

Seminar article

SELECT: the selenium and vitamin E cancer prevention trial

Eric A. Klein^{a,*}, Ian M. Thompson^b, Scott M. Lippman^c, Phyllis J. Goodman^d,
Demetrius Albanes^e, Philip R. Taylor^e, Charles Coltman^f

^a Section of Urologic Oncology, Department of Urology, Cleveland Clinic Foundation, Cleveland, OH, USA

^b Division of Urology, University of Texas Health Sciences Center, San Antonio, TX, USA

^c Department of Clinical Cancer Prevention, M.D. Anderson Cancer Center, Houston, TX, USA

^d Southwest Oncology Group Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

^e Cancer Prevention Studies Branch, Division of Clinical Sciences, National Cancer Institute, Washington, DC, USA

^f Southwest Oncology Group, San Antonio, TX, USA

Abstract

Purpose: Growing evidence suggests that both selenium and vitamin E may reduce the risk of prostate cancer. SELECT is a randomized, prospective, double-blind study designed to determine if selenium and vitamin E can reduce the risk of prostate cancer among healthy men. **Materials and methods:** The preclinical and epidemiologic evidence regarding chemoprevention with selenium and vitamin E were reviewed. Secondary analyses from randomized trials of both agents were included in the analysis. Data from these analyses as well as evidence from the Prostate Cancer Prevention Trial were used to develop the schema of SELECT. **Results:** Preclinical, epidemiologic, and Phase III data suggest that both selenium and vitamin E have potential efficacy in prostate cancer prevention. The experience of the Prostate Cancer Prevention Trial and the rapid accrual of SELECT during its first year demonstrate the interest and dedication of healthy men to long-term studies of cancer prevention. A total of 32,400 men are planned to be randomized in SELECT. **Conclusions:** SELECT is the second large-scale study of chemoprevention for prostate cancer. Enrollment began in 2001 with final results anticipated in 2013. © 2003 Elsevier Science Inc. All rights reserved.

Keywords: Prostate cancer; Chemoprevention; Selenium; Vitamin E

1. Introduction

Prostate cancer has been the most common visceral malignancy in U.S. 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 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 preventing disease occurrence.

Chemoprevention of prostate cancer is based on an understanding of the underlying molecular events which lead to neoplastic growth, leading to opportunities for both primary and secondary prevention (Figs. 1 and 2). A number of

hypotheses regarding the pathogenesis of prostate cancer has lead to several large clinical trials with oral agents meant to prevent its development. The Prostate Cancer Prevention Trial (PCPT), the first population-based prostate prevention study, was based on the hypothesis that inhibition of a specific enzymatic reaction (the blocking of 5- α -reductase by finasteride) could prevent androgen-driven prostate cell growth and development into cancer. The PCPT opened in 1993 and easily exceeded the goal of 18,000 randomized men during a 3-year accrual period. Final results of this trial are expected in 2003, when end-of-study biopsies will be completed. Recent research suggests that selenium and vitamin E are promising candidates for prostate cancer prevention, based primarily on secondary analyses of large-scale chemoprevention trials for other cancers [2,3]. SELECT, the Selenium and Vitamin E Cancer Prevention Trial, is based on the presumed antioxidant and anticancer properties of these agents that inhibit specific cellular processes in the development of cancer. SELECT is

* Corresponding author. Tel.: +1-216-444-5591; Fax: +1-216-445-3532.

E-mail address: kleine@ccf.org (E.A. Klein).

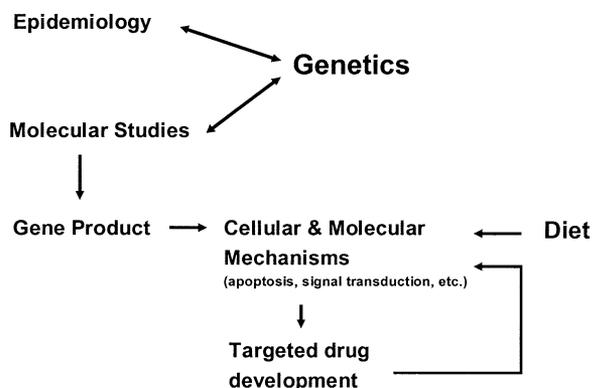


Fig. 1. Overview of chemoprevention.

an intergroup phase III, randomized, double-blind, placebo-controlled, population-based trial designed to test the efficacy of selenium and vitamin E alone and in combination in the prevention of prostate cancer.

