

ABSTRACTS**Alcohol****ALCOHOL AND HEALTH: A DRINK A DAY WON'T KEEP THE DOCTOR AWAY.**

We should not advise patients to start drinking alcohol for its alleged cardiovascular benefits. The negative effects of alcohol are well established, and the evidence of alcohol's benefits comes mainly from epidemiologic studies that were not well controlled for other influences, such as lifestyle factors. Moreover, we have other means of lowering cardiovascular risk that are safe and proven. Those who are healthy and whose drinking history shows little risk of developing alcohol dependency may continue to drink moderate amounts. Heavy drinkers should be advised to quit.

Cleve Clin J Med . 2003 Nov;70(11):945-6

ALCOHOL CONSUMPTION AND RISK OF LARYNGEAL CANCER.

Epidemiological studies consistently showed that alcohol drinking increases the risk of laryngeal cancer. This risk increases with the amount of alcohol consumed: in recent studies conducted in North America, Europe, Japan and Korea the multivariate relative risks for the highest levels of consumption ranged between 2 and 10, and were 1.94 for 50g/day and 3.95 for 100g/day in a meta-analysis of 20 studies. Further, the risk increases by concomitant tobacco smoking, each agent approximately multiplying the effect of the other. In the absence of smoking the risks are small for moderate alcohol consumption. After stopping drinking, some fall in risk becomes apparent in the long term. The role of age at starting and stopping drinking is still unclear. In various studies, the most commonly used alcoholic beverage appears to be the most associated with laryngeal cancer risk, suggesting that no meaningful difference exists for different types of alcoholic beverages. The supraglottis is more closely related to alcohol consumption, as compared to the glottis/subglottis. Alcohol drinking may influence laryngeal cancer risk particularly through its direct contact or solvent action, perhaps by enhancing the effects of tobacco or other environmental carcinogens.

Oral Oncol . 2005 May 28

HISTORY OF CIRRHOSIS AND RISK OF DIGESTIVE TRACT NEOPLASMS.

Background: Cirrhosis is strongly related to liver cancer. Data on the possible association between cirrhosis and risk at other cancer sites are scanty. Patients and methods: We analysed data from a network of case-control studies conducted in Italy between 1983 and 1997, including patients with cancers of the oral cavity and pharynx (520), oesophagus (405), stomach (731), colon (943), rectum (613), liver (425), gallbladder (63) and pancreas (395). The controls were 4297 patients admitted to hospitals for acute non-neoplastic conditions. Results: After strict allowance for alcohol drinking, tobacco smoking and history of hepatitis, the multivariate odds ratios for a history of cirrhosis were 4.7 [95% confidence interval (CI) 2.2-9.8] for neoplasms of the oral cavity and pharynx, 2.6 (95% CI 1.2-5.7) for the oesophagus, 1.0 (95% CI 0.4-2.5) for the stomach, 1.0 (95% CI 0.4-2.4) for the colon, 1.7 (95% CI 0.7-4.1) for the rectum, 20.5 (95% CI 12.3-34.2) for the liver, 2.1 (95% CI 0.3-16.8) for the gallbladder and 0.9 (95% CI 0.3-3.0) for the pancreas. Conclusions: Our study confirms and further quantifies the increased risk of liver cancer in cirrhotic patients and is compatible with an increased risk of oral, pharyngeal and oesophageal cancers.

Ann Oncol . 2005 Sep;16(9):1551-1555

EXPRESSION OF ALDEHYDE DEHYDROGENASE 2 IN THE NORMAL ESOPHAGEAL EPITHELIUM AND ALCOHOL CONSUMPTION IN PATIENTS WITH ESOPHAGEAL CANCER.

Alcohol consumption is a risk factor for esophageal cancer. Acetaldehyde, a highly toxic intermediate produced from ethanol, is converted to acetic acid mainly by aldehyde dehydrogenase 2 (ALDH2) in the metabolic pathway of ethanol. Fifty percent of Japanese have inactive ALDH2 due to genetic polymorphism, which is considered to be a risk factor associated with esophageal cancer. In our previous study, we have demonstrated that ALDH2 is expressed in the esophagus with a considerable variation among individuals. In this study, we further investigated the expression of ALDH2 in esophagus and its relationship with risk factors of esophageal cancer. Tissue specimens resected from 51 patients with esophageal cancer were analyzed by

immunohistochemistry using ALDH2-antibody. The immuno-staining of ALDH2 in the esophageal epithelium was compared with both the drinking habit and the occurrence of flushing that is closely associated with the ALDH2 deficiency. ALDH2 was not detectable in 8 (16%) among 51 specimens. All of the 8 patients were non- or light-drinkers but not heavy-drinkers. Among 18 patients showing the high level ALDH2 expression in the esophagus, 15 patients (83%) were heavy-drinkers. Although the relationship between the ALDH2 deficiency and drinking habit is not clear, the patients with ALDH2 deficiency tend to be non- or light drinkers while heavy-drinkers tend to have the active form of ALDH2. These results suggest that both inactive and active forms of ALDH2 are induced in the esophagus by heavy drinking and also support a hypothesis that ALDH2 deficiency might be a high-risk factor of esophageal cancer for the individuals having a heavy-drinking habit. To our knowledge, this is the first study demonstrating the induction of ALDH2 in the esophagus by ethanol consumption.

Front Biosci . 2005 Sep 1;10:2319-24

ALCOHOL DRINKING AND RISK OF LOCALIZED VERSUS ADVANCED AND SPORADIC VERSUS FAMILIAL PROSTATE CANCER IN SWEDEN.

BACKGROUND: It is unknown whether the association of alcohol consumption with prostate cancer risk varies between localized and advanced cases, or between sporadic and familial cases. **METHODS:** We assessed recent alcohol drinking in a population-based case-control study of Swedish men, including 1499 cases and 1130 controls. Drinking status and average volume, frequency, and type of alcohol consumed were evaluated. Unconditional logistic regression was performed to estimate the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for associations between alcohol consumption and prostate cancer risk. **RESULTS:** Prostate cancer cases were more likely than controls to be current or former, rather than never, drinkers. However, there was no association between recent total alcohol, beer, wine, and liquor consumption and risk of overall prostate cancer, nor advanced, sporadic, or familial prostate cancer. The OR for risk of overall disease among men who drank more than 135 g of total alcohol per week versus non-drinkers was 1.2 (95% CI: 0.9, 1.5), $p(\text{trend})=0.12$. There was a marginal positive association between alcohol intake and risk of localized disease. **CONCLUSIONS:** We detected no association between recent alcohol consumption and risk of advanced, sporadic, or familial prostate cancer, and a borderline positive association with localized disease.

Cancer Causes Control . 2005 Apr;16(3):275-84

ALCOHOL IN HEPATOCELLULAR CANCER.

