SESSION 5
TRACE ELEMENTS, MINERALS AND CANCER

POSSIBLE PROTECTIVE ROLE OF TRACE ELEMENTS IN HUMAN CANCER: A REVIEW OF RECENT EPIDEMIOLOGICAL STUDIES

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The interest in the role of trace elements in cancer is increasing, particularly for those with a possible protective action, such as selenium and zinc. Despite the vast amount of epidemiological studies already conducted, there is a need for further investigations to better understand what compounds, at what levels and with which mechanism trace elements are involved in the protection of a specific cancer or groups of cancer. From our studies, we observed that cancer type and patient characteristics can substantially affect plasma concentrations of trace elements such as Se, Zn and Cu. However, serum/plasma analyses may be insufficient to evaluate trace element status. A better evaluation of the body burden of trace elements should include analysis of other indicators such as hair, cells or tissue specimens, which tends to reflect long-term exposure to these elements. Despite trace elements at physiological levels are not definitively associated with a decreased cancer risk, many studies on the efficacy of supplemented doses of Se and other compounds were carried out with contradictory results. In addition, both absorption and biological effects might vary according with chemical form, as confirmed in our «in vitro» studies on selenium. The narrow safe range of intake for Se suggests caution in supplementing this element by tablets, and further analyses on the actual Se intake with diet in European countries are needed. The epidemiological studies are aimed to provide the basis for developing and evaluating preventive procedure and public health practices. In this context, it appears of particular importance to better define adequate trace element dietary intake and/or to verify the efficacy of supplementation in the cancer prevention, avoiding undue collateral or even toxic effects.

THE EFFECTS OF DI-(2-ETHYLHEXYL) PHTHALATE ON TESTICULAR ELEMENT STATUS IN SELENIUM-DEFICIENT AND SELENIUM-SUPPLEMENTED RATS

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Di (2-ethylhexyl) phthalate (DEHP), a widely used plasticizer for synthetic polymers, is known to have endocrine disruptive potential, reproductive toxicity, and induce hepatic carcinogenesis in rodents. The question in this study was whether DEHP causes alterations in trace element balance and distribution, and the study was designed to investigate the effects of DEHP exposure in normal, selenium (Se) deficient and Se-supplemented rats. Se-deficiency was produced by feeding 3-week old Sprague-Dawley rats with $\leq$ 0.05 Se mg/kg diet for 5 weeks, and supplementation group were on 1 mg Se/kg diet. DEHP treated groups received 1 g/kg dose by gavage during the last 10 days of feeding period. Se, Zn, Cu, Mn and Fe levels were measured by ICP-MS in plasma and tissue homogenates of liver, kidney and testis. In Se-deficient animals, Se concentration was maintained only in testes. The other significant trace element alterations were elevation of Zn and Cu in testes, and decreased Mn and Cu in kidney. Se-supplementation caused significant increases only in liver and kidney Se, and a decrease of Mn in kidney. With DEHP exposure, trace element balance was maintained in testes and liver. But plasma Se and Zn concentrations were significantly lowered, and the kidney was the most affected tissue with a significant increase of Zn and decreases in Se, Cu and Mn concentrations. DEHP exposure in both Se-deficient and Se-supplemented animals seemed to affect mostly the kidney and liver Mn concentrations. These results showed the potential of DEHP exposure to modify the distribution pattern of essential trace elements in various tissues, the importance of which needs to be further evaluated.

THE USE OF OVINE PULMONARY ADENOMATOSIS AS AN ANIMAL MODEL OF PROGRESSIVE LUNG CANCER IN A LONG-TERM STUDY OF THE IMPACT OF NUTRITIONAL SELENIUM SUPPLY

