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Relation of Vitamin E and Selenium Intakes to Prostate Cancer Risk by Smoking Status: A Review and Meta-Analysis

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Degree to be awarded: MPH

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Abstract

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By Yeunjung Kim

Both observational studies and clinical trials have investigated the association between antioxidants and prostate cancer risk. However, reports on the efficacy of antioxidants, namely selenium and vitamin E, in reducing the risk of prostate cancer have shown no clear benefit. It has been noted that smoking status may modify this effect of antioxidants through a variety of mechanisms. In this study, we performed a review of the literature and meta-analysis to examine the associations of vitamin E and selenium with prostate cancer in three groups of participants: never smokers, former smokers and non-smokers. In total, 20 studies met the inclusion criteria and provided necessary data. Summary analyses produced overall meta-relative risk (RR) estimates for vitamin E of 0.99 [95% confidence interval (CI), 0.90-1.09] in never smokers, 0.97 (95% CI, 0.90-1.04) in former smokers, and 0.94 (95% CI, 0.72-1.23) in current smokers. For selenium studies, overall meta-RRs were 1.09 (95% CI, 0.78-1.53), 0.63 (95% CI, 0.45-0.87) and 0.84 (95% CI, 0.57-1.25) for never former and current smokers, respectively. Most sensitivity analyses using subgroups of studies with different exposure assessment methods and outcome definitions produced null results that did not differ appreciably in smokers and non-smokers. The only possible exception is the analysis of studies that relied on serum selenium, which produced ORs (95% CIs) of 1.08 (0.75-1.56), 0.79 (0.65-0.95), and 0.75 (0.56-1.00), respectively, for never, former and current smokers. The interpretation of overall summary analyses is limited by small number of observations, varying definitions of smoking status, and methodological limitations of the available studies. Nevertheless, the findings for serum selenium are noteworthy and may require additional evaluation.

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INTRODUCTION

Prostate cancer is a major public health concern with more than 200,000 new cases diagnosed each year in the United States (Siegel et al., 2012). This corresponds to a lifetime risk estimate of 1 in 6 men (16.2%) and a lifetime probability of 1 in 33 men (3%) dying from the disease (Brawley, 2012). Today, it is estimated that nearly 2.8 million Americans live with a history of prostate cancer, making it the leading cancer in US men (Siegel et al., 2012). Although prostate cancer is rarely fatal within five years of diagnosis, particularly if the disease is localized, survivors experience many treatment complications that may compromise quality of life (Potosky et al., 2000; Siegel et al., 2012). Screening has done little to mitigate the problems in management of prostate cancer (Lumen et al., 2012). For all of the above reasons, preventive measures have been and are of great interest (Brawley, 2012).

The development of effective preventive measures requires understanding of disease causation. While several environmental and genetic risk factors for prostate cancer have been proposed in the literature, the list of established determinants of this disease is short and includes age, race/ethnicity and family history, all of which are not modifiable (Gupta-Elera, Garrett, Robison, & O'Neill, 2012; Thapa & Ghosh, 2012). One of the proposed underlying mechanisms of prostate carcinogenesis is oxidative stress (Gupta-Elera et al., 2012; Thapa & Ghosh, 2012). The most common sources of oxidative stress are reactive oxygen species (ROS), which are produced at increased and harmful concentrations within the cell in response to chemicals, various types of radiation, cigarette smoke, and certain dietary factors (Gupta-Elera et al., 2012; Mehraein-Ghomi, Basu, Church, Hoffmann, & Wilding, 2010). Chronic exposure to high levels ROS may overwhelm the antioxidant capacity of various tissues including prostate parenchyma, causing damage to multiple cellular components essential for cell development and homeostasis—ultimately leading to carcinogenesis (Thapa & Ghosh, 2012).

Limiting the exposure to ROS and stimulating antioxidant systems have been proposed as a possible way of reducing prostate cancer risk (Thapa & Ghosh, 2012). Two antioxidants – vitamin E and selenium have attracted particular attention as candidate preventive agents (Li et al., 2004; Tsavachidou et al., 2009).

Experimental biology studies demonstrate that selenium may induce apoptosis of damaged cells, inhibit proliferation, and protect cellular structures from peroxide damage (Griffin, 1979; Redman et al., 1997; Shamberger & Willis, 1971; Waters et al., 2003). Additional evidence comes from ecological studies, which have shown an inverse relation between selenium levels in the environment and cancer incidence (Clark, Cantor, & Allaway, 1991).

Vitamin E and its 8 subunits (4 tocopherols and 4 tocotrienols) act as free-radical scavengers, which inhibit lipid peroxidation and block the formation of carcinogens (Burton, Cheeseman, Doba, Ingold, & Slater, 1983; Traber, 1997). Vitamin E has been reported to play a protective role for many malignancies including cancers of the colon and rectum, lung and breast (Bostick et al., 1993; Longnecker et al., 1992; Menkes et al., 1986; Ratnasinghe et al., 2000; White, Shannon, & Patterson, 1997; Yong et al., 1997).

Both vitamin E and selenium have been examined as possible chemopreventive agents for prostate cancer in several observational studies and clinical trials. On balance the reports on the efficacy of these two agents in reducing the risk of prostate cancer have shown no clear benefit, with findings varying considerably across studies (Allen et al., 2008; Eichholzer, Stahelin, Ludin, & Bernasconi, 1999; Goodman, Schaffer, Bankson, Hughes, & Omenn, 2001; Hartman et al., 1998; Klein et al., 2011; Lippman et al., 2009; Nomura, Lee, Stemmermann, & Combs, 2000; Peters et al., 2008; Vogt et al., 2003).

