BRIEF COMMUNICATIONS

Selenium Supplementation and Secondary Prevention of Nonmelanoma Skin Cancer in a Randomized Trial

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The Nutritional Prevention of Cancer Trial was a double-blind, randomized, placebo-controlled clinical trial designed to test whether selenium as selenized yeast (200 μg daily) could prevent nonmelanoma skin cancer among 1312 patients from the Eastern United States who had previously had this disease. Results from September 15, 1983, through December 31, 1993, showed no association between treatment and the incidence of basal and squamous cell carcinomas of the skin. This report summarizes the entire blinded treatment period, which ended on January 31, 1996. The association between treatment and time to first nonmelanoma skin cancer diagnosis and between treatment and time to multiple skin tumors overall and within subgroups, defined by baseline characteristics, was evaluated. Although results through the entire blinded period continued to show that selenium supplementation was not statistically significantly associated with the risk of basal cell carcinoma (hazard ratio [HR] = 1.09, 95% confidence interval [CI] = 0.94 to 1.26), selenium supplementation was associated with statistically significantly elevated risk of squamous cell carcinoma (HR = 1.25, 95% CI = 1.03 to 1.51) and of total nonmelanoma skin cancer (HR = 1.17, 95% CI = 1.02 to 1.34). Results from the Nutritional Prevention of Cancer Trial conducted among individuals at high risk of nonmelanoma skin cancer continue to demonstrate that selenium supplementation is ineffective at preventing basal cell carcinoma and that it increases the risk of squamous cell carcinoma and total nonmelanoma skin cancer. [J Natl Cancer Inst 2003;95: 1477–81]

The Nutritional Prevention of Cancer Trial *(1)* was designed to test the efficacy of selenium supplementation in preventing nonmelanoma skin cancer in men and women with a history of two or more basal cell carcinomas or one or more squamous cell carcinomas of the skin. During the intervention, an unexpected deficit of other cancer and mortality among selenium-supplemented participants became apparent, so that in 1993, end points for the trial were expanded to include several secondary ones: lung, prostate, and colorectal cancer incidence, total cancer incidence, and total cancer mortality. Analysis of the complete observation period through January 31, 1996, revealed a 25% decrease in total cancer incidence, a 52% decrease in prostate cancer incidence, a 26% decrease in lung cancer incidence, a 54% decrease in colorectal cancer incidence, and a 41% decrease in total cancer mortality *(2).* This report extends the previous results (September 15, 1983, through December 31, 1993; total subject follow-up = 8271 person-years) through the end of blinded treatment (September 15, 1983, through January 31, 1996; total subject follow-up = 9904 person-years).

The protocol for the Nutritional Prevention of Cancer Trial was described by Clark et al. *(1).* Briefly, this study was a randomized, double-blind, placebo-controlled trial conducted among 1312 patients in the Eastern United States with a history of two or more basal cell carcinomas or one or more squamous cell carcinomas of the skin *(1).*

Patients were randomly assigned in a double-blinded manner to experimental treatment (200 μg of selenium per day in a 0.5-g high-selenium baker's yeast tablet) or to placebo. The total selenium content of tablets was monitored by G. F. Combs, Jr., and I. S. Palmer (South Dakota State University, Brookings), who used the diaminonaphthalene fluorometric procedure after digestion in a mixture of nitric acid and perchloric acid *(3).*

The baseline interview of each patient gathered sociodemographic, occupational, and behavioral information *(1).* The baseline examination addressed sun exposure and sensitivity. A dermatologic examination included the assessment of sun damage for each temple and the dorsum of each hand. Each area was assessed and classified into one of the following nine clinical categories: 1 = mild$^-$; 2 = mild; 3 = mild$^+$; 4 = moderate$^-$; 5 = moderate; 6 = moderate$^+$; 7 = severe$^-$; 8 = severe; 9 = severe$^+$. For each participant, the sun damage variables for the four assessment areas were averaged to provide the index of clinical sun damage. Although this index has not been directly validated *(4,5),* it has proved a powerful predictor of risk for nonmelanoma skin cancer. Patients were scheduled to be examined every 6 months. Incident basal cell carcinomas and squamous cell carcinomas were diagnosed by biopsy and confirmed by board-certified dermatopathologists. Recurrent and retreated skin tumors and skin tumors without biopsy confirmation were excluded from the study.

