

Selenium in Breast Cancer.

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AIM: Controversy surrounds the hypothetical relationship between low serum levels of selenium and reduced activity of selenium-dependent enzymes, such as glutathione peroxidase, and an increased risk of cancer in humans. This study investigated serum concentrations of selenium in women with and without breast cancer. METHODS: In this case-control study, we compared serum concentrations of selenium in women with breast cancer (n = 200), healthy women (n = 100), and women with chronic diseases (n = 100). Patients with breast cancer were divided into premenopausal (n = 99) and postmenopausal subjects (n = 101). RESULTS: Mean serum concentrations of selenium were 81.1 $\mu\text{g/l}$ in women with breast cancer and 98.5 $\mu\text{g/l}$ in women with non-tumoral disease ($p < 0.001$). CONCLUSION: Alterations in serum concentrations of selenium in women with breast cancer appear to be a consequence, rather than a cause of cancer. In accordance with the hypothesis, the findings suggest that very low selenium status could be due to the nature of cancer. Copyright 2003 S. Karger AG, Basel

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Reactive oxygen species, antioxidant mechanisms, and serum cytokine levels in cancer patients: impact of an antioxidant treatment.

Mantovani G, Maccio A, Madeddu C, Mura L, Massa E, Gramignano G, Lusso MR, Murgia V, Camboni P, Ferreli L.

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OBJECTIVE: It has not been well established whether the oxidative stress found in cancer patients results from an increased production of oxidants in the body or from a failure of physiological antioxidant systems. To further investigate this question, we have assessed the blood levels of reactive oxygen species as a marker of free radicals producing oxidative stress and the most relevant of the physiological body enzymes counteracting reactive oxygen species, namely glutathione peroxidase and superoxide dismutase. We also investigated serum levels of proinflammatory cytokines and IL-2. All of these parameters were studied in relation to the most important clinical index of disease progression--namely, the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS). We also tested the reducing ability of different antioxidant agents on reactive oxygen species levels by measuring the increase in glutathione peroxidase activity and the reduction of serum levels of IL-6 and TNF-alpha. PATIENTS AND METHODS: We carried out an open nonrandomized study on 28 advanced stage cancer patients (stage III, 10.7% and stage IV, 89.3%) with tumors at

different sites. The patients were divided into 5 groups, and a different antioxidant treatment was administered to each group. The antioxidants were alpha lipoic acid 200 mg/day orally; N-acetylcysteine 1800 mg/day i.v. or carboxycysteine-lysine salt 2.7 g/day orally; amifostine 375 mg/day i.v.; reduced glutathione 600 mg/day i.v.; and a combination of vitamin A 30,000 IU/day orally, vitamin E 70 mg/day orally, and vitamin C 500 mg/day orally. The antioxidant treatment was administered for 10 consecutive days. RESULTS: We found that all but one of the antioxidants tested were effective in reducing reactive oxygen species levels, and two of them (cysteine-containing compounds and amifostine) had the additional effect of increasing glutathione peroxidase activity. Comprehensively, the antioxidant treatment was found to have an effect on both reactive oxygen species levels and glutathione peroxidase activity. The antioxidant treatment also reduced the serum levels of IL-6 and TNF-alpha. Patients in both ECOG PS 0-1 and ECOG PS 2-3 responded to antioxidant treatment.

PMID: 12678402 [PubMed - indexed for MEDLINE]

Biol Trace Elem Res 2003;91(3):203-215

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Oxidative-Stress Markers in Blood of Lung Cancer Patients Occupationally Exposed to Carcinogens

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The study covered 152 lung cancer patients and 210 controls. The results of the study indicated decreased selenium (Se) concentrations and lowered activity of erythrocyte antioxidant enzymes (glutathione peroxidase, superoxide dismutase, glutathione-S-transferase) in the blood of lung cancer patients, as well as significantly increased concentrations of vitamin E in erythrocytes and thiobarbituric acid reactive substances in the plasma of the study population. Low plasma Se concentrations ($< 45.7 \mu\text{g/L}$) enhance the estimated risk of lung cancer (odds ratio = 3.047, $p < 0.001$). A more precise exposure assessment is required to identify the association between lung cancer incidence and occupational exposure to carcinogens.