It is important to emphasize that the effects of vitamin E and/or selenium may differ in populations with different levels of exposure to free radicals, such as in smokers and non-smokers (Bruno & Traber, 2005; Hakim et al., 2012). Evidence shows there may be a strong biological interaction between cigarette smoke and antioxidant levels (Bruno & Traber, 2005). Previous studies have shown the depletion of plasma levels of vitamin E, selenium, and other antioxidants in smokers compared to nonsmokers (Handelman, Packer, & Cross, 1996; Leonard et al., 2003; Munro, Burton, & Kelly, 1997).

Although several previous reviews examined the weight of evidence regarding the effects of vitamin E and selenium on prostate cancer risk (Hurst et al., 2012; Stratton & Godwin, 2011; Yang, Suh, & Kong, 2012), no studies examined the data by smoking status. To address this knowledge gap, the present review and meta-analysis will analyze published literature on the roles of vitamin E and selenium as possible prostate cancer prevention agents among current, former and never smokers.

MATERIALS AND METHODS

Criteria for inclusion in the study were as follows: 1) assessment of exposure to vitamin E and/or selenium in an observational setting or in a clinical trial; 2) data presented separately for current, former, or never smokers; 3) results presented as risk, odds, or hazard ratios with corresponding 95% confidence interval (CI) or data included in the article allowing calculation of these values. Results of ever smokers, which combines former and current smokers, or non-smokers, which combines never and former smokers, were not included in the meta-analysis because of the heterogeneity of these groups.

We searched electronic literature databases Pubmed, Ovid, and EMBASE for relevant journal articles published through March 2013 using multiple combinations of keywords such as *smoking, prostate cancer, vitamin E, and selenium*. Following electronic search, we examined the references listed in each study and extracted additional relevant articles using the same inclusion criteria. Two authors performed this process independently, and articles were consolidated into a single list.

The association of each antioxidant with prostate cancer risk was assessed in three groups of subjects: never smokers, former smokers, and current smokers. Data extracted from each study included the location and name of the study, author and date of publication, study design, exposure assessment (e.g., questionnaire or biomarker based measurement of vitamin E or its subunits), primary outcome, and risk ratio estimates (95% CI) for never, former, and current smokers (Tables 1a and 1b).

For the purposes of the meta-analysis, the main result of interest from each study was the relative risk (RR) or the odds ratio (OR) estimate along with the corresponding 95% confidence interval (CIs) presented according to the smoking category. The OR was assumed to arithmetically approximate the RR allowing a comparison between case control and cohort studies (Zhang & Yu, 1998).

When pooling the results to obtain meta-estimates, we used RRs or ORs comparing the highest and lowest levels of exposure. If a study did not provide an effect estimate, the appropriate contingency (e.g., 2-by-2) tables were constructed from the numbers provided in the article and the ORs or RRs and the corresponding 95% CIs were calculated using OpenEpi software (Dean A, 2007).

All results were summarized by constructing forest plots for each exposure interest and for each smoking category. A summary meta-RR estimate for association between the antioxidant under study and prostate cancer risk was also calculated for each smoking category. The meta-RRs were calculated as weighted averages of the individual study results based on inverse variances as the weights (Rothman KJ, 1998). The corresponding 95% CI and tests for heterogeneity were also recorded. The test for heterogeneity examines the hypothesis that the underlying effect estimates across studies are equal, and is based on the chi-square distribution as described by Fleiss and Gross (Fleiss & Gross, 1991). We also calculated the I^2 statistic, which gives the percentage of the total variation across studies due to heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). We considered I^2 values of 25%, 50%, and 75% as cutoffs for low, moderate, and high levels of heterogeneity, respectively. The main meta-analysis was followed by sub-analyses and sensitivity analyses based on various study characteristics. A sub- or sensitivity analysis was considered feasible if there were at least three studies of the same or similar type. All analyses were performed used using Episheet, a spreadsheet based analytical calculator (Andersson & Ahlbom, 2003) or MIX Pro 2.0 an add-on to Microsoft Excel statistical software package (BiostatXL).

RESULTS

Overview of the literature

A total of 34 studies examined the association of the two antioxidants of interest (vitamin E and selenium) with prostate cancer risk or mortality. Of those, 13 studies assessed the effects of selenium, and 22 studies focused on vitamin E. After exclusion of studies, in which data was not presented separately for current, former, or never smokers, 20 studies were available for analysis, consisting of 7 and 13 studies assessing selenium and vitamin E, respectively (Tables 1a and 1b).

Selenium studies were published between 1993 and 2008 involving patients from the United States, Finland, Netherlands, as well as from countries involved in the European prospective investigation into Cancer and Nutrition (EPIC) study, which included Denmark, Germany, Greece, Italy, Spain, Sweden, and the United Kingdom. Vitamin E studies were published between 1994 and 2009 with patients from the United States, Canada, Finland, and Switzerland. Most selenium studies used relied on nested case control design while a cohort design was more common in vitamin E studies. In addition, the meta-analyses for vitamin E included three clinical trials. The large clinical trial of selenium (Lippman et al., 2009) was not included because it did not present data by smoking status.

Meta analysis of selenium studies

A total of 7 selenium studies were included (Table 1a). Stratum specific data including the RR estimate and the associated 95% CI were available in 6 studies for current smokers, 4 studies for former smokers, and 5 studies for never smokers. Exposure characterization involved mostly serum or plasma measurement of selenium, usually divided into quartiles or quintiles. In addition, one study used toenail selenium levels to characterize exposure.

