Published in final edited form as:
Cancer Causes Control. 2011 June ; 22(6): 827–836. doi:10.1007/s10552-011-9753-4.

Association of Serum α-Tocopherol with Sex Steroid Hormones and Interactions with Smoking: Implications for Prostate Cancer Risk

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Abstract

Background—Vitamin E may protect against prostate cancer, possibly only in smokers and, we hypothesize, through altered sex steroid hormones. A controlled trial in smokers showed that sex hormone levels were inversely associated with baseline serum α-tocopherol and decreased in response to vitamin E supplementation. The vitamin E-hormone relation is understudied in non-smokers.

Methods—Serum sex steroid hormones and α-tocopherol were measured for 1,457 men in NHANES III. Multivariable-adjusted geometric mean hormone concentrations by α-tocopherol quintile were estimated.

Results—We observed lower mean testosterone, estradiol, and SHBG concentrations with increasing serum α-tocopherol (Q1=5.5 and Q5=4.6 ng/mL, *p-trend=0.0007*; Q1=37.8 and Q5=33.1 pg/mL, *p-trend*=0.02; Q1=38.8 and Q5=30.6 pg/mL, *p-trend=0.05*, respectively). Interactions between serum α-tocopherol and exposure to cigarette smoke for total testosterone, total estradiol, and SHBG were found with the inverse relation observed only among smokers.

Conclusions—Results from this nationally representative, cross-sectional study indicate an inverse association between serum α-tocopherol and circulating testosterone, estradiol, and SHBG, but only in men who smoked. Our findings support vitamin E selectively influencing sex hormones in smokers, and afford possible mechanisms through which vitamin E may impact prostate cancer risk.

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Keywords

Gonadal Steroid Hormones; alpha-Tocopherol; Smoking; Prostatic Neoplasms; Cross-Sectional Studies

Introduction

Vitamin E, which refers to a family of four tocopherols and four tocotrienols, is thought to have promise as a chemopreventive agent for prostate and possibly other cancers. Of these compounds, α-tocopherol is the most biologically active in humans and has been the most commonly studied for its cancer prevention potential. The Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study, a large randomized controlled trial of vitamin E and β-carotene supplementation in smokers in Finland, found a statistically significant 32% reduction in prostate cancer incidence in the vitamin E supplemented arm (1). Subsequently, two other large randomized trials tested vitamin E, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (2) and the Physician's Health Study II (PHS II) (3), but found no effect of supplementation on the development of prostate cancer. One major difference between the ATBC Study and the other two trials is that the former study enrolled only men who were current smokers, whereas the prevalence of smoking in the other two studies was quite low. Observational studies provide some evidence that the protective effect of vitamin E for prostate cancer may differ by smoking status. For example, although findings regarding dietary or supplemental vitamin E intake or serum levels of α-tocopherol and prostate cancer have been inconsistent, showing either null or inverse associations (4-22), many studies have observed inverse associations between intake or blood levels of vitamin E and prostate cancer risk in smokers (5, 12, 15-21, 23), particularly for advanced or high-grade disease (12, 17, 20, 21, 23).

One hypothesized mechanism through which vitamin E might prevent prostate cancer in smokers is by influencing steroid hormone concentrations. Epidemiologic studies show little direct association between circulating testosterone concentrations in middle age and prostate cancer risk (24). However, a role for androgens in prostate cancer etiology is supported by other evidence. Hormone deprivation therapy is an effective treatment for prostate cancer, and the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial showed lower prostate cancer incidence in men randomized to receive finasteride or dutasteride, respectively, agents which block the conversion of testosterone to its more active form, dihydrotestosterone (DHT), compared to men who received placebo (25, 26). Male smokers are known to have higher serum levels of testosterone, free testosterone, total estradiol, or sex hormone-binding globulin (SHBG) than nonsmokers (27-36). Therefore, if vitamin E status is related to lower sex steroid concentrations, it could theoretically reduce the increased prostate cancer risk in smokers that may result from greater exposure to circulating androgens (and possibly estrogens).

Few epidemiologic studies have examined the association between circulating α-tocopherol and steroid hormone concentrations. Investigations of the ATBC Study cohort found serum α-tocopherol to be inversely associated with serum androstenedione, testosterone, SHBG, and estrone at baseline (37), and lower on-study androstenedione and testosterone levels among men who received the vitamin E supplements compared to men who received a placebo (38). By contrast, one small pilot trial of 28 men conducted in the U.S. observed no change in testosterone in response to α-tocopherol supplementation; the smoking status of the participants in this trial was not mentioned, however (39). Thus, the relationship between circulating α-tocopherol, vitamin E supplementation, and circulating sex steroid hormones remains unclear, particularly with respect to smoking status.

We examined the association of serum α-tocopherol and supplemental vitamin E intake with sex steroid hormones overall and with respect to smoking status and other potential modifying factors among male participants in the Third National Health and Nutrition Examination Survey (NHANES III), a large study designed to be nationally representative of the United States population.