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Lung Cancer 2003 Apr;40(1):25-32

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Association between glutathione S-transferase p1 polymorphisms and lung cancer risk in Caucasians: a case-control study.

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Glutathione transferases (GSTs), a multiple gene family of phase II enzymes, catalyze detoxifying endogenous reactions with glutathione and protect cellular macromolecules from damage caused by cytotoxic and carcinogenic agents. Glutathione S-transferase p1 (GSTP1), the most abundant GST isoform in the lung, metabolizes numerous carcinogenic compounds including benzo[a]pyrene, a tobacco carcinogen. Previous studies suggest that genetic polymorphisms of GSTP1 exon 5 (Ile105Val) and exon 6 (Ala114Val) have functional effects on the GST gene product resulting in reduced enzyme activity. Individuals with reduced GST enzymatic activity may be at a greater risk for cancer due to decreased detoxification of carcinogenic and mutagenic compounds. Utilizing a hospital-based case-control study, we investigated the association between GSTP1 polymorphisms at exons 5 and 6 with lung cancer risk. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was used to successfully genotype the GSTP1 exons 5 and 6 polymorphism in 582 Caucasian lung cancer cases and 600 frequency matched Caucasian controls. There was no association between the exon 5 variant genotypes (A/G+G/G) and overall lung cancer risk (OR=1.09; 95% CI 0.82-1.45) nor when stratified by age, gender, and smoking status. However, the exon 6 variant genotypes (C/T+T/T) were associated with a statistically significant elevated lung cancer risk (OR=1.40; 95% CI 1.06-1.92). Additionally, there was an increase in lung cancer risk for the exon 6 variant genotypes in younger individuals (<62 years) (OR=1.63; 95% C.I. 1.07-2.49) but no effect in older individuals (OR=1.14; 95% CI 0.72-1.81). A statistically significant increased risk of lung cancer was also observed for the exon 6 variant genotypes among men (OR=2.17; 95% CI 1.41-3.33), but not among women (OR=0.80; 95% CI 0.51-1.28). Among ever smokers, the exon 6 variant genotypes were associated with an elevated lung cancer risk (OR=1.58; 95% CI 1.14-2.19), which was not evident for never smokers (OR=0.53; 95% CI 0.21-1.33). These data demonstrate that the GSTP1 exon 6 polymorphism, but not the exon 5 polymorphism, is associated with lung cancer risk that is especially evident in men, younger individuals, and ever smokers.

PMID: 12660004 [PubMed - in process]

Free Radic Res 2003 Feb;37(2):213-23

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The impact of different antioxidant agents alone or in combination on reactive oxygen species, antioxidant enzymes and cytokines in a series of advanced cancer patients at different sites: correlation with disease progression.

Mantovani G, Maccio A, Madeddu C, Mura L, Gramignano G, Lusso MR, Murgia V, Camboni P, Ferreli L, Mocci M, Massa E.

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In the present study we tested the ability of different antioxidant agents, used alone or in combination, to reduce the reactive oxygen species (ROS) levels and to increase the glutathione peroxidase (GPx) activity. Moreover, we tested the ability of such

antioxidant agents to reduce the serum levels of proinflammatory cytokines IL-6 and TNFalpha. Fifty-six advanced stage cancer patients with tumors at different sites were included in the study: they were mainly stage III (12.5%) and stage IV (82.1%). The study was divided into two phases. In the 1st phase 28 patients were divided into five groups and a single different antioxidant agent was administered to each group. The selected antioxidant agents were: alpha lipoic acid or carboxycysteine-lysine salt, amifostine, reduced glutathione, vitamin A plus vitamin E plus Vitamin C. In the 2nd phase of the study 28 patients were divided into five groups and a combination of two different antioxidant agents was administered to each group. The antioxidant treatment was administered for 10 consecutive days. The patients were studied at baseline and after antioxidant treatment. Our results show that all single antioxidants tested were effective in reducing the ROS levels and three of them in increasing GPx activity, too. Among the combinations of antioxidant agents, three were effective in reducing ROS, while three were effective in increasing GPx activity (arm 4 was effective in both instances). Comprehensively, the "antioxidant treatment" was found to be effective both on ROS levels and GPx activity. Moreover, the antioxidant treatment was able to reduce serum levels of IL-6 and TNFalpha. Furthermore, a correlation was shown between the Eastern Cooperative Oncology Group Performance Status of patients and blood levels of ROS, GPx activity, serum levels of proinflammatory cytokines.