The results of meta-analyses are presented in Figures 1-3. For never smokers, the meta-RR estimate was 1.09, 95% CI 0.78-1.53, and the results were highly homogenous (p=0.909; I^2=0.00%) (Figure 2). The corresponding meta-RRs (95% CIs) for former and current smokers were 0.63 (0.45-0.87) and 0.84 (0.57-1.25), respectively (Figure 1 and 3). Analysis of heterogeneity indicated that the studies were in good agreement for former smokers (p=0.359; I^2=6.75%) but less so for current smokers (p=0.065; I^2=49.42%). Sensitivity analyses are presented on Table 2. For serum only studies, meta-RR estimate was 1.08 (95% CI: 0.75-1.56) for never smokers, 0.79 (95% CI: 0.65-0.95) for former smokers and 0.75 (95% CI; 0.56-1.00) for current smokers. The studies were homogeneous for current and former smokers and less so (p=0.10) for current smokers.

Meta analysis of vitamin E

The meta-analysis for vitamin E was based on 14 studies (Table 1b). The majority of observational studies relied on food frequency questionnaires to ascertain vitamin E intakes, although 4 studies tested patients' serum or plasma for vitamin E or its subunits (α-tocopherol or γ-tocopherol). In clinical trials, vitamin E interventions included supplementation of racemic α-tocopheryl acetate, or α-tocopherol.

As shown in Figures 4-6 for never smokers, meta-RR estimate was 0.99 (95% CI: 0.90-1.09) And the corresponding estimates meta-RRs (95% CIs) for former and current smokers were 0.97 (0.90-1.04) and 0.94 (0.72-1.23), respectively. Only for current smokers there was a significant heterogeneity across studies (p=0.008; I^2=63.31%).

Stratified and subanalyses were based on different methods of exposure characterization and different outcome definitions (Table 2). For advanced/extraprostatic cases, the meta-RR estimates (95% CIs) were 1.01 (0.68-1.50) for never smokers 1.01 (0.82-1.25) for former smokers and 0.75 (0.39-1.25) for current smokers. The results were in reasonable agreement in former smokers (p=0.363), less so in current smokers (p=0.06), and were significantly heterogeneous for never smokers (p=0.024). For localized cases of prostate cancer, the meta-RR (95% CI) for never smokers was 1.06 (0.90-1.25). The corresponding meta-RRs (95% CIs) were 0.90 (0.80-1.02) for former smokers and 1.30 (0.97-1.74) for current smokers. In the analyses of studies that relied on blood tocopherol levels, the results were generally comparable with the overall meta-analysis (Table 2).

DISCUSSION

In the past two decades, observational and clinical studies have investigated the use of antioxidants in decreasing prostate cancer risk (Thapa & Ghosh, 2012) . Mechanistically, targeting the source of carcinogenesis was a practical strategy, and early pre-clinical studies have supported the use of antioxidants as chemopreventive agents (ATBC, 1994; Duffield-Lillico et al., 2003). However, uncertainty regarding the ideal dose, the time of intervention, and the type of antioxidants required have presented considerable challenges for researchers. Recent randomized clinical trials have shown that antioxidant supplementation did not decrease the risk of prostate cancer and may even have an opposite effect (Chan et al., 1999; Gaziano et al., 2009; Klein et al., 2011; Lippman et al., 2009).

Nevertheless, late onset of prostate cancer provides an excellent opportunity for prevention, and clinical trials with 5α-reductase inhibitors have shown that this is feasible (Andriole et al., 2010; Thorpe et al., 2007) although effective androgen deprivation therapy (ADT) carries serious side effects including but not limited to osteoporosis, treatment-resistant prostate cancer, neurodegenerative and cardiovascular diseases (Feldman & Feldman, 2001; Jones, 2011; Taylor, Canfield, & Du, 2009). Moreover, the long-term effects of ADT in healthy men are unknown. Therefore, the hypothesized benefits of antioxidants and their presumed clinical safety make them a promising agent of primary prevention (Gupta-Elera et al., 2012).

Smoking is not an identified risk factor for prostate cancer. One meta-analysis of 24 cohort studies reported that current smokers had an increased risk of fatal prostate cancer (meta-RR 1.14, 95% CI 1.06-1.19) yet this effect was not statistically significant when looking at all prostate cancers (meta-RR 1.04, 95% CI 0.87-1.24) (Huncharek, Haddock, Reid, & Kupelnick, 2010).   Smoking status, however, is believed to cause significant decrease in the levels of antioxidants in the serum or plasma (Alberg, 2002; Bolton-Smith, Casey, Gey, Smith, & Tunstall-Pedoe, 1991; Bruno & Traber, 2005; Lloyd et al., 1983). It is hypothesized that smokers often require higher dietary α-tocopherol intake to maintain the same plasma levels as nonsmokers (Bruno & Traber, 2005; Church & Pryor, 1985). Due to the free radical content of cigarette smoke, the half-life of α-tocopherols is reduced, and its fractional disappearance rates are increased in smokers (Bruno & Traber, 2005). Ferritin reducing ability of plasma (FRAP), indicative of antioxidant capacity, is also greatly reduced in smokers (Bruno & Traber, 2005). Furthermore, tissues and other cell types experience depletion of antioxidants with smoking. One study of human subjects found that with age selenium content in the prostate decreases in smokers, while there is an increase in selenium content for nonsmokers with age (Schopfer, Drasch, & Schrauzer, 2010). Also, platelet and lymphocyte levels of α-tocopherol are significantly lower among smokers compared to nonsmokers (Jeanes, Hall, Proteggente, & Lodge, 2004). Similarly, selenium levels in whole blood, plasma, red blood cells are significantly lower in cigarette smokers compared to nonsmokers (Lloyd et al., 1983)

Our study is the first to perform meta-analyses for never, former, and current smokers in the association between antioxidants, vitamin E and/or selenium intakes, and prostate cancer risk. Although many studies have discussed the possibility of interaction by smoking status, reports have been inconclusive. On balance our results do not show that the effects of vitamin E or selenium on prostate cancer risk is appreciably modified by smoking. Nevertheless, in one specific sub-analysis in which selenium exposure was measured using serum levels, the risk appeared to be 20-25% lower in current and former smokers but did not differ in persons who never smoked.

