several documented an inverse association.[12–14] Most studies examining the relationship between α-tocopherol on prostate cancer risk were over a short period, whereas whether the relationship changes over a long follow-up period remains understudied.[13]

Genome-wide association studies (GWAS) have identified genetic determinants of circulating nutrient concentrations (e.g., vitamins A, D, and E).[15,16] For example, a large GWAS meta-analysis of circulating α-tocopherol concentration identified three associated vitamin E single-nucleotide polymorphisms (SNPs), (rs964184, rs2108622, and rs11057830).[17] The impact of these vitamin E-related genetic variants on cancer risk remains not well understood, particularly alleles associated with higher serum α-tocopherol concentration. Therefore, examining the joint effects of vitamin E–related

variants and serum α-tocopherol on prostate cancer risk is of importance to develop a greater understanding on the disease mechanism.

In the present study, we investigated whether serum α-tocopherol is prospectively associated with long-term prostate cancer risk (over a 28-year period), and whether three genetic variants involved in vitamin E transport or metabolism have any beneficial risk association on vitamin E status. We also examined whether the serum α-tocopherol-prostate cancer risk association was modified by polygenic risk score (PRS) using the three identified genetic variants.

Methods

Study population

The Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention study enrolled 29 133 Finnish male smokers, ages 50–69 years. Details of the ATBC Study design have been previously published.[18] Briefly, the ATBC study was a double-blind, placebo-controlled primary cancer prevention trial conducted in Finland to investigate whether β-carotene or α-tocopherol supplementation were associated with reduced cancer risk. In this 2×2 factorial randomized controlled trial, each participant was assigned to one of four intervention groups: β-carotene (20mg/day), α-tocopherol (50mg/day), both (β-carotene and α-tocopherol), or placebo.

Participants were given capsules for 5–8 years (median of 6.1) until conclusion of study on April 30, 1993. At baseline (e.g., pre-supplementation) and at three years (follow-up), overnight fasting blood samples were collected from all participants and blood samples were stored at −70°C and protected from light until assayed. Anthropometric measurements were obtained at enrollment, and demographic information and medical history were captured through a detailed questionnaire. A validated food-frequency questionnaire was administrated during this period as well. Participants were evaluated at each visit for medical signs and symptoms, all hospital visits were documented, and diagnosis at hospitals were monitored through the National Hospital Discharge Register. Finally, comparisons between treatment groups on cause-specific dropout rates and capsule compliance were performed. Greater detail on the study protocol are described elsewhere.[18] All participants provided written informed consent. The ATBC study was approved by the Institutional Review Boards at Finnish National Public Health Institute and U.S. National Cancer Institute. This study was conducted in accordance with relevant guidelines and regulations.

Using high-performance liquid chromatography, serum α-tocopherol and β-carotene concentrations were assayed for the entire cohort in the same laboratory.[19] Enzymatic assay was used to measure total and high-density lipoprotein cholesterol concentrations.[20] The inter-batch coefficient of variation for serum α-tocopherol was 2.2%. We excluded participants that had missing baseline serum α-tocopherol measurement (n=31). Supplemental Figure 1 presents the inclusion criteria for the overall study cohort.

Vitamin E genotypes

Genotyping was previously conducted among 8 383 participants by genome-wide scans as previously described.[17,21] We selected three SNPs identified in previous GWAS analyses to be associated with higher circulating serum α-tocopherol concentration: rs964184 (located on 11q23.3 near *BUD13, ZNF259 and APOA1/C3/A4/A5*), rs2108622 (19pter-p13.11 near *CYP4F2*), and rs11057830 (12q24.31 near *SCARB1*).[17]

Identification of prostate cancer cases

The Finnish Cancer Registry representing approximately 100% case coverage nationwide was used to ascertain prostate cancer cases (n=2 724).[22] All cancer diagnoses prior to April 1994 were also confirmed through oncology and pathology review of medical records collected from pathology laboratories and hospitals. We further examined whether the participant had aggressive prostate cancer at diagnosis. Aggressive prostate cancer was defined as TNM stage III or IV, American Joint Committee on Cancer (AJCC), stage 3, or Gleason sum 8. Cases diagnosed after that date were reviewed by at least one study physician. Cases were diagnosed through December 31, 2012

