

29 Cu	25 Mn	3 Li
30 Zn	79 Au	47 Ag
92 U	28 Ni	63 Eu
14 Si	27 Co	76 Os
82 Pb	80 Hg	34 Se
		11 Na

Many decades ago, selenium was considered to be carcinogenic. Although it was known that lack of selenium in New Zealand grasslands caused the so-called "white muscle" disease, a degenerative disease characterized by weak, discoloured muscle tissues in farm animals, soil supplementation was not allowed in fear that the element could pass on to man. Then, in the 1960s, thanks to R. Foltz, K. Schwarz, and W. Mertz, the concept changed. Far from being a carcinogen, selenium was found to be instead an essential element. In China, vast areas of selenium-poor soils were associated with Keshan disease, from the name of the area, a cardiomegaly affecting mostly women and young children, a situation which then improved through selenium food supplementation. More recently, selenium was found to be an antioxidant protecting cells from free-radical oxidation and possibly even beneficial in preventing prostate cancer. It is definitely a promising element in nutrition and human health. For these reasons, it was thought of interest to dedicate this issue of the newsletter to selenium.

The Editorial Board

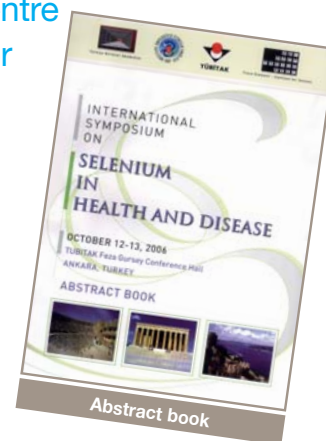
The International Symposium on Selenium in Health and Disease, held in Ankara, Turkey on 12-13 October 2006 was organized by Pr A.O. Cavdar, Coordinator of the satellite centre to Trace Element - Institute for UNESCO in Turkey.



Pr Cavdar

In this newsletter, we have chosen to publish :

- Pr Gerald F. Combs' paper on the interest of selenium in cancer prevention, presented at the symposium.
- Dr Filiz Hincal's report on iodine and selenium status in Turkish children.



Abstract book



Organizers and participants at the international symposium

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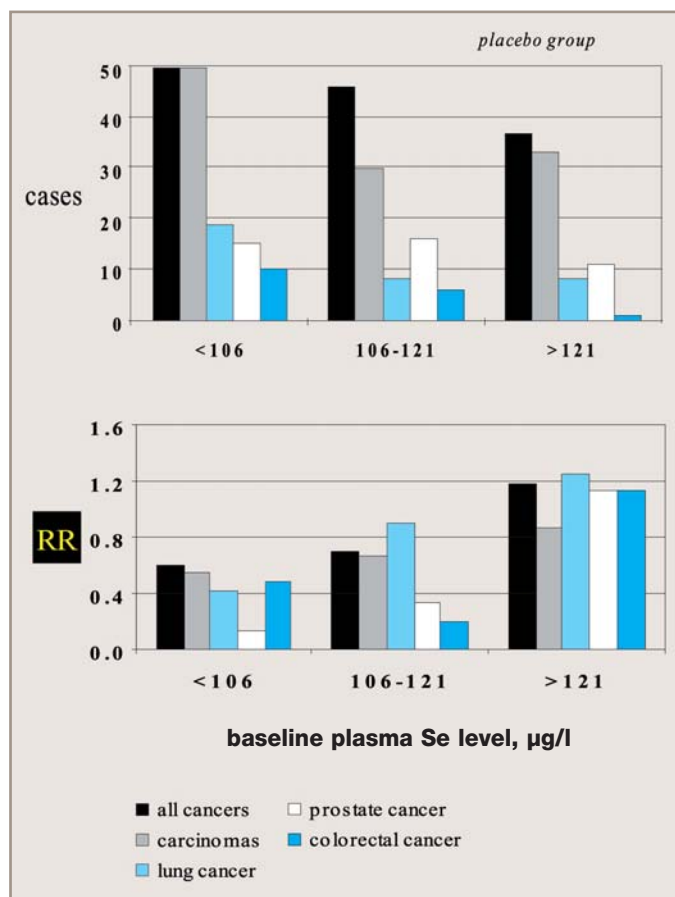


● The role of selenium in cancer prevention

Gerald F. Combs, Jr, Director of Grand Forks Human Nutrition Research Center, USDA-ARS, Grand Forks, ND, USA.