A noticeable difference between selenium and vitamin E studies was exposure characterization. While most selenium studies measured serum or plasma levels of selenium intake, vitamin E intakes were ascertained by food frequency surveys in vitamin E studies. Although validated food frequency questionnaires serve as good correlates for actual vitamin E intake, in general, more objective measurements provide better estimation of exposure (Pietinen et al., 1988). For vitamin E studies, however, the difficulty may be due to inconclusive relationship between serum levels of vitamin E subunits and oral supplementation of vitamin E (Dietrich et al., 2003; Helzlsouer et al., 2000; Huang & Appel, 2003). Hence, the selenium studies may better reflect the true relationship between its intake and prostate cancer risk.

One of the limitations of our study is the small number of available articles that stratified results by smoking status. Another challenge in our analyses was the variable definitions of smoking status. In particular an accurate distinction between former and current smokers may be difficult without more detailed information.

Despite inconclusive evidence, many patients regularly take antioxidants including selenium and vitamin E in their daily multivitamins marketed "*for prostate health*" (Locke, Hersey, Margel, Sorokin, & Fleshner, 2013). Determining the benefits of such nutritional supplements, and identifying those who will likely benefit most will present valuable information in terms of preventive care, and in terms of understanding the mechanism of action of antioxidants.

In summary, the question of whether or not the effect of antioxidants on prostate cancer risk is modified by smoking remains unresolved. The current literature is limited by a small number of independent observations, varying definitions of smoking status, and methodological limitations. Nevertheless, the findings for serum selenium are noteworthy and may require additional evaluation.

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Table 1a: Selenium. Studies investigating selenium supplementation as prostate cancer prevention agents or selenium levels as a predictor of prostate cancer risk (measures of association either calculated from data in the original articles or from reported data).

Study name, location	Study population	Reference(s)	Study design	Comparison	Primary outcome	Strata definition	Smoking status-specific measure of association		
							Never RR estimate (95% CI)*	Former RR estimate (95% CI)*	Current RR estimate (95% CI)*
Beta-Carotene and Retinol Efficacy Trial (CARET), USA	235 prostate cancer cases and 456 matched controls ages 45-74 years of age with some history of smoking or asbestos exposure	Goodman et al. (2001)	Case control	Serum selenium levels, µg/dl (quartiles: 5.07-10.12, 10.13-11.25, 11.26-12.59, 12.60-21.96)*	Lung or prostate cancer	never/former, current	0.82 (.43-1.55)		1.38 (0.73-2.59)
Alpha-tocopherol and beta-carotene (ATBC) study, Finland	127 prostate cancer cases from 50 mg α-tocopherol, versus 190 prostate cancer cases from placebo group	Hartman et al.	Case cohort	Selenium (including supplements), µg/day (quartile: <71.52, 71.52-89.12, 89.13-111.05, >111.05)**	Prostate Cancer	all smokers	NA	NA	0.84 (0.43-1.67)
				placebo group: No α-tocopherol					1.27 (0.70-2.20)
				Selenium, µg/day (quartiles: <70.11, 70.11-85.63, 85.64-105.63, >105.64)**	Prostate Cancer	all smokers	NA	NA	0.72 (0.33-1.55)
				placebo group: No α-tocopherol					1.32 (0.70-2.47)
Honolulu Heart Program, USA	249 Hawaiian Japanese men who are diagnosed with prostate cancer during more than 20 years follow up and 249 matched controls	Nomura et al.	Case control	Serum selenium, ng/ml (quartiles: <119.3, 119.3<130.6, 130.6<147.2, ≥147.2)*	Prostate Cancer	nonsmoker, past, current	0.80 (0.40-1.90)	0.50 (0.20-1.10)	0.20 (0.10-0.80)
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), USA	724 incident prostate cancer cases and 879 matched control subjects from PLCO (29361 men followed up to 8 years)	Peters et al. (2007)	Nested case control	serum selenium, ng/ml (quartiles: 50.5<126.8, 126.8<141.9, 141.9<158, 158<253.0 ng/ml)*	Prostate Cancer	never, current/former	1.32 (0.72-2.40)	0.65 (0.44-0.97)	
European Prospective Investigation into Cancer and Nutrition (EPIC), European countries	959 men with incident prostate cancer and 1059 matched controls	Allen et al. (2008)	Nested case control	Plasma selenium, µg/l (quintiles: <62, 62.0-68.5, 68.6-75, 75.1-84.0, ≥84.1)*	Prostate cancer	current, former, never	1.06 (.58-1.94)	0.86 (.53-1.39)	0.82 (0.53-1.65)
Netherlands Cohort Study (NLCS), Netherlands	58,279 men 55-69 years of age with 6.3 years of follow up	Van den Brandt et al.	Case cohort	Toenail selenium level, µg/g (quintiles: <=0.467, 0.467 <=0.514, 0.514 <=0.560, 0.560 <=0.616, >0.616)*	Prostate cancer	never, former, current	1.19 (0.48-2.92)	0.46 (0.27-0.79)	0.97 (0.42-2.22)
Atlanta, GA; Detroit Michigan; New Jersey; USA	212 prostate cancer cases and 233 controls from white and black men between 40-79 years of age	Vogt et al.	Population based case control	Serum selenium, µg/ml (quartiles: <=0.119, 0.120-0.135, 0.136-0.150, ≥0.151)*	Prostate cancer	never, former, current	0.94 (0.31-2.84)	0.67 (0.25-1.78)	0.60 (0.20-1.85)

Table 1b: Vitamin E and/or lipophilic components (α, γ, β, δ tocopherol and α, γ ,β, δ tocotrienol). Studies investigating vitamin E (or its lipophilic components) supplementation as prostate cancer prevention agents or vitamin E (or its lipophilic component) levels as a predictor of prostate cancer risk (measures of association either calculated from data in the original articles or from reported data).