Statistical analysis

Continuous variables were reported as the mean ± standard deviation, and categorical variables as percent to describe the study population characteristics. Cox proportional hazard regression models were fit to assess the association between serum α-tocopherol at baseline by quintile and on prostate cancer risk, while adjusting for confounders. Person-years was used as the underlying time metric and calculated from the beginning of each time-period to date of prostate cancer diagnosis or censor date (December 31, 2012). Potential confounders were selected *a priori* including baseline age (continuous), body mass-index (continuous), years of cigarette smoking (continuous), number of cigarettes smoked daily (continuous), serum total cholesterol concentration (continuous), family history of prostate cancer (categorical), and trial intervention group (categorical). We further examined education, physical exercise, dietary γ-tocopherol, height, and history of diabetes which were not ultimately included as confounders as they did not change the risk estimate by at least 10%. We performed tests for linear trend across quintiles by assigning participants the median value of serum α-tocopherol for each quintile. For prostate cancer risk, unadjusted cumulative incidence functions were represented by Kaplan-Meier plots, and the differences in cumulative prostate cancer incidence across baseline serum α-tocopherol quintiles were tested using the log-rank test.

Multivariable Cox proportional hazards models were repeated with stratification by age at randomization (<55, 55–59, or 60), years of smoking (<32, 32–39, or 40), number of cigarettes smoked daily (<20 or 20), BMI (<24.5, 24.5–27.6, or 27.6), intervention group (yes or no), and history of diabetes (yes or no). *P* values for interaction were evaluated through likelihood ratio tests by taking the difference between −2log likelihood for models with and without the interaction terms between baseline serum α-tocopherol (quintiles) and the covariate of interest, with degrees of freedom equal to differences between the number of parameters in the two models. We tested proportional hazards assumptions for all models, with no evidence of violation.

Logistic regression was performed to estimate risk of prostate cancer by individual SNP alleles. Unweighted polygenic risk score (PRS) was sum of the number of high α-tocopherol risk alleles, and for a weighted-polygenic risk score (weighted sum of alleles across the three SNPs)[23] where the weight for each individual SNP was the log-odds ratio of its association with prostate cancer risk. The PRS variable was then categorized as tertiles (1st tertile [low risk], 3rd tertile [high risk]) based on the distribution among non-cases.

We also examined whether the association between baseline serum α-tocopherol and prostate cancer risk was modified by the change in α-tocopherol concentration from baseline to three years of follow-up (low: <10.5 mg/L and high: 10.5 mg/L) and by the trial α-tocopherol supplementation. All statistical tests were two-sided and p-value less than 0.05 was considered statistically significant. Analyses were conducted using R version 4.0.2 and SAS version 9.4.

Results

The analytical cohort included 29 102 men, of whom 2 724 were diagnosed with prostate cancer over a 28-year period. Table 1 presents the baseline cohort risk factor, dietary, and demographic characteristics by quintile of serum α-tocopherol concentration. The cohort median concentration was 11.5 mg/L and median of the fifth quintile was 15.9 mg/L. Compared to men in the lowest quintile, those in the highest quintile had slightly greater weight, fewer years of smoking, greater fruit and vegetable consumption, and higher education.