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Cancer Res 2003 Mar 15;63(6):1297-303

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The role of manganese superoxide dismutase in the growth of pancreatic adenocarcinoma.

Cullen JJ, Weydert C, Hinkhouse MM, Ritchie J, Domann FE, Spitz D, Oberley LW.

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Chronic pancreatitis, K-ras oncogene mutations, and the subsequent generation of reactive oxygen species (ROS) appear to be linked to pancreatic cancer. ROS have also been suggested to be mitogenic and capable of stimulating cell proliferation. Cells contain antioxidant enzymes to regulate steady state levels of ROS produced by products of metabolism. The aims of our study were to determine antioxidant enzyme activity in pancreatic cancer cells and correlate enzyme activity with tumor growth, as well as determine whether tumor cell growth could be altered with antioxidant gene transfection. Western blots, enzyme activity, and enzyme activity gels were performed for manganese superoxide dismutase (MnSOD), copper/zinc, catalase, and glutathione peroxidase in normal human pancreas and in the human pancreatic cancer cell lines BxPC-3, Capan-1, MIA PaCa-2, and AsPC-1. Cell population doubling times were determined and correlated with antioxidant enzyme activity. MnSOD was overexpressed in MIA PaCa-2 using an adenoviral vector, and the effect on cell growth was determined. The cell pancreatic cancer lines BxPC-3, MIA PaCa-2, and AsPC-1 had decreased levels of MnSOD immunoreactive protein as well as activity

and decreases in MnSOD levels correlated well with increased rates of tumor cell proliferation as determined by cell doubling time. No correlation could be found between cell growth and levels of copper/zinc superoxide dismutase, catalase, or glutathione peroxidase. Enforced expression of MnSOD by adenovirus transfection in the rapid growing cell line MIA PaCa-2 increased MnSOD immunoreactivity and MnSOD activity and decreased growth rate. Overexpression of MnSOD may be effective in growth suppression of pancreatic cancer.

PMID: 12649190 [PubMed - indexed for MEDLINE]

Int J Mol Med 2003 Apr;11(4):479-84

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Reactive oxygen species and antioxidants in apoptosis of esophageal cancer cells induced by As₂O₃.

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To explore the relationship between the reactive oxygen species (ROS) and apoptosis in esophageal carcinoma cells (SHEE85) induced by arsenic trioxide (As₂O₃), we focused on changes of apoptosis, ROS, and antioxidants. Apoptosis of SHEE85 was confirmed by means of DNA fragmentation stained by Hoechst 33342, Sub-G1 cells scored by flow cytometry and ultrastructure of cells by electron microscopy. To evaluate the level of ROS, the chemiluminescent method was used for measuring the production of superoxide anion (O₂⁻). Lipid peroxide (malondialdehyde, MDA), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were measured respectively by the photometry method. In the cells treated with As₂O₃ at a concentration of 5.0 micro mol/l for 2-24 h, the content of cellular O₂⁻ and MDA was increased, but SOD and GSH-Px were significantly lower in the process of apoptosis in SHEE85. As₂O₃ at concentration of 0.5 micro mol/l did not cause cell apoptosis but promoted cell proliferation. These results suggest that As₂O₃ at a high dosage (5 micro mol/l) causes cell apoptosis and at a low dosage (0.5 micro mol/l) causes cell proliferation. The essential mechanisms of cell apoptosis induced by As₂O₃ may be related to the increase of ROS and decrease of anti-oxidation. ROS and antioxidants participate in the apoptotic pathway of esophageal carcinoma cells.

PMID: 12632101 [PubMed - in process]

Hepatogastroenterology 2003 Jan-Feb;50(49):126-31

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Antioxidant potential in esophageal, stomach and colorectal cancers.

