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

Duffield-Lillico et al. (1) reported an increase in skin cancer for those taking selenium supplementation as a secondary prevention for nonmelanoma skin cancer in a randomized trial. Importantly, the National Cancer Institute (NCI) in the early 1980s evaluated selenium sulfide (SeS₂, CAS No. 7446-34-6) and a shampoo formulation containing SeS₂ (Selsun) for potential carcinogenicity in experimental animals (2–4; Huff J: unpublished data). These were selected for study on the basis of widespread worker and consumer exposures. Selenium finds considerable and rising use as a nutritional additive to animal and human diets and in hair shampoos, and it is being evaluated for chemoprevention of human cancers. Four carcinogenesis bioassays were conducted via oral or dermal routes of exposure. SeS₂ in 0.5% aqueous carboxymethylcellulose was given by oral intubation 7 days/week for 2 years to Fischer rats at 0, 3, and 15 mg/kg per day and to B6C3F1 mice at 0, 20, and 100 mg/kg per day. Dermally, SeS₂ in 0.5% aqueous carboxymethylcellulose was applied to the clipped backs of ICR Swiss mice at 0, 0.5, or 1.0 mg three times a week for 86 weeks. Likewise, Selsun shampoo (2.5% SeS₂) was applied to ICR Swiss mice at 0.05 mL of a 25% (0.31 mg of SeS₂) or a 50% (0.625 mg of SeS₂) solution in distilled water three times per week.

Oral exposure of SeS₂ caused primarily liver tumors in male and female rats and liver and lung tumors in female mice. Male rats also exhibited increases in interstitial cell tumors of the testes and of the hematopoietic system (leukemias). Despite early deaths from amyloidosis and the limited lifespan of Swiss mice, dermal application of SeS₂ was associated with tumors of the lung and circulatory system in female mice, and dermal exposure to SeS₂ shampoo showed increases in lung tumors in male mice.

In addition to causing skin cancers in humans (1), these experimental carcinogenic results (2–4; Huff J: unpublished data)—tumors of the liver, lung, and testes and the hematopoietic and circulatory systems—should caution us that long-term selenium intake may be more hazardous than previously realized. Thus, we should be equally concerned about and on the lookout for other potential cancer sites in humans in occupational settings as well as in those taking selenium-containing supplements.

Notably however, Dufield-Lillico et al. (5) show a protective effect of selenium supplementation on the overall incidence of prostate cancer, although the effect was restricted to those with lower baseline prostate-specific antigen and plasma selenium concentrations. Additionally, beginning in mid 2001, the NCI began a large prostate cancer prevention trial with 32,000 men aged 55 years or older who will be taking neither, either, or both selenium and vitamin E (6), the premise being that selenium and vitamin E are both naturally occurring antioxidants capable of neutralizing free radicals that might otherwise damage genetic material and possibly lead to cancer. Perhaps during the NCI prostate cancer prevention trial using selenium and vitamin E, these men should be monitored closely for signs of cancer development as well as for gauging protective effects against prostate cancer. Meanwhile, prospective experimental long-term...
bioassays might be undertaken with this chemical combination.

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REFERENCES


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RESPONSE

We are grateful to Dr. Huff for his comments.

The biologic activity of selenium is very much dependent on its chemical form (I–3). Elemental selenium, for example, has virtually no biologic activity. Selenite and selenate, inorganic forms, are toxic at fairly low doses. In the Nutritional Prevention of Cancer (NPC) trial, selenium was administered in selenized yeast. The major form of selenium in the selenized yeast most commonly available today is selenomethionine, an organic form; the form that predominated in the selenized yeast used in the NPC trial was also selenomethionine, although a number of other selenium compounds were recently identified (4). Selenomethionine, now being tested in two ongoing prostate cancer chemoprevention trials (5,6), has low toxicity and is absorbed by the body in the same manner as methionine. Catabolism of selenomethionine initiates a cascade of metabolites, including selenocysteine, hydrogen selenide (which is an active oxidant), and methylselenol (which may be most directly protective against cancer). Methylselenocysteine, a possibly important compound now under investigation, is metabolized to methylselenol in a single-step cleavage (I–3).

The toxicity, the carcinogenicity, and, conversely, the anticancer activity of selenium compounds likely vary widely. The form of selenium mentioned by Huff, selenium disulfide, may well be carcinogenic in a number of applications. Nonetheless, the fact that one selenium compound has deleterious effects does not mean all others do. The hazard of extrapolating from nonhumans to humans also bears emphasizing. The NPC trial has, on average, 7.9 years of follow-up on human subjects. It is fair to question whether the results for the NPC participants are fully generalizable, but it must be qualitatively less difficult to generalize from these subjects to other humans than from Fischer or B6C3F1 rats or ICR Swiss mice to humans.

The primary end point of the NPC study was nonmelanoma skin cancer (NMSC); NPC tested selenium supplementation as a means of preventing NMSC recurrence among high-risk individuals and found that it increased risk. Nonetheless, the enthusiastic response to the first presentation of the NPC results emphasized secondary end points. The editorial that accompanied that first NPC report cautioned that the results demanded replication before they could be regarded as in any sense definitive or confirmed (7). Our finding is that selenium increased the risk of our primary end point, a finding that requires additional testing in other clinical trials.

Huff’s comments are a useful reminder of the high standard necessary for chemoprevention: Trials of selenium in men with an average risk, whose results will figure prominently in decisions about chemopreventive strategies, should attend carefully to the clinical trial evidence that selenium may increase the risk of NMSC.

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REFERENCES


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