Materials and Methods

Study Population

NHANES III, a cross-sectional study undertaken by the National Center for Health Statistics from 1988 to 1994, was designed to represent the total United States civilian, noninstitutionalized population over 2 months of age. This was accomplished using a stratified multistage probability design; to be able to more precisely calculate estimates in certain subgroups of the population, Mexican-Americans, non-Hispanic blacks, and the elderly were over-sampled.

The study was conducted in two phases (1988-1991 and 1991-1994); unbiased national estimates can be obtained from either phase 1 or phase 2 separately or from both combined. For each phase, participants were randomly assigned to either the morning or the afternoon examination session. A total of 33,944 people were interviewed in NHANES III, 30,818 of whom gave a blood sample and underwent a physical examination. Sex steroid hormone concentrations were assayed for 1,637 males ages 12 and older who participated in the morning examination of phase 1 of NHANES III and for whom stored serum was still available in the repository. We measured hormones only for those participants who were examined in the morning to minimize measurement error due to diurnal variation in hormone levels. Men were excluded if they were younger than 20 years of age (10.2%), had ever been diagnosed with prostate cancer (0.7%), were missing information on total cholesterol (0.1%), were missing information on percent body fat or waist circumference (8.6%), or were missing information on serum α-tocopherol concentration (0.6%). After these exclusions, 1,307 men remained for analysis.

Measurement of Serum Sex Steroid Hormone and α-Tocopherol Concentrations

Blood was drawn after an overnight fast for all participants in the morning sample. Concentrations of total testosterone; total estradiol, the major estrogen in men; and sex hormone binding globulin (SHBG), their major carrier in circulation, were measured using a competitive electrochemiluminescence immunoassay on the 2010 Elecsys autoanalyzer (Roche Diagnostics, Indianapolis IN). Androstanediol glucuronide, an indicator of the conversion of testosterone to DHT, was measured using an enzyme immunoassay (Diagnostic Systems Laboratories, Webster, TX). All samples were analyzed at Children's Hospital Boston where laboratory personnel were blinded to participants' ages and identities and samples were arranged in random order for testing. The lowest detection limits were 0.02 ng/mL for testosterone, 5 pg/mL for estradiol, 3 nmol/L for SHBG, and 0.33 ng/mL for androstanediol glucuronide. The coefficients of variation for embedded quality control samples were: testosterone 5.9% and 5.8% at 2.5 and 5.5 ng/mL, respectively; estradiol 6.5% and 6.7% at 102.7 and 474.1 pg/mL, respectively; SHBG 5.3% and 5.9% at 5.3 and 16.6 nmo/L, respectively; and androstanediol glucuronide 9.5% and 5.0% at 2.9 and 10.1 ng/mL, respectively. Serum concentrations of testosterone and estradiol detected in this population were consistent with what are considered normal values for adult US men (testosterone, 1.94 – 8.33 ng/mL; estradiol, <50 pg/mL) (40). Free testosterone and free estradiol were estimated from total testosterone and total estradiol, respectively, SHBG, and albumin concentrations using mass action equations (41, 42).

Serum α-tocopherol was measured previously in NHANES III using isocratic high performance liquid chromatography with detection at three different wavelengths. The coefficient of variation for α-tocopherol ranged from 2.2 – 4.3% (43).

Assessment of Vitamin E Supplement Use

During the household interview, participants were asked if they took any vitamin or mineral supplements and, if so, how many. For each supplement a participant reported taking, the interviewer asked to see the container and recorded the supplement name and the manufacturer or distributor. This information was later used by National Center for Health Statistics staff to develop a database of the nutrients in each supplement reported by NHANES participants. Participants were also asked how many times per month they took the supplement and how many doses they took each time. We used this information to calculate whether the men were regular users of vitamin E-containing supplements and, if so, how many IUs of supplemental vitamin E (including from multivitamins) they took daily. Men who reported taking supplements 15 or more times per month were considered regular users and men who reported taking supplements fewer than 15 times per month were considered occasional users.

Assessment of Covariates

Information on physical activity, cigarette smoking, and alcohol intake was collected during in-person interviews, which included a food frequency questionnaire. Height, weight, and waist circumference were measured by NHANES III study personnel. Percent body fat was calculated from bioelectrical impedance analysis (BIA), measured height and weight, and age as described previously (44). Serum total cholesterol and serum cotinine, an indicator of active and passive exposure to cigarette smoke, were measured for all NHANES participants (43).

