



Review

SELECT: the Selenium and Vitamin E Cancer Prevention Trial: rationale and design

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Prostate cancer is the commonest non-skin malignancy in the United States and has a substantial mortality rate despite the use of PSA-based screening. Furthermore, therapy for prostate cancer by surgery, radiotherapy or hormonal manipulation carries a significant risk of treatment-related morbidity. Recent analysis of secondary endpoints of several large-scale randomized prospective clinical trials for other malignancies has suggested that selenium or vitamin E may result in a decreased incidence and mortality from prostate cancer. *In vitro* and preclinical studies of these antioxidants support this hypothesis.

This review outlines the rationale and design of SELECT, the Selenium and Vitamin E Cancer Prevention Trial, designed to test the hypothesis that selenium or vitamin E alone or in combination can reduce the clinical incidence of prostate cancer in a population-based cohort of men at risk. SELECT is a phase III, randomized, double-blinded, prospective, 2 × 2 factorial clinical trial which will randomize 32,400 healthy men with normal DRE and serum PSA to one of four study arms: selenium alone, vitamin E alone, selenium + vitamin E, or placebo. Study agents will be taken orally for a minimum of 7 and maximum of 12 y with assessments of general health, incident prostate cancer and toxicity performed at 12 month intervals. Under the assumptions described, the detectable risk reduction is 25% for an effective single agent relative to placebo, with an additional 25% reduction for the combination relative to an effective single agent. The estimated power for the comparison of a single agent *vs* placebo is 96% and the power for the comparison of an effective single agent *vs* combination is 89%. Secondary endpoints will include prostate cancer-free survival, all-cause mortality, and the incidence and mortality of other cancers and diseases potentially impacted by the chronic use of selenium and vitamin E. Other trial objectives will include periodic quality of life assessments, assessment of serum micronutrient levels and prostate cancer risk, and studies of the evaluation of biological and genetic markers with the risk of prostate cancer. *Prostate Cancer and Prostatic Diseases* (2000) 3, 145–151.

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Introduction

Prostate cancer has been the most common visceral malignancy in US men for the last decade. The estimated lifetime risk of disease is 16.6% for Caucasians and 18.1% for African-Americans, with a lifetime risk of death of

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3.5% and 4.3%, respectively.¹ The dramatic increase in the number of cases and the steady increase in mortality from prostate cancer, which has only recently begun to decline, have peaked interest in developing ways of improving early diagnosis for institution of therapy at a more curable stage. Although PSA-based screening regimens have resulted in a substantial stage migration and greatly reduced the frequency of tumors which are metastatic at the time of diagnosis, there is no direct evidence that screening results in improved survival.^{2,3} Furthermore, the morbidity of various treatments remains substantial. An ideal method to reduce the mortality and morbidity of prostate cancer is through primary prevention, either by reducing the number of life-threatening, clinically evident cases or through a reduced age-dependent rate of disease development, ie the disease would become evident 5, 10 or 15 y later than it otherwise would occur.⁴

The recognition that the androgenic milieu is important in the development of prostate cancer led to the Prostate Cancer Prevention Trial (PCPT, SWOG-9217) with finasteride. The PCPT is an ongoing Phase III, double-blind, placebo-controlled, randomized trial to determine the efficacy of finasteride in reducing the period prevalence of prostate cancer. Finasteride is a testosterone analog that competitively inhibits the enzyme 5- α reductase (type 2) that converts testosterone to dihydrotestosterone (DHT) and causes a profound reduction in circulating and cellular DHT.⁵ Finasteride inhibits growth of prostate cancer cells *in vitro* and is an active preventive agent in certain animal models of prostate carcinogenesis.^{6,7} The PCPT opened in 1993 and easily exceeded the goal of 18,000 randomized men during a 3y accrual period, demonstrating broad public support for chemoprevention efforts to thwart this common malignancy.

Recent research suggests that selenium and vitamin E are promising candidates for prostate cancer prevention.⁸ Compelling data supporting the use of both agents in this setting come from secondary analyses of large-scale chemoprevention trials for other cancers.^{9,10} These analyses have suggested that selenium and vitamin E may prevent the development or progression of prostate cancer. SELECT, a Phase III randomized, double-blind, placebo-controlled, population-based clinical trial has been designed to test the efficacy of selenium and vitamin E alone and in combination in the prevention of prostate cancer. SELECT is funded by the National Cancer Institute and will be coordinated by the Southwest Oncology Group, with participation from major cooperative groups in North America, including ECOG, CALGB, NCCTG, RTOG, the Veterans Administration, and the Canadian Urologic Oncology Group. The trial is anticipated to open in the fourth quarter of 2000.