Study name, location	Study population	Reference(s)	Study Design	Comparison	Primary Outcome (definitions)	Strata definition	Smoking status-specific measure of association		
							Never RR estimate (95% CI)*	**Former** RR estimate (95% CI)*	**Current** RR estimate (95% CI)*
The Selenium and Vitamin E Cancer Prevention Trial (SELECT), USA, Canada, Puerto Rico	35,533 men 50 years or older (African American men) and 55 years or older (all other men) from 427 sites followed for 5.46 years	Lippman et al.	Clinical trial	Vitamin E (racemic α-tocopheryl acetate) vs. placebo	Prostate cancer	never, former/current	1.23 (1.03-1.48)	1.04 (0.87-1.25)	
Alpha-tocopherol and beta-carotene (ATBC) study, Finland	29133 male smokers 50-69 years of age followed up to 9 years	ATBC group (original study)	Clinical trial	α-tocopherol (50 mg) vs. placebo	Lung cancer (Secondary: prostate cancer)	all smokers			0.66 (0.51- 0.84)
				non-α-tocopherol (50 mg) vs. placebo					1.53 (1.19-1.96)+
"	"	Heinonen et al.	Clinical trial (follow-up)	α-tocopherol (50 mg) vs. placebo	Prostate cancer	"	NA	NA	0.64 (0.44-0.94)
				non-α-tocopherol (50 mg) vs. placebo					1.56 (1.06-2.28)+
"	100 incident prostate cancer cases and 200 matched controls randomly selected from ATBC	Weinstein et al. (2005)	Nested case-control	Serum α-tocopherol, mg/dl (tertiles: <1.260, 1.260-1.577, ≥1.578)**	Prostate Cancer	"	NA	NA	0.31 (0.09-1.10)
				non-α-tocopherol (50 mg) arm					0.63 (0.26-1.53)
				γ-tocopherol, mg/dl (tertiles: <0.076, 0.076-0.107, ≥0.108)**	Prostate Cancer	"			0.24 (0.08-0.76)
				non-α-tocopherol (50 mg) arm					0.85 (0.40-1.83)
	ATBC cohort from 1985-2004	Weinstein et al. (2007)	Cohort (follow-up)	Serum α-tocopherol, mg/l (quintiles: <9.33, 10.80-12.20, ≥14.17)	Prostate Cancer		NA	NA	0.80 (0.66-0.96)
					Advanced cases		NA	NA	0.56 (0.36-0.85)
"		Hartman et al.	Case-cohort	vitamin E (including supplements), mg/day (quartiles: <8.40, 8.41-11.25, 11.26-15.96, >15.96)**	Prostate Cancer	"	NA	NA	0.52 (0.29-0.95)
				non-α-tocopherol (50 mg) arm					1.19 (0.76-1.86)

				vitamin E, mg/day (quartiles: <8.17, 8.17-10.70, 10.71-14.44, >14.44)**	Prostate Cancer	"	NA		0.65 (0.36-1.18)
				non-α-tocopherol (50 mg) arm					1.26 (0.80-2.00)
				serum α-tocopherol, mg/l (quartiles: <9.78, 9.78-11.47, 11.48-13.60, >13.60)**	Prostate Cancer	"	NA	NA	0.76 (0.42-1.37)
				non-α-tocopherol (50 mg) arm					1.30 (0.82-2.07)
				α-tocopherol, mg/day (quartiles: <7.03, 7.03-9.21, 9.22-12.43, >12.43)**	Prostate Cancer	"	NA	NA	0.70 (0.44-1.31)
				non-α-tocopherol (50 mg) arm					1.30 (0.82-2.07)
				β-tocopherol, mg/day (quartiles: <0.54, 0.54-0.77, 0.78-1.09, >1.09)**	Prostate Cancer	"	NA	NA	0.81 (0.46-1.44)
				non-α-tocopherol (50 mg) arm					1.42 (0.90-2.25)
				γ-tocopherol, mg/day (quartiles: <3.00, 3.00-5.75, 5.76-11.02, >11.02) **	Prostate Cancer	"	NA	NA	0.56 (0.32-0.98)
				non-α-tocopherol (50 mg) arm					1.33 (0.88-1.99)
				δ-tocopherol, mg/day (quartiles: <0.36, 0.36-0.71, 0.72-2.32, >2.32)**	Prostate Cancer	"	NA	NA	0.70 (0.38-1.26)
				non-α-tocopherol (50 mg) arm					1.48 (0.99-2.22)
				α-tocotrienol, mg/day (quartiles: <1.30, 1.30-1.84, 1.85-2.53, >2.53)**	Prostate Cancer	"	NA	NA	1.04 (0.56-1.95)
				non-α-tocopherol (50 mg) arm					0.93 (0.57-1.52)
				β-tocotrienol mg/day (quartiles: <1.77, 1.77-2.41, 2.42-3.19, >3.19)**	Prostate Cancer	"	NA	NA	1.04 (0.55-1.97)
				non-α-tocopherol (50 mg) arm					1.08 (0.64-1.80)
				γ-tocotrienol mg/day (quartiles: <0.12, 0.12-0.20, 0.21-0.13, >0.31)**	Prostate Cancer	"	NA	NA	0.74 (0.42-1.29)
				non-α-tocopherol (50 mg) arm					1.17 (0.77-1.77)
				δ-tocotrienol, mg/day (quartiles: <0.02, 0.02-0.05, 0.06-0.11, >0.11)**	Prostate Cancer	"	NA	NA	0.72 (0.40-1.21)
				non-α-tocopherol (50 mg) arm					1.17 (0.78-1.77)
Physicians' Health Study II (PHS II), USA	14,641 male physicians aged 50 years or older, including 1307 men with a history of prior cancer followed for a mean of 8 years	Gaziano et al.	Clinical trial	vitamin E, 400IU every other day, vs. placebo	Prostate Cancer	never, former, current	0.98 (0.83-1.16)	0.92 (0.76-1.12)	1.50 (0.74-3.04)