2. Rationale for study agents

2.1. Selenium

Selenium is a nonmetallic trace element recognized as a nutrient essential to human health. Selenium is an essential constituent of at least 4 extracellular and cellular glutathione peroxidases, 3 thyroidal and extrathyroidal iodothyronine 5'-deiodinases, thioredoxin reductase, and other selenoproteins. Typical dietary intake of selenium in the U.S. is 80–120 $\mu\text{g}/\text{day}$, and the recommended dietary allowance is 0.87 $\mu\text{g}/\text{kg}$ [4].

Selenium inhibits tumorigenesis in a variety of experimental models [5]. Of the more than 100 reported studies in more than two dozen animal models, two thirds have shown reductions in tumor incidence in response to selenium supplementation [6,7]. There are a number of potential mechanisms proposed for the antitumorigenic effects of selenium, including 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 [8–14].

Epidemiologic evidence in humans also suggests that selenium status may be inversely related to the risk of at least some cancers, including prostate cancer [5]. A recent nested case-control study found that the risk of advanced prostate cancer was reduced by one half to two thirds for men with the highest selenium status [15]. Two large, randomized trials have reported findings, suggesting that selenium supplementation can reduce overall cancer mortality and mortality from stomach and esophageal cancers in China [16,17]. Recent enthusiasm for selenium in the prevention of prostate cancer arose after publication of results

of the clinical trial conducted by Clark et al. [3]. 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 years for the development of basal or squamous cell carcinoma of the skin and other cancers. While no difference was noted in rates of skin cancer further analysis found that prostate cancer incidence was reduced by two thirds among those in the selenium supplemented 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 years old, and those with low serum PSA values [18]. There also were significant reductions in lung and colon cancer incidences in this trial [15].

2.2. 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 [19]. 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 [20]. 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 [21,22].

Alpha-tocopherol may influence the development of cancer through several mechanisms. 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 [20]. Alpha-tocopherol inhibits protein kinase-C activity and the proliferation of smooth muscle cells and melanoma cells [23–26]. Vitamin E also induces the detoxification

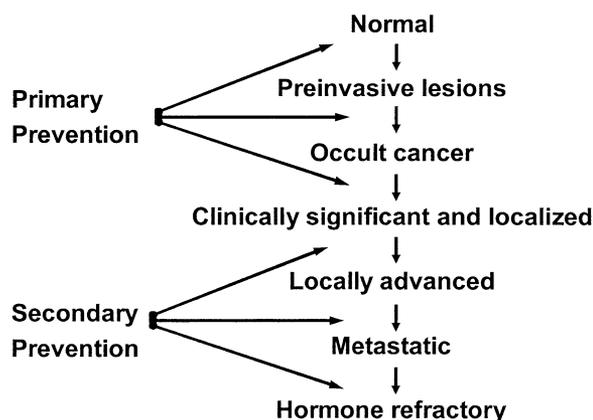


Fig. 2. Targeting of primary and secondary chemoprevention to steps in the development and progression of prostate cancer.

enzyme NADPH:quinone reductase in cancer cell lines, and inhibits arachadonic acid and prostaglandin metabolism [27,28]. Effects on hormones which can increase cellular oxidative stress and proliferative activity and on cell-mediated immunity have also been reported [28].

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 [29–32]. In the same studies, 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 [29–32].

The average dietary vitamin E intake among men and women in the U.S. is estimated to be 10 mg/day and 7 mg/day, respectively [33,34]. The recommended dietary allowance of the National Research Council are set at 10 mg for men and 8 mg for women daily [35].

Evidence currently suggests that vitamin E status or intake is inversely related to risk of lung and colorectal cancers [36–47]. 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 [48–50]. A study of 2,974 subjects over a 17-year follow-up period found low α -tocopherol to be associated with higher prostate cancer risk [51]. These studies all noted lower serum or plasma vitamin E concentrations among prostate cancer cases years prior to diagnosis [49–51]. In a 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 [52]. One case-control study reported no association between vitamin E intake and risk of prostate cancer [53].