Hepatocellular cancer accounts for almost half a million cancer deaths a year, with an escalating incidence in the Western world. Alcohol has long been recognized as a major risk factor for cancer of the liver and of other organs including oropharynx, larynx, esophagus, and possibly the breast and colon. There is compelling epidemiologic data confirming the increased risk of cancer associated with alcohol consumption, which is supported by animal experiments. Cancer of the liver associated with alcohol usually occurs in the setting of cirrhosis. Alcohol may act as a cocarcinogen, and has strong synergistic effects with other carcinogens including hepatitis B and C, aflatoxin, vinyl chloride, obesity, and diabetes mellitus. Acetaldehyde, the main metabolite of alcohol, causes hepatocellular injury, and is an important factor in causing increased oxidant stress, which damages DNA. Alcohol affects nutrition and vitamin metabolism, causing abnormalities of DNA methylation. Abnormalities of DNA methylation, a key pathway of epigenetic gene control, lead to cancer. Other nutritional and metabolic effects, for example on vitamin A metabolism, also play a key role in hepatocarcinogenesis. Alcohol enhances the effects of environmental carcinogens directly and by contributing to nutritional deficiency and impairing immunological tumor surveillance. This review summarizes the epidemiologic evidence for the role of alcohol in hepatocellular cancer, and discusses the mechanisms involved in the promotion of cancer.

Clin Liver Dis . 2005 Feb;9(1):151-69

NEXT DAY EFFECTS OF A NORMAL NIGHT'S DRINKING ON MEMORY AND PSYCHOMOTOR PERFORMANCE.

AIM: To investigate in social drinkers the effects of a 'normal' evening of drinking alcohol on cognitive performance. **METHODS:** Aiming for ecological validity, the study required participants to consume their usual quantity of any type of alcoholic beverage in their chosen company (hangover situation). However, the timing of drinking was restricted to the period between 22:00 and 02:00 hours on the night before testing. Testing included memory and psychomotor performance tests; testing was also performed after an evening of abstinence (no hangover situation), following a counterbalanced design using repeated measures, with time of testing (09:00, 11:00 and 13:00 hours) and order of testing (hangover/no hangover; no hangover/hangover) as 'between participant' factors in the analysis. **RESULTS:** Forty-eight social drinkers (33 women, 15 men) aged between 18 and 43 years were tested, with a 1-week interval between test sessions. The morning after alcohol (mean consumption: 14.7 units for men; 10.4 units for women), free recall was impaired at 09:00 hours and delayed recognition and psychomotor performance were impaired throughout the morning, despite blood alcohol levels of zero or very near zero. **CONCLUSION:** Memory and psychomotor performance is impaired on the morning after heavy 'social' drinking.

A PHYSIOLOGICALLY BASED MODEL FOR ETHANOL AND ACETALDEHYDE METABOLISM IN HUMAN BEINGS.

Pharmacokinetic models for ethanol metabolism have contributed to the understanding of ethanol clearance in human beings. However, these models fail to account for ethanol's toxic metabolite, acetaldehyde. Acetaldehyde accumulation leads to signs and symptoms, such as cardiac arrhythmias, nausea, anxiety, and facial flushing. Nevertheless, it is difficult to determine the levels of acetaldehyde in the blood or other tissues because of artifactual formation and other technical issues. Therefore, we have constructed a promising physiologically based pharmacokinetic (PBPK) model, which is an excellent match for existing ethanol and acetaldehyde concentration-time data. The model consists of five compartments that exchange material: stomach, gastrointestinal tract, liver, central fluid, and muscle. All compartments except the liver are modeled as stirred reactors. The liver is modeled as a tubular flow reactor. We derived average enzymatic rate laws for alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH), determined kinetic parameters from the literature, and found best-fit parameters by minimizing the squared error between our profiles and the experimental data. The model's transient output correlates strongly with the experimentally observed results for healthy individuals and for those with reduced ALDH activity caused by a genetic deficiency of the primary acetaldehyde-metabolizing enzyme ALDH2. Furthermore, the model shows that the reverse reaction of acetaldehyde back into ethanol is essential and keeps acetaldehyde levels approximately 10-fold lower than if the reaction were irreversible.

Alcohol. 2005 Jan;35(1):3-12

OXIDATION OF ETHANOL TO ACETALDEHYDE AND FREE RADICALS BY RAT TESTICULAR MICROSOMES.

A large number of epidemiological studies evidencing that excessive alcohol consumption is associated with impaired testosterone production and testicular atrophy are available in the literature. One hypothesis to explain the deleterious action of alcohol involves the in situ biotransformation to acetaldehyde, but it strongly suggests the need to learn more about the enzymatic processes governing alcohol metabolism to acetaldehyde in different cellular fractions since limited information is available in the literature. In this article we report studies on the metabolic conversion of alcohol to acetaldehyde and to 1-hydroxyethyl radicals in rat testicular microsomal fractions. The oxidation of ethanol to acetaldehyde in rat testes microsomal fraction was mostly of enzymatic nature and strongly dependent on the presence of NADPH and oxygen. Several compounds were able to significantly decrease the production of acetaldehyde: SKF 525A; diethyldithiocarbamate; esculetin; gossypol; curcumin; quercetin; dapsone; and diphenyleneiodonium. Microsomal preparations in the presence of NADPH were also able to produce both hydroxyl and 1-hydroxyethyl free radicals. Their generation was modulated by the presence of diphenyleneiodonium, gossypol, and deferoxamine. Results show that rat microsomal fractions are able to metabolize alcohol to deleterious chemicals, such as acetaldehyde and free radicals, that may be involved in ethanol toxic effects. Enzymes involved could include CYP2E1, P450 reductase, and other enzymes having lipoygenase- /peroxidase-like behavior.

Arch Toxicol . 2005 Jan;79(1):25-30

THE DISCOVERY OF THE MICROSOMAL ETHANOL OXIDIZING SYSTEM AND ITS PHYSIOLOGIC AND PATHOLOGIC ROLE.

Oxidation of ethanol via alcohol dehydrogenase (ADH) explains various metabolic effects of ethanol but does not account for the tolerance. This fact, as well as the discovery of the proliferation of the smooth endoplasmic reticulum (SER) after chronic alcohol consumption, suggested the existence of an additional pathway which was then described by Lieber and DeCarli, namely the microsomal ethanol oxidizing system (MEOS), involving cytochrome P450. The existence of this system was initially challenged but the effect of ethanol on liver microsomes was confirmed by Remmer and his group. After chronic ethanol consumption, the activity of the MEOS increases, with an associated rise in cytochrome P450, especially CYP2E1, most conclusively shown in alcohol dehydrogenase negative deer mice. There is also cross-induction of the metabolism of other drugs, resulting in drug tolerance. Furthermore, the conversion of hepatotoxic agents to toxic metabolites increases, which explains the enhanced susceptibility of alcoholics to the adverse effects of various xenobiotics, including industrial solvents. CYP2E1 also activates some commonly used drugs (such as acetaminophen) to their toxic metabolites, and promotes carcinogenesis. In addition, catabolism of retinol is accelerated resulting in its depletion. Contrasting with the stimulating effects of chronic consumption, acute ethanol intake inhibits the metabolism of other drugs. Moreover, metabolism by CYP2E1 results in a significant release of free radicals which, in turn, diminishes reduced glutathione (GSH) and other defense systems against oxidative stress which plays a major pathogenic role in alcoholic liver disease. CYP1A2 and CYP3A4, two other perivenular P450s, also sustain the metabolism of ethanol, thereby contributing to MEOS activity and possibly liver injury. CYP2E1 has also a physiologic role which comprises gluconeogenesis from ketones, oxidation of fatty acids, and detoxification of xenobiotics other than ethanol. Excess of these physiological substrates (such as seen in obesity and diabetes) also leads to CYP2E1 induction and nonalcoholic fatty liver disease (NAFLD), which includes nonalcoholic fatty liver and nonalcoholic steatohepatitis (NASH), with pathological lesions similar to those observed in alcoholic steatohepatitis. Increases of CYP2E1 and its mRNA prevail in the perivenular zone, the area of maximal liver damage. CYP2E1 up-regulation was also demonstrated in obese patients as well as in rat models of