Statistical Analysis

All analyses were conducted using SUDAAN v 9.0 software (Research Triangle Park, NC) as implemented in SAS v 9.2 (Cary, NC). In all analyses we used the Phase I morning sampling weights to account for the NHANES complex survey design (45). We calculated the age-adjusted means or percentages of characteristics of the participants by categories of serum α-tocopherol by directly standardizing to the age distribution of the US population according to the 2000 Census. We estimated geometric mean concentrations of total and free testosterone, total and free estradiol, SHBG, androstanediol glucuronide, and the molar ratio of testosterone to estradiol and their 95% confidence intervals by quintile of serum α-tocopherol concentration (<809, 809 - <949, 949 - <1,096, 1,096 - <1,324, ≥1,324 μg/dL) and by categories of supplemental vitamin E (none, occasional use, regular use ≤30 IU/day, regular use ≤100 IU/day, regular use >100 IU/day) using linear regression. Because hormone concentrations were not normally distributed these values were transformed using the natural logarithm. We also estimated geometric mean hormone concentrations by decile and clinical cut points of serum α-tocopherol to determine whether modeling by quintile cut points accurately captured the shape of the association between hormone and α-tocopherol concentrations. The inferences were similar using both of these sets of cut points, so we report the results by quintiles of α-tocopherol. We evaluated the beta for the change in the natural log of serum hormone concentration per 100 μg/dL change in serum α–tocopherol as well as the trend across categories by modeling serum α–tocopherol as a continuous variable and evaluating its statistical significance using the Wald test.

Multivariable models included factors that have been associated with hormone concentrations in previous NHANES analyses. Age in years (continuous) and race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other) were included in all

models; the results did not differ when age was parameterized as a restricted cubic spline with knots at the 5th, 50th, and 95th percentiles. Multivariable models were further adjusted for the following: percent body fat (quintiles), waist circumference (quintiles), total serum cholesterol (quintiles of mg/dL), moderate or vigorous physical activity (quintiles of times/week), cigarette smoking (never, current, former), and alcohol intake (non-drinker, < 1 drink/week, 1 drink/week - < 1 drink/day, ≥ 1 drink/day). None of the factors included in the multivariable model appeared to confound the association between serum α-tocopherol and any of the examined hormones. Results did not differ after further adjustment for serum cotinine. Because α-tocopherol is carried in circulation bound to lipoproteins, there is a strong relationship between serum concentrations of α-tocopherol and cholesterol. Thus, we conducted additional analyses adjusting serum α-tocopherol for serum cholesterol using the residual method (46).

We conducted analyses stratified by age (20-39, 40-59, ≥ 60 years), race (non-Hispanic white, non-Hispanic black, Mexican-American), cigarette smoking status (never, current, former), serum cotinine (no exposure: below the limit of detection of 0.035 ng/mL, passive exposure: <10 ng/mL, active exposure: ≥10 ng/mL), serum cholesterol (<200, 200 - <240, ≥240 mg/dL), percent body fat (tertiles), and alcohol intake (none, <1 drink/day, ≥1 drink/day). Statistical interaction was assessed by entering main effects terms and a cross-product term for the stratification variable and serum α-tocopherol into the model, and evaluating its statistical significance using the Wald test. Stratified results were adjusted for age in years (continuous), serum cholesterol (continuous), and, with the exception of the models stratified by race, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other).

All protocols for the implementation of NHANES III were approved by the Institutional Review Board of the National Center for Health Statistics, Centers for Disease Control and Prevention; informed consent was obtained for all participants. The Institutional Review Boards at the Johns Hopkins Bloomberg School of Public Health and the National Center for Health Statistics, Centers for Disease Control and Prevention approved the assay of stored serum specimens for the Hormone Demonstration Program.

Results

Characteristics of the study population by quintiles of serum α-tocopherol are shown in Table 1. Men with higher serum α-tocopherol tended to be older, and with adjustment for age, they were more likely to be non-Hispanic white, physically active, and use vitamin E supplements, had higher mean waist circumference and serum cholesterol, and were less likely to be current smokers, actively exposed to cigarette smoke (as indicated by cotinine concentration) or heavy drinkers (Table 1).

Adjusting for age and race/ethnicity, serum α-tocopherol was statistically significantly inversely associated with testosterone, estradiol, and SHBG (Table 2). These associations persisted after adjusting for several factors (Table 2), with mutual adjustment for testosterone and estradiol (data not shown), and after adjusting testosterone and estradiol for SHBG (data not shown). The results did not differ when men using vitamin E supplements were excluded from the analysis (data not shown). We observed no association between serum α-tocopherol and free testosterone, free estradiol, or AAG after multivariable adjustment (Table 2). Analyses of the association between serum α-tocopherol and the testosterone to estradiol ratio were not informative beyond the contribution of the individual hormones presented in Table 2 (data not shown). When we used serum α-tocopherol adjusted for serum cholesterol using the residual method, the results were very similar (geometric mean, 95% CI; testosterone: Q1 α-tocopherol = 5.4, 5.0 – 5.9 ng/mL, Q5 α-

tocopherol = 4.7, 4.4-5.0 ng/mL, *p-trend = 0.02*; estradiol : Q1 α-tocopherol = 36.9, 34.5 - 39.4 pg/mL, Q5 α-tocopherol = 34.6, 33.2 – 36.1 pg/mL, *p-trend = 0.11*; SHBG: Q1 α-tocopherol = 37.2, 34.7 – 39.9 ng/mL, Q5 α-tocopherol = 31.7, 29.4 – 34.1 ng/mL, *p-trend = 0.005*). We observed no association between vitamin E supplement use and testosterone, free testosterone, estradiol, free estradiol, SHBG, or AAG (data not shown).

