Reply to Dr. Schrauzer

Dear Editor,

The comments of Dr. Schrauzer concerning our article (1) in particular, and the context and findings of the SU.VI.MAX study (2) in general, raise several issues.

Although not central to the hypothesis or conclusions of our study, the first issue is the long-standing controversy concerning the biological properties of zinc (Zn). This relates to the relative importance of the physiological properties of Zn as an essential cofactor for enzymatic activity, as an antioxidant, its supposed interactions with selenium (Se) compounds, and its influence on oncogenesis.

We think that the influence of antioxidants and free radicals on the acquisition and stabilization of cancerous features in cells is not black and white, with this influence varying as a function of dose, the oxidative environment of the cell, and the stage of the cell cycle. In this respect, although Se, a potent mediator of cellular redox reactions, is widely proposed to be an antioxidant and, thus, to protect against cancer development, a recent study indicates Se has a more complex role with respect to cancer development (3). Moreover, within the catalytic cycle of glutathione peroxidase, Se undergoes redox changes that can trigger prooxidant reactions under certain circumstances (4). In parallel, recent research has revealed complex interactions between Se and cellular Zn homeostasis, indicating, for example, that Zn finger motifs are highly reactive toward oxidizing Se compounds (5). Inhibitory interactions of Se with Zn finger motifs of transcription factors have repeatedly been claimed to contribute to the presumed protective properties of Se compounds with respect to tumor development. However, it should be remembered that Zn finger proteins are also involved in many cellular reactions required to maintain genomic stability. Thus, Zn finger inactivation may lead to increased genetic instability under certain circumstances (6), which could be expected to have detrimental consequences on cancer development. Functioning DNA repair mechanisms are required to protect the genome from DNA damage induced by environmental agents, such as ultraviolet radiation, as well as from endogenous DNA damage. Because redox reactions are important for the regulation of Zn finger proteins and their related cellular pathways, an imbalance in intracellular Se levels, whether due to Se deficiency or oversupply, may considerably lessen genomic stability. For these reasons, it seems difficult to implicate individual oligo-elements or vitamins in the changes in risk of skin cancer development revealed in our study.

Second, we have always emphasized that our goal in the SU.VI.MAX study was to evaluate the impact of a combination of vitamins and essential minerals, on the hypothesis that such a combination may be more efficacious than single molecules given alone, due to potential complementarity and synergy in their mechanism of action (7). Indeed, the SU.VI.MAX study was not designed to discriminate the effects of an isolated nutrient at a specific dosage from the other components of the combination used in the trial (2,8). In our analysis, the opposite effect of supplementation on skin cancer incidence in men and women was confirmed by building a Cox proportional hazard regression model that showed an interaction term between gender and treatment group (P = 0.013) in addition to gender and treatment group effects.

With respect to Zn, no effect of baseline levels on cancer incidence was observed in either women (hazard ratio = 1.88; 95% CI [0.05; 75.65]) or men (HR = 1.86; 95% CI [0.04; 88.10]). In contrast, a significant relationship between baseline levels was observed in both women (HR = 6.38) and men (HR = 3.35) for vitamin C. With respect to longitudinal data, serum Zn concentrations did not differ between women in the 2 treatment groups 2 or 7 y after randomization, whereas serum Se concentrations increased significantly in both women and men in the antioxidant intervention group. Therefore, the hypothesis of an interaction between Zn and Se in terms of absorption or circulation is not supported by our data, which show minimal changes in serum Zn levels due to supplementation. We emphasize that a categorical link between intake estimators for individual elements, such as Zn and Se on the one hand and mortality rates related to skin cancer (presumably melanoma) on the other cannot be inferred from the data of our study. Although a causative role for Zn in the increased incidence of skin cancer, as suggested by Schrauzer, cannot be ruled out, a study evaluating specific Zn supplementation would be required to demonstrate this.

Finally, the results published in 1977 suggesting evidence for a protective role of Se and a deleterious role of Zn against cancer development came from studies initiated at a time when reference values for dietary Se were unavailable for many of the 27 participating countries. Therefore, it seems hazardous to implicate a definite impact of specific Se intake on the incidence of cancers using such findings.

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Literature Cited


