Chapter 23
Prostate Cancer Prevention and the Selenium and Vitamin E Cancer Prevention Trial (SELECT): A Selenium Perspective

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Abstract The Selenium and Vitamin E Cancer Prevention Trial (SELECT) randomized 35,533 healthy men, ≥55 years (≥50 years if African American), with normal digital rectal exams and prostate-specific antigens <4 ng/mL, to (i) 200 μg/day *l*-selenomethionine, (ii) 400 IU/day all-rac-alpha-tocopheryl acetate (vitamin E), (iii) both supplements, or (iv) placebo for a median of 5.5 years (range 4.2–7.3 years). The hypotheses underlying SELECT, that selenium and vitamin E individually and together decrease prostate cancer incidence, derived from epidemiologic and laboratory evidence and significant secondary endpoints in the Nutritional Prevention of Cancer (NPC) (selenium) and Alpha-Tocopherol Beta-Carotene (vitamin E) trials. Results from SELECT showed that prostate cancer incidence did not differ among the four arms: hazard ratios (HRs) (99% CIs) for prostate cancer: 1.13 (99% CI, 0.95–1.35; $p=0.06$; $n=473$) for vitamin E, 1.04 (99% CI, 0.87–1.24; $p=0.62$; $n=432$) for selenium, and 1.05 (99% CI, 0.88–1.25; $p=0.52$; $n=437$) for selenium + vitamin E vs. 1.00 ($n=416$) for placebo. Statistically nonsignificant increased risks of prostate cancer with vitamin E alone (RR 1.13; $p=0.06$) and newly diagnosed type 2 diabetes mellitus with selenium alone (RR 1.07; $p=0.16$) were observed. SELECT data show that neither selenium nor vitamin E, alone or together, in the doses and formulations used, prevented prostate cancer in this heterogeneous population of healthy men. Although there are many potential explanations for the null findings in SELECT, the most likely reasons appear to be a mismatch between the target population and the intervention agents selected, or that effects were limited to as-yet-undetermined subgroups of susceptible men.

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23.1 Background

Documentation of the anticancer properties of selenium and vitamin E as secondary endpoints in two nutrition intervention trials, the NPC Study [1] and the ATBC Cancer Prevention Trial [2, 3], formed the foundation upon which the Selenium and Vitamin E Cancer Prevention Trial (SELECT) was based. SELECT was only the second NCI-sponsored cancer prevention trial, specifically designed and implemented with the primary objective to prevent prostate cancer [4–7].

23.2 Study Objectives

The hypotheses underlying SELECT, that selenium and vitamin E prevent prostate cancer, were the basis for its primary objective: to assess the effects of selenium and vitamin E alone and in combination on incidence of prostate cancer. Prespecified secondary endpoints included: prostate cancer-free survival; all cause mortality; the incidence and mortality of other cancer types such as lung and colorectal; overall cancer incidence and survival; and disease potentially impacted by chronic administration of selenium and vitamin E. Serious cardiovascular events were also monitored because of concerns over the safety of vitamin E with regard to the risk of hemorrhagic stroke [5, 6]. Additional trial objectives included periodic quality of life assessment, serum micronutrient measurement and prostate cancer risk, and the evaluation of biological and genetic markers associated with the risk of prostate cancer [8].

23.3 Selection of Study Agents

Advice from an NCI-sponsored panel of experts led to selection of *l*-selenomethionine over selenized yeast for SELECT. Although selenized yeast was the form used in the hypothesis-generating NPC trial [1], marked batch-to-batch variability in various forms of selenium in the selenized yeast, lack of commercial availability of the selenized yeast used in the NPC study, and laboratory analysis which showed that *l*-selenomethionine was the predominant selenium species in commercially available selenized yeast at the time the trial was being designed led to the panel's recommendation of the essential nutrient form. A daily dose of 200 μg was selected to mimic the NPC trial dose. The optimum dose and formulation of vitamin E was also the subject of debate. Ultimately, α-tocopherol (*all rac* (*dl*)-α-tocopheryl acetate) was selected because of the observed association of long-term supplementation with this form of vitamin E with reduction in prostate cancer incidence in the ATBC trial [3, 9]. The chosen daily dose of 400 mg was based on its potential benefits for other non-cancer diseases (e.g., cardiovascular disease, Alzheimer's disease, age-related macular degeneration), as well as its inclusion in widely used vitamin supplements, suggesting its safety [10–12].