The associations between some hormones, especially total and free estradiol, and serum α-tocopherol differed somewhat by self-reported smoking status (Table 3), although the patterns did not appear to differ between never and current smokers. However, alternative classification of active, passive, and no exposure to cigarette smoke based on serum cotinine levels, revealed no association with serum α-tocopherol among men who were unexposed to cigarette smoke, but we saw progressively stronger inverse associations between serum α-tocopherol and total testosterone, total estradiol, and SHBG as exposure to cigarette smoke increased (Table 4). The interactions with total testosterone and SHBG were statistically significant or, in the case of total testosterone, of borderline significance.

Stratification by serum total cholesterol concentration with additional adjustment for serum cholesterol revealed that the inverse associations between serum α-tocopherol and total testosterone and SHBG were strongest among men with higher serum cholesterol (*p for interaction 0.002 and 0.07*, respectively) (Table 5). Further, we noted a suggestion of an inverse association between free testosterone and serum α-tocopherol among men with the highest cholesterol concentrations (*p for interaction = 0.01*) (Table 5).

The association between some of the measured hormones and serum α-tocopherol varied somewhat by race. The inverse association between total testosterone and serum α-tocopherol appeared limited to non-Hispanic white and Mexican-American men, with no association among non-Hispanic black men, although the interaction was not statistically significant (*p for interaction = 0.12*)(data not shown). There was also a suggestion of qualitative interaction with free testosterone: the association with serum α-tocopherol appeared inverse for non-Hispanic white and Mexican-American men, and positive for non-Hispanic black men (*p for interaction = 0.07*). Similar race differences for total and free estradiol were not statistically significant, however (data not shown). The inverse association between SHBG and serum α-tocopherol evident in all racial groups appeared strongest among non-Hispanic black men (*p for interaction = 0.33*) (data not shown).

The serum hormone-α-tocopherol associations were also examined by subgroups of age, percent body fat, and alcohol intake, and we observed a modest inverse association with free testosterone among younger (20 – 59 years) men, but no association among older men (*p for interaction = 0.02*) (data not shown). The inverse association between serum α-tocopherol and SHBG appeared to be stronger among men who did not drink (*p for interaction = 0.02*) (data not shown). We observed no statistically significant interaction between any of the measured hormones and percent body fat (data not shown).

Discussion

To our knowledge this is the first report on the association between serum or supplemental vitamin E and sex steroid hormones in a nationally representative sample of men in the U.S. After controlling for age and other potential confounding factors, we observed that serum α-tocopherol was inversely associated with total testosterone, total estradiol, and SHBG. These relationships were limited to men who were actively exposed to cigarette smoke and men with high (>200 mg/dL) serum cholesterol, and appeared to vary by race. Our findings are consistent with those from two analyses within the ATBC Study, a cohort of Finnish male smokers, which showed inverse associations between α-tocopherol and these hormones

cross-sectionally (37) as well as prospectively in response to controlled vitamin E supplementation (38). Although the biologic mechanism through which vitamin E may influence circulating hormones is unknown, one hypothesis involves vitamin E lowering prostaglandin levels, particularly prostaglandin E2 (PGE2), which, in turn, are known to increase the secretion of hormones that stimulate androgen production in the testis (38). Alternatively, animal studies demonstrate that vitamin E supplementation down-regulates expression of genes involved in the synthesis of androgen precursors (e.g., cholesterol) in the testis and adrenal glands (47), as well as the gene for 5-α-steroid reductase type 1 in the liver (48). Thus, vitamin E may influence sex steroid hormone production at the transcription level.

Given the evidence that vitamin E supplement use may be protective for prostate cancer among smokers, (1, 12, 15, 17, 21, 23) and the known role of androgens in prostate tumorigenesis and progression, a hormone-lowering influence of vitamin E in the setting of exposure to cigarette smoke would be consistent with the prostate cancer preventive effect. We observed inverse relations between total testosterone, total estradiol, and SHBG among men exposed to cigarette smoke, as determined by serum cotinine concentrations, but not among men who were unexposed, pointing to a selective impact of vitamin E on sex steroid hormones in smokers. How vitamin E might alter hormone concentrations specifically in the setting of exposure to cigarette smoke is at this time unclear. Despite our data being cross-sectional and our resulting inability to establish a cause-and-effect temporal relationship between α-tocopherol and the sex hormones, the present findings support a hormonal mechanism through which vitamin E might influence prostate cancer risk in smokers. It is important to note that our results differed markedly by whether smoking status was classified by serum cotinine concentration or self-reported smoking status, with the former, more objective definition yielding tronger vitamin E-hormone associations. This may be due, in part, to the categorization of some individuals as “never smokers” who either underreported their smoking behaviors or were passively exposed to cigarette smoke (49). In fact, in our analysis only 8% of self-reported never smokers were unexposed to cigarette smoke as measured by serum cotinine concentration; 84% were passively exposed and 8% were actively exposed according to serum cotinine concentration. Our results suggest that self-reported smoking status is subject to some misclassification and may not discriminate sufficiently between those exposed and unexposed to the myriad of compounds delivered by cigarette smoke for the purpose of testing effect modification of the circulating hormone - vitamin E association by smoking.