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Jaagsiekte sheep retrovirus (JSRV) is known to induce ovine pulmonary adenocarcinoma (OPA). The tumour has been considered as a large animal model for human lung adenocarcinoma. Several studies suggested an influence of Se status on cancer incidence, but specific data are limited. Thus, the combination of OPA with a defined Se supply might give further information about the impact of Se on cancer progression. 16 sheep, naturally infected with JRSV, were divided into 2 groups with different Se levels in diet (< 0.05 and 0.2 mg Se/kg dry matter, resp.). Computed tomography (CT) with general inhalation anaesthesia as well as x-ray was performed every three months. A new CT-OPA score system was generated to classify cancer progression. Liver biopsies were performed immediately after CT. Blood samples were collected biweekly, broncho-alveolar lavage (BAL) was performed 2—3 times per animal. Cell pellets from BAL fluid (BALF) were tested for JSRV by PCR as well as for cytology. To date, three animals of the ongoing study have been euthanized. Postmortem and histopathology were performed and correlation to CT findings was reassessed. Progression of lung tumours could clearly be visualised by CT. Postmortem findings showed good correlation with CT data. The advantage of score-based CT for quantifying tumour progression in contrast to x-rays is evident. Routine haematology, clinical chemistry as well as analysis of Se and seleno-enzymes were available to demonstrate the metabolic effects of distinguished feeding. The liver tissue was sufficient to determine Se, glutathione peroxidase as well as thioredoxin reductase. JRSV was detected in BALF cell pellets. In conclusion, OPA turns out to be a useful cancer model when integrated into advanced tumour imaging by CT, providing a sensitive basis for following up of cancer proliferation consecutively. Moreover, the ongoing study will give further insights into the impact of Se on tumour progression in a long-term, large animal study.

INTEGRIN BETA3 LEU33PRO POLYMORPHISM AND TRACE ELEMENTS CONCENTRATION AND RISK OF CANCER

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The incidence of prostate cancer (PC) and bladder cancer (BC) increase gradually. The genetic variations alone do not explain the observed differences in incidence of PC and BC, indicated that environmental and dietary factors are of importance. The recent 10 years to discover the trace elements are related to cancer. Cell adhesion molecules play an important role in the development and progression of cancer. The glycoprotein alpha (IIb)beta3a (GPIIb/IIIa) is the main fibrinogen receptor on platelets. The gene *gp3a* encodes the beta chain of this receptor and demonstrates the Leu33Pro (PLA) polymorphism. The association of the beta3 Leu33Pro polymorphism (allelic variants *PLA1* and *PLA2*) and the concentration of zinc (Zn) and iron (Fe) with cancer development and progression were studied. We assessed the risk of PC and BC in individuals with the Leu33Pro polymorphism (heterozygote and homozygote) relative to those without the polymorphism (non-carriers). A study group of patients with PC, patients with BC and age-matched controls healthy volunteers were measured for genotype of gp3a with polymerase chain reaction using DNA extracted from freshly drawn blood. Detection of trace elements in the hairs was done by using XRF. In population 76% are non-carriers (PLA1/PLA1), 22% are heterozygote (PLA1/PLA2), and 2% are homozygote (PLA2/PLA2). Among the patients with cancer 57.8% were non-carries, 37.8% were heterozygote and 4.4% were homozygote. The frequency of PLA2 carries was significantly higher in patients with PC and BC, comparing to population frequency ($p<0.02$). The zinc content in hair of volunteers were 73.33 ± 12.75 μg/g; iron — 77.10 ± 5.86 μg/g. For the patients with PC: zinc — 55.20 ± 5.17 μg/g; iron — 86.50 ± 7.29 μg/g. For the patients with BC: zinc — 60.1 ± 16.32 μg/g; iron — 90.30 ± 10.03 μg/g. The tumour progression, local invasion and metastases have a greater rate for the patients with lower concentration of zinc and for the carries of Leu33Pro polymorphism (PLA1/PLA2) than that for non-carries patients (PLA1/PL1).