obesity and NASH. Furthermore, NASH is increasingly recognized as a precursor to more severe liver disease, sometimes evolving into "cryptogenic" cirrhosis. The prevalence of NAFLD averages 20% and that of NASH 2% to 3% in the general population, making these conditions the most common liver diseases in the United States. Considering the pathogenic role that up-regulation of CYP2E1 also plays in alcoholic liver disease (vide supra), it is apparent that a major therapeutic challenge is now to find a way to control this toxic process. CYP2E1 inhibitors oppose alcohol-induced liver damage, but heretofore available compounds are too toxic for clinical use. Recently, however, polyenylphosphatidylcholine (PPC), an innocuous mixture of polyunsaturated phosphatidylcholines extracted from soybeans (and its active component dilinoleoylphosphatidylcholine), were discovered to decrease CYP2E1 activity. PPC also opposes hepatic oxidative stress and fibrosis. It is now being tested clinically.

Drug Metab Rev . 2004 Oct;36(3-4):511-29

CYP2E1: FROM ASH TO NASH.

The pathology of the liver in alcoholic steatosis and alcoholic steatohepatitis (ASH) is remarkably similar to that of nonalcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis (NASH), suggesting some common pathogenic mechanism. Studies carried out over the last three decades of possible mechanisms involved revealed one common link, namely the induction of cytochrome P4502E1. Its substrates include fatty acids, ketones and ethanol. These substances, when present chronically in large amounts, induce the activity of the enzyme which thereby contributes to the disposition of these substrates. This reaction, however, is associated with the release of free radicals which can cause lipid peroxidation and liver injury, including mitochondrial damage. Mitochondrial damage in turn exacerbates the oxidative stress. CYP2E1 can also convert various xenobiotics to toxic metabolites. When unchecked, this toxicity eventually results in inflammation and fibrosis, culminating in cirrhosis. Prevention of this disorder is based on limiting the substrates that induce the system, such as excessive fatty acid associated with obesity and excessive alcohol consumption. No effective pharmacologic treatment is presently available but there is ongoing research on possible inhibitors of CYP2E1, innocuous enough to be suitable for chronic human consumption and sufficiently effective to attenuate the CYP2E1 induction to avoid the consequences of its excessive activity while maintaining its physiologic role.

Hepatol Res . 2004 Jan;28(1):1-11

OXIDATIVE STRESS AND ANTIOXIDANT STATUS IN PATIENTS WITH ALCOHOLIC LIVER DISEASE.

BACKGROUND: Alcoholic liver diseases (ALD) are very common in lower socio-economical strata due to heavy drinking habits and multiple nutritional deficiencies. Ethanol causes liver damage by many mechanisms. The generation of lipid peroxidation by free radicals has been proposed as a mechanism for ethanol induced hepatotoxicity. These free radicals are destroyed by anti-oxidants. Many anti-oxidants are present in the diet, e.g., vitamin E, vitamin C etc. However, poor nutrition or malabsorption leads to deficiency of these vitamins. This may impair the anti-oxidative defense leading to ethanol induced oxidative stress and then to liver damage. **METHODS:** Oxidative stress and antioxidant defense were assessed in patients with alcoholic liver disease. Serum malondialdehyde (MDA) concentrations were measured as an index of lipid peroxidation, i.e., oxidative stress; and serum vitamins E and C concentrations were measured as an index of antioxidant status. **RESULTS:** Serum MDA concentrations were increased with the increase in severity of the disease. Concentrations of serum vitamins E and C were decreased in patients with alcoholic liver disease as compared to controls. **CONCLUSIONS:** Our observations may be due to increased demands of the same or increased utilization.

Clin Chim Acta . 2005 May;355(1-2):61-5

ABSTRACTS

Green tea

ANTIOXIDANTS OF THE BEVERAGE TEA IN PROMOTION OF HUMAN HEALTH.

Tea that contains many antioxidants is a pleasant and safe drink that is enjoyed by people across the globe. Tea leaves are manufactured as black, green, or oolong. Black tea represents approximately 78% of total consumed tea in the world, whereas green tea accounts for approximately 20% of tea consumed. The concept of "use of tea for promotion of human health and prevention and cure of diseases" has become a subject of intense research in the last decade. Diseases for which tea drinkers appear to have lower risk are simple infections, like bacterial and viral, to chronic debilitating diseases, including cancer, coronary heart disease, stroke, and osteoporosis. Initial work on green tea suggested that it possesses human health-promoting effects. In recent years, the research efforts have been expanded to black tea as well. Research conducted in recent years reveals that both black and green tea have very similar beneficial attributes in lowering the risk of many human diseases, including several types of cancer and heart diseases. For cancer prevention, evidence is so overwhelming that the Chemoprevention Branch of the National Cancer Institute has initiated a plan for developing tea compounds as cancer-chemopreventive agents in human trials. Thus, modern medical research is confirming the ancient wisdom that therapy of many diseases may reside in an inexpensive beverage in a "teapot."

Antioxid Redox Signal . 2004 Jun;6(3):571-82

UPDATE ON CHEMOPREVENTION OF PROSTATE CANCER.

PURPOSE OF REVIEW: Prostate cancer remains the most commonly diagnosed visceral cancer in men in the United States, with almost 200,000 newly diagnosed cases in 2003. Prevention of this disease would have a major impact on disease-associated cost, morbidity, and mortality for a large segment of the population. A major advance in prevention of prostate cancer came in 2003 with the publication of the Prostate Cancer Prevention Trial. This overview summarizes the results of that trial, the design of other large-scale trials, and advances in understanding of the molecular mechanisms underlying the effect of other promising agents. **RECENT FINDINGS:** The Prostate Cancer Prevention Trial demonstrated that use of finasteride is associated with a 25% reduction in the 7-year period prevalence of prostate cancer in men over age 55 years with normal digital rectal exam and initial prostate specific antigen <3.0 ng/ml. Use of finasteride was associated with a slightly higher risk of Gleason sum 7-10 tumors, some sexual side effects, and fewer urinary symptoms. A substantial body of new molecular evidence supports the existing body of clinical and epidemiological data leading to testing of vitamin E and selenium as preventative agents in men at risk for prostate cancer. Epidemiologic and molecular evidence also makes cyclooxygenase-2 inhibitors, lycopene, soy, and green tea promising agents. **SUMMARY:** Results of a population-based, randomized phase III trial demonstrates that finasteride can prevent prostate cancer. A large amount of data supports the use of other agents as potential preventatives, including selenium, vitamin E, vitamin D, other 5-alpha-reductase inhibitors, cyclooxygenase-2 inhibitors, lycopene, and green tea. Some of these agents are being tested in new large-scale phase III clinical trials.