Given that non-Hispanic black race is one of the few established risk factors for prostate cancer in the United States, and substantial research is focused on understanding and eliminating this disparity, our observation of a different relationship between serum α-tocopherol and sex hormone concentrations among non-Hispanic black men compared to other racial/ethnic groups may have important implications for preventive efforts in the former group. We were unable to examine the associations stratified by exposure to cigarette smoke within each racial group because of our study sample size, however the distribution of serum cotinine did not differ markedly by group, making it unlikely that a different racial/ethnic distribution of cigarette smoke exposure could explain our findings.

The inverse associations between α-tocopherol and both testosterone and SHBG were strongest among men with higher serum cholesterol, even after additional adjustment for cholesterol within strata. α-tocopherol is carried in circulation bound to lipoproteins and individuals with higher cholesterol concentrations generally have higher α-tocopherol concentrations as well (50). Cholesterol might influence the vitamin E – hormone relation by facilitating greater α-tocopherol delivery on lipoproteins (particularly LDL) to tissues, particularly the testes, adrenal glands, and liver. Our observation of statistical interactions

with both age and alcohol consumption further highlights the complexity of the relation between vitamin E and hormones, particularly in the context of other factors that influence the hormonal milieu. Further research of this area is likely to clarify some of the underlying biologic interactions and their relevance to prostate carcinogenesis.

Interestingly, we observed no association between vitamin E supplement use and hormone concentrations in our study, but only 22% of the cohort was using a vitamin-E containing supplement. Users and non-users of vitamin E supplements had broad, overlapping distributions of serum α-tocopherol (median, IQR (μg/mL); users= 979, 821-1,183; non-users=1,219, 997-1,593), however. Thus, comparing supplement users to non-users does not capture the differences in hormone concentrations accounted for by high and low vitamin E biochemical status. Our findings support the idea that serum α-tocopherol concentration is a better indicator of vitamin E status than estimated dietary or supplemental intake.

Our study has several strengths including its large sample size and use of nationally representative data. We were able to adjust for many potential confounding factors and examine interactions. Despite our large sample size, however, we were limited in our ability to adjust for multiple covariables in stratified models. Given that the overall associations did not differ markedly between the multivariable models and those adjusted only for age and race, it seems unlikely that residual confounding could explain the associations observed in our subgroup analyses.

Conclusions

Results from this nationally representative, cross-sectional study indicate an inverse relationship between serum α-tocopherol and circulating testosterone, estradiol, and SHBG concentrations in men actively exposed to cigarette smoke (as measured by serum cotinine concentration), with similar, albeit not statistically significant, associations among men with lower cigarette smoke exposure levels. Our findings will require further study but provide support for the hypothesis that vitamin E may selectively protect against prostate cancer in smokers, at least in part, through a hormonal mechanism.

Acknowledgments

Funding: This is the 26th paper from the Hormone Demonstration Program funded by the Maryland Cigarette Restitution Fund at Johns Hopkins.

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Table 1

Age-Adjusted[a] Weighted Characteristics by Quintiles of Serum α–tocopherol, Adult Men, NHANES III 1988-1991

	Serum α–tocopherol (μg/dL)				
	Q1 <809	**Q2 809 - <949**	**Q3 949 - <1,096**	**Q4 1,096 - <1,324**	**Q5 ≥1,324**
N	261	260	262	261	263
Age (years)					
Race (%)					
Non-Hispanic white	65.7	74.5	79.5	86.9	80.2
Non-Hispanic black	19.2	11.6	9.7	5.5	5.7
Mexican-American	5.1	4.1	4.3	4.5	6.6
Other race/ethnicity	10.0	9.8	6.5	3.1	7.6
BMI (kg/m^2)	25.3	26.1	26.4	27.3	26.2
Body Fat (%)	24.8	24.7	25.7	26.0	25.3
Waist Circumference (cm)	92.5	94.5	95.7	97.7	95.2
Physical Activity (times/week)	5.4	6.6	6.7	6.1	7.8
Cigarette Smoking (%)					
never	29.0	28.4	37.1	26.9	37.2
current	43.8	36.2	31.5	32.9	27.0
former	27.2	35.4	31.5	40.2	35.9
Cigarette Smoke Exposure (based on serum cotinine concentration) (%)					
unexposed	1.3	4.6	5.5	5.0	7.5
passively exposed	44.9	51.2	57.6	52.9	70.6
actively exposed	53.2	43.5	36.7	42.1	20.6
Alcohol Intake (%)					
non-drinker	26.7	37.3	35.7	33.1	24.6
>0 - <1 drink/week	10.7	7.6	10.4	10.4	12.7
≥ 1/week - <1 drink day	33.9	37.5	38.9	39.6	46.6

	Serum α–tocopherol (μg/dL)				
	Q1 <809	**Q2 809 - <949**	**Q3 949 - <1,096**	**Q4 1,096 - <1,324**	**Q5 ≥1,324**
≥ 1 drink/day	25.7	17.6	15.0	16.9	16.1
Vitamin E Supplement Use (%)	8.0	14.1	16.2	29.8	51.5
Total Cholesterol (mg/dL)	172	191	213	216	231

[a]Standardized to the 2000 US Census age distribution (except age); means unless noted otherwise.