One large-scale randomized, placebo-controlled trial supports the role for vitamin E in the prevention of prostate cancer: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC) Study conducted in Finland. The ATBC Study was a 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) among 29,133 male smokers 50–69 years old at entry [2,54]. During the median follow-up period of 6.1 years, 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 ($n = 14,569$) [2]. 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 (i.e., 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%). 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.

Table 1
Schema

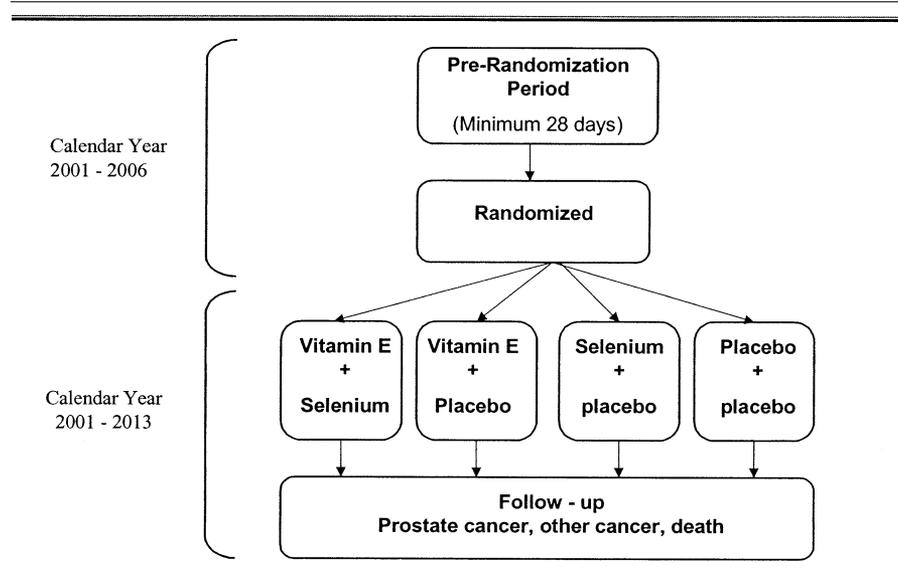


Table 2
Eligibility criteria

○ Age
≥55 years for Caucasians
≥50 years for African-Americans
○ 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, except low-dose aspirin
○ Normal blood pressure (systolic BP < 150 mm Hg and diastolic BP < 90 mm Hg)
○ Willing to restrict supplementation of selenium and vitamin E during participation

3. SELECT

SELECT is a 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 years for Caucasians and 50 years for African-Americans, as African-Americans aged 50–55 have comparable prostate cancer incidence rates as Caucasians aged 55–60. Randomized men will be equally distributed among 4 study arms (Table 1). Intervention will consist of a daily oral dose of study supplement and/or matched placebo according to the randomization (Table 1). Study duration will be 12 years, with a 5-year uniform accrual period and a minimum of 7 and maximum of 12 years of intervention depending on the time of randomization.

The study supplements include 200 μg of 1-selenomethionine, 400 mg of racemic α-tocopherol, and an optional multivitamin containing no selenium or vitamin E. The racemic mix of α-tocopherol will include both the *d*- and *l*-isomers, and except for a higher dose (400 mg vs. 50 mg) is the same supplement used in the ATBC trial.

Table 3
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 4
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.

3.1 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 by the chronic use of selenium and vitamin E (Table 3). 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.

4. Statistical considerations

4.1. Sample size calculation

The primary analysis of the study includes five prespecified comparisons:

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

The study design will permit detection of a 25% reduction in the incidence of prostate cancer for selenium or vitamin E alone, with an additional 25% reduction for the combination of selenium and vitamin E compared to either agent alone. The study allows for the potential interaction between vitamin E and selenium, and additional statistical analyses will include tests for vitamin E vs. no vitamin E,

Table 5
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	.066	533
Vitamin E	8100	.050	403
Selenium	8100	.050	403
Vitamin E + selenium	8100	.038	304

selenium vs. no selenium, and for interactions between the two agents.