23.4 Study Cohort, Design, and Statistical Methods

SELECT was a prospective, randomized, double-blind, placebo-controlled, 2×2 factorial design clinical trial, which tested selenium and vitamin E alone and in combination in eligible healthy men. Eligibility was based mainly on elevated risk of disease due to age: ≥55 years in Caucasian men and ≥50 years in African-American men since 50 to 55-year-old black American men have a prostate cancer incidence rate comparable to that of 55 to 60-year-old white men. Full eligibility criteria are shown in Fig. 23.1. At completion of accrual, 35,533 eligible men enrolled in SELECT, exceeding the goal of 32,400. A great strength and advantage in the SELECT study design is that the randomization process should lead to equal participant distribution among the four study arms for all factors (beyond the agents being tested) that might otherwise influence study endpoints, thus avoiding unmeasured or hidden sources of bias in participant characteristics. The study design with randomization groups is shown in Fig. 23.1.

SELECT had a planned sample size of 32,400 men to address five prespecified comparisons – (i) vitamin E vs. placebo, (ii) selenium vs. placebo, (iii) combined vitamin E plus selenium vs. placebo, (iv) combined vitamin E plus selenium vs. vitamin E, and (v) combined vitamin E plus selenium vs. selenium. Each comparison was powered to detect a ≥25% decrease in the incidence of prostate cancer for selenium or vitamin E alone, and an additional 25% decrease for selenium and vitamin E combined, compared with either agent alone. Prostate cancer was assessed based on a recommended routine clinical diagnostic evaluation, including yearly digital rectal exam (DRE) and serum prostate specific antigen (PSA) measurement.

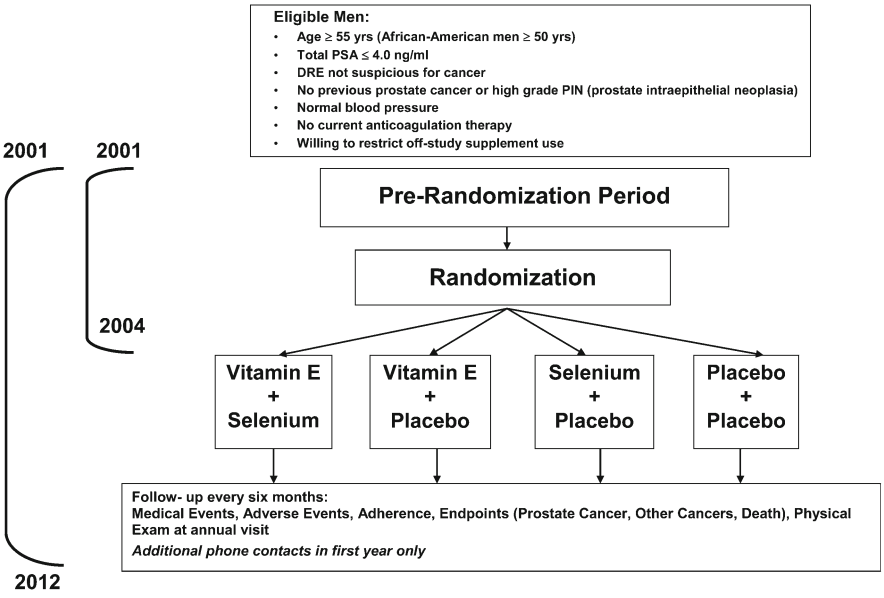

Fig. 23.1 SELECT: study eligibility, schema, and follow-up schedule

23.5 Study Implementation, Recruitment Strategies, and Participant Baseline Characteristics

Eligible men from the US, Canada, and Puerto Rico were enrolled from July 2001 to June 2004, a period 2 years shorter than projected. Although the accrual target was 32,400, a total of 35,533 participants, including 21% minorities (12% African American, 7% Hispanic, and 2% other) were randomized [13] (Table 23.1). Not only was SELECT the largest randomized chemoprevention trial ever conducted, it also had the largest percentage of black participants ever randomized to this type of study [14].