Rationale for study agents

Selenium

Selenium is a nonmetallic trace element recognized as a nutrient essential to human health. Its primary function was first elucidated in 1973 when it was identified as a component of glutathione peroxidase, an enzyme that protects against oxidative damage by catalyzing reduction of lipid hydroperoxides.^{11,12} Selenium is an essential

constituent of at least four extracellular and cellular glutathione peroxidases, three thyroidal and extra-thyroidal iodothyronine 5' deiodinases, thioredoxin reductase, and selenoproteins P (from plasma) and M (from muscle) whose functions are unknown. Typical dietary intake of selenium in the US is 80–120 $\mu\text{g}/\text{day}$, and the recommended dietary allowance is 0.87 $\mu\text{g}/\text{kg}$.¹³

Selenium is present in nature in both organic and inorganic forms. Foods contain both forms, predominantly as the amino acids selenomethionine and selenocysteine. The enteric absorption of selenomethionine is essentially complete, and the estimated whole body half-life is 252 days.¹⁴ Selenomethionine is metabolized by competition with the sulfur-containing analog methionine in protein synthesis or is catabolized to yield selenide, which is either used in the co-translational synthesis of selenocysteine or is methylated and excreted.

Selenium compounds can inhibit tumorigenesis in a variety of experimental models.¹⁵ Of the more than 100 reported studies in more than two dozen animal models that monitored tumor production and/or preneoplastic changes, two-thirds have shown reductions in tumor incidence in response to selenium supplementation. Although a few of the reports ($n = 4$) found that selenium treatment enhanced tumorigenesis, the preponderance of evidence indicates that high-level exposure to selenium compounds can be anti-tumorigenic. Data relating selenium specifically to prostate cancer in animals is limited, in part due to the paucity of valid model systems. Male rats pretreated with DMBA fed an antioxidant-rich diet that included selenium did not show a reduction in the incidence of prostate cancer compared to controls.¹⁶ Selenium has been shown, however, to inhibit the growth of DU-145 human prostate carcinoma cells *in vitro*.¹⁷

There are a number of potential mechanisms proposed for the anti-tumorigenic effects of selenium, and it is likely that many of them are operational. These include antioxidant effects, enhancement of immune function, induction of apoptosis, inhibition of cell proliferation, alteration of carcinogen metabolism, cytotoxicity of metabolites formed under high-selenium conditions, and an influence on testosterone production (Figure 1).^{18–24}

Antitumor Activity of Selenium

- Antitumorigenic in many laboratory models
- Inhibits growth *in vitro*
- Potential mechanisms
 - antioxidant effects
 - induction of apoptosis
 - inhibition of cell proliferation
 - metabolites cytotoxic

Figure 1 Antitumor activity of selenium

Human observational studies of selenium and prostate cancer. Epidemiologic evidence suggests that selenium status may be inversely related to the risk of at least some cancers.¹⁵ Data relating selenium status specifically to prostate cancer are limited but suggestive. Two small prospective studies in the United States have been reported in subjects with selenium values in the normal range.^{25,26} These studies hinted that a benefit could be achieved with higher selenium status, but very small sample sizes (11 and 13 cases, respectively) limit their interpretation. Another prospective study in Finland ($n = 51$) assessed the benefit of increasing serum selenium levels in individuals with very low initial levels and found that there was no association between selenium level and cancer risk.²⁷ A recent nested case-control study of selenium on advanced prostate cancer risk embedded in a prospective design included time-integrated assessment of selenium status by measurement in toenails, careful appraisal and control of other potential confounds, and the largest number of advanced prostate cancer cases ($n = 181$) studied to date.²⁸ The results suggest that the risk of advanced prostate cancer was reduced by one-half to two-thirds for men with the highest selenium status compared to those with the lowest status.