ANALYSIS OF COPPER, ZINC AND IRON CONCENTRATIONS IN TISSUES OF TUMOUR-INOCULATED ANIMALS ON BEING TREATED WITH OZONE AND DOXORUBUCIN

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The work was aimed at testing copper, zinc and iron content in the tissues of experimental tumour-inoculated animals on having been injected with ozone and doxorubicin. The tests were done on plasma and tissues of different organs (heart, liver, kidneys, lungs, brain). The animals were divided into 5 groups: (1) controls — rats with re-inoculated malignant tumour of mammary gland; (2) tumour-inoculated animals that were on doxorubicin injections; (3) tumour-inoculated animals that were on ozonated saline injections; (4) tumour-inoculated animals that were on combined injections of ozonated saline and doxorubicin; (5) intact animals. The study was done in accordance with European Community principles of humanity. The test samples were taken by mineralization autoclave method. To evaluate the Zn, Cu, Fe content in blood plasma and tissue there was used atomic-emission spectrometer ICAP 6300 INTERTECH Corporation (USA). All the examined tissues of the control group showed the decrease of Fe, Cu, Zn levels compared with intact animals. The most vivid decrease was seen in brain tissue for Fe (as much as 2.5 times) and Zn (as much as 7.6 times). The most marked changes compared with the controls were in the second group. Fe content in the tumour of animals from the second group decreases due to doxorubicin influence as much as 2.4 times, Zn — 6.6 times and Cu — 6.7 times. Intraperitoneal ozonated saline infusions caused less marked microelements changes than with doxorubicin injections. Combined effect of doxorubicin and ozone was not marked by sharp changes in Fe, Cu, Zn levels in tissues. It can testify of ozone having a corrective effect on doxorubicin, thus preventing further changes in microelements levels in tissues.

ASSOCIATION BETWEEN LEVELS OF PROSTATE SPECIFIC ANTIGEN AND LEVELS OF BLOOD CADMIUM AND URINARY CADMIUM

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BACKGROUND AND OBJECTIVE: If the risk of prostate cancer is associated with cadmium exposure, there may have association between prostate-specific antigen (PSA) and levels of blood cadmium (BCd) and urinary cadmium (UCd). The associations between them were determined. METHODS: We recruited 295 men 50 years of age and above for health check up program at medical centres. With consent, study subjects completed a self-reported questionnaire and provided fasting samples of blood and urine for cadmium assay, using atomic absorption spectrophotometry. Blood samples were also collected for assays of total cholesterol and high density lipoprotein measures. RESULTS: The age specific mean levels of BCd and UCd increased with age with the overall means of 1.19 ± 1.04 ug/l and 1.37 ± 1.76 ug/g creatinine, respectively. The PSA level was positively associated with the lipid level, but reversely associated with BCd and UCd levels. Multivariate logistic regression analysis showed that the odds ratio (OR) of PSA > 4 ng/g was 0.4 (95% confidence interval (CI) = 0.1—0.9) for having the BCd greater than the mean level. The OR of PSA > 4 ng/g was also 0.4 (95% CI = 0.2—1.0) for having the UCd greater than the mean level. CONCLUSION: This study shows that the PSA level is negatively associated with both BCd and UCd.

SPECIFIC CORRELATIONS BETWEEN BIOGENIC ELEMENTS AND AMINO ACIDS IN THE BLOOD OF PATIENTS WITH BENIGN TUMOURS OF MAMMARY GLAND

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Mammary gland benign tumour is a widespread disease. 20 to 60% women have various forms of mastopathy. Mastopathy is the background for the possible development of mammary gland cancer. We estimated the contents of macro- and microelements and amino acids in the blood serum of somatically healthy women and cases of various mastopathy forms. All diagnoses were histologically verified. In cases of mammary gland fibroadenoma the levels of Zn and Ca were significantly higher in the blood serum — an evidence of a possible role of these essential microelements in the mastopathy development ($p < 0.05$). A strong direct correlation was revealed between biogenic Zn and isoleucine contents ($r = 0.900$; $p < 0.037$) and strong reverse correlation between Zn and asparagine ($r = -0.975$; $p < 0.005$), Zn and serine ($r = -0.900$; $p < 0.037$) — an evidence of an important relationship between biogenic Zn and amino acids. Significant direct correlations were observed between Fe on the one hand and serine, phenylalanine, tryptophan ($r = 0.900$; $p < 0.037$) on the other hand. Fe levels in the blood serum were not limited by metabolism of replaceable amino acids — proline and cystine, as evidenced by the reverse correlation between them ($r = -0.900$; $p < 0.037$). Direct correlations were between Mn and histidine, Mn and ornithine ($r = 0.900$; $p < 0.037$). Mg and arginine, Mg and alanine ($r = 0.900$; $p < 0.037$). The results obtained conclude of a relationship between biogenic elements and a number of amino acids in the blood of ill women. Estimation of correlations between the contents of amino acids and biogenic elements in the blood serum of patients with benign tumours of mammary gland, and may be used in diagnostics and prognosis.