Table 23.1 Select: baseline characteristics – age, race/ethnicity, PSA, serum levels

	Number (%) of participants[a]			
	Placebo	Vitamin E	Selenium	Selenium + vitamin E
Age (year)				
Median (interquartile range)	62.6 (58.1–67.8)	62.3 (58.0–67.8)	62.6 (58.2–68.0)	62.4 (58.1–67.8)
50–54	355 (4)	402 (5)	337 (4)	385 (4)
55–64	5,078 (58)	5,143 (59)	5,076 (58)	5,052 (58)
65–74	2,702 (31)	2,641 (30)	2,733 (31)	2,731 (31)
≥75	561 (6)	551 (6)	606 (7)	535 (6)
Race/ethnicity				
White	6,863 (79)	6,890 (79)	6,942 (79)	6,874 (79)
African American	1,078 (12)	1,107 (13)	1,053 (12)	1,076 (12)
Hispanic (non-AA)	492 (6)	477 (5)	481 (5)	484 (6)
Hispanic (AA)	76 (1)	103 (1)	86 (1)	95 (1)
Other	187 (2)	160 (2)	190 (2)	174 (2)
PSA (ng/mL)				
0.1–1.0	4,122 (47)	4,208 (48)	4,218 (48)	4,213 (48)
1.1–2.0	2,728 (31)	2,653 (30)	2,661 (30)	2,666 (31)
2.1–3.0	1,168 (13)	1,228 (14)	1,211 (140	1,149 (13)
3.1–4.0	666 (8)	634 (7)	652 (7)	659 (8)
>4.0	5 (<1)	3 (<1)	2 (<1)	1 (<1)
Unknown/missing	7 (<1)	11 (<1)	8 (<1)	15 (<1)
Serum levels (μg/mL)[b]				
Median, interquartile range				
Selenium (μg/L)	138 (125–152)	136 (122–148)	135 (123–146)	136 (123–150)
α-tocopherol (μg/mL)	12.5 (10.7–15.0)	12.8 (10.7–15.4)	12.6 (10.4–14.8)	12.2 (10.1–15.4)

SELECT Selenium and Vitamin E Cancer Prevention Trial; *PSA*, prostate-specific antigen; *AA*, African American

[a]Number (%) of participants refers to all entries in this section except for age and serum values where median and interquartile ranges are shown

[b]Serum α-tocopherol levels are cholesterol-adjusted

Table 23.2 Select: study adherence – pill counts by supplement type and study year

	% of Men adherent[a,b] (range)			
	Placebo	Vitamin E	Selenium	Selenium + vitamin E
Selenium/matching placebo				
Year 1 ($n = 34{,}708$)	85 (76–85)	85 (77–85)	84 (76–84)	85 (77–84)
Year 2 ($n = 34{,}163$)	81 (72–81)	80 (72–81)	79 (71–80)	80 (72–80)
Year 3 ($n = 33{,}616$)	76 (68–77)	77 (69–77)	75 (68–76)	76 (69–77)
Year 4 ($n = 32{,}976$)	69 (65–73)	73 (66–74)	71 (64–72)	72 (65–74)
Year 5 ($n = 23{,}419$)	69 (63–71)	71 (64–73)	69 (62–70)	70 (64–71)
Vitamin E/matching placebo				
Year 1 ($n = 34{,}708$)	85 (76–85)	85 (77–85)	85 (76–85)	85 (77–85)
Year 2 ($n = 34{,}163$)	80 (71–80)	80 (71–80)	79 (70–79)	79 (71–80)
Year 3 ($n = 33{,}616$)	75 (67–75)	75 (67–76)	74 (67–75)	76 (69–77)
Year 4 ($n = 32{,}976$)	70 (63–72)	70 (63–72)	69 (62–71)	70 (63–72)
Year 5 ($n = 23{,}419$)	67 (61–69)	69 (62–71)	67 (61–69)	68 (61–70)

SELECT, Selenium and Vitamin E Cancer Prevention Trial

[a]Percent of men adherent defined as taking at least 80% of their study supplements

[b]Ranges are estimates which include those with missing data and assumes that those with missing data were either all not adherent (low estimate) or all adherent (high estimate)

Adherence in SELECT was assessed via pill count (Table 23.2), participant diary, and serum levels (in a bioadherence subcohort), and is described in detail elsewhere [13].