Health Professionals Follow-up Study (HPFS), USA	47,780 male health professionals between 40-75 years of age without history of cancer (except nonmelanoma skin cancer)	Chan et al.	Cohort	Supplemental vitamin E, IU/day (0.1-15.0, 15.1-99.9, ≥100.0)*	Prostate cancer	never, quit (>=10years), current (quit within 10 years)	1.02 (0.86-1.21)	1.04 (0.86-1.26)	1.27 (0.97-1.66)
					Extraprostatic cases		1.45 (1.05-2.02)	1.15 (0.80-1.68)	1.00 (0.61-1.64)
					Metastatic/fatal cases		1.42 (0.87-2.32)	1.49 (0.82-2.69)	0.44 (0.18-1.07)
Cancer Prevention Study II (CPS-II) Nutrition Cohort, USA	72,704 men between 50-74 years of age from CPS-II nutrition cohort	Rodriguez et al.	Cohort	Supplemental vitamin E, IU/day (0, 1-31, 32 <400, ≥400)*	Prostate Cancer	current, former, never	0.95 (0.80-1.13)	1.02 (0.90-1.16)	0.87 (0.58-1.31)
National Institutes of Health (NIH) AARP Diet and Health Study, USA	295,344 men between 50-71 years of age, without history of cancer with 5 years of follow up	Wright et al.	Cohort	Supplemental vitamin E, IU/day (0, >0-399, 400-799, ≥800)*	All Prostate Cancer	current, former, never	1.04 (0.86-1.25)	0.91 (0.8-1.04)	1.15 (0.81-1.63)
					Localized cases		1.10 (0.91-1.34)	0.91 (0.79-1.05)	1.14 (0.78-1.67)
					Advanced cases		0.66 (0.38-1.17)	0.90 (0.64-1.26)	1.18 (0.49-2.89)
				γ-tocopherol, mg/day (tertiles: <11.5, 11.6-15.9, >15.9)*	All Prostate Cancer		0.97 (0.87-1.08)	0.95 (0.88-1.02)	1.17 (0.96-1.43)
					Localized cases		1.01 (0.90-1.13)	0.97 (0.89-1.06)	1.19 (0.96-1.47)
					Advanced cases		0.77 (0.58-1.02)	0.82 (0.67-1.00)	1.08 (0.66-1.00)
Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) screening Trial, USA	29361 men between 55-74 years of age without history of prosate, colon, lung cancer with 8 years of follow up	Kirsh et al.	Cohort	Supplemental vitamin E, IU/day (0, 0-30, >30-400, >400)*	All Prostate cancer	never, current/quit<10, former (quit >= 10 years)	1.05 (0.79-1.38)	0.93 (0.73-1.18)	0.78 (0.52-1.17)
					Nonadvanced cases		1.09 (0.75-1.59)	0.90 (0.64-1.25)	1.47 (0.87-2.47)
					Advanced cases		0.93 (0.65-1.40)	0.95 (0.65-1.40)	0.29 (0.12-0.68)
				vitamin E supplement use, years (quintiles: 0, >0-2, 3-4, 5-9, ≥10)*	All Prostate cancer	never, former (quit >=10 years), current/quit within past 10 years	0.87 (0.62-1.23)	0.85 (0.51-1.41)	0.85 (0.63-1.15)
					Advanced cases	"	1.11 (0.66-1.88)	0.30 (0.09-0.96)	0.93 (0.58-1.49)
					Nonadvanced cases	"	0.87 (0.54-1.40)	1.73 (0.95-3.15)	0.73 (0.47-1.14)

Basel, Switzerland	2974 healthy men from major chemical/pharmaceutical companies in Basel, Switzerland	Eichholzer et al.	Cohort	Plasma vitamin E, µmol/l (median: <30.02, ≥30.02)	All Prostate cancer mortality	nonsmoker and *light* smokers (<=5 cig/day), smokers	1.32 (0.42-4.00)+	NA	0.31 (0.12-0.79)+
					Excluding first 2 years of follow-u.8p	"	5.66 (0.88-36.34)	NA	0.05 (0.01-0.28)
Vitamins and lifestyle study (VITAL), Washington State	35,242 men between 50-76 years of age from western Washington State	Peters et al. (2008)	Cohort	supplemental intake vitamin E, IU/day (tertiles: 0-30, 30 <400, ≥400)*	All Prostate cancer	Never, former quit >=10), current/recent smokers (quit <10 years)	0.69 (0.43-1.10)	0.79 (0.53-1.20)	1.80 (0.84-3.70)
					Organ confined		0.77 (0.46-1.30)	0.84 (0.55-1.30)	1.80 (0.79-4.20)
					Advanced cases		0.17 (0.03-1.10)	0.47 (0.15-1.50)	1.50 (0.25-8.80)

*highest vs lowest; IU: international units; **highest versus lowest in intervention group; +calculated using available data

Table 2. Sensitivity Meta-Analyses.