Data from controlled intervention trials of selenium. The real enthusiasm for selenium in the prevention of prostate cancer comes from the results of the clinical trial conducted by Clark *et al* in the US among individuals with low-to-normal selenium status.¹⁰ In this study, 1312 subjects with a prior history of skin cancer were randomized to receive 200 $\mu\text{g}/\text{day}$ of elemental selenium in the form of selenized yeast or placebo and followed for an average of 4.5 y for the development of basal or squamous cell carcinoma of the skin and other cancers. The study findings for the primary endpoint (non-melanoma skin cancer incidence reduction) were negative. Analysis of the data for secondary endpoints revealed that prostate cancer incidence was reduced by two-thirds among those in the selenium-supplemented group as compared to placebo group. Based on a small number of cases additional stratified analyses suggested a greater reduction in prostate cancer in those having low baseline selenium blood levels, those less than 65 y old, and those with low serum PSA values.²⁹

Vitamin E (α -tocopherol)

Vitamin E is a family of naturally occurring, essential, fat-soluble vitamin compounds. Its importance in mammalian biology was first revealed by earlier fertility research.³⁰ Vitamin E functions as the major lipid-soluble antioxidant in cell membranes; it is a chain-breaking, free-radical scavenger and inhibits lipid peroxidation, specifically biologic activity relevant to carcinogen-induced DNA damage.³¹

At least eight different tocopherols and tocotrienols have vitamin E biological activity, all sharing a common 6-hydroxychroman ring and long, saturated phytol side chain structure. The tocopherols (α -, β -, γ - and δ -) are characterized by a fully saturated phytol chain, while the

Antitumor Activity of Vitamin E

- Antitumorigenic in many laboratory models
- Inhibits prostate cancer in rat models
- Potential mechanisms
 - free radical scavenger/antioxidant
 - blocks nitrosamine synthesis
 - antiproliferative
 - inhibits fatty acid metabolism
 - inhibits prostaglandins

Figure 2 Antitumor activity of vitamin E.

tocotrienols represent the same α -, β -, γ - and δ -moieties but with three unsaturated chain bonds. The most active form of vitamin E is α -tocopherol; it is also among the most abundant and is widely distributed in nature and the predominant form in human tissues.^{32,33}

Alpha-tocopherol may influence the development of cancer through several mechanisms (Figure 2). It has a strong inherent potential for antioxidation of highly reactive and genotoxic electrophiles, such as hydroxyl, superoxide, lipid peroxy and hydroperoxy, and nitrogen radicals, thereby preventing propagation of free radical damage in biological membranes, and decreasing mutagenesis and carcinogenesis.³¹ Vitamin E also blocks nitrosamine formation. Alpha-tocopherol inhibits protein kinase-C activity and the proliferation of smooth muscle cells and melanoma cells, thus possibly affecting tumor growth or aggressiveness.³⁴⁻³⁷ Vitamin E also induces the detoxification enzyme NADPH: quinone reductase in cancer cell lines, and inhibits arachadonic acid and prostaglandin metabolism.^{38,39} Effects on hormones which can increase cellular oxidative stress and proliferative activity and on cell-mediated immunity have also been reported.³⁹

In vitro studies suggest that vitamin E can inhibit the growth of certain human cancer cell lines, including prostate, lung, melanoma, oral carcinoma and breast, while animal experiments show prevention of various chemically induced tumors, including hormonally mediated tumors.⁴⁰⁻⁴³ Similarly, vitamin E has been shown to slow the growth of prostate tumors *in vitro* and *in vivo* in rats receiving various doses of chemotherapeutic agents. In another study, vitamin E inhibited dietary-fat promoted growth of LNCaP xenografts in an athymic mouse model.⁴⁴

Vitamin E is present in small quantities in a wide range of foods, including vegetable oils, nuts, vegetables, milk fat and egg yolk. Vegetable oils and vegetable oil-containing products such as margarine, mayonnaise and shortening are the richest vitamin E sources in the US diet, followed by whole-wheat products and nuts.⁴⁵

Approximately 20–50% of dietary vitamin E is absorbed. Tissue levels vary considerably, with highest concentrations in platelets, the testis and prostate, adrenal and pituitary glands. The average dietary vitamin E intake among men and women in the US is estimated to be 10 and 7 mg/day, respectively.^{46,47} For dietary purposes, vitamin E activity is expressed as α -tocopherol equivalents; ie, biological effects equivalent to those from 1 mg of α -tocopherol. The recommended dietary allowance of the National Research Council is set at 10 mg for men and 8 mg for women daily.⁴⁸ The planned formulation for SELECT is synthetic dl- α -tocopheryl acetate, which encompasses the eight possible stereoisomers resulting from methyl group positioning at the 2', 4', and 8' asymmetric chroman carbon atoms. It is the same form used in the ATBC Study (discussed below) that resulted in a one-third reduction in prostate cancer incidence and a 41% reduction in prostate cancer mortality.⁹

Human observational studies of vitamin E and prostate cancer. Epidemiologic evidence for a protective effect for vitamin E in human cancer is growing but varies across cancer sites. In general, the case-control and cohort studies are most supportive of a protective role for vitamin E in lung and colorectal cancer, with some data also available for prostate cancer.