Selenium and vitamin E intervention supplements were discontinued on October 23, 2008 based on an assessment of the SELECT data as of August 1, 2008 by the Data and Safety Monitoring Committee, with a median overall follow-up of 5.5 years (range, 4.2–7.3 years) [13]. This independent committee concluded that the null hypothesis – that no convincing evidence of benefit existed with either selenium or vitamin E or the two in combination – prevailed, according to the SELECT results.

23.6 Results

23.6.1 Adherence to Study Supplements

Adherence, assessed both by pill count and in a subset of men by "bioadherence" metrics (i.e., serum levels of selenium and vitamin E), was high and comparable in all four study arms. Importantly, serum selenium and α-tocopherol levels rose only in participants assigned to the selenium- and vitamin E-containing arms, respectively.

Table 23.3 Select: clinically diagnosed prostate cancers

	Placebo ($n=8,696$)	Vitamin E ($n=8,737$)	Selenium ($n=8,752$)	Selenium + vitamin E ($n=8,703$)
Prostate cancers				
Number[a]	416	473	432	437
5-year incidence[b] (%)	4.43	4.93	4.56	4.56
HR (99% CI)	1.00	1.13 (0.95–1.35)	1.04 (0.87–1.24)	1.05 (0.88–1.25)
p-value	–	$p=0.06$	$p=0.62$	$p=0.52$
Diagnosis by prostate biopsy				
Number[b]	404 (97%)	458 (97%)	419 (97%)	420 (97%)
Reason for biopsy (positive biopsies)[b]				
Elevated PSA[b]	259 (64%)	324 (71%)	296 (71%)	263 (63%)
Abnormal DRE[b]	66 (16%)	58 (13%)	46 (11%)	56 (13%)

SELECT, Selenium and Vitamin E Cancer Prevention Trial; *HR*, hazard ratio; *CI*, confidence interval; *PSA*, prostate-specific antigen; *DRE*, digital rectal exam

[a]Total number of prostate cancers diagnosed

[b]Number or % of participants per treatment arm

These measurements indicated both good compliance with assigned study agents and conversely, minimal "drop-ins" to unassigned supplements from taking over-the-counter selenium and/or vitamin E off-study.

23.6.2 Primary Endpoint: Prostate Cancer

Rates of prostate cancer did not differ statistically among the four intervention arms, with HRs for prostate cancer relative to placebo of 1.13 (99% CI, 0.95–1.35; $p=0.06$) for the vitamin E-alone group, 1.05 (99% CI, 0.88–1.25; $p=0.52$) for the selenium + vitamin E group, and 1.04 (99% CI, 0.87–1.24; $p=0.62$) for the selenium-alone group (Table 23.3). The graph depicting the cumulative incidence of prostate cancer detected during each study year indicated that the vitamin E-alone curve showed some divergence from the placebo and other two intervention curves at about 4 years of follow-up which, although statistically nonsignificant, was of potential concern (Fig. 23.2). Most prostate cancers were diagnosed by prostate biopsy, constituting histological diagnoses (Table 23.2). The majority were early stage and low Gleason grade, which were similar in all four groups [13]. The clinical presentation that prompted biopsy was primarily increased PSA (approximately two-thirds of cases in each of the four groups) or abnormal DRE (11–16% of cases in the four groups). Importantly, the proportion of participants undergoing PSA testing and DREs was similar in all groups, obviating any concern that observed outcomes reflected detection bias associated with differential screening.