Skrzydowska E, Kozusko B, Sulkowska M, Bogdan Z, Kozlowski M, Snarska J, Puchalski Z, Sulkowski S, Skrzydlewski Z.

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BACKGROUND/AIMS: The gastrointestinal tract is particularly susceptible to reactive oxygen species attack which lead to carcinogenesis. An important role in defense strategy against reactive oxygen species is played by antioxidants. The present study aims at examining antioxidant parameters and malondialdehyde--the product of lipid peroxidation as well as the marker of cancer progression--and cancer procoagulant in esophageal, gastric and colorectal cancer patients. **METHODOLOGY:** The activity of superoxide dismutase, catalase, glutathione peroxidase and reductase and the level of glutathione, vitamin C, malondialdehyde and cancer procoagulant were determined in tumors and normal mucous from 18 patients with esophageal cancer, 18 patients with stomach tumor and 62 patients with colorectal cancer. **RESULTS:** In esophageal tumor the activity of all enzymes has been increased compared with normal mucous. Stomach tumor has been also characterized by an increase in antioxidant enzymes activity except glutathione peroxidase and reductase whose activities have been decreased. However in colorectal tumor the activity of enzymes has been increased apart from catalase. In all cases the glutathione level has been increased while the vitamin C content has been significantly decreased. Tumor malondialdehyde level was significantly increased, too. The level of cancer procoagulant also increased in cancer tissues as well as in the serum. **CONCLUSIONS:** Antioxidant potential in all cases of gastrointestinal tract cancer has been unbalanced which has lead to increase in reactive oxygen species action and enhancement of lipid peroxidation and cancer procoagulant generation.

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Int J Cancer 2003 Mar 1;103(6):810-4

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Association between a glutathione S-transferase A1 promoter polymorphism and survival after breast cancer treatment.

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Glutathione S-transferase (GST) enzymes detoxify chemotherapeutic drugs, and several studies have reported differences in survival for cancer patients who have variant genotypes for GSTP1, GSTM1 or GSTT1 enzymes. A recently described polymorphism alters hepatic expression of GSTA1, a GST with high activity in glutathione conjugation of metabolites of cyclophosphamide (CP). To consider the possible influence of the reduced-expression GSTA1*B allele on cancer patient survival, we have conducted a pilot study of breast cancer patients treated with CP-containing combination chemotherapy. GSTA1 genotype was determined by polymerase chain reaction and restriction fragment length polymorphism. Kaplan-Meier methods and Cox proportional hazards models were used to evaluate survival in relation to genotype. Among 245 subjects, 35% were GSTA1*A/*A, 49% GSTA1*A/*B and 16% GSTA1*B/*B; the genotype distribution did not differ by ethnic group, age or stage at diagnosis. Among patients who had 0 or 1 GSTA1*B

allele, the proportion surviving at 5 years was 0.66 (95% CI = 0.59-0.72), whereas for GSTA1*B/*B subjects the proportion was higher, 0.86 (95% CI = 0.67-0.95). Significantly reduced hazard of death was observed for GSTA1*B/*B subjects during the first 5 years after diagnosis, hazard ratio (HR) = 0.3, 95% CI = 0.1-0.8. The association varied with time, with no survival difference observed for subjects who survived beyond 5 years. These results, although based on a small study population, describe an apparent difference in survival after treatment for breast cancer according to GSTA1 genotype. Further studies should consider the possible association between the novel GSTA1*B variant and outcomes of cancer therapy. Copyright 2002 Wiley-Liss, Inc.

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Acta Haematol 2003;109(2):108-9

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Polymorphisms of glutathione S-transferase mu1 (GSTM1) and theta1 (GSTT1) genes in multiple myeloma.

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PMID: 12624497 [PubMed - indexed for MEDLINE]

Biochem Biophys Res Commun 2003 Mar 14;302(3):593-600

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A phase II detoxification enzyme inducer from lemongrass: identification of citral and involvement of electrophilic reaction in the enzyme induction.