● That selenium (Se) might be anti-carcinogenic came when it was noted that cancer mortality rates appeared to vary inversely with forage crop Se contents in the US. Most, but not all, of the subsequent literature has found Se status to be inversely associated with cancer risk, prospective cohort studies have shown cancer cases to have significantly lower mean pre-diagnostic serum Se levels than controls, and negative associations have been found for parameters of Se status and risk of cancer or pre-cancerous lesions of several tissues. These findings have been supported by studies in various animal models, which have shown Se treatment to reduce and/or delay tumorigenesis.

Figure 1: Effect of baseline Se status on cancer cases in placebo-treated individuals (upper panel), and of supplemental Se (200 µg/d) on relative risks (RR) to cancers (lower panel) in the NPC Trial.



● Only a few clinical trials have been conducted to test the hypothesis that Se can reduce cancer risk in humans, the most robust being the Nutritional Prevention of Cancer (NPC) Trial, a double-blind, randomized, placebo-controlled clinical trial that used a daily dose of Se (200 µg/d as Se-yeast) conducted with 1 312 high-risk, older Americans with histories of non-melanoma skin cancer. The results (ca. 8 yrs/subject follow-up) showed that Se-treatment significantly reduced risk of total cancers (RR=0.63), carcinomas of the prostate (RR=0.51) and colon-rectum (RR=0.46) (Figure 1) [1-4]. It did not, however, protect against recurrent non-melanoma skin cancer [4].

● The NPC Trial results indicate that Se treatment protects against early stages of prostate cancer. Se-treated men with plasma prostate specific antigen (PSA) concentrations ≤ 4 ng/ml showed 65% less prostate cancer than non-treated controls (P=0.01) [2], while men with PSA>4 ng/ml did not benefit from Se-treatment. Protection from prostate cancer by Se occurred mostly for subjects with baseline plasma Se levels in the lower tertile (<106 µg/l) of the cohort (RR=0.14, P=0.002), while subjects in the middle tertile (107-123 µg/l) experienced a modestly protective effect (RR=0.39, P=0.03) and those highest tertile (>123 µg/l) experienced no protection (RR=1.20, P=0.66) (Figure 1). This suggests that subjects with plasma Se levels <106 µg/l (1.35 µM/l) may benefit from increases in Se intake.

● Cancer risk reduction in the NPC Trial occurred in subjects who, with baseline plasma Se levels of 114±23 ng/ml, were not deficient in Se: only two subjects had levels <80 µg/l, above which healthy adults show no increases in Se-dependent glutathione peroxidase activity when supplemented with Se [5] (these plasma Se levels suggest average Se intakes of 85 µg/day). That cancer protection by Se can occur in non-deficient individuals likely to have fully expressed Se-enzymes suggests anti-carcinogenic mechanisms in addition to the physiological functions of the selenoenzymes [6,7]. Indeed, animal model studies show Se to be anticarcinogenic at dietary levels exceeding by an order of magnitude those required to prevent clinical signs of Se deficiency and to support maximal selenoprotein expression. Studies have shown certain Se-metabolites, namely methylated selenides, to function in anti-carcinogenesis [6-8].

● Thus, Se may function in anti-carcinogenesis as both an essential constituent of metabolically important selenoproteins, and as a source of anticarcinogenic metabolites. Because the former function appears to be optimized at lower levels of Se exposure than are required to support the latter function, minimization of cancer risk appears to require Se intakes greater than those required for maximal selenoprotein expression.