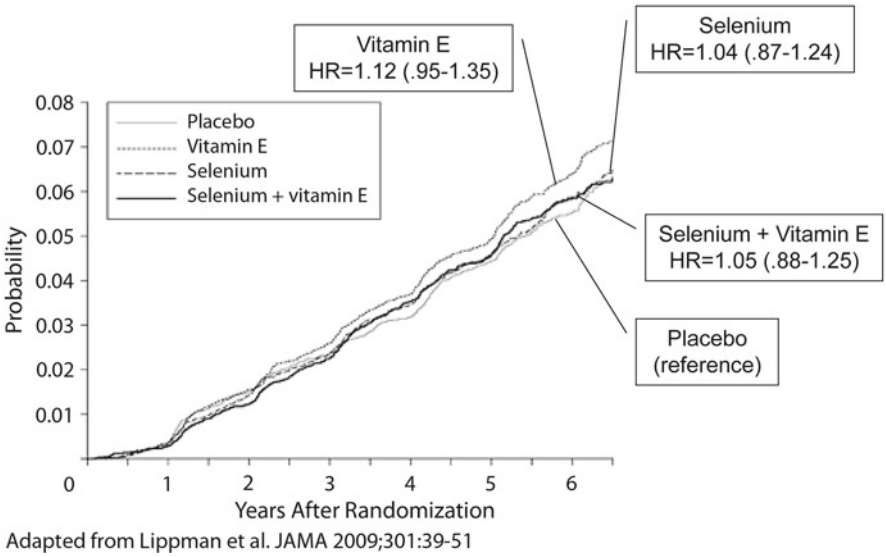

Fig. 23.2 SELECT: cumulative incidence of prostate cancer over time

23.6.3 Secondary Endpoints

Prespecified secondary endpoints included other cancers, especially those influenced by a study supplement in prior nutritional trials [1]. None of these cancers differed significantly in any of the intervention arms compared to the placebo group; all p-values were >0.15 (Table 23.4). Non-cancer secondary outcomes included cardiovascular outcomes, none of which showed a significant difference from the reference placebo arm [13]. In particular, hemorrhagic stroke, which was a potential concern due to the known association of vitamin E with bleeding propensity [15] and the previous association observed at a lower dose (50 mg daily) in the ATBC trial [2], did not differ among the four groups (Table 23.4). Type 2 diabetes mellitus was of interest because of earlier reports linking increased prevalence with higher serum selenium levels, and higher incidence following long-term selenium supplementation [16]. Although there was a hint of increased risk of type 2 diabetes in the selenium-alone arm based on patient-reported outcomes, the observed effect was small and statistically nonsignificant (relative risk (RR), 1.07; 99% CI, 0.94–1.22; $p = 0.16$). Deaths, total and those due to predesignated causes, also did not differ among the four arms (Table 23.4). The only adverse effects that were statistically significantly increased were alopecia and low-grade dermatitis in the selenium-alone group, and halitosis in the selenium + vitamin E group; these are previously known side effects of the interventional supplements (Table 23.4).

Table 23.4 Select: secondary endpoints

	Treatment arm (number of participants)			
	Placebo ($n=8,696$)	Vitamin E ($n=8,737$)	Selenium ($n=8,752$)	Selenium + vitamin E ($n=8,703$)
	No. events HR (99% CI)			
Cancers				
Any cancer	824	856	837	846
(including prostate)	1 (reference)	1.03 (0.91–1.17)	1.01 (0.89–1.15)	1.02 (0.90–1.16)
Lung	67	67	75	78
	1 (reference)	1.00 (0.64–1.55)	1.12 (0.73–1.72)	1.16 (0.76–1.78)
Colorectal	60	66	63	77
	1 (reference)	1.09 (0.69–1.73)	1.05 (0.66–1.67)	1.28 (0.82–2.00)
Cardiovascular events				
Any (including death)	1,050	1,034	1,080	1,041
	1 (reference)	0.98 (0.88–1.09)	1.02 (0.92–1.13)	0.99 (0.89–1.10)
Hemorrhagic stroke	11	7	11	12
	1 (reference)	0.63 (0.18–2.20)	0.99 (0.33–2.98)	1.09 (0.37–3.19)
Diabetes[a]	669	700	724	660
	1 (reference)	1.04 (0.91–1.18)	1.07 (0.94–1.22)	0.97 (0.85–1.11)
Deaths				
Total	382	358	378	359
	1 (reference)	0.93 (0.77–1.13)	0.99 (0.82–1.19)	0.94 (0.77–1.13)
All cancers	125	106	128	117
	1 (reference)	0.84 (0.60–1.18)	1.02 (0.74–1.41)	0.93 (0.67–1.30)