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We have developed a simple system for the sensitive detection and measurement of glutathione S-transferase (GST) activity that detoxifies polycyclic aromatic hydrocarbons using the cultured rat normal liver epithelial cell line, RL34 cells. Citral (3,7-dimethyl-2,6-octadienal) was isolated from the methanol extract of lemongrass (*Cymbopogon citratus*) and identified as a novel inducer of GST. Citral, a mixture of the two stereoisomers geranial and neral, dose- and time-dependently induced the total and pi-class-specific activities of GST. The structure-activity relationship study revealed that geranial, an E-isomer, was mainly responsible for the inducing activity of citral mixture and the aldehyde group conjugated with a trans-double bond is an essential structural factor. The data were consistent with the in vitro observation that both glutathione (GSH) and protein thiol quickly and specifically reacted with the

active isomer geranial, but not neral. Pretreatment of the cells with diethyl maleate significantly enhanced not only the basal activity but also the citral-stimulated activity of GST, while pretreatment with N-acetyl-cysteine inhibited it. Moreover, the treatment of RL 34 cells with geranial for 30min significantly attenuated the intracellular GSH level, while application for 18h enhanced it. These results strongly suggested that the electrophilic property characterized by the reactivity with intracellular nucleophiles including protein thiol or glutathione (GSH) plays an important role in the induction of GST. The present study also implied the antioxidant role of GST induction by citral in mouse skin, providing a new insight into skin cancer prevention.

PMID: 12615076 [PubMed - in process]

Breast Cancer Res Treat 2003 Mar;78(1):89-96

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Reproductive factors, glutathione S-transferase M1 and T1 genetic polymorphism and breast cancer risk.

Park SK, Kang D, Noh DY, Lee KM, Kim SU, Choi JY, Choi IM, Ahn SH, Choe KJ, Hirvonen A, Strickland PT, Yoo KY.

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We conducted a hospital-based case-control study to evaluate the interactive effect of reproductive factors and glutathione S-transferase (GST) M1 and T1 genetic polymorphisms in individual susceptibility to breast cancer. The study population consisted of 189 incident breast cancer cases and 189 age-matched controls with no known malignant diseases. GSTM1/T1 genotypes were determined by a multiplex polymerase chain reaction (PCR) method, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by conditional logistic regression model. The parity factors were grouped as (1) high-risk status defined as nullipara or para with experience of first full-term pregnancy (FFTP) at or over 30 years, and (2) low-risk status defined as para with experience of FFTP under 30 years. A significant multiplicative interaction was observed between GSTM1 and GSTT1 null genotypes and high-risk status of parity factor in all women and in premenopausal women ($P < \text{or} = 0.01$), but not in postmenopausal women ($P > 0.05$). The interaction between the combined genotypes of GSTM1 and GSTT1 and status of parity factor was also significant in all women and in premenopausal women ($P < 0.01$). Our findings suggest that genetic polymorphisms GSTM1/T1 could modify estrogen-related breast cancer risk.

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Curr Drug Metab 2003 Feb;4(1):45-58

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Cancer and phase II drug-metabolizing enzymes.

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Cancer development results from the interaction between genetic factors, the environment, and dietary factors have been identified as modulators of carcinogenesis process. The formation of DNA adducts is recognized as the initial step in chemical carcinogenesis. Accordingly, blocking DNA adducts formation would be the first line of defense against cancer caused by carcinogens. Glutathione-S-transferases inactivate chemical carcinogens into less toxic or inactive metabolite through reduction of DNA adducts formation. There are many different types of glutathione S-transferase isozymes. For example, GST delta serves as a marker for hepatotoxicity in rodent system, and also plays an important role in carcinogen detoxification. Therefore, inhibition of GST activity might potentiate the deleterious effects of many environmental toxicants and carcinogens. In addition, approximately half of the population lacks GST Mu expression. Epidemiological evidence showed that persons possessing this genotype are predisposed to a number of cancers including breast, prostate, liver and colon cancers. In addition, individual risk of cancer depends on the frequency of mutational events in target oncogenes and tumor suppressor genes which could lead to loss of chromosomal materials and tumor progression. The most frequent genetic alteration in a variety of human malignant tumors is the mutation of the coding sequence of the p53 tumor suppressor gene. O(6)-alkylguanine in DNA leads to very high rates of G:C deltaA:T transitions in p53 gene. These alterations will modulate the expression of p53 gene and consequently change DNA repair, cell division, and cell death by apoptosis. Also, changes in the expression of Bcl-2 gene results in extended viability of cells by over-riding programmed cell death (apoptosis) induced under various conditions. The prolonged life-span increases the risk of acquiring genetic changes resulting in malignant transformation. In addition, a huge variety of food ingredients have been shown to affect cell proliferation rates. They, therefore, may either reduce or increase the risk of cancer development and progression. For example, it has been found that a high intake of dietary fat accelerates the development of breast cancer in animal models. Certain diets have been suggested to act as tumor promoters also in other types of cancer such as colon cancer, where high intake of fat and phosphate have been linked to colonic hyper-proliferation and colon cancer development. Different factors such as oncogenes, aromatic amines, alkylating agents, and diet have a significant role in cancer induction. Determination of glutathione S-transferase isozymes in plasma or serum could be used as a biomarker for cancer in different organs and could give an early detection.