Curr Opin Urol . 2004 May;14(3):143-9

MEDICINAL BENEFITS OF GREEN TEA: PART I. REVIEW OF NONCANCER HEALTH BENEFITS.

Tea, in the form of green or black tea, is one of the most widely consumed beverages in the world. Extracts of tea leaves also are sold as dietary supplements. However, with the increasing interest in the health properties of tea and a significant rise in scientific investigation, this review covers recent findings on the medicinal properties and noncancer health benefits of both green and black tea. In Part II, a review of anticancer properties of green tea extracts is presented. Green tea contains a unique set of catechins that possess biological activity in antioxidant, anti-angiogenesis, and antiproliferative assays potentially relevant to the prevention and treatment of various forms of cancer. Although there has been much focus on the biological properties of the major tea catechin epigallocatechin gallate (EGCg) and its antitumor properties, tea offers other health benefits; some due to the presence of other important constituents. Characteristics unrelated to the antioxidant properties of green and black teas may be responsible for tea's anticancer activity and improvement in cardiac health and atherosclerosis. Theanine in green tea may play a role in reducing stress. Oxidized catechins (theaflavins in black tea) may reduce cholesterol levels in blood. Synergistic properties of green tea extracts with other sources of polyphenolic constituents are increasingly recognized as being potentially important to the medicinal benefits of black and green teas. Furthermore, due to presumed antioxidant and antiaging properties, tea is now finding its way into topical preparations. Each of these aspects is surveyed.

J Altern Complement Med. 2005 Jun;11(3):521-8

THE ANTIFOLATE ACTIVITY OF TEA CATECHINS.

A naturally occurring gallated polyphenol isolated from green tea leaves, (-)-epigallocatechin gallate (EGCG), has been shown to be an inhibitor of dihydrofolate reductase (DHFR) activity in vitro at concentrations found in the serum and tissues of green tea drinkers (0.1-1.0 micromol/L). These data provide the first evidence that the prophylactic effect of green tea drinking on certain forms of cancer, suggested by epidemiologic studies, is due to the inhibition of DHFR by EGCG and could also explain why tea extracts have been traditionally used in "alternative medicine" as anticarcinogenic/antibiotic agents or in the treatment of conditions such as psoriasis. EGCG exhibited kinetics characteristic of a slow, tight-binding inhibitor of 7,8-dihydrofolate reduction with bovine liver DHFR ($K(I) = 0.109$ micromol/L), but of a classic, reversible, competitive inhibitor with chicken liver DHFR ($K(I) = 10.3$ micromol/L). Structural modeling showed that EGCG can bind to human DHFR at the same site and in a similar orientation to that observed for some structurally characterized DHFR inhibitor complexes. The responses of lymphoma cells to EGCG and known antifolates were similar, that is, a dose-dependent inhibition of cell growth ($IC_{50} = 20$ micromol/L for EGCG), G₀-G₁ phase arrest of the cell cycle, and induction of apoptosis. Folate depletion increased the sensitivity of these cell lines to antifolates and EGCG. These effects were attenuated by growing the cells in a medium containing hypoxanthine-thymidine, consistent with DHFR being the site of action for EGCG.

Cancer Res. 2005 Mar 15;65(6):2059-64

GREEN TEA AND TEA POLYPHENOLS IN CANCER PREVENTION.

The cancer-preventive effects of green tea and its main constituent (-)-epigallocatechin gallate [(-)-EGCG] are widely supported by results from epidemiological, cell culture, animal and clinical studies in the recent decade. In vitro cell culture studies show that tea polyphenols potently induce apoptotic cell death and cell cycle arrest in tumor cells but not in their normal cell counterparts. Green tea polyphenols affect several signal transduction pathways, including growth factor-mediated, the mitogen-activated protein kinase (MAPK)-dependent, and ubiquitin/proteasome degradation pathways. Epidemiological studies have suggested that the consumption of green tea lowers the risk of cancer. Various animal studies have revealed that treatment by green tea inhibits tumor incidence and multiplicity in different organ sites such as skin, lung, liver, stomach, mammary gland and colon. Phase I and II clinical trials were carried out recently to explore the anticancer effects of green tea in patients with cancer. At this time, more mechanistic research, animal studies, and clinical trials are necessary to further evaluate the role of green tea in cancer prevention.

Front Biosci. 2004 Sep 1;9:2618-31

BODY WEIGHT LOSS AND WEIGHT MAINTENANCE IN RELATION TO HABITUAL CAFFEINE INTAKE AND GREEN TEA SUPPLEMENTATION.

OBJECTIVE: Investigation of the effect of a green tea-caffeine mixture on weight maintenance after body weight loss in moderately obese subjects in relation to habitual caffeine intake. **RESEARCH METHODS AND PROCEDURES:** A randomized placebo-controlled double blind parallel trial in 76 overweight and moderately obese subjects, (BMI, 27.5 ± 2.7 kg/m²) matched for sex, age, BMI, height, body mass, and habitual caffeine intake was conducted. A very low energy diet intervention during 4 weeks was followed by 3 months of weight maintenance (WM); during the WM period, the subjects received a green tea-caffeine mixture (270 mg epigallocatechin gallate + 150 mg caffeine per day) or placebo. **RESULTS:** Subjects lost 5.9 ± 1.8 (SD) kg ($7.0 \pm 2.1\%$) of body weight ($p < 0.001$). At baseline, satiety was positively, and in women, leptin was inversely, related to subjects' habitual caffeine consumption ($p < 0.01$). High caffeine consumers reduced weight, fat mass, and waist circumference more than low caffeine consumers; resting energy expenditure was reduced less and respiratory quotient was reduced more during weight loss ($p < 0.01$). In the low caffeine consumers, during WM, green tea still reduced body weight, waist, respiratory quotient and body fat, whereas resting energy expenditure was increased compared with a restoration of these variables with placebo ($p < 0.01$). In the high caffeine consumers, no effects of the green tea-caffeine mixture were observed during WM. **DISCUSSION:** High caffeine intake was associated with weight loss through thermogenesis and fat oxidation and with suppressed leptin in women. In habitual low caffeine consumers, the green tea-caffeine mixture improved WM, partly through thermogenesis and fat oxidation.

Obes Res. 2005 Jul;13(7):1195-204

EFFECTS OF PURIFIED GREEN AND BLACK TEA POLYPHENOLS ON CYCLOOXYGENASE- AND LIPOXYGENASE-DEPENDENT METABOLISM OF ARACHIDONIC ACID IN HUMAN COLON MUCOSA AND COLON TUMOR TISSUES.