Observational studies are inconsistent with regard to a beneficial association between serum vitamin E and prostate cancer. These studies have assessed cancer risk through estimated dietary intake or through determination of plasma or serum α -tocopherol concentrations. Of the few prospective studies having a sufficient number of prostate cancers for analysis, two reported no dose-response association, and one reported a statistically significant protective association.^{49–52} The Basel Study of serum vitamin E among 2974 subjects over a 17 y follow-up period found low α -tocopherol to be associated with higher prostate cancer risk.⁵³ These studies share the observation of lower serum or plasma vitamin E concentrations among prostate cancer cases years prior to diagnosis compared to controls.^{50–53} In a trial-based cohort analysis, the associations between prostate cancer and baseline serum and dietary α -tocopherol differed significantly according to the α -tocopherol intervention status, with the suggestion of a protective effect for total vitamin E intake among those men who also received α -tocopherol supplementation.⁵⁴ One other case-control study reported no association between vitamin E intake and risk of prostate cancer.⁵⁵

Data from controlled intervention trials of α -tocopherol. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC) a large, randomized, double-blind, placebo-controlled trial of α -tocopherol (50 mg synthetic dl- α -tocopheryl acetate daily) and beta-carotene (20 mg daily, alone or in combination) reported a protective effect for vitamin E and prostate cancer among 29,133 male smokers aged 50–69 y at entry.^{9,57} During the median follow-up period of 6.1 y, there were 246 new cases of prostate cancer and 64 deaths from prostate cancer. Among those assigned to the α -tocopherol supplementation arm of the trial ($n = 14,564$), there were 99 incident prostate cancers compared with 147 cases among those assigned to the

non- α -tocopherol arm ($n = 14,569$).⁹ This represented a statistically significant 32% reduction in prostate cancer incidence (95% confidence interval, 12–47%; $P = 0.002$). The observed preventive effect appeared stronger in clinically evident cases (ie stages B–D) where the incidence was decreased 40% in subjects receiving α -tocopherol (95% confidence interval, –20% to –55%). Prostate cancer mortality data, though based on fewer events, suggested a similarly strong effect of 41% lower mortality (95% confidence interval, –1% to –64%). Alpha-tocopherol supplementation did not appear to affect survival time, although relatively few participants continued taking supplements after diagnosis. Although prostate cancer was prespecified as a *secondary* endpoint in this trial, these findings suggest a potentially substantial benefit of α -tocopherol in reducing the risk prostate cancer.

In summary, the available data from controlled intervention trials, human observational studies, and preclinical models strongly support the testing of selenium and vitamin E as chemopreventative agents in prostate cancer.

SELECT study design

SELECT is a Phase III, double-blind, placebo-controlled, 2 × 2 factorial study (Table 1) of selenium and vitamin E alone and in combination in 32,400 healthy men with a digital rectal examination (DRE) not suspicious for cancer and a serum prostate specific antigen (PSA) ≤ 4 ng/ml (Table 2). Age eligibility is 55 y for Caucasians and 50 y for African-Americans, since African-Americans aged 50–55 have comparable prostate cancer incidence rates to Caucasians aged 55–60. Randomized men will be equally distributed among four study arms (Table 1). Intervention will consist of a daily oral dose of study medication and/or matched placebo according to the randomization (Table 3). Study duration will be 12 y, with a 5 y uniform accrual period and a minimum of 7 and maximum of 12 y of intervention depending on the time of randomization.

Table 1 2 × 2 factorial study design

Selenium + vitamin E	Selenium + placebo
Vitamin E + placebo	Placebo + placebo

Table 2 Eligibility criteria

- Age
 - ≥ 55 y for Caucasians
 - ≥ 50 y for African-Americans
- SWOG performance status = 0
- DRE not suspicious for prostate cancer
- Total serum PSA ≤ 4.0 ng/ml
- No prior history of prostate cancer or high-grade prostatic intraepithelial neoplasia (PIN)
- No anticoagulation therapy
- Normal blood pressure
- Willing to restrict supplementation of selenium and vitamin E during participation

Table 3 Treatment doses and schedule

Agents	Dose	Route	Frequency	Duration
Selenium + matched vitamin E placebo	200 µg/1 capsule +	p.o.	qd	7-12y
Vitamin E + matched selenium placebo	1 capsule +			
Selenium + vitamin E	400 mg/1 capsule +	p.o.	qd	7-12y
Matched selenium placebo + matched vitamin E placebo	1 capsule +			
	200 µg/1 capsule +	p.o.	qd	7-12y
	400 mg/1 capsule +			
	1 capsule +	p.o.	qd	7-12y
	1 capsule			

p.o. = orally.
qd = daily.