Publication Types:

- Review
- Review, Tutorial

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Glutathione S-transferase M1 and T1 genetic polymorphisms, alcohol consumption and breast cancer risk.

Zheng T, Holford TR, Zahm SH, Owens PH, Boyle P, Zhang Y, Zhang B, Wise JP Sr, Stephenson LP, Ali-Osman F.

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Alcohol consumption has been inconsistently associated with breast cancer risk. Recent studies suggest that genetic polymorphisms of glutathione S-transferases (GSTs) may modify this relation. To determine if breast cancer risk is associated with GSTM1 and GSTT1 genetic polymorphisms, and to evaluate the effect modification between GST genotypes and alcohol consumption in the risk of breast cancer, we conducted a case-control study in the state of Connecticut in the period 1998 and 2001. Cases were histologically confirmed, incident breast cancer patients in New Haven County, CT. Controls were randomly selected from women histologically confirmed to be without breast cancer. The study results show that, while GSTM1 genotypes were not associated with breast cancer risk, GSTT1-null genotype was associated with a significant 90% increased risk for postmenopausal women (OR=1.9, 95% CI 1.2-3.0). Analysis by GST genotypes and alcohol consumption shows that GSTM1A ever-drinking women had a 2.5-fold (OR=2.5, 95% CI 1.1-5.5) increased risk of breast cancer compared to the GSTM1A never-drinkers, and the risk increases with duration and daily amount of alcohol consumption. Postmenopausal women with GSTT1-null genotype, who consumed a lifetime of >250 kg of spirit-equivalents, had an almost seven-fold increased risk (OR=6.8, 95% CI 1.4-33.9), and drinking commencing at younger ages appears to carry a higher risk. An OR of 8.2 (95% CI 1.2-57.4) was observed for those with GSTM1A, and GSTT1-null genotypes who had consumed a lifetime of >250 kg of spirit-equivalents. In conclusion, alcohol consumption may increase breast cancer risk among those who carry susceptible GST genotypes.

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Anticancer Res 2002 Nov-Dec;22(6B):3647-52

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Glutathione S-transferase (GST) polymorphisms as risk factors for cancer in a highly homogeneous population from southern Italy.

Sgambato A, Campisi B, Zupa A, Bochicchio A, Romano G, Tartarone A, Galasso R, Traficante A, Cittadini A.

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Glutathione S-Transferase (GST) is a phase II enzyme and catalyses reactions between

glutathione and a variety of electrophilic compounds, including some environmental carcinogens. In man, at least 20 isoenzymatic forms of GST have been identified and many of them show genetically-based individual variability of enzyme activity. The GSTM1 and GSTT1 isoenzymes display several polymorphisms, including a homozygotic deletion, which have been associated with an increased risk for developing neoplastic diseases. There is geographical and ethnic variation in genotype frequencies for both genes. The available data suggest that cancer incidence varies amongst Italian regions, being higher in Northern than in Southern areas, though it is unknown whether this phenomenon is to be attributed to genetic and/or environmental factors. We performed a case-control study to evaluate the GSTM1 and GSTT1 polymorphisms in a series of cancer patients in Basilicata, a Southern Italian region, and in corresponding controls. The results obtained demonstrate that the occurrence of GST polymorphisms in the Basilicata population is not different from other Italian regions and suggest that the population attributable risk associated with these genotypes may be quite high. GSTM1 homozygous null genotype was associated with an increasing risk of cancer, especially in females. The strongest association was with colon and breast cancers. For the GSTT1 gene, the results obtained were suggestive of a decreased risk of cancer associated with the null genotype. Thus, similar studies on these and other susceptibility genes are warranted since they can help to identify susceptible subgroups of people who can be targeted for cancer prevention.