The overall α level for the study is 5% (two-sided), with each of the five comparisons 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. the combination of selenium and vitamin E is 89% (Table 4). The median time under observation is estimated to be 8.8 years.

4.2. Incidence rate

Based on PCPT, expectations are that participants will have a mean age of 63 years at study entry. The yearly prostate cancer incidence figures used in the sample-size calculations are derived from observations of the PCPT and SEER databases. The estimated incidence of prostate cancer begins at 0% at randomization, reaches 0.14% at year 1, and rises steadily to 1.36% 12 years later. The number of prostate cancer cases expected in each study arm is listed in Table 5, based on 8100 participants per arm.

4.3. Medication rate

Medication rate is an estimate of the percentage of participants who actually take the study supplements. It is

quantified as the percent of full active drug dose taken by men in each 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 years of treatment. These estimates are based on observed rates in the PCPT. Compliance with daily medication use in SELECT may be higher than PCPT because finasteride has more side-effects than is known for selenium or vitamin E.

4.4. Drop-in rate

The drop-in rate, defined as the rate of those randomized to placebo who obtain and take selenium and/or vitamin E on their own is assumed to be constant at 10% for the 12 years of treatment. Recent Heart Outcomes Prevention Evaluation (HOPE) data support this estimate [55]. 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.

4.5. 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 years of treatment and then adjusted upwards to the 1995 U.S. 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.

4.6. Other factors

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.

Table 6
Differences between the PCPT and SELECT study designs

Variable	PCPT	SELECT
Agent	Finasteride	1-Selenomethionine and α -tocopherol
Eligibility criteria		
Age	≥ 55 yr	≥ 50 yrs for African Americans; ≥ 55 all others
DRE	Not suspicious	Not suspicious
Total PSA	≤ 3.0 ng/mL	≤ 4.0 ng/mL
Primary endpoint	7-year prevalence	Incidence
Placebo run-in	Yes	No
Follow-up intervals	Every 3 months	Every 3 months year 1, then every 6 months
Disease ascertainment	Biopsy required	Biopsy recommended per community standard
End-of-study biopsy	Yes	No
Central lab facility	All PSAs	None
Pathology review	All biopsies	Prostate cancers only
Quality of life studies	All participants	Subset only
Secondary endpoints	Prostate cancer and screening issues	All cancer issues
African American participation	4%	Projected 20%

PSA levels at baseline and after 2 years of vitamin E use were analyzed on a subsample of participants from the HOPE trial and after 3 years in the ATBC study [2,56]. There was no evidence of an effect on the PSA concentrations in these studies.

5. Differences between SELECT and PCPT

The experience with PCPT has influenced the design of SELECT. These differences include broader eligibility criteria, elimination of the placebo run-in period, less frequent follow-up contacts, and reliance on community standards for the diagnosis of prostate cancer (Table 6). These changes reflect the larger sample size for SELECT, the minimal side effects expected with the study agents, and an effort to simplify data management.

6. 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. As of July 25, 2001, selected had already reached 40% of planned accrual (>13,000 of a planned 32,400 men) in the first year of enrollment.