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Iodine and selenium status in Turkish children

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Iodine is the primary requirement for thyroid hormone synthesis and regulation, and iodine deficiency (ID) is a major public health problem particularly for young children and women and a significant threat to national, social and economic developments in several parts of the world. Selenium (Se) is also essential for the regulation of thyroid hormone synthesis, metabolism and

functions, and inadequately available for men and livestock in many countries. Turkey is one of those countries where iodine deficiency is widespread and Se levels are marginal. In this overview, iodine and Se status of Turkish children, salt-iodization experience and related studies are summarized.

Iodine deficiency in Turkey

Until recently, endemic goiter has prevailed in all geographical regions of Turkey and there has been no region with less than 2% goiter prevalence [1]. A national survey conducted in 1995 showed a prevalence rate of 30.3%, and in a study conducted prior to the mandatory iodization of salt started in June 1999, the prevalence was found to be 26-52% [2]. The survey covered 1 226 children aged 9-11 years from 4 cities of Central Anatolia and the Black Sea region, and the median urinary iodine (UI) levels observed (25, 30, 16, 14 $\mu\text{g/l}$) indicated the presence of severe to moderate ID. In a following survey, covering 20 cities of Anatolia and 5 948 school-age children, goiter prevalence ranged from 5 to 56% and median UI (14 to 78 $\mu\text{g/L}$) indicated moderate to severe ID in 14 of the provinces surveyed [3]. In the same period, in an endemic goiter area of Central Anatolia, goiter prevalence was 44% and mean UI levels of 7-12 year-old children was 39 ± 38 $\mu\text{g/l}$ [4]. Two years later, iodized-salt usage was 44% among 1 573 primary school children in Istanbul, the

median UI level was found to be in the normal range, but more than half of them had mild to moderate ID [5]. A report covering 1 046 school children and 18 606 neonates from 3 cities of western Black Sea region pointed out a rate of 52% goiter prevalence and 1/2326 congenital hypothyroidism [6]. Three years after the mandatory iodization, goiter prevalence was found as 15% in the same area [7] and 13% in Ankara (central Anatolia) [8]. While iodized salt usage rate was still 52% among the children of rural and urban areas of West Coast five years after the mandatory iodine prophylaxis, goiter prevalence was found to be 12% [9]. Despite these improvements, there is still a big difference between rural and urban populations in iodized-salt use [10], and there are certain isolated mountainous areas of the country where the current program of salt iodization solely will not be adequate [11]. Moreover, high incidence of congenital hypothyroidism being observed over the years warrants a country-wide neonatal screening program [12].

Selenium in Turkey

There is a lack of detailed information regarding the soil content of Se in Turkey. Data on the Se content of foodstuff produced in the country is also limited and confined to grain levels. The first data on Se status in Turkey was reported by our group as 88 ± 12 $\mu\text{g/l}$ serum Se for 76 children (aged from 2 months to 13 years) from middle to middle-upper income families in Ankara [13]. In the following years, the mean Se levels were found to be 45 ± 10 $\mu\text{g/l}$ in cord blood; 69 ± 13 $\mu\text{g/l}$ in 2-12 month-old infants; 77 ± 12 $\mu\text{g/l}$ in children aged >12 mo-16 years, and 74 ± 16 $\mu\text{g/l}$ in

adults aged 18-48 years old [14]. The results of other studies were also in the same range: Mengubas *et al* [15] reported 75 ± 9 $\mu\text{g/l}$ for boys and 65 ± 10 $\mu\text{g/l}$ for girls; in a study covering 250 school-age children from four different regions, the average values were 51-58 $\mu\text{g/l}$ serum Se [16]; and recently a mean value of 74 ± 11 $\mu\text{g/l}$ Se for 43 healthy children was reported [17]. However, as low as 31 ± 23 $\mu\text{g/l}$ Se levels were also reported for school-children coming from a severely endemic goiter area [4].