Table 2

Geometric Mean (95% Confidence Intervals) Serum Sex Hormone Concentrations by Quintile of Serum α–tocopherol, Adult Men, NHANES III 1988-1991

	Serum α–tocopherol (μg/dL)						
	Q1 <809	**Q2 809 - <949**	**Q3 949 - <1,096**	**Q4 1,096 - <1,324**	**Q5 ≥1,324**	**β** [a]	***p trend***
Testosterone (ng/mL)							
Age and Race Adjusted[b]	5.6 (5.3 – 6.0)	5.3 (5.1 – 5.5)	4.8 (4.5 – 5.2)	5.2 (4.9 – 5.6)	4.6 (4.3 – 4.9)	-0.01	*0.002*
Multivariable Adjusted[c]	5.5 (5.1 – 6.0)	5.2 (5.0 – 5.4)	4.8 (4.5 – 5.2)	5.4 (5.1 – 5.6)	4.6 (4.3 – 4.9)	-0.01	*0.0007*
Free Testosterone (ng/dL)							
Age and Race Adjusted[b]	10.6 (10.0 – 11.2)	10.7 (10.3 – 11.2)	9.4 (8.5 – 10.4)	10.4 (9.9 – 11.0)	9.6 (8.8 – 10.5)	-0.006	*0.08*
Multivariable Adjusted[c]	10.5 (9.7 – 11.2)	10.7 (10.3 – 11.2)	9.5 (8.6 – 10.5)	10.5 (10.0 – 11.1)	9.6 (8.8 – 10.5)	-0.005	*0.27*
AAG (ng/mL)							
Age and Race Adjusted[b]	11.5 (10.5 – 12.6)	11.2 (10.3 – 12.2)	11.6 (10.5 – 12.7)	11.6 (10.5 – 12.7)	11.7 (10.9 – 12.5)	0.002	*0.73*
Multivariable Adjusted[c]	12.1 (11.0 – 13.2)	11.3 (10.5 – 12.2)	11.4 (10.4 – 12.5)	11.4 (10.4 – 12.5)	11.4 (10.6 – 12.3)	-0.004	*0.38*
Estradiol (pg/mL)							
Age and Race Adjusted[b]	38.9 (37.3 – 40.7)	35.8 (33.4 – 38.4)	35.2 (32.6 – 38.0)	37.2 (35.8 – 38.6)	32.1 (30.2 – 34.1)	-0.01	*<0.0001*
Multivariable Adjusted[c]	37.8 (36.1 – 39.7)	35.3 (32.9 – 37.9)	35.5(33.0 – 38.1)	37.4 (35.9 – 39.0)	33.1 (31.0 – 35.3)	-0.008	*0.02*
Free Estradiol (pg/mL)							
Age and Race Adjusted[b]	0.96 (0.91 – 1.02)	0.93 (0.86 – 1.00)	0.89 (0.83 – 0.95)	0.95 (0.91 – 0.99)	0.84 (0.79 – 0.91)	-0.009	*0.0003*
Multivariable Adjusted[c]	0.94 (0.89 – 0.99)	0.92 (0.86 – 0.99)	0.89 (0.84 – 0.95)	0.94 (0.90 – 0.99)	0.87 (0.81 – 0.94)	-0.004	*0.21*
SHBG (nmol/L)							
Age and Race Adjusted[b]	39.2 (36.7 – 42.0)	33.8 (31.2 – 36.5)	35.1 (32.8 – 37.5)	34.8 (31.9 – 37.8)	31.0 (28.8 – 33.3)	-0.01	*0.006*
Multivariable Adjusted[c]	38.8 (35.6 – 42.2)	33.2 (31.2 – 35.2)	35.2 (33.6 – 37.0)	35.9 (33.7 – 38.3)	30.6 (28.2 – 33.2)	-0.01	*0.05*

[a] Beta for difference in ln serum hormone concentration per 100 μg/dL difference in serum α–tocopherol.