Serum α-tocopherol appeared inversely associated with prostate cancer risk comparing the highest vs. lowest quintile (HR=0.87; 95% CI 0.75, 1.02), although none of the HRs or trend test were statistically significant (Table 2). This finding is substantiated by the Kaplan-Meier plot demonstrating lower cumulative incidence for Q5, albeit with a log-rank test that was not statistically significant (Supplemental Figure 2). Similarly, for aggressive prostate cancer a reduced risk was observed comparing the highest versus lowest quintile of serum α-tocopherol, though findings were not statistically significant (HR=0.87; 95% CI 0.70, 1.09). We further assessed effect modification of the serum α-tocopherol (quintile)-prostate cancer association by risk factors and trial intervention subgroups and observed no striking patterns, although the inverse vitamin E association appeared stronger for men receiving the trial α-tocopherol supplement, suggesting synergism (HR=0.79; 95% CI 0.64, 0.99) (Table 3). None of the interaction terms were significant. Additionally, we examined whether the association between serum α-tocopherol and prostate cancer risk was modified by the change in serum α-tocopherol concentration from baseline to three years of follow-up or by α-tocopherol supplementation (Supplemental Table 1). Our findings showed an elevated prostate cancer risk among supplemented men who had a low baseline serum α-tocopherol (<10.5 mg/L) and the highest concentrations at follow-up (median change of 3 mg/L, HR=1.56; 95% 1.07, 2.27).

We further assessed the association between vitamin E-related genes and their PRS on prostate cancer risk. For each SNP, the mean α-tocopherol concentration increased with increasing number of minor alleles (i.e., 1 or 2 copies of the variant) (Table 4). However,

no association was observed between any of the SNP and prostate cancer, and neither the unweighted-PRS nor the weighted-PRS was associated with risk (Supplemental Figure 3 and Table 5).

Discussion

In this large cancer prevention trial-based cohort of male smokers, no clear long-term dose-dependent association was observed between prospectively measured serum α-tocopherol concentration and prostate cancer risk based on nearly 3 000 cases. We did observe that men assigned to receive the trial α-tocopherol supplementation who were in the highest serum quintile had an associated 21% lower prostate cancer risk compared to their counterparts in the lowest quintile. Additionally, there were no significant interactions with risk factors for the serum α-tocopherol-prostate cancer association, and genetic variants associated with higher vitamin E concentrations did not modify the relationship.

Epidemiological studies examining the relationship between vitamin E or α-tocopherol and prostate cancer risk have reported a reduced risk, although not all risk estimates were statistically significant.[13,24,25] For example, an early finding from the ATBC Study demonstrated that low-dose, 50 IU α-tocopherol supplementation reduced the incidence of prostate cancer by 34% over a 5–8 year period,[26] and an 18-year post-intervention follow-up showed that the effects on prostate cancer risk were attenuated within two years after the end of the trial supplementation.[27] Another study among the same cohort up to nineteen years of follow-up reported a reduced risk for those with high baseline α-tocopherol but not dietary vitamin E intake.[13] In the present study, we observed no association over 28 years of follow-up, suggesting the relationship was further attenuated over time.

Findings from both the Physicians' Health Study II (PHS-II) and the Heart Outcomes Prevention Evaluation (HOPE) trial observed no effect of vitamin E supplementation (200 IU and 400 IU daily, respectively) on prostate cancer incidence.[28,29] The Selenium and Vitamin E Cancer Prevention Trial (SELECT) reported that with up to twelve years of follow-up post-intervention, supplementation with vitamin E 400 IU daily was associated with 17% increased prostate cancer incidence.[30] However, the SELECT cohort consisted of 43% never smokers and only 10% current smokers, whereas the present study consisted of only long-term smokers. This distinction is important as smoking is associated with oxidative stress, and long-term use results in faster vitamin E depletion compared to nonsmoking individuals.[31,32] Differences in findings between these trials may also be attributed to the vitamin E dosages and formulations of the supplements; e.g., ATBC=50 IU and SELECT=400 IU daily of all *rac*-α-tocopheryl acetate, and PHS-2= 400 IU of *RRR*-α-tocopherol every other day.

To date, the association between the three genes associated with circulating vitamin E and prostate cancer risk has not been elucidated.[17,33,34] Although we observed no formal interaction between the SNPs and PRS and prostate cancer risk, we did find a reduced prostate cancer risk for rs2108622 near the *CYP4F2* region with increasing number of higher vitamin E alleles (T). Additionally, a study from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial reported an association between rs964184 near

the *BUD13/ZNF259/APOA5* region and lower prostate cancer risk for the heterozygous (CG) genotype.[33] Although we observed lower prostate cancer risk for the same rs964184 allele pairing, our findings were not statistically significant. A possible explanation for the differing findings could be the beneficial impact the rs964184 high vitamin E allele may have on higher α-tocopherol concentration was buffered by the adverse impact cigarette smoking has on vitamin E and antioxidant status in the present cohort, thereby counteracting the potential benefit on prostate cancer.