Comparison	Smoking status-specific measure of association: Never Meta-RR estimate (95%CI)	Former Meta-RR estimate (95%CI)	Current Meta-RR estimate (95%CI)
Vitamin E (supplement)			
Advanced/extraprostatic cases (Chan et al., 1999; Kirsh et al., 2006; Peters et al., 2008; Wright et al., 2007)	1.01 (0.68-1.50)	1.01 (0.82-1.25)	0.70 (0.39-1.25)
P-heterogeneity	0.024	0.363	0.060
Localized cases (Kirsh et al., 2006; Peters et al., 2008; Wright et al., 2007)	1.06 (0.90-1.25)	0.90 (0.80-1.02)	1.30 (0.97-1.74)
P-heterogeneity	0.452	0.943	0.539
Vitamin E (subunit)			
α-tocopherol (serum/plasma) (Hartman et al., 1998; Weinstein et al., 2007; Weinstein et al., 2005)	NA	NA	0.83 (0.62-1.11)
P-heterogeneity	-	-	0.165
α-tocopherol (serum/plasma) (Eichholzer et al., 1999; Hartman et al., 1998; Weinstein et al., 2007; Weinstein et al., 2005)	NA	NA	0.74 (0.52-1.04)
P-heterogeneity	-	-	0.060
γ-tocopherol (All studies) (Hartman et al., 1998; Weinstein et al., 2005; Wright et al., 2007)	NA	NA	0.85 (0.56-1.29)
P-heterogeneity	-	-	0.008
Selenium			
Serum levels (Allen et al., 2008; Goodman et al., 2001; Nomura et al., 2000; Peters et al., 2008; Vogt et al., 2003)	1.08 (0.75-1.56)	0.79 (0.65-0.95)	0.75 (0.56-1.00)
P-heterogeneity	0.811	0.316	0.099

NA (not available); meta-RR estimates from highest vs lowest measure from appropriate measure of association from at least 3 values

Removed Goodman 2003, alpha toco serum levels statistically significant with ever smokers from Goodman)

Figure 1: Meta-analysis for selenium among former smokers

Study (year)	OR (95% CI)
Nomura et al. (2009)	0.5 (0.20-1.10)
Allen et al. (2008)	0.86 (0.53-1.39)
Van den Brandt et al. (2003)	0.46 (0.27-0.79)
Vogt et al. (2003)	0.67 (0.25-1.78)
Meta-result	0.63 (0.45-0.87)

P-heterogeneity = 0.359
I^2 = 6.75%

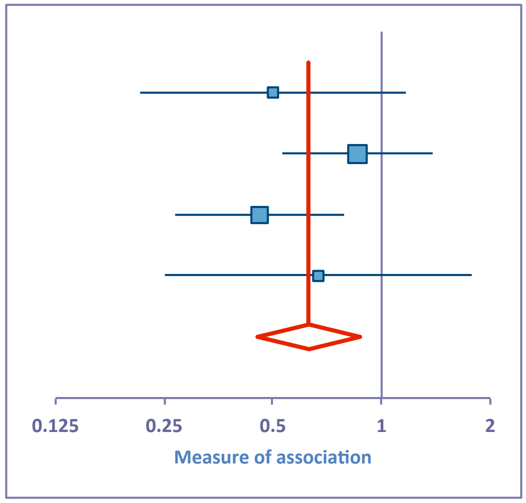

Figure 2: Meta-analysis for selenium among never smoker

Study (year)	OR (95% CI)
Nomura et al. (2009)	0.80 (0.20-1.10)
Peters et al. (2007)	1.32 (0.72-2.40)
Allen et al. (2008)	1.06 (0.58-1.94)
Van den Brandt et al. (2003)	1.19 (0.48-2.92)
Vogt et al. (2003)	0.94 (0.31-2.84)
Meta-result	1.09 (0.78-1.53)

P-heterogeneity = 0.909

I^2 = 0.00%

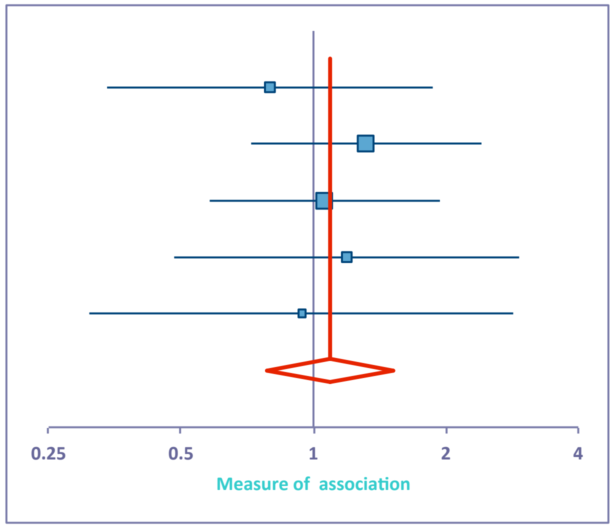

Figure 3: Meta-analysis for selenium among current smokers

Study (year)	OR (95% CI)
Goodman et al. (2001)	1.38 (0.73-2.59)
Hartman et al. -A (1998)	0.84 (0.43-1.67)
Hartman et al. -B (1998)	1.27 (0.70-2.20)
Nomura et al. (2009)	0.20 (0.10-0.80)
Allen et al. (2008)	0.82 (0.53-1.65)
Van den Brandt et al. (2003)	0.97 (0.42-2.22)
Vogt et al. (2003)	0.60 (0.20-1.85)
Meta-result	0.84 (0.57-1.25)