References

- Ries LAG, Kosary CL, Hankey BF, Miller BA, Edwards BK, editors. SEER Cancer Statistics Review, 1973–1995, National Cancer Institute. Bethesda, MD, 1998.
- Heinonen OP, Albanes D, Huttunen JK, et al. Prostate cancer and supplementation with alpha-tocopherol and β -carotene: incidence and mortality in a controlled trial. *JNCI* 1998;90:440–6.
- Clark LC, Combs Jr GF, Turnbull BW, 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;276:1957–63.
- National Academy of Sciences. Recommended Dietary Allowances. 10th ed. Washington, DC: National Academy Press, 1989, 217–24.
- Combs Jr GF, Clark LC. Selenium and cancer. In: Garewal H, editor. Antioxidants and disease prevention. New York: CRC Press; 1997.
- Nakamura A, Shirai T, Takahashi S, Ogawa K, Hirose M, Ito N. Lack of modification by naturally occurring antioxidants of 3,2'-dimethyl-4-aminobiphenyl initiated rate prostate carcinogenesis. *Cancer Letters* 1991;58:241–6.
- Webber MM, Perez-Ripoli EA, James GT. Inhibitory effects of selenium on the growth of DU-145 human prostate carcinoma cells in vitro. *Biochemical and Biophysical Research Communications* 1985; 130:603–9.
- Ip C, Medina D. Current concept of selenium and mammary tumorigenesis. In: Medina D, Kidwell W, Heppner G, Anderson EP, editors. Cellular and molecular biology of breast cancer. New York: Plenum Press; 1987, p. 479.
- Kiremidjian-Schumacher L, Stotzky G. Review: selenium and immune response. *Environmental Res* 1987;42:277–303.
- Thompson HJ, Wilson A, Lu J, et al. Comparison of the effects of an organic and an inorganic form of selenium on a mammary carcinoma cell line. *Carcinogenesis* 1994;15:183–6.
- Redman C, Scott JA, Baines AT, Basye JL, Clark LC, Calley C, Roe D, Payne CM, Nelson MA. Inhibitory effect of selenomethionine on the growth of three selected human tumor cell lines. *Cancer Letters* 1998;125:103–10.
- Shimada T, El-Bayoumy K, Upadhyaya P, Sutter TR, Guengerich FP, Yamazaki H. Inhibition of human cytochrome P450-catalyzed oxidations of xenobiotics and procarcinogens by synthetic organoselenium compounds. *Cancer Res* 1997;57:4757–64.
- El-Bayoumy K. The role of selenium in cancer prevention. In: DeVita VT, Hellman S, Rosenberg SS, editors. Practice of oncology. Philadelphia: Lippincott; 1991, p. 1–15.
- Bedwal RS, Nair N, Sharma MP, Mathur RS. Selenium—its biological perspectives. *Medical Hypotheses* 1993;41:150–9.
- Yoshizawa K, Willett WC, Morris SJ, et al. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst* 1998;90:1219–24.
- Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, Yang CS, Zheng SF, Gail M, Li GY, Yu Y, Liu BQ, Tangrea J, Sun YH, Liu F, Fraumeni Jr JF, Zhang YH, Li B. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 1993;85:1483–92.
- Li JY, Taylor PR, Li B, Dawsey S, Wang GQ, Ershow AG, Guo W, Liu SF, Yang CS, Shen Q, Wang W, Mark SD, Zou XN, Greenwald P, Wu YP, Blot WJ. Nutrition intervention trials in Linxian, China: multiple vitamin/mineral supplementation, cancer incidence, and disease-specific mortality among adults with esophageal dysplasia. *J Natl Cancer Inst* 1993;85:1492–8.
- Clark LC, Dalkin B, Krongrad A, et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol* 1998;81:730–4.
- Evans HM, Bishop KS. On the existence of a hitherto unrecognized dietary factor essential for reproduction. *Science* 1922;56:650–1.
- 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.
- Machlin LJ. Vitamin E. In: Machlin LJ, editor. Handbook of vitamins. 2nd ed. New York: Marcel Dekker; 1991.
- Pappas AM. Vitamin E: tocopherols and tocotrienols. In: Pappas AM, editor. Antioxidant status, diet, nutrition, and health. Boca Raton: CRC; 1998.
- Azzi A, Boscoboinik D, Marilley D, Ozer NK, Stauble B, Tasinato A. Vitamin E: a sensor and an information transducer of the cell oxidation state. *Am J Clin Nutr* 1995;62:1337s–46s.
- Mahoney CW, Azzi A. Vitamin E inhibits protein kinase C activity. *Biochem Biophys Res Commun* 1988;154:694–7.
- Chatelain E, Boscoboinik DO, Bartoli GM, et al. Inhibition of smooth muscle cell proliferation and protein kinase C activity by tocopherols and tocotrienols. *Biochim Biophys Acta* 1993;1176:83–9.
- 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;22:1145–51.
- 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;98:63–9.
- Traber MG, Packer L. Vitamin E: beyond antioxidant function. *Am J Clin Nutr* 1995;62;1501s–9s.
- 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(2):161–9.