In humans, α-tocopherol is the most biologically active form of vitamin E.[6] Previous studies have reported that α-tocopherol was associated with lower cancer risk by reducing oxidative injury.[6] Since humans are unable to synthesize vitamin E, α-tocopherol is primarily acquired through dietary sources (vegetable oils, seeds, fruits, whole grains, nuts, and some animal products) and supplementation.[35,36] To explore some of the differences in findings, we investigated prostate cancer risk by quintile of α-tocopherol concentration, and changes in α-tocopherol concentration from baseline to follow-up. Additionally, prior studies documented that cigarette smokers require higher α-tocopherol intake to maintain similar plasma α-tocopherol concentrations compared to their nonsmoking counterparts.[31,32] Greater plasma α-tocopherol depletion is largely contributed to elevated oxidative stress and its associated inflammatory response.[31,32,37] Previous studies also support the influence of genetic variants involved in vitamin E transport and metabolism on the association between α-tocopherol and prostate cancer risk, but these genetic associations for higher vitamin E status requires further study in more racially and ethnically diverse populations.[14,38]

Although our study provides insights on the relationship between α-tocopherol concentration and reduced prostate cancer risk over a long follow-up period, several limitations must be noted. First, the present cohort was a relatively homogenous population of Finnish male smokers, potentially hindering the generalizability to non-smokers and those of non-majority European ancestry. Second, vitamin E was measured only at baseline and 3-years, allowing for subsequent changes in status to not be captured. Third, our definition of aggressive prostate cancer included only data for Gleason sum and not the specific grades which would have permitted ISUP grading and distinguishing Group 2 vs. Group 3 cases. As a result, our data may reflect an underreporting of aggressive cases. Finally, the possibility of unmeasured confounders affecting the observed association, though we did adjust for many relevant risk factors and genetic variation should not be susceptible to such biases.

Our study limitations are offset by notable strengths including being a large prospective cohort with prostate cancers ascertained through population-based registries. The fasting serum α-tocopherol exposure assessment utilized a state-of-the-science high-performance liquid chromatography platform and provided an integrated assessment of endogenous and exogenous vitamin E exposures and metabolism. Moreover, we were able to examine the interactions of variants in vitamin E–related genes on the relationship between α-tocopherol concentration and prostate cancer risk.

Conclusion

Although previous studies have documented that high serum α-tocopherol concentrations or vitamin E supplementation might be beneficial in reducing prostate cancer risk, our findings indicate that the serologic association may attenuate over time. Genetic variants reflecting higher vitamin E status also showed no clear association with risk and did not modify the serum α-tocopherol-prostate cancer risk association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Abbreviations:

ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
GWAS	Genome-wide association study
SNP	Single-nucleotide polymorphism
PRS	Polygenic risk score

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Table 1.

Population baseline characteristics by quintile of serum α-tocopherol concentration