Study endpoints

The primary endpoint for the trial is the clinical incidence of prostate cancer as determined by a recommended routine clinical diagnostic work-up, including yearly DRE and serum PSA level. A centrally reviewed histologic diagnosis of prostate cancer will be required in all cases, except for those based on a total PSA > 50 ng/ml and a positive bone scan. Prostate biopsy will be performed at the discretion of study physicians according to local community standards. The study protocol recommends biopsy for study participants who have a DRE suspicious for cancer and/or for elevations in serum PSA. Unlike the PCPT, no biopsy will be required at the end of SELECT.

Secondary endpoints will include prostate cancer-free survival, all-cause mortality, and the incidence and mortality of other cancers and diseases potentially impacted

Table 4 Study endpoints

• Primary	Incident prostate cancer as determined by routine clinical care
• Secondary	Prostate cancer-free survival
	Overall survival
	Incidence and survival
	All cancers
	Lung cancer
	Colorectal cancer
	Serious cardiovascular events
• Other	Quality of life measures
	Molecular epidemiology
	Dietary nutrient assessment
	Biomarker studies

Table 5 Power calculations

Comparison	Baseline hazard (incidence)	Relative risk reduction	Power
Single agent vs placebo	PCPT/SEER	25%	96%
Placebo vs combination	PCPT/SEER	44%	> 99%
Effective single agent vs combination	0.75 × PCPT/SEER	25%	89%

PCPT = Prostate Cancer Prevention Trial, SEER = Surveillance, Epidemiology, and End Results.

by the chronic use of selenium and vitamin E (Table 4). Other trial objectives will include periodic quality of life assessments, assessment of serum micronutrient levels and prostate cancer risk, and studies of the evaluation of biological and genetic markers with the risk of prostate cancer.

Statistical considerations

Sample size calculation

The primary analysis of the study includes five pre-specified comparisons:

- vitamin E vs placebo;
- selenium vs placebo;
- combination (vitamin E + selenium) vs placebo;
- combination vs vitamin E;
- combination vs selenium.

Based on the reported secondary analyses of the ATBC and Nutritional Prevention of Cancer studies showing approximately one-third and two-thirds reductions in prostate-cancer incidence achieved by vitamin E and selenium, respectively, the target risk reduction (intervention effect) has been conservatively estimated. For the factorial design, the detectable risk reduction is 25% for an effective single agent relative to placebo, with an additional 25% reduction for the combination relative to an effective single agent. Under the null hypothesis, there will be no difference in prostate cancer incidence between the specified intervention and placebo (relative risk = 1.0). The alternative hypothesis is that the incidence of prostate cancer will be reduced by 25% or more for a single agent vs placebo or for the combination vs an effective single agent (relative risk 0.75).

The study allows for the potential interaction between vitamin E and selenium, and additional analyses will include tests for the main effects (vitamin E vs no vitamin E and selenium vs no selenium) and for interactions.

The overall α level for the study is 5% (two-sided). Each of the five pre-specified comparisons will be tested at the 1% level to maintain an overall 5% level for the study. With a sample size of 32,400, the estimated power for the comparison of a single agent vs placebo is 96% and the power for the comparison of an effective single agent vs combination is 89% (Table 5). The underlying assumptions used to derive this sample size and power are based on study duration, prostate cancer incidence, drop-in rate, medication rate and competing risks (cumulative loss to death and lost to follow-up), all of which are discussed below.

Under the assumptions outlined below, the effective relative risk of 0.75 translates to a relative risk of 0.58

under conditions of perfect compliance. The median time under observation is estimated to be 8.8 y.

Incidence rate

Based on PCPT, expectations are that participants will average 63 y of age at study entry. Baseline hazard rates of prostate cancer for men on placebo are given by PCPT rates for years 0–3 and SEER 1991–1995 rates for men age 63 + *s* (*s* = subject time in years since randomization) for all races combined for years 4–12. The yearly prostate cancer incidence figures (PCPT/SEER rates) used in the sample-size calculations begin at 0% at randomization, reach 0.14% at year 1, and rise steadily to 1.36% 12 y later.