The effects of green and black tea polyphenols on cyclooxygenase (COX)- and lipoxygenase (LOX)-dependent arachidonic acid metabolism in normal human colon mucosa and colon cancers were investigated. At a concentration of 30 microg/mL, (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), and (-)-epicatechin-3-gallate (ECG) from green tea and theaflavins from black tea inhibited LOX-dependent activity by 30-75%. The formation of 5-, 12-, and 15-LOX metabolites was inhibited to a

similar extent. Tea polyphenols also inhibited COX-dependent arachidonic acid metabolism in microsomes from normal colon mucosa, with ECG showing the strongest inhibition. The formation of thromboxane (TBX) and 12-hydroxyheptadecatrienoic acid (HHT) was decreased to a greater extent than other metabolites. The inhibitory effects of tea polyphenols on COX activity, however, were less pronounced in tumor microsomes than in normal colon mucosal microsomes. Theaflavins strongly inhibited the formation of TBX and HHT, but increased the production of prostaglandin E(2) (PGE(2)) in tumor microsomes. The enhancing effect of theaflavins on PGE(2) production was related to the COX-2 level in the microsomes. Although theaflavin inhibited ovine COX-2, its activity in the formation of PGE(2) was stimulated by theaflavin when ovine COX-2 was mixed with microsomes, suggesting that theaflavin affects the interaction of COX-2 with other microsomal factors (e.g. PGE synthase). The present results indicate that tea polyphenols can affect arachidonic acid metabolism in human colon mucosa and colon tumors, and this action may alter the risk for colon cancer in humans.

Biochem Pharmacol . 2001 Nov 1;62(9):1175-83

INHIBITION OF COLLAGENASES FROM MOUSE LUNG CARCINOMA CELLS BY GREEN TEA CATECHINS AND BLACK TEA THEAFLAVINS.

Theaflavin and theaflavin digallate, which are components of black tea were examined by in vitro invasion assay with mouse Lewis lung carcinoma LL2-Lu3 cells, which are highly metastatic. The compounds inhibited invasion by the tumor cells. Gelatin zymography showed that the cells secreted matrix metalloproteinases (MMPs), probably including MMP-2 and MMP-9, which may be involved in tumor cell invasion and metastasis. Theaflavin and theaflavin digallate also inhibited MMPs from the culture medium of these tumor cells, as did (-)-epigallocatechin gallate. These results suggest that theaflavin, theaflavin digallate, and (-)-epigallocatechin gallate inhibit tumor cell invasion by inhibiting type IV collagenases of the LL2-Lu3 cells.

Biosci Biotechnol Biochem . 1997 Sep;61(9):1504-6

SCAVENGING EFFECT OF EXTRACTS OF GREEN TEA AND NATURAL ANTIOXIDANTS ON ACTIVE OXYGEN RADICALS.

With the use of the spin trapping methods, the scavenging effects of the extracts of green tea and other natural foods are studied. In stimulated polymorphonuclear leukocytes (PMN) system, water extract fraction 6 (F6) from green tea and green tea polyphenols (GTP) have the strongest scavenging effect on the active oxygen radicals, much stronger than vitamin C (Vc) and vitamin E (VE). Rosemary antioxidants (RA) and Curcumin (Cur) have weaker scavenging effects than Vc, but stronger than VE. In Fenton Reaction, Cur has the strongest scavenging effect (69%) on hydroxyl radicals. In irradiation, riboflavin system F6(74%) and GTP(72%) have very strong scavenging effects that are weaker than Vc, but much stronger than VE (23%). With the use of spin probe oxymetry, the oxygen consumption in respiratory burst of stimulated PMN were measured when the antioxidants existed in these systems. The results demonstrated that these antioxidants did not affect the respiratory burst of human polymorphonuclear leukocytes stimulated with PMA.

Cell Biophys . 1989 Apr;14(2):175-85

EFFECTS OF TEA POLYPHENOLS AND FLAVONOIDS ON LIVER MICROSOMAL GLUCURONIDATION OF ESTRADIOL AND ESTRONE.

Administration of 0.5 or 1% lyophilized green tea (5 or 10 mg tea solids per ml, respectively) as the sole source of drinking fluid to female Long-Evans rats for 18 days stimulated liver microsomal glucuronidation of estrone, estradiol and 4-nitrophenol by 30-37%, 15-27% and 26-60%, respectively. Oral administration of 0.5% lyophilized green tea to female CD-1 mice for 18 days stimulated liver microsomal glucuronidation of estrone, estradiol and 4-nitrophenol by 33-37%, 12-22% and 172-191%, respectively. The in vitro addition of a green tea polyphenol mixture, a black tea polyphenol mixture or (-)-epigallocatechin gallate inhibited rat liver microsomal glucuronidation of estrone and estradiol in a concentration-dependent manner and their IC50 values for inhibition of estrogen metabolism were approximately 12.5, 50 and 10 microg/ml, respectively. Enzyme kinetic analysis indicates that the inhibition of estrone glucuronidation by 10 microM (-)-epigallocatechin gallate was competitive while inhibition by 50 microM (-)-epigallocatechin gallate was noncompetitive. Similarly, several flavonoids (naringenin, hesperetin, kaempferol, quercetin, rutin, flavone, alpha-naphthoflavone and beta-naphthoflavone) also inhibited rat liver microsomal glucuronidation of estrone and estradiol to varying degrees. Naringenin and hesperetin displayed the strongest inhibitory effects (IC50 value of approximately 25 microM). These two hydroxylated flavonoids had a competitive mechanism of enzyme inhibition for estrone glucuronidation at a 10 microM inhibitor concentration and a predominantly noncompetitive mechanism of inhibition at a 50 microM inhibitor concentration.

J Steroid Biochem Mol Biol . 1998 Feb;64(3-4):207-15

INHIBITORY EFFECTS OF ANTIOXIDANTS ON FORMATION OF HETEROCYCLIC AMINES.

It is important to search for effective antioxidants to suppress formation of mutagenic and carcinogenic heterocyclic amines (HCAs), like 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), because these HCAs are considered to be probable human carcinogens. The effects of various food-derived antioxidants on MeIQx formation were examined by their addition (0.2 mmol each) to mixtures of creatine (0.4 mmol), glycine (0.4 mmol) and glucose (0.2 mmol), and heating at 128 degreesC for 2 h. Glycine was replaced by l-phenylalanine in the case of PhIP formation. Among the 14 kinds of antioxidants tested, green tea catechins and the major component [(-)-epigallocatechin gallate], two flavonoids (luteolin and quercetin) and caffeic acid were found to clearly suppress the formation of both MeIQx and PhIP, being 3.2-75% of the level of the controls. These phenolic antioxidants also reduced the total mutagenicity of the heated mixtures. The results suggest that foodstuffs containing catechins, flavonoids and caffeic acid may suppress the formation of HCAs in cooked foods.

Mutat Res . 1998 Jun 18;402(1-2):237-45

SELECTIVE INHIBITION OF STEROID 5 ALPHA-REDUCTASE ISOZYMES BY TEA EPICATECHIN-3-GALLATE AND EPIGALLOCATECHIN-3-GALLATE.

Inhibitors of 5 alpha-reductase may be effective in the treatment of 5 alpha-dihydrotestosterone-dependent abnormalities, such as benign prostate hyperplasia, prostate cancer and certain skin diseases. The green tea catechins, (-)epigallocatechin-3-gallate and (-)epicatechin-3-gallate, but not (-)epicatechin and (-)epigallocatechin, are potent inhibitors of type 1 but not type 2 5 alpha-reductase. (-)Epigallocatechin-3-gallate also inhibits accessory sex gland growth in the rat. These results suggest that certain tea gallates can regulate androgen action in target organs.