Characteristics	Quintile of baseline serum α-tocopherol				
	Q1 9.3 mg/L (n=5 806)	Q2 > 9.3 and 10.8 mg/L (n=5 882)	Q3 > 10.8 and 12.2 mg/L (n=5 653)	Q4 > 12.2 and 14.2 mg/L (n=5 938)	Q5 > 14.2 mg/L (n=5 823)
Age at randomization, y	57 (53–62)	57 (53–61)	56 (53–61)	56 (53–61)	56 (53–60)
Weight, kg	75.7 (67.3–84.8)	77.2 (69.2–85.7)	78.3 (70.9–86.9)	78.7 (71.4–87.3)	80.9 (73.7–89.4)
Height, cm	173 (169–177)	173 (169–178)	174 (170-1-78)	174 (169–178)	174 (170–178)
BMI, kg/m^2	25.2 (22.7–28.0)	25.6 (23.3–28.2)	25.9 (23.7–28.4)	26.2 (24.0–28.6)	26.8 (24.7–29.3)
History of diabetes (%)					
Yes	4.1	3.4	3.7	3.6	6.4
No	95.9	96.6	96.3	96.4	93.6
Cigarettes per day	20 (15–25)	20 (15–25)	20 (15–25)	20 (15–25)	20 (15–25)
Years of cigarette smoking	38 (32–43)	37 (31–42)	36 (30–41)	36 (30–41)	36 (30–41)
Education (%)					
Less than high school	40.2	37.5	33.7	31.5	27.3
High school graduate and above	59.8	62.5	66.3	68.5	72.7
Physical exercise in leisure time (%)					
< 1 per week	54.9	53.8	51.1	48.5	49.5
1–2 per week	25.4	26.8	29.1	30.9	30.3
3 or more per week	19.6	19.2	19.6	20.5	20.1
Family history of prostate cancer n (%)[a]					
Yes	1.8	2.2	2.4	2.3	2.0
No	56.2	62.2	63.4	65.3	65.2
Baseline serum β-carotene, μg/L	123 (77–189)	164 (110–242)	182 (122–270.5)	195 (130–293)	196 (127–309)
Baseline serum retinol, μg/L	538.3 (464–624)	560 (489–639)	575 (503–654)	590 (515–673)	619 (542–710)
Baseline serum total cholesterol, mmol/L	5.2 (4.7–5.8)	5.8 (5.3–6.3)	6.2 (5.6–6.8)	6.6 (6.0–7.2)	7.2 (6.5–7.9)
Dietary intake					
Total energy, kcal	2 617 (2161–3159)	2 629 (2165–3148)	2 628 (2188–3131)	2 588 (2153–3106)	2 538 (2117–3060)
Fruits, g	61 (26–112)	68 (30–120)	77 (34–127)	80.5 (38.3–132.4)	84.2 (40–138)
Vegetables. g	57 (34–91)	65 (40–101)	71 (44–109)	76 (47–116)	82 (51–123)
Red meat, g	64 (47–85)	65 (48–88)	66 (50–88)	66 (48–88)	66 (49–88)
Coffee, g	550 (330–770)	560 (420–770)	600 (440–770)	560 (440–770)	550 (420–770)
Alcohol, g ethanol	12.9 (3.2–29.3)	10.9 (2.3–25.9)	10.7 (2.5–25.0)	10.3 (2.4–24.0)	10.7 (2.7–24.4)
Vitamin A, μg	1 556.4 (1071–2251)	1 619 (1116–2365)	1 639 (1129–2413)	1 641 (1110–2418)	1 631 (1100–2354)
Vitamin C, mg	85 (60–114)	90 (65–119)	94 (70–125)	96 (70–128)	98 (73–131)
Vitamin E, mg	9.2 (7.1–12.0)	10.1 (7.8–13.3)	10.9 (8.3–14.3)	11.4 (8.6–15.7)	12.4 (9.3–17.0)
α-Tocopherol, mg	7.9 (6.2–10.3)	8.7 (6.7–11.5)	9.3 (7.2–12.2)	9.8 (7.4–13.4)	10.7 (8.0–14.7)
γ-Tocopherol, mg	3.9 (2.1–7.2)	5.0 (2.7–9.2)	5.9 (3.1–10.8)	6.8 (3.5–12.8)	8.3 (4.3–14.9)

	Quintile of baseline serum α-tocopherol				
Characteristics	Q1 9.3 mg/L (n=5 806)	Q2 > 9.3 and 10.8 mg/L (n=5 882)	Q3 > 10.8 and 12.2 mg/L (n=5 653)	Q4 > 12.2 and 14.2 mg/L (n=5 938)	Q5 > 14.2 mg/L (n=5 823)
Trial intervention group					
α-tocopherol only, n (%)	1501 (25.9)	1473 (25.0)	1369 (24.2)	1473 (24.8)	1463 (25.1)
β-carotene only, n (%)	1461 (25.2)	1485 (25.3)	1384 (24.5)	1459 (24.6)	1489 (25.6)
α-tocopherol and β-carotene, n (%)	1404 (24.2)	1438 (24.5)	1426 (25.2)	1530 (25.8)	1470 (25.2)
Placebo, n (%)	1440 (24.8)	1486 (25.3)	1474 (26.1)	1476 (24.9)	1401 (24.1)

Note: Median (interquartile range) unless otherwise indicated.