Patient medical records were periodically reviewed. For patients who be-

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came inactive, annual contact was attempted. Medical, surgical, and pathology documentation of new illness or medical procedures was requested.

Plasma selenium concentration was determined by Dr. Combs, as described *(1)*. Quality control included testing multiple aliquots of human plasma. A coefficient of variation of less than 7% (for duplicate analyses) was required *(6)*.

Statistical analyses were based on data from the 1250 patients with initial blood samples drawn within 4 days of randomization. No statistically significant differences were observed among the total cohort of 1312 and the subsample of 1250 patients with valid baseline selenium values (621 in the selenium treatment group and 629 in the placebo group) *(2)*. In addition, no statistically significant differences were detected in occurrence among the total and subsample groups.

Person-years of follow-up were calculated from the date of randomization as the start date and the earlier of January 31, 1996, or the date of death as the end date *(2)*. For time to first new nonmelanoma skin cancer occurrence analyses, person-years of follow-up for participants with new basal cell carcinomas or squamous cell carcinomas were calculated through the date the first skin tumor was diagnosed. First nonmelanoma skin cancer occurrence data were compared by treatment groups by use of Nelson–Aalen cumulative hazard function estimates and the two-sided log-rank test. Relative risks were based on the ratio of the incidence densities for the treatment groups, and corresponding 95% confidence intervals were calculated. *P* values were derived from log-rank tests. Supporting analyses included hazard ratios and 95% confidence intervals, calculated with the Cox proportional hazard model to adjust for potential confounders. These data met assumptions for using the Cox model.

Effect modification by median age (65 years), sex, smoking (never, former, or current), and baseline selenium was considered by the Mantel–Haenszel test for heterogeneity and by the interaction of each characteristic and treatment group. All statistical tests were two-sided. The occurrence of multiple skin tumors was examined by negative binomial regression analysis *(7)*. This model was used because the parameter that captures extra-Poisson variation was statistically significant.

Selected baseline characteristics of the 1250 patients by treatment group have been published *(2)*. Treatment groups were well balanced; no statistically significant differences were observed in mean clinical sun damage, sun sensitivity, sunscreen use, or nonmelanoma skin cancer (basal cell carcinoma and squamous cell carcinoma), defined as new diagnoses within the 12 months before randomization.

At the end of blinded treatment on January 31, 1996, 36% (37% of placebo and 35% of selenium) of patients were still on treatment, 17% (15% of placebo and 19% of selenium) of patients were off treatment but still having routine dermatologic examinations, 22% of placebo and selenium patients were censored for dermatologic end points, and 25% (26% of placebo and 24% of selenium) of patients had died. After 9904 person-years of follow-up, no patients were lost to vital follow-up and only seven (three in the selenium group and four in the placebo group) declined to provide additional illness information. Patient-reported compliance was similar in the two treatment groups, with 79% (80% of placebo and 78% of selenium) reportedly missing a pill less than twice a month.

Estimates from the 1983–1993 analysis revealed more cases of basal cell carcinoma (relative risk [RR] = 1.10, 95% confidence interval [CI] = 0.95 to 1.28) and squamous cell carcinoma (RR = 1.14, 95% CI = 0.93 to 1.39) in the group supplemented with selenium than in the placebo group. These differences were not statistically significant *(1)*.