Biochem Biophys Res Commun. 1995 Sep 25;214(3):833-8

ABSTRACTS

Milk thistle

Milk thistle and prostate cancer: differential effects of pure flavonolignans from *Silybum marianum* on antiproliferative end points in human prostate carcinoma cells.

Extracts from the seeds of milk thistle, *Silybum marianum*, are known commonly as silibinin and silymarin and possess anticancer actions on human prostate carcinoma in vitro and in vivo. Seven distinct flavonolignan compounds and a flavonoid have been isolated from commercial silymarin extracts. Most notably, two pairs of diastereomers, silybin A and silybin B and isosilybin A and isosilybin B, are among these compounds. In contrast, silibinin is composed only of a 1:1 mixture of silybin A and silybin B. With these isomers now isolated in quantities sufficient for biological studies, each pure compound was assessed for antiproliferative activities against LNCaP, DU145, and PC3 human prostate carcinoma cell lines. Isosilybin B was the most consistently potent suppressor of cell growth relative to either the other pure constituents or the commercial extracts. Isosilybin A and isosilybin B were also the most effective suppressors of prostate-specific antigen secretion by androgen-dependent LNCaP cells. Silymarin and silibinin were shown for the first time to suppress the activity of the DNA topoisomerase II α gene promoter in DU145 cells and, among the pure compounds, isosilybin B was again the most effective. These findings are significant in that isosilybin B composes no more than 5% of silymarin and is absent from silibinin. Whereas several other more abundant flavonolignans do ultimately influence the same end points at higher exposure concentrations, these findings are suggestive that extracts enriched for isosilybin B, or isosilybin B alone, might possess improved potency in prostate cancer prevention and treatment.

Cancer Res. 2005 May 15;65(10):4448-57

The effect of revised populations on mortality statistics for the United States, 2000.

OBJECTIVES: This report presents revised mortality statistics for the year 2000 based on April 1, 2000, population figures from the 2000 census. Death rates are presented by race, Hispanic origin, sex, age, and cause of death. Life expectancies are presented by race (white and black), sex, and age. The revised statistics are compared with previously published statistics that used July 1, 2000, postcensal population estimates based on the 1990 census. **METHODS:** Data in this report are based on information from all death certificates filed in the 50 States and the District of Columbia. The statistics presented in this report are computed on the basis of two sets of population figures provided by the U.S. Census Bureau. The first set includes July 1, 2000, postcensal population estimates based on the 1990 decennial census. The second set includes April 1, 2000, populations from the 2000 decennial census bridged to single race categories. **RESULTS:** Crude death rates were lower for all groups using the April 1, 2000, populations. Age-specific death rates were generally lower for most age groups, except for infants and the very old for which death rates were higher. Age-specific death rates for males were lower for most age groups, except infants and those 75 years and over. For females, with the exception of infants, age-specific death rates were lower. Race-specific patterns by age for the white and black populations were similar to all races combined. For the American Indian population, age-specific death rates were substantially lower for ages under 75 years. For ages 75 years and over, American Indian death rates were dramatically higher. Age-specific death rates for the Asian or Pacific Islander (API) population were higher for ages under 15 years; lower for ages 15-84 years, especially for the 15-34 year age group; and higher for those 85 years and over. For the Hispanic population, age-specific death rates were substantially lower for those age 15-34 years and higher for those age 55 years and over, especially for those age 85 years and over. For the total white and total black populations, the age-adjusted death rate was somewhat higher for males and lower for females. For API the pattern was reversed. For the American Indian and Hispanic populations, age-adjusted death rates were higher for both males and females. For the 15 leading causes of death, age-adjusted death rates based on the April 1, 2000, population figures were lower for heart disease, cancer, chronic liver disease, septicemia, diabetes, chronic lower respiratory diseases, unintentional injuries, homicide, suicide, and hypertension. Age-adjusted death rates were higher for pneumonitis, Alzheimer's disease, and stroke. Rates were unchanged for influenza and pneumonia and nephritis, nephrotic syndrome and nephrosis. Life expectancy at birth was higher for the entire population and both the white and black populations using the April 1, 2000, population figures. It was 0.1 year higher for the whole population as well as for the total white and total black populations. For the total male population, life expectancy at birth was 0.1 year higher while it was 0.2 years higher for the female population. The increase in life expectancy at birth was 0.1 year for both sexes within the white and black populations. This observed gain in life expectancy at birth based on the revised population figures is reversed for life expectancy at the oldest age groups for the whole population and for males. A similar pattern is observed for both white and black males; however, the magnitude of the decline in life expectancy at older ages is much greater among black males. Among females of both race groups and the total population, there is either no change or an increase in life expectancy in the oldest age groups. **CONCLUSIONS:** Revised death rates and life expectancies are, in many cases, significantly different from previously published mortality statistics calculated using 1990-based postcensal estimates for 2000. Thus, previously published mortality statistics for 2000 using the 1990-based populations will not be comparable to the corresponding statistics that will be

published for 2001. The data in this report will provide comparable 2000 data. Efforts are also underway to revise previously published mortality tables for 2000 as well as previously published data for 1991-99.

Natl Vital Stat Rep . 2003 Jun 5;51(9):1-24

Prostate-specific antigen levels in the United States: implications of various definitions for abnormal.

BACKGROUND: The finding that some men with a normal prostate-specific antigen (PSA) level (i.e., less than 4 ng/mL) nonetheless have microscopic evidence of prostate cancer has led to some suggestions that the threshold defining abnormal should be lowered to 2.5 ng/mL. We examined the effect of this lower threshold on the number of American men who would be labeled abnormal by a single PSA test. **METHODS:** We obtained PSA data on a nationally representative sample of American men 40 years of age and older with no history of prostate cancer and no current inflammation or infection of the prostate gland (n = 1308) from the 2001-2002 National Health and Nutrition Examination Survey. We obtained data on the 10-year risk of prostate cancer death in the pre-PSA era from DevCan, the National Cancer Institute's software to calculate the probability of dying of cancer. **RESULTS:** Based on NHANES data, approximately 1.5 million American men aged 40 to 69 years have a PSA level over 4.0 ng/mL. Lowering the threshold to 2.5 ng/mL would label an additional 1.8 million men as abnormal, if all men were screened. For men aged 70 years or older, the corresponding numbers are 1.5 and 1.2 million. The proportion of the population affected by different thresholds would vary with age. Among men in their 60s, for example, 17% have a PSA level over 2.5 ng/mL, 5.7% have a PSA level over 4.0 ng/mL, and 1.7% have a PSA level over 10.0 ng/mL. For context, only 0.9% of men in their 60s are expected to die from prostate cancer in the next 10 years. **CONCLUSION:** Lowering the PSA threshold to 2.5 ng/mL would double the number of men defined as abnormal, to up to 6 million. Until there is evidence that screening is effective, increasing the number of men recommended for prostate biopsy--and the number potentially diagnosed and treated unnecessarily--would be a mistake.

J Natl Cancer Inst . 2005 Aug 3;97(15):1132-7

The unreasonableness of prostate-cancer screening and the ethical problems pertaining to its investigation.