[a] Family history of prostate cancer was not captured at baseline but on-study

Abbreviations: Q, quintile; BMI, Body mass index;

Table 2.

Multivariable-adjusted hazard ratios and 95% confidence intervals of prostate cancer by quintile of serum α-tocopherol concentration at baseline, among 29,102 Finnish male smokers in the ATBC Study

Serum measure	Events/Total person-years of follow-up	Prostate cancer incidence rate[a]	HR (95%CI)[b]
Baseline α-tocopherol, range, mg/L			
All prostate cancer			
Q1 9.3	497/86 812	5.7	1.00 (Ref)
Q2 > 9.3 and 10.8	543/96 890	5.6	0.93 (0.82, 1.06)
Q3 > 10.8 and 12.2	569/95 589	6.0	0.99 (0.87, 1.12)
Q4 > 12.2 and 14.2	599/102 060	5.9	0.96 (0.84, 1.10)
Q5 > 14.2	516/98 227	5.3	0.87 (0.75, 1.02)
P_{trend}[c]			0.57
Aggressive prostate cancer[d]			
Q1 9.3	223/83 247	2.7	1.00 (Ref)
Q2 > 9.3 and 10.8	307/93 895	3.3	1.12 (0.94, 1.34)
Q3 > 10.8 and 12.2	267/91 580	2.9	0.98 (0.81, 1.18)
Q4 > 12.2 and 14.2	317/98 341	3.2	1.04 (0.86, 1.26)
Q5 > 14.2	257/94 755	2.7	0.87 (0.70, 1.09)
P_{trend}			0.27
Non-aggressive prostate cancer			
Q1 9.3	365/85 349	4.3	1.00 (Ref)
Q2 > 9.3 and 10.8	373/94 762	3.9	0.87 (0.75, 1.01)
Q3 > 10.8 and 12.2	420/93 797	4.5	0.99 (0.85, 1.15)
Q4 > 12.2 and 14.2	452/100 192	4.5	0.99 (0.85, 1.15)
Q5 > 14.2	383/96 651	4.0	0.89 (0.75, 1.06)
P_{trend}			0.57

[a] Crude prostate cancer incidence rate per 1000 person-years; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention.

[b] Cox proportional hazards regression using person-years as the time metric to calculate hazard ratios and 95% confidence intervals of associations between measures of serum α-tocopherol (quintiles) and incidence of prostate cancer, and adjusted for age at randomization, body mass index, years of cigarette smoking, number of cigarettes smoked daily, serum total cholesterol concentration, and trial intervention group

[c] Two-sided P-trend is based on the statistical significance of the coefficient of the quintile variable (median value within each quintile).

[d] Aggressive prostate cancer was defined as TNM stage III or IV, AJCC, stage 3, or Gleason sum 8.

Abbreviations: HR, hazard ratio; 95% CI, 95 % confidence interval, Q, quintile; AJCC, American Joint Committee on Cancer;

Table 3.

Multivariable-adjusted hazard ratios and 95% confidence intervals of prostate cancer risk by quintile of baseline serum α-tocopherol concentration, stratified by study population characteristics, among 29,102 Finnish male smokers in the ATBC Study