Daily intake of selenium

For the evaluation of dietary daily intake, double portion technique is the most precise method but not convenient for applying to large numbers of samples. We, therefore, estimated the daily intake of Se by using two statistical formulas [18,19]. The derived values for the children of Ankara region were 45 ± 10 $\mu\text{g/d}$ [18] and 43 $\mu\text{g}\pm 10$ $\mu\text{g/d}$ Se [19] and very similar to those obtained by

duplicate portion technique [20]. When all the available data for children was considered and an estimation for a range of ~50-70 $\mu\text{g/l}$ serum Se was made, daily intakes of Se were found to range from 30 to 40 $\mu\text{g/d}$. These values are at the borderline or lower than those of RDA values for children established as 40 $\mu\text{g/d}$ for 9-13 years and 55 $\mu\text{g/d}$ for 14-18 year-olds [21].

Selenium, thyroid and antioxidant/oxidant status

The effects of Se on thyroid derive from the fact that it is the essential part of the antioxidant defense system and that the enzymes, iodothyronine deiodinases, that catalyze the deiodination of thyroid hormones are selenoenzymes. With the aim of investigating the alterations of oxidant and antioxidant status and oxidative DNA-based damage in iodine-deficient goitrous children, we conducted a study in high schools of two towns of the eastern Black Sea region where the prevalence rate of endemic goiter is the highest of Turkey [22]. Prevalence of goiter was 39.6%, and the goitrous group (severely and moderately iodine-deficient children), had significantly lower Se levels and antioxidant enzyme activities (erythrocyte glutathione peroxidase, superoxide dismutase and catalase) than non-goitrous controls (normal iodine or mildly iodine-deficient status). Modified DNA base levels (8-OH-guanine, 5-OH-cytosine, 8-OH-adenine) were

also found to be significantly higher in the goitrous group [23]. Hence, these results indicated the presence of oxidative activity and enhancement of free radical reactions in severely and moderately iodine-deficient goitrous children. It is known that consistently low iodine intake (< 50 $\mu\text{g/d}$) usually results in goiter, but not all people with iodine deficiency develop goiter. Whether the high level of oxidant stress encountered in goitrous populations is a cause or a consequence needs to be further investigated. However, in the study presented, highly iodine-deficient non-goitrous children existed within the control group and their antioxidant enzyme and Se status were not different from controls. Therefore, it may be speculated that goiter development is more likely to occur in individuals having lower status of antioxidant enzymes and Se.

Conclusions

Considering the important physiological functions of iodine and Se and available data in the literature suggesting that higher Se intake may be beneficial for protection against several diseases including cancer [24, 25], it is necessary to ensure consumption of a balanced diet adequate in both nutrients and to continue effective salt iodization programs.

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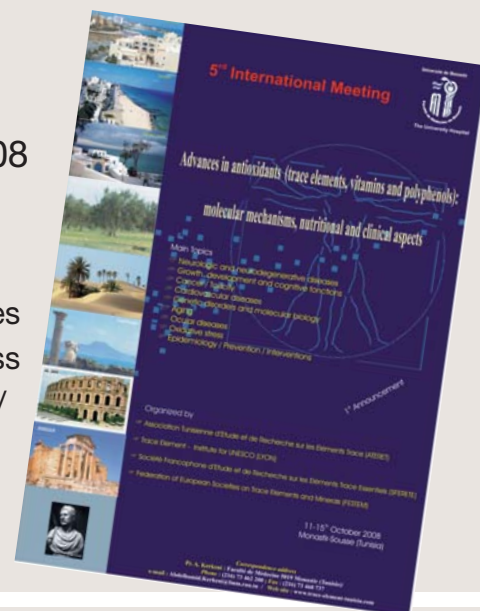
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