Since the early 1990s, screening with prostate-specific antigen (PSA) testing has increased the incidence of prostate cancer. Any decrease in mortality will not be seen for at least a decade, due to the long natural history of prostate cancer. Death due to prostate cancer is rare, while the prevalence of localised tumours is high. The prognosis of these early-detected localised tumours is uncertain, because most patients will die from other causes. Complications of prostate-cancer therapy are common, with high rates of impotence, incontinence and gastrointestinal problems after prostatectomy or radiotherapy. Randomised trials of prostate-cancer screening, notably the 'European randomised screening for prostate cancer' (ERSPC) trial, began with the consent of ethical committees. There is a real uncertainty regarding the benefits of prostate-cancer screening. However, it is clear that these benefits are limited, because prostate-cancer death is rare before the age of 75 years. There is no real uncertainty about the harms of prostate-cancer screening. High prevalence and high rates of treatment complications deduct many disease- and disability-free years from the eligible population (men aged 55-74 years). Therefore, there has been no real uncertainty over the balance of harms and benefits in prostate-cancer screening trials. Days may be added to old age, at the cost of months of disease- and disability-free living. It is not in the best interest of eligible men to participate in these trials. Randomised trials evaluating prostate-cancer screening violate in principle and practice the Helsinki Declaration of the rights of human subjects in medical research.

Ned Tijdschr Geneeskd . 2005 Apr 30;149(18):966-71

Role of Mammalian lignans in the prevention and treatment of prostate cancer.

Prostate cancer is poised to become the most prevalent male cancer in the Western world. In Japan and China, incidence rates are almost 10-fold less those reported in the United States and the European Union. Epidemiological data suggest that environmental factors such as diet can significantly influence the incidence and mortality of prostate cancer. The differences in lifestyle between East and West are one of the major risk factors for developing prostate cancer. Traditional Japanese and Chinese diets are rich in foods containing phytoestrogenic compounds, whereas the Western diet is a poor source of these phytochemicals. The lignan phytoestrogens are the most widely occurring of these compounds. In vitro and in vivo reports in the literature indicate that lignans have the capacity to affect the pathogenesis of prostate cancer. However, their precise mechanism of action in prostate carcinogenesis remains unclear. This article outlines the possible role of lignans in prostate cancer by reviewing the current in vitro and in vivo evidence for their anticancer activities. The intriguing concept that lignans may play a role in the prevention and treatment of prostate cancer over the lifetime of an individual is discussed.

Nutr Cancer . 2005;52(1):1-14

Synergistic anti-cancer effects of silibinin with conventional cytotoxic agents doxorubicin, cisplatin and carboplatin against human breast carcinoma MCF-7 and MDA-MB468 cells.

Significant emphasis is being placed on combination chemotherapy of cancer using cytotoxic agents and naturally occurring chemopreventive agents, having different mechanisms of action with non-overlapping toxicity. In this regard, here we assessed whether a cancer preventive agent silibinin synergizes the therapeutic potential of doxorubicin (Dox), cisplatin or carboplatin, the chemotherapeutic drugs, in both estrogen-dependent and -independent human breast carcinoma, MCF-7 and MDA-MB468 cells, respectively. When tested alone, each of the four agents showed growth inhibition in both the cell lines in a dose- and a time-dependent manner. Based on their growth inhibitory effects, several combinations of silibinin (25-100 microM) with Dox (10-75 nM), cisplatin (0.2-2 microg/ml) or carboplatin (2-20 microg/ml) were next assessed for their synergistic, additive and/or antagonistic efficacy towards cell growth inhibition and apoptotic death. The strongest synergistic effects for cell growth inhibition [combination index (CI) 0.35 for MCF-7 and 0.45 for MDA-MB468 cells] were evident at a silibinin dose of 100 microM plus 25 nM Dox, in both the cell lines. Most of the CIs for other combinations of these three drugs with silibinin also suggested strong synergistic effects for cell growth inhibition in both MCF-7 and MDA-MB468 cells. In quantitative apoptosis studies, combination of silibinin with Dox resulted in much stronger apoptotic death compared to each agent alone in both cell lines. In case of silibinin combination with cisplatin, it showed no additional apoptotic effect in either cell line. Similarly, silibinin plus carboplatin combination showed stronger apoptotic effect only in MCF-7 cells. Together, these results suggest a possible synergism between silibinin and conventional cytotoxic agents for breast cancer treatment, and warrant further in vivo studies in pre-clinical breast cancer models.

Oncol Rep. 2004 Feb;11(2):493-9

Prostate cancer prevention by silibinin.

Several epigenetic alterations leading to constitutively active mitogenic and cell-survival signaling, and loss of apoptotic response are causally involved in self-sufficiency of prostate cancer (PCA) cells toward uncontrolled growth, and increased secretion of pro-angiogenic factors. Therefore, one targeted approach for PCA prevention, growth control and/or treatment could be inhibition of epigenetic molecular events involved in PCA growth, progression and angiogenesis. In this regard, silibinin/silymarin (silibinin is the major active compound in silymarin) has shown promising efficacy. Our extensive studies with silibinin/silymarin and PCA cells have shown the pleiotropic anticancer effects leading to cell growth inhibition in culture and nude mice. The underlying mechanisms of silibinin/silymarin efficacy against PCA involve alteration in cell cycle progression, and inhibition of mitogenic and cell survival signaling, such as epidermal growth factor receptor, insulin-like growth factor receptor type I and nuclear factor kappa B signaling. Silibinin also synergizes the therapeutic effects of doxorubicin in PCA cells, making it a strong candidate for combination chemotherapy. Silibinin/ silymarin also inhibits the secretion of proangiogenic factors from tumor cells, and causes growth inhibition and apoptotic death of endothelial cells accompanied by disruption of capillary tube formation on Matrigel. More importantly, silibinin inhibits the growth of in vivo advanced human prostate tumor xenograft in nude mice. Recently, due to its non-toxic and mechanism-based strong preventive/therapeutic efficacy, silibinin has entered in phase I clinical trial in prostate cancer patients.

Curr Cancer Drug Targets . 2004 Feb;4(1):1-11

A cancer chemopreventive agent silibinin, targets mitogenic and survival signaling in prostate cancer.

There are many epigenetic variables that affect the biological responses of autocrine, paracrine and endocrine regulatory molecules, which determine the growth and development of different cancers including prostate cancer (PCA). One of the focuses of the current cancer chemoprevention studies is the search for non-toxic chemopreventive agents that inhibit mitogenic and cell survival signaling in cancer cells. In general, advanced stage cancer cells harbor many constitutively active mitogenic signaling and anti-apoptotic mechanisms, which make them less dependent on external growth factors as well as resistant to chemotherapeutic agents. In this regard, silibinin (a naturally occurring flavanone) has shown the pleiotropic anticancer effects in different cancer cells. Our extensive studies with PCA have shown that inhibition of mitogenic and cell survival signaling, such as epidermal growth factor receptor, insulin-like growth factor receptor type I and nuclear factor kappa B signaling are the most likely molecular targets of silibinin's efficacy in PCA. We have observed that silibinin inhibits prostate tumor growth in animal models without any apparent signs of toxicity. At the same time, silibinin is also physiologically available in different organs of the body including plasma and prostate, which is generally required for the pharmacological dosing and translational mechanistic studies of the compound. There are substantial amount of data to support the inhibitory effect of silibinin on mitogenic and cell survival signaling in PCA, which are reviewed in the present communication.