Environ Mol Mutagen 2003;41(1):69-76

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Polymorphisms for chemical metabolizing genes and risk for cervical neoplasia.

Sierra-Torres CH, Au WW, Arrastia CD, Cajas-Salazar N, Robazetti SC, Payne DA, Tyring SK.

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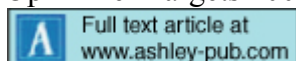
Infection with high-risk human papillomavirus (HPV) plays a major role in the etiology of cervical cancer (CC). However, most infected women do not develop cancer. Therefore, exposure to other carcinogenic agents may be a contributing risk factor for CC. We investigated the hypothesis that environmental exposure to cigarette smoke and inheritance of polymorphic chemical metabolizing genes (CYP2E1, GSTM1, and mEH) significantly increase the risk for neoplasia. We selected 76 cases with high-grade cervical neoplasia or with invasive CC and 75 matched healthy controls. The collected data support the well-established observation that infection with high-risk HPV is the major risk factor for CC (OR = 7.5; 95% CI = 2.6-22.0). In addition, our data show that women who smoked more than 15 "pack-year" had a significant 6.9-fold increase in risk (95% CI = 1.2-40.3) after adjustment for HPV infection. The CYP2E1 variant genotype did not significantly increase the risk for neoplasia. A significant increase in risk for neoplasia was observed for the low-activity mEH 113 His allele after adjustment for smoking (OR = 3.0; 95% CI = 1.4-6.3). The GSTM1 null genotype was associated with a significant 3.3-fold increased

risk for neoplasia (95% CI = 1.0-11.8) compared to women who were GSTM1-positive after adjustment for smoking and HPV infection. Our study suggests that genetic differences in the metabolism of cigarette smoke, particularly GSTM1, may confer susceptibility to CC. Further studies using larger populations will be needed to confirm our observations and to validate data for disease prevention. Copyright 2003 Wiley-Liss, Inc.

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Glutathione S-transferases as emerging therapeutic targets.

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Glutathione S-transferases (GST) represent a large family of Phase II detoxification enzymes widely expressed in animals and plants. These enzymes catalyse the conjugation of glutathione with some endogenous molecules and a broad range of exogenous substrates including various anticancer drugs. Due to high expression of GSTs in tumours when compared to normal tissues and their high level in plasma from cancer patients, these enzymes are considered to be cancer markers. Their involvement in resistance to anticancer drugs and an inverse correlation between expression and prognosis in many tumours provided a rationale for the design of inhibitors and prodrugs to enhance therapeutic index. The first generation of GST inhibitors included ethacrynic acid and showed promising potentiating activity in vitro but lack of isoenzyme specificity and diuretic side effects restricted clinical use. Novel GST inhibitors include glutathione analogues and demonstrate better specificities with fewer limiting toxicities. One lead compound is a potent inhibitor of the GSTP1-1 isoform in both cell lines and animal models. A GSTP1-1 activated prodrug has also been developed. Testing of the preclinical and clinical efficacy of these agents is presently in progress. Their rational design provides a promising new approach to targeting tumour-specific characteristics in a manner consistent with improving therapeutic index.

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Cancer Lett 2003 Feb 10;190(1):37-44

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Glutathione S-transferase polymorphisms in thyroid cancer patients.

Hernandez A, Cespedes W, Xamena N, Surralles J, Creus A, Galofre P, Marcos R.