Results for the entire period of blinded treatment through January 31, 1996, are shown in Table 1. The relative risk of a new occurrence of skin cancer was increased statistically significantly for basal cell (RR = 1.17), squamous cell (RR = 1.32), and total nonmelanoma skin cancer (RR = 1.27). Multivariate-adjusted Cox proportional hazard analysis indicates statistically nonsignificant risk enhancement for basal cell skin cancer; risk remains statistically significant for squamous cell (HR = 1.25) and total nonmelanoma skin cancer (HR = 1.17). The cumulative incidence of squamous cell carcinoma throughout the period of blinded treatment is shown in Fig. 1.

Eliminating cancers that occurred within the first 2 years of treatment was used to evaluate the lag between selenium treatment and skin cancer risk (data not shown). Eliminating these cases had no impact on the relative risk of basal cell cancers. In contrast, eliminating cases that occurred during even the first year of treatment caused the relative risk of squamous cell and total nonmelanoma skin cancer associated with selenium treatment to decline slightly to statistical nonsignificance. Eliminating cases that occurred during the first 2 years of treatment caused an additional slight decline in this relative risk. Thus,

Table 1. Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) through January 31, 1996, by treatment group

	Incidence*		Unadjusted		Adjusted	
Tumor type	Placebo group	Selenium group	RR (95% CI)	*P* value	HR (95% CI)†	*P* value
BCC*,‡	0.13	0.16	1.17 (1.02 to 1.35)	.03	1.09^1 (0.94 to 1.26)	.24
SCC*,‡	0.05	0.07	1.32 (1.09 to 1.60)	.004	1.25^2 (1.03 to 1.51)	.03
NMSC§	0.16	0.20	1.27 (1.11 to 1.45)	.001	1.17^3 (1.02 to 1.34)	.03

*Incidence was calculated by dividing the number of cases by the total person-years of follow-up. RR = relative risk; NMSC = nonmelanoma skin cancer.

†Hazard ratio (HR), confidence interval (CI), and *P* values were derived from Cox proportional hazard models adjusted for sex, age, smoking status, clinic site, plasma selenium concentration, clinical sun damage, sunscreen use at baseline, and number of previous BCCs (superscript 1), SCCs (superscript 2), or total NMSCs (superscript 3) in the 12 months before randomization. All statistical tests were two-sided.

‡Participants diagnosed with new BCCs and SCCs are represented in both BCC and SCC analyses.

§Number of participants in total NMSC analysis does not equal the sum of participants included in the separate BCC or SCC analyses because individuals diagnosed both with new BCCs and SCCs were counted only once.

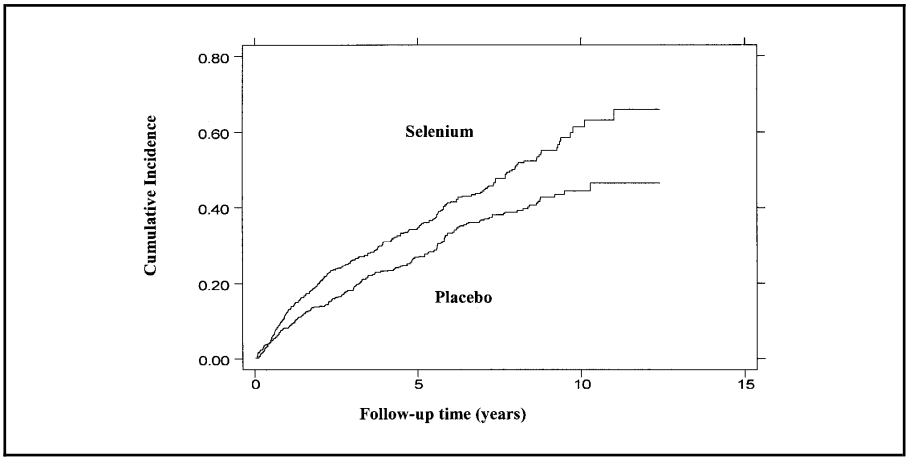

Fig. 1. Nelson–Aalen cumulative incidence estimates (95% confidence intervals) for both treatment groups at 5 years and 10 years of follow-up. Placebo group: 5-year follow-up = 0.27 (0.23 to 0.32); 10-year follow-up: 0.44 (0.38 to 0.52). Treatment group: 5-year follow-up = 0.34 (0.30 to 0.40); 10-year follow up = 0.61 (0.53 to 0.71). Log-rank test *P* value = .004.

for example, eliminating cases during the first 2 years of treatment caused the unadjusted relative risk of total nonmelanoma skin cancer to decline from 1.27 (95% CI = 1.11 to 1.45) to 1.20 (95% CI = 0.98 to 1.47).