Prostate cancer	0	0	1	0
	1 (reference)	N/A	N/A	N/A
Cardiovascular	142	119	129	117
	1 (reference)	0.84 (0.61–1.15)	0.91 (0.66–1.24)	0.82 (0.60–1.13)
Supplement-specific adverse events[b]				
Alopecia	206	220	265	238
	1 (reference)	1.06 (0.83–1.36)	1.28 (1.01–1.62)	1.15 (0.91–1.47)
Dermatitis, grades 1–2	516	591	605	554
	1 (reference)	1.14 (0.98–1.32)	1.17 (1.00–1.35)	1.07 (0.92–1.25)
Halitosis	427	493	503	531
	1 (reference)	1.15 (0.97–1.36)	1.17 (0.99–1.38)	1.24 (1.06–1.46)

SELECT, Selenium and Vitamin E Cancer Prevention Trial; *HR*, hazard ratio; *CI*, confidence interval; *N/A*, not applicable

[a]Diagnoses based on self-report or reported use of diabetes medication excluding prevalent cases at randomization

[b]Point estimates expressed as relative risk (RR) and 99% CIs

23.7 Discussion

The results of SELECT – that neither selenium nor vitamin E supplementation alone or in combination reduced prostate cancer incidence – are at odds with results from the NPC and ATBC trials, upon which the SELECT hypotheses were based. Furthermore, the nonsignificant increased prostate cancer incidence in the vitamin E-alone arm raises a largely unexpected concern that vitamin E might, in fact, has undesirable effects in prostate carcinogenesis. These outcomes of SELECT have been debated extensively, generating a series of potential explanations for the negative results.

23.7.1 Why Didn't Selenium Reduce the Clinical Incidence of Prostate Cancer?

Kristal enumerated a general list of categorical reasons why cancer prevention trials can fail [17]: the intervention dose was too high or low, the intervention period was too short, unexpected side effects resulted in early termination, adherence was poor, too many controls "dropped in," susceptibility was limited to subgroups, and the intervention itself affected detection of the endpoint. It is also possible that a lag-to-effect may occur such that benefit (or harm) appears only much later, after the conclusion of the intervention, as was evident in one of the tamoxifen vs. placebo breast cancer prevention trials [18]. Yet, another alternative is that intervening in middle-aged to elderly adults is simply too late in life and misses the true prevention window of opportunity to alter early carcinogenic events.

For SELECT in general and selenium in particular, a number of potential explanations for the null findings stand out as most likely, including, the dose and form of selenium chosen, the study population targeted for the intervention, effects were restricted to subgroups, and among others, the play of chance, as discussed below.

23.7.1.1 Selenium Dose

The dose and, more importantly, the formulation (see below) of selenium used in SELECT have been cited as major contributors to the failure of the selenium-containing arms to show a reduction in prostate cancer incidence. Yet, these features of the selenium intervention were chosen with great care. Although an optimum dose of selenium supplementation for cancer prevention has not been established, the selenium dose chosen for SELECT was the same 200 μg/day dose used in the hypothesis-generating NPC trial. Based on this, plus the efficacy and safety data derived from a series of preclinical studies, an expert panel convened in December 1998 concurred that 200 μg would be an appropriate daily dose. One idea is that a narrow window exists for the most beneficial dose of dietary selenium. Selenium intake, and more importantly the actual selenium concentration in tissues,

does not exhibit a linear relationship to DNA damage, the regulation of which is a major mechanism by which selenium is presumed to serve as a chemopreventive agent in the prostate. Waters et al. [19] demonstrated that a nonlinear U-shaped dose-response curve characterized the relation between selenium (as toenail selenium concentration) and genotoxic stress in the prostate of dogs. Tissue concentrations either above or below the optimal selenium range might be either ineffectual or even toxic. Importantly, this U-shaped relationship between intake/concentration and biological function appears to have more general applicability to trace elements beyond just selenium [20].