[b] Adjusting for age in years (continuous) and race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other)

[c] Adjusting for age in years (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other), percent body fat (quintiles), waist circumference (continuous), physical activity (quintiles of times/week), cigarette smoking (never, current, former), alcohol intake (non-drinker, <1 drink/week, 1 drink/week - <1 drink/day, ≥1 drink/day), and serum total cholesterol concentration (continuous)

Table 3

Geometric Mean[a] (95% Confidence Interval) Serum Sex Hormone Concentrations by Lowest and Highest Quintiles of Serum α–tocopherol, Stratified by Smoking Status, Adult Men, NHANES III 1988-1991

	Never Smokers		Former Smokers		Current Smokers		
Serum α–tocopherol Quintile (μg/dL)	**Q1 and Q2 <949**	**Q5 ≥ 1,324**	**Q1 and Q2 <949**	**Q5 ≥ 1,324**	**Q1 and Q2 <949**	**Q5 ≥ 1,324**	***p for interaction***
Testosterone (ng/mL)	5.0 (4.6 – 5.4)	4.1 (3.4 – 4.9)	4.9 (4.5 – 5.3)	4.7 (4.4 – 5.0)	6.2 (5.8 – 6.6)	5.5 (4.9 – 6.2)	
β [b]	-0.02		-0.002		-0.01		
p trend	*0.10*		*0.72*		*0.19*		*0.09*
Free Testosterone (ng/dL)	9.7 (9.0 – 10.4)	8.5 (7.0 – 10.3)	9.8 (9.1 – 10.6)	9.9 (9.2 – 10.7)	12.3 (11.7 – 13.0)	11.1 (9.7 – 12.7)	
β [b]	-0.01		0.0004		-0.004		
p trend	*0.53*		*0.95*		*0.65*		*0.04*
AAG (ng/mL)	12.3 (11.5 – 13.3)	10.5 (9.3 – 11.7)	10.7 (9.7 – 11.8)	11.2 (8.7 – 14.5)	11.9 (10.6 – 13.4)	12.3 (10.6 – 14.4)	
β [b]	-0.006		-0.009		0.001		
p trend	*0.43*		*0.21*		*0.94*		*0.21*
Estradiol (pg/mL)	33.2 (31.3 – 35.1)	29.3 (26.3 – 32.8)	33.2 (30.6 – 35.9)	33.1 (31.6 – 34.6)	42.3 (40.4 – 45.0)	39.2 (36.9 – 41.6)	
β [b]	-0.01		-0.001		-0.01		
p trend	*0.04*		*0.76*		*0.07*		*0.002*
Free Estradiol (pg/mL)	0.84 (0.78 – 0.89)	0.76 (0.67 – 0.87)	0.86 (0.80 – 0.93)	0.88 (0.83 – 0.92)	1.08 (1.02 – 1.14)	1.00 (0.92 – 1.10)	
β [b]	-0.006		-0.0003		-0.007		
p trend	*0.33*		*0.95*		*0.29*		*0.01*
SHBG (nmol/L)	34.6 (31.9 – 37.5)	30.5 (27.8 – 33.5)	34.0 (30.3 – 38.1)	30.6 (27.4 – 34.2)	37.7 (35.3 – 40.3)	35.6 (29.7 – 42.6)	
β [b]	-0.02		-0.005		-0.01		
p trend	*0.003*		*0.45*		*0.24*		*0.90*

[a] Adjusting for age in years (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other), and serum total cholesterol concentration (continuous)

[b] Beta for difference in ln serum hormone concentration per 100 μg/dL difference in serum α–tocopherol.

Table 4

Geometric Mean[a] (95% Confidence Interval) Serum Sex Hormone Concentrations by Lowest and Highest Quintiles of Serum α–tocopherol, Stratified by Exposure to Cigarette Smoke[b], Adult Men, NHANES III 1988-1991

		No Exposure		Passive Exposure		Active Exposure		
Serum α–tocopherol Quintile (μg/dL)		**Q1 and Q2 <949**	**Q5 ≥ 1,324**	**Q1 and Q2 <949**	**Q5 ≥ 1,324**	**Q1 and Q2 <949**	**Q5 ≥ 1,324**	***p for interaction***
Testosterone (ng/mL)		4.2 (3.3 – 5.3)	2.9 (2.0 – 4.2)	5.0 (4.8 – 5.3)	4.8 (4.4 – 5.3)	5.9 (5.4 – 6.3)	5.1 (4.4 – 5.9)	*0.07*
	β [c]	-0.003		-0.0008		-0.01		
	p trend	*0.90*		*0.86*		*0.03*		
Free Testosterone (ng/dL)		8.6 (7.5 – 9.9)	6.4 (4.2 – 9.8)	10.0 (9.6 – 10.4)	9.8 (9.0 – 10.8)	11.6 (10.8 – 12.4)	10.9 (9.4 – 12.6)	*0.25*
	β [c]	0.003		0.001		-0.003		
	p trend	*0.91*		*0.79*		*0.56*		
AAG (ng/mL)		14.7 (11.1 – 19.5)	9.7 (6.6 – 14.2)	11.9 (11.2 – 12.6)	11.7 (10.5 – 13.1)	11.1 (10.1 – 12.3)	11.4 (8.7 – 14.8)	*0.09*
	β [c]	-0.05		-0.0006		-0.006		
	p trend	*0.09*		*0.93*		*0.40*		
Estradiol (pg/mL)		31.2 (29.4 – 33.2)	29.8 (26.7 – 33.4)	33.5 (31.5 – 35.6)	32.1 (29.6 – 34.8)	40.3 (37.7 – 43.1)	38.1 (35.5 – 40.9)	*0.16*
	β [c]	-0.00003		-0.003		-0.01		
	p trend	*0.99*		*0.58*		*0.006*		
Free Estradiol (pg/mL)		0.8 (0.72 – 0.89)	0.81 (0.72 – 0.92)	0.85 (0.80 – 0.91)	0.83 (0.76 – 0.90)	1.03 (0.96 – 1.10)	1.01 (0.92 – 1.10)	*0.22*
	β [c]	0.004		-0.001		-0.005		
	p trend	*0.77*		*0.82*		*0.14*		
SHBG (nmol/L)		29.1 (22.2 – 38.3)	25.1 (20.9 – 30.1)	34.5 (32.3 – 36.8)	32.8 (29.9 – 36.0)	37.4 (34.7 – 40.3)	31.1 (26.3 – 36.7)	*0.006*
	β [c]	-0.008		-0.005		-0.01		
	p trend	*0.65*		*0.48*		*0.11*		