P-heterogeneity = 0.065
I^2 = 49.42%

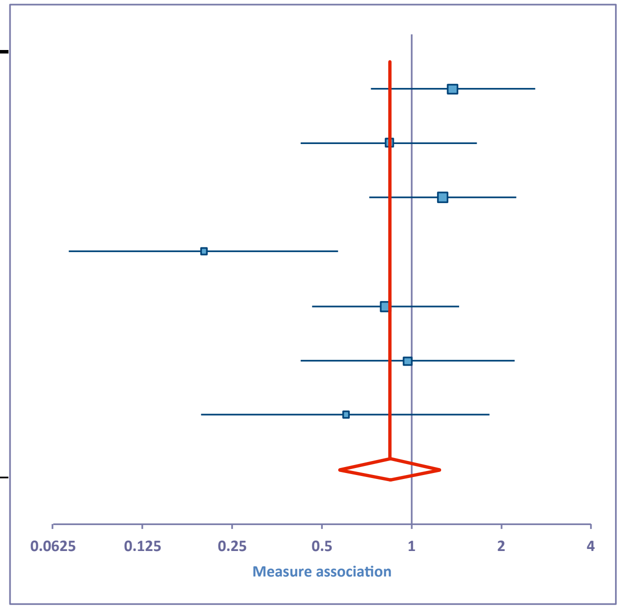

Figure 4: Meta-analysis for vitamin E among never smokers

Study (year)	OR (95% CI)
Chan et al. (1999)	1.02 (0.86-1.21)
Rodriguez et al. (2004)	0.95 (0.80-1.13)
Wright et al. (2007)	1.04 (0.86-1.25)
Kirsh et al. (2006)	1.05 (0.79-1.38)
Peters et al. (2008)	0.69 (0.43-1.10)
Meta-result	0.99 (0.90-1.09)

P-heterogeneity = 0.551
I^2 = 0.00%

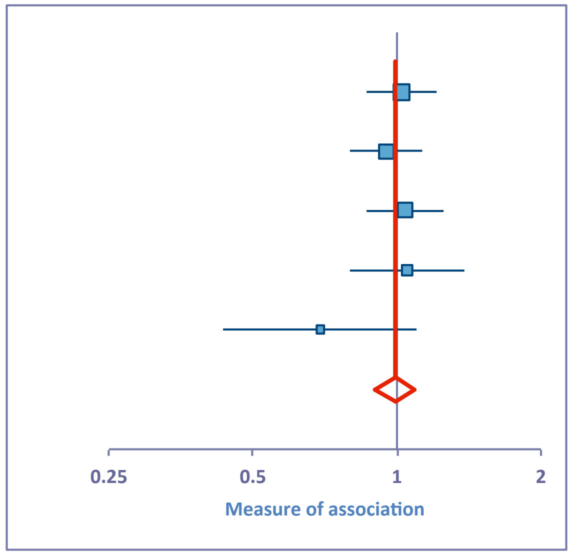

Figure 5: Meta-analysis for vitamin E among former smokers

Study (year)	OR (95% CI)
Chan et al. (1999)	1.04 (0.86-1.26)
Wright et al. (2007)	0.91 (0.80-1.04)
Rodriguez et al. (2004)	1.02 (0.90-1.16)
Kirsh et al. (2006)	0.93 (0.73-1.18)
Peters et al. (2008)	0.79 (0.53-1.20)
Meta-result	0.97 (0.90-1.04)

P-heterogeneity = 0.541
I^2 = 0.00%

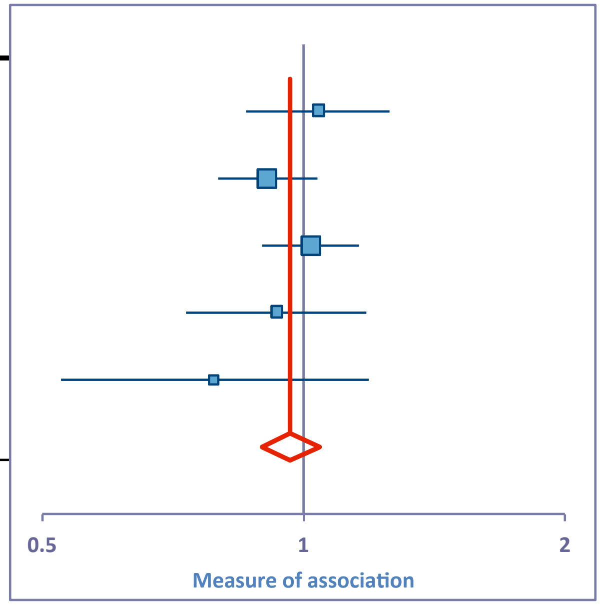

Figure 6: Meta-analysis for vitamin E among current smokers

Study (year)	OR (95% CI)
Hartman et al. -A (1998)	0.52 (0.29-0.95)
Hartman et al. -B (1998)	1.19 (0.76-1.86)
Chan et al. (1999)	1.27 (0.97-1.66)
Eichholzer et al. (1999)	0.31 (0.12-0.79)
Rodriguez et al. (2004)	0.87 (0.58-1.31)
Wright et al. (2007)	1.15 (0.81-1.63)
Peters et al. (2008)	1.80 (0.84-3.7)
Kirsh et al. (2006)	0.78 (0.52-1.17)
Meta-result	0.94 (0.72-1.23)

P-heterogeneity = 0.008
I^2 =63.31%