With 8100 participants randomized to each of four arms, the number of prostate cancer cases expected under the alternative hypothesis is listed in Table 6.

Medication rate

Medication rate is an estimate of participant adherence while assigned to study agents. It is quantified as the percentage of full active drug dose taken by men in the specified arm. It is assumed that the medication rate will vary over time, with a decline from 100% after randomization to 51% at the end of 12 y of treatment. These estimates are based on off-treatment rates of the PCPT for the first 4 y of the study and with extrapolation of the rate in the 4th year to year 12. These are conservative estimates, and the SELECT medication rates may be higher than in PCPT since finasteride has more side-effects than those known for selenium or vitamin E at the doses chosen for SELECT.

Drop-in rate

The drop-in rate for placebo subjects to active medication is assumed to be constant at 10% for the 12 y of treatment. Recent Heart Outcomes Prevention Evaluation (HOPE) data support this estimate.⁵⁷ A drop-in rate of 15% reduces the power to 92% for the comparison of placebo to either single agent and 82% for an effective single agent vs the combination.

Competing risks—death and loss

The cumulative competing risk is defined to be the estimated cumulative all-cause mortality rate plus the cumulative lost-to-follow-up (LTFU) rate. The mortality rates used were taken from PCPT for the first 4 y of

treatment and then adjusted upwards to the 1995 US rates for all races. The LTFU rate was calculated to be 0.05% per year. The cumulative loss (death + LTFU) is expected to be 0.8% at the end of the first year of the study and 33.2% by the end of year 12.

Other factors

No lag time to agent effectiveness is posited; such a lag time would have little effect on power because we are assuming a very low prostate cancer incidence rate in the first 2 y of the study.

In contrast to finasteride, it is assumed that the drugs being tested in SELECT do not affect PSA or prostate size, either of which could bias the diagnosis of prostate cancer. PSA levels at baseline and after 2 y of vitamin E use were analyzed on a subsample of participants from the HOPE trial and after 3 y in the ATBC study.^{9,57} There was no evidence of an effect on the PSA concentrations in these studies.

Sample size estimates are for the primary endpoint only. No adjustments have been made for multiple outcomes, such as incidence of and death from other cancers, cardiovascular deaths, or prostate cancer-specific survival.

Summary

Ample evidence exists from preclinical studies, epidemiologic observations, and controlled and uncontrolled clinical trials that selenium and vitamin E may prevent the development or progression of prostate cancer. SELECT is a large-scale, population-based, randomized controlled trial which will directly test the effect of these agents alone and in combination on the incidence of prostate cancer in North American males.

References

- Ries LAG et al (eds). *SEER Cancer Statistics Review, 1973–1995*. National Cancer Institute: Bethesda, MD, 1998.
- Catalona WJ et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *New Engl J Med* 1991; 324: 1156.
- Chodak GW et al. Results from two prostate cancer screening programs. *JAMA* (in press).
- Mishina T et al. Epidemiological study of prostatic cancer by matched-pair analysis. *Prostate* 1985; 6: 423.
- Russell DW, Wilson JD. Steroid 5-alpha-reductase: two genes/two enzymes. *A Rev Biochem* 1994; 63: 25–61.
- Thompson IM, Coltman CA Jr, Crowley J. Chemoprevention of prostate cancer: the Prostate Cancer Prevention Trial. *Prostate* 1997; 33: 217–221.
- Tsukamoto S et al. A five-alpha reductase inhibitor or an anti-androgen prevents the progression of microscopic prostate carcinoma to macroscopic carcinoma in rats. *Cancer* 1998; 82: 531–537.
- Marnett LJ. Peroxyl free radicals: potential mediators of tumor initiation and promotion. *Carcinogenesis* 1987; 8: 1365–1373.
- Heinonen OP et al. Prostate cancer and supplementation with α -tocopherol and β -carotene: incidence and mortality in a controlled trial. *JNCI* 1998; 90: 440–446.

