Selenium status in the body and proliferative activity of malignant cells

Sir,

Avanzini and co-workers recently reported the results of their study on serum selenium concentrations in patients with newly diagnosed lymphoid malignancies.[1] Interestingly, as compared to controls, selenium (Se) levels were significantly lower in patients with non-Hodgkin's lymphoma (in a representative sample) in IV stage and/or in those with high grade disease. However, literature reports of serum Se levels in patients with lymphoid malignancy or solid tumors are discordant.[2-4] These discrepancies may be due to case series that are not directly comparable among themselves or with healthy control cohorts.

It must be borne in mind that the elevated variability of serum Se may be due to factors other than cancer such as age, sex, body mass, dietary habits, life style (alcohol, smoking), intercurrent disease and medications.

When considering the various biological roles of Se (proliferation and expression of oncogenes by both normal and malignant cells, carcinogen metabolism, cellular immune response, prevention of oxidative stress, apoptosis) and when addressing the topic of whether Se is a risk factor or a protection against cancer,[5] one must evaluate selenium levels both in serum and in biological material that integrates selenium intake and reflects its status over the medium and long term (4 months for red blood cells, 12 months or longer nails and hair). These studies are however methodologically complex, and at present various types of investigations (prospective, environmental, epidemiological, ecological) have failed to provide conclusive results.

Several factors may influence Se exchanges between labile pools, deposits and cancer tissue, and we wish to point out one important factor which has so far received little attention but which might influence selenium profiles, namely the proliferative activity of cancer cells. Of particular interest along this line of thought is the finding by Avanzini and co-workers of an inverse relationship between serum selenium and β2-microglobulin, an important index of the turnover of neoplastic cells.

In an ongoing study on Se levels in the serum and hair of women with breast cancer (unpublished data), we observed that patients recruited at an early clinical stage had lower serum Se and higher Se hair content with respect to patients at a more advanced stage or to healthy controls:

Stage 0-I (n=42): serum Se mean value 76.2±21.7 μg/L, hair Se content geometric mean 416.5 μg/g

Stage II-IV (n=44): serum Se mean value 81.5±22.4 μg/L, hair Se content geometric mean 335.2 μg/g

Controls (n=86): serum Se mean value 88.6±26.4 μg/L, hair Se content geometric mean 370.5 μg/g

Though our data fell short of statistical significance, due in part to the wide spread of values in the series, the findings are suggestive in light of the kinetic properties of tumor cells.[6] Indeed the relationship between Se and cellular growth emerged from our *in vitro* studies that showed different Se accumulation and effect according to cell density in the lymphocyte cultures used in our experiments.[7] Breast cancer shows a Gompertz-type growth curve with an exponential increase in the early proliferative phases. These events, whose underlying mechanisms also require further investigation in terms of host-tumor interactions, might influence different aspects of Se distribution in various body districts.

In conclusion, further experimental and epidemiological studies are warranted to better elucidate the relationships between Se status and carcinogenesis; however, determination of Se levels in subjects with malignancies will only contribute data useful for the clinician when it is performed across several body districts (blood, depots, healthy and diseased tissue) and interpreted in the light of the proliferative characteristics of the tumor and of the intricate tumor host relationships.

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Selenium and lymphoid malignancies (Reply)

Sir,

Piccinini *et al.*'s hypothesis that the proliferative activity of malignant lymphoid cells and of cancer cells in general might influence selenium status is interesting and is partially supported by prior data, including our own.[1] However, due to the limited evidence available on this topic, further data are needed to confirm that enhanced selenium uptake by neoplastic tissue may vary according to the mitotic activity of the cancer cells.

Piccinini and colleagues also addressed a fundamental issue in epidemiologic and clinical research on the health effects of selenium: the methodology for exposure assessment and, in particular, the use of biomarkers as surrogate measures of selenium exposure (represented in most individuals by dietary intake). Selenium content of serum, plasma, erythrocytes, whole blood, hair, toenails, and urine are among the biomarkers most frequently used in epidemiologic and clinical studies. Serum, plasma and urine selenium are short-term markers of exposure, whereas the remaining indicators tend to reflect long-term selenium intake. The limitations of these indicators as surrogate measures of intake have been reviewed.[2] Selenium-dependent glutathione peroxidase activity has also been evaluated as a possible biomarker of exposure, but it does not appear to be a reliable indicator of selenium intake since the correlation between the two parameters is not linear[2] and, what is more, glutathione peroxidase activity may be induced by oxidizing agents[3] (including selenium itself).[4,5]

In our clinical studies[1,6] we evaluated selenium exposure through determination of serum selenium content, a sensitive short-term selenium marker,[2] because we were interested in a possible relationship between the clinical characteristics of lymphoid malignancies and recent changes in selenium status. Obviously the characteristic that makes serum selenium content of interest in clinical research, i.e. its ability to reflect short-term selenium intake, also represents a limitation in an epidemiologic setting, particularly in retrospective studies where selenium status is likely to be affected by the disease, at least in some body tissues. This is why we did not consider our results to be contradictory to the prior hypothesis of a direct association between selenium exposure and the risk of lymphoid malignancies,[7] though they did not add any evidence to support this hypothesis.

Biomarkers, however, may not adequately reflect selenium intake due to factors such as gender, body mass, medical