[a] Adjusting for age in years (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other), and serum total cholesterol concentration (continuous)

[b] Defined based on cotinine concentration (no exposure: below the limit of detection of 0.035 ng/mL, passive exposure: <10 ng/mL, active exposure: ≥10 ng/mL)

[c] Beta for difference in ln serum hormone concentration per 100 μg/dL difference in serum α–tocopherol.

Table 5

Geometric Mean[a] (95% Confidence Interval) Serum Sex Hormone Concentrations by Lowest and Highest Quintiles of Serum α–tocopherol, Stratified by Serum Total Cholesterol, Adult Men, NHANES III 1988-1991

	Total Cholesterol (mg/dL)						
	<200		200 - <240		≥240		
Serum α–tocopherol Quintile (μg/dL)	**Q1 and Q2 <949**	**Q5 ≥ 1,324**	**Q1 and Q2 <949**	**Q5 ≥ 1,324**	**Q1 and Q2 <949**	**Q5 ≥ 1,324**	***p for interaction***
Testosterone (ng/mL)	5.4 (5.0 – 5.8)	5.2 (4.7 – 5.8)	5.3 (4.8 – 5.8)	4.5 (4.1 – 5.0)	7.5 (5.8 – 9.6)	4.5 (3.9 – 5.2)	*0.002*
β [b]	0.001		-0.02		-0.01		
p trend	*0.87*		*0.03*		*0.02*		
Free Testosterone (ng/dL)	10.7 (10.1 – 11.3)	10.3 (9.3- 11.4)	10.6 (9.6 – 11.7)	9.7 (8.6 – 10.9)	13.0 (112 – 15.2)	9.2 (7.9 – 10.7)	*0.01*
β [b]	-0.001		-0.003		-0.006		
p trend	*0.83*		*0.74*		*0.32*		
AAG (ng/mL)	11.9 (10.9 – 13.0)	13.6 (10.3 – 18.0)	11.1 (9.9 – 12.6)	10.6 (9.2 – 12.3)	12.4 (9.8 – 15.7)	10.9 (8.9 – 13.2)	*0.09*
β [b]	0.01		-0.01		-0.01		
p trend	*0.39*		*0.38*		*0.12*		
Estradiol (pg/mL)	35.4 (33.6 – 37.3)	33.4 (30.8 – 36.3)	37.7 (33.5 – 42.4)	33.0 (29.8 – 36.6)	41.7 (34.7 – 50.1)	34.1 (30.7 – 37.8)	*0.69*
β [b]	-0.005		-0.01		-0.008		
p trend	*0.33*		*0.06*		*0.05*		
Free Estradiol (pg/mL)	0.91 (0.85 – 0.97)	0.85 (0.76 – 0.94)	0.97 (0.86 – 1.09)	0.88 (0.78 – 0.99)	0.97 (0.85 – 1.12)	0.88 (0.79 – 0.99)	*0.99*
β [b]	-0.007		-0.007		-0.002		
p trend	*0.08*		*0.41*		*0.64*		
SHBG (nmol/L)	35.3 (31.6 – 39.5)	35.5 (29.2 – 43.2)	34.2 (32.0 – 36.6)	29.7 (26.9 – 32.8)	51.0 (40.3 – 64.5)	32.7 (29.3 – 36.4)	*0.07*
β [b]	0.003		-0.03		-0.02		
p trend	*0.73*		*0.002*		*0.03*		

[a] Adjusting for age in years (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other), and serum total cholesterol concentration (continuous)

[b] Beta for difference in ln serum hormone concentration per 100 μg/dL difference in serum α–tocopherol.

Cancer Causes Control. Author manuscript; available in PMC 2012 November 16.