Table 6 Expected incidence of prostate cancer in each arm under the alternative hypothesis

	Number at risk	Proportion with prostate cancer	Number with prostate cancer
Placebo	8100	0.066	533
Vitamin E	8100	0.050	403
Selenium	8100	0.050	403
Vitamin E + selenium	8100	0.038	304

- 10 Clark LC *et al.* Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA* 1996; 276: 1957-1963.
- 11 Rotruck JT *et al.* Selenium: biochemical role as a component of glutathione peroxidase. *Science* 1973; 179: 588-590.
- 12 Medina D. Mechanisms of selenium inhibition of tumorigenesis. *Adv Exp Med Biol* 1986; 206: 465-472.
- 13 National Academy of Sciences. *Recommended Dietary Allowances*, 10th edn. National Academy Press: Washington, DC, 1989, pp 217-224.
- 14 Swanson CA *et al.* Human [74Se]selenomethionine metabolism: a kinetic model. *Am J Clin Nutr* 1991; 54: 917-926.
- 15 Combs GF Jr, Clark LC. Selenium and cancer. In: Garewal H (ed). *Antioxidants and Disease Prevention*. CRC Press: New York, 1997.
- 16 Nakamura A *et al.* Lack of modification by naturally occurring antioxidants of 3,2'-dimethyl-4-aminobiphenyl-initiated rate prostate carcinogenesis. *Cancer Lett* 1991; 58: 241-246.
- 17 Webber MM, Perez-Ripoli EA, James GT. Inhibitory effects of selenium on the growth of DU-145 human prostate carcinoma cells *in vitro*. *Biochem Biophys Res Commun* 1985; 130: 603-609.
- 18 Ip C, Medina D. Current concept of selenium and mammary tumorigenesis. In: Medina D, Kidwell W, Heppner G, Anderson EP (eds). *Cellular and Molecular Biology of Breast Cancer*. Plenum Press: New York, 1987, p 479.
- 19 Kiremidjian-Schumacher L, Stotzky G. Review: selenium and immune response. *Environ Res* 1987; 42: 277-303.
- 20 Thompson HJ *et al.* Comparison of the effects of an organic and an inorganic form of selenium on a mammary carcinoma cell line. *Carcinogenesis* 1994; 15: 183-186.
- 21 Redman C *et al.* Inhibitory effect of selenomethionine on the growth of three selected human tumor cell lines. *Cancer Lett* 1998; 125: 103-110.
- 22 Shimada T *et al.* Inhibition of human cytochrome P450-catalyzed oxidations of xenobiotics and procarcinogens by synthetic organo-selenium compounds. *Cancer Res* 1997; 57: 4757-4764.
- 23 El-Bayoumy K. The role of selenium in cancer prevention. In: DeVita VT, Hellman S, Rosenberg SS (eds). *Practice of Oncology*. Lippincott: Philadelphia, 1991, p 1-15.
- 24 Bedwal RS, Nair N, Sharma MP, Mathur RS. Selenium—its biological perspectives. *Med Hypotheses* 1993; 41: 150-159.
- 25 Willett WC *et al.* Prediagnostic serum selenium and risk of cancer. *Lancet* 1983; 2: 130-134.
- 26 Coates RJ *et al.* Serum levels of selenium and retinol and the subsequent risk of cancer. *Am J Epidemiol* 1988; 128: 515-523.
- 27 Knekt P *et al.* Serum selenium and subsequent risk of cancer among Finnish men and women. *J Natl Cancer Inst* 1990; 82: 864-868.
- 28 Yoshizawa K *et al.* Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst* 1998; 90: 1219-1224.
- 29 Clark LC *et al.* Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol* 1998; 81: 730-734.
- 30 Evans HM, Bishop KS. On the existence of a hitherto unrecognized dietary factor essential for reproduction. *Science* 1922; 56: 650-651.
- 31 Burton GW, Ingold KU. Autoxidation of biological molecules. 1. The antioxidant activity of vitamin E and related chain-breaking phenolic antioxidants *in vitro*. *J Am Chem Soc* 1981; 103: 6472.
- 32 Machlin LJ. Vitamin E. In: Machlin LJ (ed). *Handbook of Vitamins*, 2nd edn. Marcel Dekker: New York, 1991.
- 33 Pappas AM. Vitamin E: tocopherols and tocotrienols. In: Pappas AM (ed). *Antioxidant Status, Diet, Nutrition, and Health*, CRC: Boca Raton, FL, 1998.
- 34 Azzi A *et al.* Vitamin E: a sensor and an information transducer of the cell oxidation state. *Am J Clin Nutr* 1995; 62: 1337s-1346s.
- 35 Mahoney CW, Azzi A. Vitamin E inhibits protein kinase C activity. *Biochem Biophys Res Commun* 1988; 154: 694-697.