No variation in effects by age, sex, or smoking status was statistically significant. The association between selenium supplementation and squamous cell carcinoma by tertile of baseline plasma selenium is shown in Table 2. The adverse effect of selenium supplementation appeared to increase with increasing baseline plasma selenium concentration; the interaction of selenium treatment and baseline selenium was statistically significant. Regardless of adjustment for a wide range of possible confounders, skin cancer patients with baseline plasma selenium in the upper tertile experienced a 60% increase in probability of a new skin cancer as a result of selenium supplementation.

Negative binomial regression analysis of time to the occurrence of multiple tumors and time to first occurrence showed similar associations (data not shown). Negative binomial models were also used to investigate the effect of selenium supplementation within subgroups defined by baseline characteristics.

The Nutritional Prevention of Cancer Trial tested selenium supplementation for preventing nonmelanoma skin cancer occurrence in high-risk individuals. This study was originally designed to provide statistical power of 80% with an α value of .05 to detect a 22% change in basal cell carcinoma and a 35% change in squamous cell carcinoma. It was expected that, with 4 years of follow-up, there would be 550 patients with new basal cell carcinoma and 175 with new squamous cell carcinoma. The numbers of basal cell carcinomas and squamous cell carcinomas observed are greater than expected, albeit with longer follow-up.

With complete follow-up (mean = 7.9 years), positive associations between selenium treatment and nonmelanoma skin cancer occurrence persist. Indeed, analyses through the end of treatment (January 31, 1996) reveal statistically significant increases of 25% and 17% in the risk of squamous cell carcinoma and total nonmelanoma skin cancer, respectively. These appear to be concentrated among participants in the highest two tertiles of baseline plasma selenium. Modification of the effect of supplementation by baseline selenium, not hypothesized *a priori,* could also reflect a chance finding or methodologic nuance.

Compliance with this intervention was high; the blood selenium level of patients in the treatment group was substantially higher than that of patients in the placebo group *(1).* Furthermore, total cancer incidence and mortality were lower in patients in the treatment group than in those in the placebo group *(1,2).* This effect, however, apparently did not translate into protection against nonmelanoma skin cancer. Selenium-treated patients could have been less cautious than placebo-treated control patients about sun exposure after the study began, although we have no evidence that this was true.

These clinical trial results are inconsistent with findings of a protective association between plasma selenium level and the risk of nonmelanoma skin cancer *(8–11)* and with findings that topical application of selenium protects humans against ultraviolet B radiation (UVB) *(12).* The results are inconsistent with animal experiments in which dietary and topically applied selenium decrease UVB-induced skin damage, tumor formation, and overall mortality *(13–17). In vitro* studies have shown that organic (50–200 n*M*) and inorganic (1–100 n*M*) selenium compounds can protect keratinocytes *(17,18),* melanocytes *(18),* and fibroblasts *(19)* from UVB. Sodium selenite (1–50 n*M*) and selenomethionine (50–200 n*M*) alter immune function in murine keratinocytes, preventing the release of UVB-induced cytokines that promote inflammatory damage (i.e., interleukins 6 and 8) *(20)*

Table 2. Squamous cell carcinoma and selenium supplementation, by baseline plasma selenium concentration

Baseline plasma selenium tertile, ng/mL	Referent	Unadjusted*			Adjusted†		
		RR (95% CI)	*P* value	P_{int}	HR (95% CI)	*P* value	P_{int}
⩽105.2	1.00	0.95 (0.68 to 1.31)	.73	.04	0.87 (0.62 to 1.22)	.42	.04
105.6–122.0	1.00	1.55 (1.10 to 2.19)	.009		1.49 (1.05 to 2.12)	.03	
⩾122.4	1.00	1.62 (1.14 to 2.32)	.005		1.59 (1.11 to 2.30)	.01	

*RR = relative risk; CI = confidence interval. *P* values and *P* for interaction (P_{int}) values were derived from incident rate ratios.