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Glutathione S-transferases (GST) are enzymes involved in the metabolism of many carcinogens and mutagens, also acting as important free-radical scavengers. The existence of different genetic polymorphisms in human populations has proven to be a susceptibility factor for different tumours. Nevertheless, as far as we know, for thyroid cancer no study has been conducted until now linking its incidence to genetic susceptibility biomarkers. The present investigation has been conducted to detect the possible association between polymorphism at the GSTM1, GSTT1 and GSTP1 genes and thyroid cancer incidence. Thus, 134 thyroid cancer patients and 116 controls, all from the urban district of Barcelona (Spain), have been included in this study. The results indicate that, according to the calculated odds ratio, the frequencies of the different genotypes found in the group of cancer patients do not significantly differ from those values obtained in the controls. This is true for the overall data as well as for the tumour characterization as follicular and papillary types. In addition, none of the possible combinations of mutant genotypes were shown to be risk factors. Finally, when the sex of the patients, the age of tumour onset, and life-style habits were also taken into account, no influence was observed related to the different genotypes. In conclusion, the results obtained in this study clearly suggest that those susceptibility factors related to the different GST polymorphic enzymes are not a predisposing factor in thyroid cancer disease.

PMID: 12536075 [PubMed - indexed for MEDLINE]

Rocz Akad Med Białymst 2002;47:113-22

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The decrease in antioxidant potential in human brain tumours.

Dudek H, Farbiszewski R, Michno T, Witek A, Kozłowski A, Rydzewska M.

Department of Neurosurgery, Medical Academy of Białystok, Białystok, Poland.

The objective of our research was to estimate the activity of superoxide dismutase (SOD-1), glutathione peroxidase (GSH-Px) and glutathione reductase (GSSG-R), as well as the concentrations of free oxygen radicals "sweepers" (GSH, Vit.C) and the concentrations of the substances reacting with thiobarbituric acid in brain tumours with II, III and IV level of biological malignancy. The research was conducted on 61 samples obtained from the patients operated in the Department of Neurosurgery of the Medical Academy of Białystok between the years 1996 and 2000. The obtained values of the above enzyme activities and of the concentrations of the examined substances in brain tumours were compared to the adequate values determined in 10 samples of histopathologically unchanged nerve tissue. The results: the increase of all enzymes activities in brain tumours is statistically significant ($p < 0.05$) as compared to the adequate activity level in normal nerve tissue. The significant decrease ($p < 0.05$) of the GSH and ascorbate concentration and the significant increase ($p < 0.05$) of the level of the thiobarbituric acid--reactive substances in the examined brain tumours was found in comparison to the adequate concentration of the above substances in normal nerve tissue.

PMID: 12533953 [PubMed - indexed for MEDLINE]



Sodium selenite, dietary micronutrient, prevents the lymphocyte DNA damage induced by N-nitrosodiethylamine and phenobarbital promoted experimental hepatocarcinogenesis.

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Department of Medical Biochemistry, Dr. ALM Post-Graduate Institute of Basic Medical Sciences, University of Madras, Chennai, India.

Selenium (Se), a micronutrient, has a long history in chemoprevention of mammary and colon cancers in rodent models. Se is a current clinical trial, having shown promise in prevention of prostate and other human cancers. The mechanisms involved in the *in vivo* anti-carcinogenic activity of Se remain to be elucidated. In the present study, we examined the effect of sodium selenite supplementation in lymphocytes, obtained from hepatoma bearing rats on DNA damage in correlation with oxidative stress. In addition, this study examined the supplementation of Se at 4-ppm levels in the form of sodium selenite either before initiation or during initiation and/or promotion phase's increases lymphocyte Se concentrations. This in turn improves lymphocyte resistance to oxidative stress and protection against the lymphocytes DNA damage. Supplementation of Se increased lymphocyte Se concentration and reduced lymphocytes DNA damage as determined by single cell gel electrophoresis. The enzymatic antioxidants such as superoxide dismutase, glutathione peroxidase, and catalase were found to be decreased while the thiobarbituric acid reactive substances level was increased in the lymphocytes of hepatoma bearing rats. Furthermore, the reactive oxygen species such as superoxide radicals and hydroxyl radicals were also found to be high in lymphocytes. Our present results explain the understanding of unique association between anti-peroxidative effect of Se and ultimately the capability of Se to prevent cancer. Copyright 2002 Wiley-Liss, Inc.

PMID: 12532333 [PubMed - in process]

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[Article in German]

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