- 36 Ottino P, Duncan JR. Effect of alpha-tocopherol succinate on free radical and lipid peroxidation levels in BL6 melanoma cells. *Free Radic Biol Med* 1997; 22: 1145-1151.
- 37 Chatelain E *et al.* Inhibition of smooth muscle cell proliferation and protein kinase C activity by tocopherols and tocotrienols. *Biochim Biophys Acta* 1993; 1176: 83-89.
- 38 Wang W, Higuchi CM. Induction of NAD(P)H:quinone reductase by vitamins A, E and C in Colo205 colon cancer cells. *Cancer Lett* 1995; 98: 63-69.
- 39 Traber MG, Packer L. Vitamin E: beyond antioxidant function. *Am J Clin Nutr* 1995; 62: 1501s-1509s.
- 40 Israel K, Sanders BG, Kline K. RRR-alpha-tocopheryl succinate inhibits the proliferation of human prostatic tumor cells with defective cell cycle/differentiation pathways. *Nutr Cancer* 1995; 24: 161-169.
- 41 Kishimoto M *et al.* The inhibitory effect of vitamin E on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis in mice based on the regulation of polyamine metabolism. *Cancer Lett* 1998; 24: 173-178.
- 42 Sigounas G, Anagnostou A, Steiner M. DL-Alpha-tocopherol induces apoptosis in erythroleukemia, prostate, and breast cancer cells. *Nutr Cancer* 1997; 28: 30-35.
- 43 Umeda F, Kato K-I, Muta K, Ibayashi H. Effect of vitamin E on function of pituitary-gonadal axis in male rats and human studies. *Endocrin Japon* 1982; 29: 287-292.
- 44 Fleshner N, Fair WR, Huryk R, Heston WD. Vitamin E inhibits the high-fat diet promoted growth of established human prostate LNCaP tumors in nude mice. *J Urol* 1999; 161: 1651-1654.
- 45 Bauernfeind J. Tocopherols in foods. In: Machlin LJ ed. *Vitamin E: a Comprehensive Treatise*. Marcel Dekker: New York, 1980.
- 46 USDA (US Department of Agriculture). *Nationwide Food Consumption Survey Continuing Survey of Food Intake by Individuals: Women 19-50 Years and their Children 1-5 Years, 4 Days, 1985*, report no. 85-4, Nutrition and Monitoring Division, Human Nutrition Information Economic research Service, US Department of Agriculture: Hyattsville, MD, 1987.
- 47 USDA (US Department of Agriculture). *Nationwide Food Consumption Survey Continuing Survey of Food Intake by Individuals: Men 19-50 Years 1 Day, 1985*, report no. 85-3, Nutrition and Monitoring Division, Human Nutrition Information Economic research Service, US Department of Agriculture: Hyattsville, MD, 1987.
- 48 National Research Council (NRC). *Recommended Dietary Allowances*, 10th edn. National Academy Press, Washington, DC, 1989.
- 49 Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States. *J Natl Cancer Inst* 1981; 66: 1192-1308.
- 50 Comstock GW, Helzlsouer KJ, Bush TL. Prediagnostic serum levels of carotenoids and vitamin E as related to subsequent cancer in Washington County, Maryland. *Am J Clin Nutr* 1991; 53: 260S-264S.
- 51 Knekt P *et al.* Serum vitamin E and risk of cancer among Finnish men during a 10-year follow-up. *Am J Epidemiol* 1988; 127: 28-41.
- 52 Hsing AW, Comstock GW, Abbey H, Polk BF. Serologic precursors of cancer: retinol, carotenoids, and tocopherol and risk of prostate cancer. *JNCI* 1990; 82: 941-966.
- 53 Eichholzer M *et al.* Prediction of male cancer mortality by plasma levels of interacting vitamins: 17-year follow-up of the prospective Basel study. *Int J Cancer* 1996; 55: 145-150.
- 54 Hartman TJ *et al.* The association between baseline vitamin E, selenium, and prostate cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Cancer Epidemiol Biomarkers Prev* 1998; 7: 335-340.
- 55 Rohan TE *et al.* Dietary factors and risk of prostate cancer: a case-control study in Ontario, Canada. *Cancer Causes Control* 1995; 6: 145-154.
- 56 The ATBC Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *New Engl J Med* 1994; 330: 1029-1035.
- 57 Yusuf S *et al.* Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *New Engl J Med* 2000; 342: 145-153.