Abstract. Background: An inverse relationship between selenium (Se) intake and cancer mortality is evident in humans. Materials and Methods: In eighty patients who had been operated on for primary gastric cancer, serum Se and carcinoembryonic antigen (CEA) levels were measured preoperatively using a fluorometric and immunoradiometric assay (IRMA), respectively. Results: The serum Se levels were 43±6.3 μg l–1 in the patient group and 68.7±4.5 μg l –1 in healthy individuals (p<0.001). The serum CEA was 12±1.9 U ml–1 in the gastric cancer patients and 2.1 U ml –1 in the control group (p<0.001). The Se tissue concentrations were 2,640±220 mg g–1 in excised neoplastic tissue and 685±115 mg g –1 in non-neoplastic tissue (p<0.001). An inverse correlation between Se and CEA serum levels was found (r=–0.782). There was no correlation between serum/tissue Se concentration and disease stage/histological type or gender in the patient group.

More than 10 million new cancer cases each year are recorded worldwide, with cancer being one of the leading causes (12%) of death (1). Gastric cancer is the second leading cause of death among cancer patients after lung cancer. Every year 800,000 new cases of gastric cancer are diagnosed worldwide (1), with prevalence in Japan, Chile, Colombia and Central America. Ninety five percent of the stomach malignancies are represented by gastric adenocarcinoma. Identifying cancer risk factors is crucial, both in prevention and treatment of these diseases (2-4).

Since the beginning of the 1970s (5, 6) the trace element selenium (Se) has received much attention and a low serum concentration has been related to increased risk for various types of cancer in humans (7, 8). The implication of Se in cardiovascular disease and other conditions involving oxidative stress and inflammation has also been established (8). Se is found naturally in the environment, although soil concentrations vary widely geographically. Diet and drinking water supplies represent the primary sources of Se intake (9, 10), with consumption from foods ranging from 71 μg to 152 μg daily. The daily Se intake in Greek people is estimated at approximately 110 μg (5, 18-20). In humans, high Se concentrations are detected in the thyroid glands, kidneys, genitals and liver, whilst lower Se concentrations are detected in the pancreas and lymph nodes (11). Several studies showed an inverse correlation with age-adjusted mortality for colorectal, prostate, breast, ovary and lung cancer, as well as for some hematological malignancies, whilst only a weak association was found for pancreatic and skin cancer. In addition, low Se is associated with risk of lung, colorectal, esophageal, stomach, liver, breast, prostate and urinary bladder cancer.

Se plays an important role in cancer prevention (12), but the homeostatic mechanisms which regulate plasma and tissue Se concentrations have not been completely elucidated. Se exists in the human body in the form of selenocysteine (SeCys), a component of selenoproteins (SePs, SPs), and appears to have important structural and enzymatic roles such as antioxidant activity. Twenty-five SPs have been identified to date, out of a possible 50 thought to exist. It is well established that oxidative stress plays an important role in the carcinogenic process. Human defense mechanisms against reactive oxygen species (ROS) which induce oxidative damage are amplified by Se. In particular, SeCys, reduces the levels of hydrogen peroxide and may act as an antitumoral agent. Glutathione peroxidase (GPx),

Key Words: Selenium, trace elements, gastric cancer, carcinoembryonic antigen.
thioredoxin reductase (TrxR) and selenoprotein P (SePP) are the main selenoproteins containing molecular Se within their active center. SePs, all of which contain molecular Se, regulate the cellular antioxidant defense system, DNA damage and protein function, furthermore controlling cell-mediated immunity and B-cell function. The antiproliferative action of Se in the G1-phase of the cell cycle has been well documented in both normal and neoplastic cells. In addition, Se impairs the expression of c-fos and c-myc oncoproteins (13). It has also been reported that Se supplementation reduces the Cox-2 protein levels in colorectal cancer cells (14, 15). However, in the literature there are many controversial studies regarding the protective/therapeutic role of Se in human cancer. Interestingly, it is well documented that high doses of Se may lead to cytotoxic effects and even to carcinogenesis due to DNA strand breaks. Although many chemoprevention trials have strongly suggested that Se supplementation may have some protective effects against certain cancer types in populations where average dietary Se concentrations from 0.002 μg and is considered the method of choice throughout Europe (17).

Patients and Methods

Eighty patients (57 males, 23 females), mean age 61±15 years, with gastric adenocarcinoma (stage I-IV) of diffuse or intestinal type (54:26, ratio 2.07:1) according to the Lauren classification, were enrolled in the study. An age/sex-matched population group of 120 individuals was selected for comparison of the serum laboratory data since serum Se level differs with age and sex. In the patients, the serum Se levels were measured at the time of diagnosis before any kind of treatment was started. A fluorometric method (Watkinson’s) modified by Thorling et al. (17) was used, which compared to others such as, spectrometric, nonflame molecular absorption, neutronic activation and volumetric methods, is specific and very sensitive, detecting Se concentrations from 0.002 μg and is considered the method of choice throughout Europe (17).