Stratified characteristics	Events	Q1 9.3 mg/L	Q2 >9.3 and 10.8 mg/L	Q3 >10.8 and 12.2 mg/L	Q4 >12.2 and 14.2 mg/L	Q5 >14.2 mg/L	P_{trend} [b]	$P_{interaction}$ [c]
				HR (95% CI) [a]				
Age at randomization, y								0.28
<55	972	1.00 (Ref)	0.89 (0.72, 1.11)	1.01 (0.81, 1.25)	0.97 (0.77, 1.22)	0.91 (0.70, 1.17)	0.99	
55–59	877	1.00 (Ref)	1.17 (0.93, 1.47)	1.17 (0.93, 1.47)	1.09 (0.86, 1.39)	0.96 (0.73, 1.26)	0.17	
60	875	1.00 (Ref)	0.80 (0.65, 0.98)	0.83 (0.66, 1.03)	0.86 (0.68, 1.07)	0.78 (0.61, 1.01)	0.71	
Years of smoking								0.67
<32	831	1.00 (Ref)	0.96 (0.76, 1.22)	1.15 (0.91, 1.46)	1.05 (0.82, 1.35)	1.01 (0.76, 1.34)	0.87	
32–39	910	1.00 (Ref)	1.05 (0.84, 1.31)	1.01 (0.81, 1.27)	1.02 (0.80, 1.29)	0.86 (0.66, 1.12)	0.31	
40	983	1.00 (Ref)	0.84 (0.70, 1.03)	0.87 (0.71, 1.07)	0.88 (0.71, 1.09)	0.81 (0.64, 1.04)	0.99	
Number of cigarettes smoked daily								0.69
<20	1 121	1.00 (Ref)	0.96 (0.79, 1.18)	0.94 (0.76, 1.15)	0.98 (0.80, 1.21)	0.84 (0.66, 1.06)	0.62	
20	1 603	1.00 (Ref)	0.91 (0.78, 1.07)	1.02 (0.87, 1.20)	0.94 (0.79, 1.12)	0.90 (0.74, 1.10)	0.61	
BMI (range), kg/m²								0.83
<24.5	857	1.00 (Ref)	0.92 (0.75, 1.13)	1.05 (0.85, 1.31)	0.94 (0.74, 1.19)	0.92 (0.69, 1.22)	0.88	
24.5–27.6	981	1.00 (Ref)	0.89 (0.72, 1.10)	0.87 (0.70, 1.08)	0.94 (0.75, 1.17)	0.75 (0.58, 0.97)	0.93	
27.6	884	1.00 (Ref)	1.00 (0.80, 1.26)	1.07 (0.85, 1.35)	1.00 (0.79, 1.26)	0.98 (0.76, 1.26)	0.36	
α-Tocopherol supplementation								0.40
Yes	1 317	1.00 (Ref)	0.95 (0.79, 1.13)	0.98 (0.81, 1.18)	1.00 (0.82, 1.21)	0.79 (0.64, 0.99)	0.69	
No	1 407	1.00 (Ref)	0.93 (0.78, 1.10)	1.00 (0.84, 1.19)	0.93 (0.77, 1.12)	0.96 (0.78, 1.19)	0.71	
β-Carotene supplementation								0.49
Yes	1 379	1.00 (Ref)	0.95 (0.80, 1.13)	0.97 (0.81, 1.16)	0.97 (0.81, 1.17)	0.83 (0.67, 1.03)	0.37	
No	1 345	1.00 (Ref)	0.92 (0.77, 1.10)	1.01 (0.85, 1.21)	0.95 (0.79, 1.15)	0.92 (0.74, 1.14)	0.92	
History of diabetes								0.10
Yes	71	1.00 (Ref)	0.60 (0.27, 1.32)	0.38 (0.16, 0.90)	0.76 (0.35, 1.66)	0.61 (0.28, 1.34)	0.63	
No	2 653	1.00 (Ref)	0.95 (0.83, 1.07)	1.01 (0.89, 1.15)	0.97 (0.85, 1.11)	0.89 (0.76, 1.03)	0.64	

[a] Cox proportional hazards regression using person-years as the time metric to calculate hazard ratios and 95% confidence intervals of associations between measures of serum α-tocopherol (quintiles) and incidence of prostate cancer, and adjusted for age at randomization, body mass index, years of cigarette smoking, number of cigarettes smoked daily, serum total cholesterol concentration, and trial intervention group

[b] Two-sided P$_{trend}$ is based on the statistical significance of the coefficient of the quintile variable (median value within each quintile).