23.7.1.2 SELECT Study Population: Baseline Selenium Status

The net tissue concentration of selenium reflects not only selenium intake, or dose, but also baseline selenium status. Thus, differences in the study populations between the SELECT and NPC trials with respect to mean baseline selenium status could explain the difference in their prostate cancer outcomes. Unlike SELECT, the NPC trial was conducted in a study population located in east coast areas of the United States where environmental selenium levels are low [1, 21, 22]. The baseline mean plasma Se levels in both the selenium and placebo arms of this trial were 114 μg/mL. The Se levels rose about 67% in the Se-treated arm, reaching a mean plasma level of 190 μg/mL. Patients with baseline plasma Se levels in the lowest (<106.4 μg/mL) and middle (106.4–121.2 μg/mL) tertiles showed significant reductions in prostate cancer, with RRs of 0.08 ($p=0.002$) and 0.30 ($p=0.03$), respectively. In contrast, among those in the highest tertile (>121.2 μg/mL), only a nonsignificant reduction was observed, with an RR of 0.85 ($p=0.75$) [23]. The low baseline selenium levels in the NPC participants appear to have accentuated the beneficial effects of selenium supplementation in reducing prostate as well as total cancer incidence [23, 24]. Unlike the NPC trial, the men participating in SELECT came from multiple regions all over the United States and Canada and were replete in selenium levels at baseline, with median serum selenium levels of 135 μg/mL (Table 23.1) compared to the median of 114 μg/mL observed in the NPC trial. In fact, 78% of SELECT participants entered the trial with serum levels that were higher than the lower two tertiles of NPC participants, namely those with lower serum selenium levels who benefited from the selenium intervention in the NPC trial [13].

23.7.1.3 SELECT Study Population: Genetics

In addition to environmental factors feeding into the response of a trial population to the selenium intervention, polymorphisms in the 25 identified selenoprotein genes [25] or in genes encoding proteins involved in selenium metabolism and activity may influence health outcomes. For example, manganese superoxide dismutase (MnSOD), a mitochondrial antioxidant enzyme encoded by the *SOD2* gene, participates in processes that depend on selenium [26]. In a case-control study nested within the Physicians' Health Study, homozygosity for a functional variant

of MnSOD containing an alanine (A) in place of a valine (V) in codon 16 in men who also had the highest pre-diagnostic levels of serum selenium was associated with a reduced risk of prostate cancer (relative risk or RR = 0.47, 95% confidence interval (CI) 0.26–0.85, compared to VV/VA genotypes and low serum selenium for all prostate cancers; and RR = 0.35, 95% CI 0.15–0.82 for aggressive prostate cancer) [26]. An analysis of prostate cancer mortality, also from the Physicians' Health Study, showed that three polymorphisms in the selenoprotein gene *SEP15* significantly affected survival time in men with prostate cancer, and that the survival effect for one of these variants was further influenced by plasma selenium levels [27]. These results suggest that stratification of SELECT participants according to allelic status for relevant genes such as *SOD2* or *SEP15* may well elicit relations between selenium supplementation and prostate cancer risk that did not emerge in the trial population as a whole.

23.7.1.4 Selenium Formulation

The choice of the formulation of selenium, which exhibits a complex metabolism [28–31], posed an even greater challenge. Inorganic forms of selenium, such as selenite, were considered because they are more active than organoselenium compounds in suppressing prostate cancer cell growth and inducing apoptosis of prostate cancer cells [32]. However, in contrast to the organoselenium compounds, the anticancer properties of inorganic forms are linked to genotoxicity, specifically the rapid induction of DNA single-strand breaks [33]. Potential genotoxicity, particularly in view of the prolonged use anticipated in the prevention setting, argued against using an inorganic selenium compound despite the potential of greater efficacy. A similar view confronted the promising compound methylseleninic acid, which exhibited greater potency in vitro and in vivo relative to its organic precursor, Se-methylselenocysteine [29]. Methylseleninic acid was new at the time SELECT was being designed and concern that its toxicity and safety were not well understood, together with its commercial nonavailability, discouraged the panel from further consideration of this form of selenium [7]. The remaining options were selenomethionine and selenized yeast. Although selenized yeast was used in the NPC trial, incomplete characterization and concern over large batch-to-batch variation in concentration of specific organoselenium compounds led the panel to reject yeast as the form of intervention. *L*-selenomethione was the primary active ingredient in the selenized yeast used in the NPC trial, pointing to this form of selenium as the optimal intervention in SELECT.