Blood samples (10 ml whole blood) were taken from the median cubital vein in the morning after the individuals had fasted during the previous night. After centrifugation, the samples were preserved at –4°C. Neoplastic and healthy non-neoplastic tissue samples from the area surrounding the tumor were taken during surgery and were preserved in liquid nitrogen. The tissue Se concentration was determined by the use of a modified fluorometric assay similar to the serum method. The serum CEA levels were measured by immunoradiometric assay (IRMA).

For statistical analysis, the t-test was used and p-values less than 0.001 were regarded as statistically significant.

Results

The serum Se concentration was 43±6.3 μg l⁻¹ in the gastric cancer patients and 68.7±4.5 μg l⁻¹ in the age-matched control group of healthy individuals (p<0.001). The neoplastic tissue Se concentration was 2640±220 μg g⁻¹ tissue; the concentration in the adjacent non-neoplastic tissue was 685±115 μg g⁻¹. Thus, an almost four-fold (statistically significant, p<0.001) increase in neoplastic tissue Se concentration compared to the surrounding healthy tissue was detected. The serum CEA level in the gastric cancer patients was 12±1.9 U ml⁻¹ and 2.1 U ml⁻¹ in the control group (p<0.001) (normal values <2.5 U ml⁻¹ in nonsmokers and <3.5 U ml⁻¹ in smokers). An inverse relationship between the Se and CEA serum levels was found (r=-0.782). No correlation between serum/tissue concentration and gender, disease stage and/or histological type, was found.

Discussion

Organic Se is present in foods mainly in the form of SeCys, selenomethionine (SeMeth) and seleno-methylselenocysteine (Se-CH₃-SeCys), whilst inorganic Se, either in the form of selenite or selenate, is found infrequently or in very low amounts. Both organic and inorganic Se is utilized with similar efficacy in the human body, producing SePs, although Se enters at different points in the metabolic process depending on the chemical form. Glutathione (GSH) reduces the inorganic forms (selenite and selenate) of Se. The originally discovered cytosolic glutathione peroxidase (GSH-Px or GPx-1), the phospholipid hydroperoxidase GSH-Px, and the secretory GSH-Px, represent three isoenzymes of glutathione peroxidase. The latter, ubiquitously expressed, is the first and best characterized SP in mammals.

Other SePs such as TrxR and SePP also contain molecular Se in their active center and act in a similar fashion. Se, apart from its preventive role in various types of human cancer such as breast, prostate and bladder cancer (3, 21, 22), additionally shows a direct antineoplastic effect acting via various enzymic pathways. Experimental data have shown that the chemopreventive effect of Se is due, at least in part, to its inhibitory effect on cell growth, DNA, RNA, and protein synthesis in transformed cells (12). Several reports have described the inhibitory effect of Se on kinase enzyme activity. Cell cycle cyclin-dependent-kinase-2 (cdk2) and/or cell signaling protein kinases and/or some redox-regulated proteins with critical transcription factors have been proposed as targets against which Se exerts its chemopreventive actions. An increase in cyclin B expression as well as phosphorylation of cdk2 coincidental with cell cycle arrest has been demonstrated (12). In a number of studies, an inverse association between serum Se levels and neoplastic development has been observed in various cancer types. It has been postulated that...
the process underlying tumor development can lead to an uptake of Se by the malignant cells, thus explaining the increased Se levels in the tumor mass (7, 23, 24). It is not clear whether the increased Se levels in the neoplastic tissue are responsible for the lower serum Se levels found in these patients, or if the latter precede the development of cancer. Also in regard to the significance of the increased Se concentration in neoplastic tissue, an attractive hypothesis is that this phenomenon reflects, at least in part, the human defense mechanisms against the neoplastic process. Of course, further studies are needed to elucidate this issue.

In the present study, a nearly four-fold increase in Se concentration was found in the neoplastic tissue compared with the adjacent healthy tissue (p<0.001). Simultaneously, the serum Se levels were significantly lower in the patient group compared to the age/sex-matched group of Greek healthy individuals, which was in agreement with our previous findings regarding patients with colorectal and breast cancer (23, 24).

The inverse relationship between Se and CEA serum levels found in the present study possibly indicate that the development and progression of gastric carcinoma are associated with decreasing levels of serum Se. This concept is greatly supported by the antioxidant action of Se.

References