- [30] Kishimoto M, Yano Y, Yajima S, Otani S, Ichikawa T, Yano T. 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* Apr 24 1998;126(2):173–8.
- [31] Sigounas G, Anagnostou A, Steiner M. dl-alpha-tocopherol induces apoptosis in erythroleukemia, prostate, and breast cancer cells. *Nutr Cancer* 1997;28(1):30–5.
- [32] 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;29:287–92.
- [33] USDA (U.S. 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, U.S. Department of Agriculture, Hyattsville, MD, 1987.
- [34] USDA (U.S. 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, U.S. Department of Agriculture, Hyattsville, MD, 1987.
- [35] National Research Council (NRC). Recommended Dietary Allowances. 10th edition. Washington, D.C.: National Academy Press, 1989.
- [36] Comstock GW, Bush TL, Helzlsouer K. Serum retinol, beta-carotene, vitamin E, and selenium as related to subsequent cancer of specific sites. *Am J Epidemiol* 1992;135:115–21.
- [37] Shibata A, Paganini-Hill A, Ross RK, Henderson BE. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. *Br J Cancer* 1992;66:673–9.
- [38] Yong LC, Brown CC, Schatzkin A, et al. Intake of vitamins E, C, and A and risk of lung cancer: the NHANES I Epidemiologic Followup study. *Am J Epidemiol* 1997;146:231–43.
- [39] Ocke MC, Bueno-de-Mesquita HB, Feskens EJ, et al. Repeated measurements of vegetables, fruits, b-carotene, and vitamins C and E in relation to lung cancer: The Zutphen study. *Am J Epidemiol* 1997;145:358–65.
- [40] Knekt P, Jarvinen R, Sepanen R, et al. Dietary antioxidants and the risk of lung cancer. *Am J Epidemiol* 1991;134:471–9.
- [41] Longnecker MP, Martin-Moreno JM, Knekt P, et al. Serum alpha-tocopherol concentration in relation to subsequent colorectal cancer: pooled data from five cohorts. *JNCI* 1992;84:430–5.
- [42] Wu AH, Paganini-Hill A, Ross RK, Henderson BE. Alcohol, physical activity and other factors for colorectal cancer: a prospective study. *Br J Cancer* 1987;55:687–94.
- [43] Bostick RM, Potter JD, McKenzie DR, et al. Reduced risk of colon cancer with high intake of vitamin E: the Iowa Women's Health Study. *Cancer Res* 1993;53:4230–7.
- [44] Ferraroni M, La Vecchia C, D'Avanzo B, et al. Selected micronutrient intake and the risk of colorectal cancer. *Br J Cancer* 1994;70:1150–5.
- [45] Lee HP, Gourley L, Duffy SW, et al. Colorectal cancer and diet in an Asian population study among Singapore Chinese. *Int J Cancer* 1989;43:1007–16.
- [46] Freudenheim JL, Graham S, Horvath PJ, et al. Risks associated with source of fiber components in cancer of the colon and rectum. *Cancer Res* 1990;50:3295–300.
- [47] Meyer F, White E. Alcohol and nutrients in relation to colon cancer in middle-aged adults. *Am J Epidemiol* 1993;136:225–36.
- [48] Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States. *J Natl Cancer Inst* 1981;66:1192–308.
- [49] 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–4S.
- [50] Knekt P, Aromaa A, Maatala J, 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.
- [51] Hsing AW, Comstock GW, Abbey H, Polk BF. Serologic precursors of cancer retinol, carotenoids, and tocopherol and risk of prostate cancer. *JNCI* 1990;82:941–6.
- [52] Eichholzer M, Stahelin HB, Gey FK, 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;55:145–50.
- [53] Hartman TJ, Albanes D, Pietinen P, 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;7:335–40.
- [54] Rohan TE, Howe GR, Burch ID, et al. Dietary factors and risk of prostate cancer: a case-control study in Ontario, Canada. *Cancer Causes Control* 1995;6:145–54.
- [55] 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. *N Engl J Med* 1994;330:1029–35.
- [56] Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145–53.