[c] Two-sided P$_{interaction}$ is based on the statistical significance of the cross-product term added to multivariable models.

Abbreviations: HR, Hazard Ratio; 95%CI, 95 % confidence interval; Ref, Referent; Q, quintile; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention

Table 4.

Association between vitamin E–related gene SNPs and prostate cancer risk among 8,383 Finnish male smokers in the ATBC Study

SNP	Gene	Chromosome	Minor allele	MAF	Number of participants	Prostate cancer diagnosis (%)	OR (95%CI)[a]	Mean serum α-tocopherol (mg/L) by genotype	P$_{trend}$[b]
rs964184	BUD13/ ZNF259/APOA5	11	G	0.15					
CC					6 096	26.4	1.00 (Ref)	11.8	0.09
GC					2 115	24.1	0.90 (0.80 1.01)	12.6	
GG					172	26.7	1.02 (0.72, 1.44)	13.6	
rs2108622	CYP4F2	19	T	0.19					
CC					5 505	26.0	1.00 (Ref)	11.9	0.50
TC					2 590	25.8	1.00 (0.89, 1.11)	12.2	
TT					288	23.6	0.89 (0.67, 1.17)	12.9	
rs11057830	SCARB1	12	A	0.13					
GG					6 314	25.5	1.00 (Ref)	11.9	0.08
AG					1 919	26.8	1.08 (0.96, 1.21)	12.3	
AA					150	31.3	1.35 (0.95, 1.92)	12.7	

[a] Models adjusted for age at randomization, body mass index, years of cigarette smoking, number of cigarettes smoked daily, serum total cholesterol concentration, and trial intervention group.

[b] Two-sided P$_{trend}$ is based on the statistical significance of the coefficient for the allele variable of each SNP

Abbreviations: MAF, minor allele frequency; OR, odds ratio; 95%CI, 95 % confidence interval; Ref, referent; BUD13, budding-site selection protein 13 (yeast); ZNF259, zinc finger protein 259; APOA5, apolipoprotein A5; CYP4F2, cytochrome p450, family 4, subfamily F, polypeptide 2; SCARB1, scavenger receptor class-B member 1; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention, SNP, single-nucleotide polymorphisms.

Table 5.

Association between weighted-polygenic risk score and prostate cancer risk by quintile of serum α-tocopherol, among 8,383 Finnish male smokers in the ATBC Study

Stratified characteristics	Mean serum α-tocopherol concentration (mg/L)	Events (%)	Baseline serum α-tocopherol quintiles, range					$P_{interaction}$ [c]
			Q1 9.3 mg/L	Q2 > 9.3 and 10.8 mg/L	Q3 > 10.8 and 12.2 mg/L	Q4 > 12.2 and 14.2 mg/L	Q5 > 14.2 mg/L	
			OR (95%CI) [b]					
PRS-ordinal [a]								0.89
Tertile 1 (lower risk)	12.7	24.4	1.00 (Ref)	1.02 (0.73, 1.43)	1.28 (0.91, 1.80)	1.14 (0.81, 1.61)	1.15 (0.79, 1.67)	
Tertile 2	11.9	24.6	1.00 (Ref)	1.17 (0.78, 1.75)	1.23 (0.81,1.88)	0.99 (0.62, 1.56)	1.04 (0.62, 1.73)	
Tertile 3 (higher risk)	11.7	27.0	1.00 (Ref)	0.95 (0.77, 1.18)	1.07 (0.86, 1.34)	1.09 (0.87, 1.38)	1.09 (0.83, 1.42)	

[a] PRS was defined for participants with complete data for all 3 SNPs

[b] Models adjusted for age at randomization, body mass index, years of cigarette smoking, number of cigarettes smoked daily, serum total cholesterol concentration, and trial intervention group

[c] Likelihood ratio test was used to assess for interaction.

Abbreviations: OR, odds ratio; 95%CI, 95 % confidence interval; Ref, referent; PRS, polygenic risk score; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention; SNP, single-nucleotide polymorphisms; Q, quintile