†HR = hazard ratio. P_{int} = *P* value for treatment group characteristic interaction (treatment group × factor), the cross-product term derived from Cox proportional hazards models adjusted for sex, age, smoking status, clinic site, clinical sun damage, sunscreen use at baseline, and number of previous squamous cell carcinomas 12 months before randomization. All statistical tests were two-sided.

and suppress cell-mediated immunity *(21,22)*.

Several large, phase III chemoprevention trials *(23–29)* have been performed in subjects at high risk of nonmelanoma skin cancer. Studies of retinoids *(30–32)* suggest that subjects at an early stage in UV-induced skin carcinogenesis can be protected by chemoprevention. Patients in the Nutritional Prevention of Cancer Trial had developed at least one nonmelanoma skin cancer and may simply be beyond protection by an agent such as selenium.

Results of the Nutritional Prevention of Cancer Trial that show no benefit of selenium supplementation in the secondary prevention of nonmelanoma skin cancer indicate that selenium will not protect against nonmelanoma skin cancer. Indeed, selenium administered at 200 μg/day appears to increase the risk of squamous cell carcinoma and total nonmelanoma skin cancer among men and women with a history of nonmelanoma skin cancer. This appearance of increased risk is dependent on specification: it declines with a 1- or 2-year lag. Moreover, it hovers at the margin of statistical significance. Weighing any detrimental effect against the protection afforded by selenium supplementation may require careful debate. Although the results of the Nutritional Prevention of Cancer Trial suggest protection against solid tumors, those results represent end points secondary to nonmelanoma skin cancer. Nonmelanoma skin cancer is rarely fatal, but these negative effects of selenium supplementation appear greatest among those with high baseline concentrations of plasma selenium, i.e., greater than 122.4 ng/mL. The average serum selenium concentration in the United States has been estimated to be 123 ng/mL *(33)*. Nonmelanoma skin cancer patients with higher baseline concentrations of plasma selenium appear to gain no protection against other cancers by selenium supplementation *(2)*: those nonmelanoma skin cancer patients with plasma selenium greater than 123 ng/mL appear most likely to suffer untoward nonmelanoma skin cancer consequences and are least likely to gain protection against cancer from selenium supplementation.

The generalizability of these observations is critical. These subjects were all skin cancer patients, with skin that had sustained heavy sun damage. We have not to date identified factors that modified the impact of selenium, other than baseline plasma selenium, but further analysis may reveal such factors. It is possible, for example, that some commonly used drugs could have nullified or even reversed the effects of selenium supplementation.

Exposure to environmental contaminants might have altered the impact of supplementation on skin cancer incidence among these subjects. For example, many of the subjects worked on farms, with great potential for arsenic pesticide exposure; arsenic exposure has been associated with nonmelanoma skin cancer *(34)*. The dermatologic examination for each NPC clinic visit evaluated punctate keratoses of the palms, which are believed to result from arsenic exposure *(35)*. Approximately 60% of the NPC participants had at least one of these lesions. Several authors *(36,37)* have shown that arsenic interferes with the metabolism of selenium and selenium incorporation into proteins. Although the effects of arsenic and other contaminant exposures on the impact of selenium chemoprevention are unknown, further evaluation of them is underway.

These results must also be considered in terms of the overall impact of supplementation by selenium as a putative chemopreventive agent. Prostate cancer prevention trials presently underway, including one testing selenium among men with high grade prostatic intraepithelial neoplasia *(38)* and one testing selenium and vitamin E among average risk men *(39)*, will help to clarify this overall impact.

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NOTES

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