SPECIFICITY OF MICROELEMENT METABOLISM IN THE BLOOD SERUM OF MEGAPOLIS-DWELLING WOMEN HAVING MALIGNANT TUMOUR OF MAMMARY GLAND

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Diagnostics and treating lactic gland diseases is presently an urgent problem. Micro- and macroelements are known to participate in cell proliferation, differentiation and apoptosis. They are present in enzyme active centres, in nucleoproteins, transcriptional factors and oncoproteins, affect the immune and antioxidant systems. Therefore the problem of specific microelement metabolism in malignant tumour tissues arouses interest. The content of macroelements in the blood serum of somatically healthy and sick (breast cancer) women was investigated. The control group was somatically healthy women without oncological pathology in the anamnesis. The second group were breast cancer cases, stages I and II. All diagnoses were histologically verified. The content of Cu, Zn, Ca, Mg, Mn, Fe, Co, Sr, Cd, Pb was estimated by the atomic absorption (device: Analist 100, firm Perkin Elmer). The sick patients had the levels of Ca and Cu 1.4 times lower ($p < 0.05$), Fe — 6.4 times higher, Pb — twice higher, Sr — thrice higher ($p < 0.05$), an evidence of a possible correlation between the imbalance of these microelements and the disease development. The content of biogenic Zn was 1.8 times higher. Statistically significant were inverse ratios: between Zn and alanine levels ($r = -0.892$; $p < 0.007$), between Zn and taurine levels ($r = -0.928$; $p < 0.003$), between Fe and glutamic acid levels ($r = -0.785$; $p < 0.038$). The levels of Fe and leucine ($r = 0.928$; $p < 0.003$) had a significantly direct correlation. Certain metabolic disturbances accompanied by microelement imbalance occur in the cancer cases. The observed changes in the levels of micro- and macroelements in the blood serum and their relationships with the amino acids levels reveal the direct or indirect participation in the cancer development. Further investigations to reveal the possible usage of some microelements in pathogenetic therapy are needed.

A POTENTIAL CHEMOPROTECTIVE AGENT AGAINST AFLATOXIN B1 TOXICITY IN HUMAN BLOOD: BORIC ACID

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Aflatoxin B1 is the most potent pulmonary and hepatic carcinogen. Since the eradication of Aflatoxin B1 contamination in agricultural products has been difficult, the use of natural or synthetic free radical scavengers could be a potential chemopreventive strategy. On the other hand, boric acid is the major component of industry and its antioxidant role has recently been reported. The present study assessed, for the first time, the effectiveness of boric acid following exposure to Aflatoxin B1 on human whole blood cultures. The biochemical characterizations of glutathione and some enzymes have been carried out in erythrocytes. Alterations in malonic dialdehyde level were determined as an index of oxidative stress. The sister-chromatid exchange and micronucleus tests were performed to assess DNA damages in lymphocytes. Aflatoxin B1 treatment significantly reduced the activities of antioxidants by increasing malonic dialdehyde level of blood. Whereas, the boric acid led to an increased resistance of DNA to oxidative damage induced by Aflatoxin B1 in comparison with control values ($P<0.05$). In conclusion, the support of boric acid was especially useful in Aflatoxin-intoxicated blood. Thus, the risk on target tissues of Aflatoxin B1 could be reduced and ensured early recovery from its toxicity.