23.7.1.5 SELECT vs. NPC Trial Designs: Statistical Issues

Perhaps the most important difference between the SELECT and NPC cancer prevention trials and their prostate cancer outcomes is that prostate cancer was the primary

endpoint in SELECT, but merely a secondary endpoint in NPC. Although statistical design in clinical trials typically focuses on assuring adequate power to address the primary endpoint, this is not necessarily true of secondary endpoints [34]. In a trial containing multiple outcomes, prospectively defining a given outcome as the primary endpoint protects that endpoint from concerns that the observed result is due to chance from multiple testing [35]. This leaves secondary endpoints at risk of precisely that, representing findings that are due to chance alone. In this manner, the NPC trial was designed to evaluate the effect of selenized yeast on the incidence of non-melanoma skin cancers as the primary endpoint. Observations regarding secondary endpoints, including other cancers such as prostate cancer, were at risk of being due to chance. In essence, it is as if "all available statistical power had been 'spent' on the primary outcome and the play of chance could have considerable influence even though the secondary outcomes seemed to be statistically significant" [35]. The NPC trial was especially vulnerable to the possibility of a chance finding in a secondary endpoint since it was a small trial, with only 1,312 participants, and it had multiple secondary endpoints.

Statistical concerns regarding interpretation of trial outcomes apply to secondary endpoints irrespective of the significance of the accompanying primary endpoint. These concerns are especially pertinent to outcome data relating to interventions being tested for cancer prevention, because prevention trials lay the foundation for broad health policy decisions affecting healthy populations. Since health policy should be based on the high level of evidence provided by rigorously conducted clinical trials, adoption of a cancer preventive intervention based on a statistically significant secondary endpoint alone is insufficient. However, a significant secondary endpoint may generate a hypothesis that, in turn, serves as the basis for the primary endpoint in a derivative clinical trial. This is exactly the role played by prostate cancer incidence in the NPC trial, which laid the groundwork for the selenium intervention incorporated into the factorial design of SELECT [36]. SELECT was justified because equipoise existed regarding the expectation that selenium would reduce prostate cancer incidence as a primary endpoint.

23.7.2 Ancillary Studies

Several ancillary studies were incorporated into SELECT and results from these studies will ultimately enrich the overall output from SELECT. These studies include: the Prevention of Alzheimer's Disease with Vitamin E and Selenium (PREADVISE), which enrolled ~6,500 men to evaluate Alzheimer's, other neurodegenerative diseases, and normal aging; the SELECT Eye Endpoints (SEE) study to evaluate cataract and macular degeneration events in SELECT participants; the Respiratory Ancillary Study (RAS), which enrolled ~2,900 men to evaluate change in pulmonary function during the intervention; and the Adenomatous Colorectal Polyp (ACP) study, which enrolled over 2,000 men to evaluate adenomatous polyps.

23.8 Conclusion

The absence of positive findings in SELECT for either selenium or vitamin E was surprising in view of the abundant laboratory and epidemiologic data that supported associations between these nutrients and decreased prostate cancer risk. Among the candidate explanations for the negative results, the most likely reasons involve a mismatch between the target population and intervention agents selected, or that effects were limited to as-yet-undetermined subgroups of susceptible men. The choice of dose and formulation for each agent tested, together with selection of a cohort most likely to benefit from supplementation, should be the focus of future trial design. In the case of selenium, a trial cohort that has low selenium intake or status would be most likely to benefit from supplementation. In general, nutritional agents appear to exhibit an optimal "window" of activity (a "U-shaped" dose-response curve), below and above which their benefits disappear and toxicity may even ensue. Unlike purely synthetic drugs, nutrients derive from natural products, and the state of endogenous nutritional repletion of an individual participant must be prospectively factored into the trial designs aimed at achieving this optimal level. Similarly, trial design in the future will be aided enormously by improved understanding of the underlying biologic effects of the intervention agents themselves, particularly as they relate to potentially susceptible subgroups (e.g., genetic susceptibility defined by genotypes, or concurrent environmental exposures such as tobacco or alcohol use).

In summary, SELECT was an enormously important effort. It was the largest nutritional intervention trial ever conducted in the US to prevent cancer, its implementation was a model of methodologic rigor and care, and it produced highly informative (albeit null) answers regarding the potential role of selenium and vitamin E in the prevention of prostate cancer under the conditions the trial was conducted. But SELECT is not yet done, and we await further analyses of these most valuable data, especially those regarding baseline serum levels, subgroups of environmental exposures such as smoking and genetic factors, as well as findings from postintervention follow-up and the several studies of ancillary endpoints incorporated into the SELECT.

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