Mutat Res. 2004 Nov 2;555(1-2):21-32

Is screening for prostate cancer with prostate specific antigen an appropriate public health measure?

Screening and treatment for prostate cancer is controversial. In the absence of randomized trials, several prominent medical organizations in the United States and Europe have formulated policies that range from enthusiastic support to significant skepticism concerning the efficacy of screening and subsequent treatment for prostate cancer. Sharp rises in the incidence of

prostate cancer have occurred whenever PSA testing has been introduced on a wide scale. Unfortunately, it is unclear whether declines in prostate cancer mortality can be attributed to PSA testing. Other explanations include the early use of anti-androgen therapy or changes in environmental factors such as diet. Repeated testing for serum PSA has produced significant shifts in the types of cases being identified and has raised the possibility of significant over-diagnosis of this disease. The European screening trial and the PLCO trial in the US will hopefully provide some insights into the value of population-based testing.

Acta Oncol. 2005;44(3):255-64

Diet, lifestyle and risk of prostate cancer.

Prostate cancer has become a major public health problem worldwide. Yet, the etiology of prostate cancer remains largely unknown. Dietary factors, dietary supplements, and physical activity might be important in the prevention of the disease. In the majority of studies, it was observed that high consumption of meat and dairy products has been linked to a greater risk. In contrast, frequent consumption of fatty fish and tomato products has been associated with a reduced risk. It has been shown consistently that high levels of circulating insulin-like growth factor 1 (IGF-1) are associated with an increased risk of prostate cancer. Dietary factors are also recognized as determinants of circulating IGF-1, thus changes in diet may influence IGF-1 concentrations in serum. Furthermore, increased intake of vitamin E and selenium (from supplements) has been shown in intervention studies to decrease the risk. Possibly, high level of physical activity is also associated with decreased risk of prostate cancer. The accumulated scientific evidence concerning the associations between diet, lifestyle, and risk of prostate cancer development suggests that there are some identified modifiable risk factors that it might be recommended to change in order to decrease the risk for this common cancer site.

Acta Oncol. 2005;44(3):277-81

ABSTRACTS

Pregnenolone

Neurosteroids: biosynthesis, metabolism and function of pregnenolone and dehydroepiandrosterone in the brain.

Pregnenolone (P) and dehydroepiandrosterone (D) accumulate in the brain as unconjugated steroids and their sulfate (S) and fatty acid (L) esters. The microsomal acyl-transferase activity is highest in immature (1-3 weeks old) male rats. The immunocytochemical and biochemical evidence for P biosynthesis by differentiated oligodendrocytes is reviewed. The importance of P synthesis for its brain accumulation is assessed by the intracisternal injection of the inhibitor aminoglutethimide. Primary glial cell cultures convert P to 20-OH-P, PL, progesterone, 5 alpha-pregnane-3,20-dione and 3 alpha-hydroxy-5 alpha-pregnane-20-one (Polone). Astroglial cell cultures also produce these metabolites, whereas neurons from 17-day mouse embryos only form 20-OH-P. P and D are converted to the corresponding 7 alpha-hydroxylated metabolites by a very active P-450 enzyme from rat brain microsomes. Several functions of neurosteroids are documented. P decreases in olfactory bulb of intact male rats exposed to the scent of estrous females. D inhibits the aggressive behavior of castrated male mice towards lactating female intruders. The D analog 3 beta-methyl-androst-5-en-17-one, which cannot be metabolized into sex steroids and is not demonstrably androgenic or estrogenic is at least as efficient as D. Both compounds elicit a marked decrease of PS in rat brain. The Cl⁻ conductance of gamma-aminobutyric (GABAA) receptor is stimulated by GABA agonists, an effect which is enhanced by Polone and antagonized by PS. Thus, P metabolites in brain as well as steroids of extraencephalic sources may be involved physiologically in GABAA receptor function. The neurosteroids accumulated in brain may be precursors of sex steroid hormones and progesterone receptors have been localized in glial cells. P and D do not bind to any known intracellular receptor. A heat stable P binding protein has been found in brain cytosol with distinct ligand specificity. A binding component specific for steroids sulfates, including Polone S, DS and PS, in the order of decreasing affinity is localized in adult rat brain synaptosomal membranes. Its relationship to the GABAA receptor is under current investigation.

J Steroid Biochem Mol Biol . 1991;40(1-3):71-81

Sex- and age-related changes in epitestosterone in relation to pregnenolone sulfate and testosterone in normal subjects.

Epitestosterone has been demonstrated to act at various levels as a weak antiandrogen. So far, its serum levels have been followed up only in males. Epitestosterone and its major circulating precursor pregnenolone sulfate and T were measured in serum from 211 healthy women and 386 men to find out whether serum concentrations of epitestosterone are sufficient to exert its antiandrogenic actions. In women, epitestosterone exhibited a maximum around 20 yr of age, followed by a continuous decline up to menopause and by a further increase in the postmenopause. In men, maximum epitestosterone levels were detected at around 35 yr of age, followed by a continuous decrease. Pregnenolone sulfate levels in women reached their maximum at about age 32 yr and then declined continuously, and in males the maximum was reached about 5 yr earlier and then remained nearly constant. Epitestosterone correlated with pregnenolone sulfate only in males. In both sexes a sharp decrease of the epitestosterone/T ratio around puberty occurred. In conclusion, concentrations of epitestosterone and pregnenolone sulfate are age dependent and, at least in prepubertal boys and girls, epitestosterone reaches or even exceeds the concentrations of T, thus supporting its role as an endogenous antiandrogen. The dissimilarities in the course of epitestosterone levels through the lifespan of men and women and its relation to pregnenolone sulfate concentrations raise the question of the contribution of the adrenals and gonads to the production of both steroids and even to the uniformity of the mechanism of epitestosterone formation.

J Clin Endocrinol Metab . 2002 May;87(5):2225-31

Antioxidant activity of dioscorea and dehydroepiandrosterone (DHEA) in older humans.

Dioscorea is a yam steroid extract used in commercial steroid synthesis and consumed by people. DHEA is a steroid which declines with age, but without known activity. This study was designed to determine whether dioscorea supplementation could increase serum dehydroepiandrosterone sulfate (DHEAS) in humans and modulate lipid levels in older people. The subjects were selected volunteers aged 65-82 years. The serum DHEAS level, lipid peroxidation and lipid profile were assessed. Three weeks of dioscorea supplementation had no effect on serum DHEAS level. However DHEA intake of 85 mg/day increased serum DHEA levels 100.3%. DHEA and dioscorea significantly reduced serum lipid peroxidation, lowered serum triglycerides, phospholipid and increased HDL levels. Both DHEA and the steroid yam extract, dioscorea, have significant activities as antioxidant to modify serum lipid levels.

The neurosteroid pregnenolone sulfate infused into the medial septum nucleus increases hippocampal acetylcholine and spatial memory in rats.

The effects of an infusion of the neurosteroid pregnenolone sulfate into the medial septum on acetylcholine release in the hippocampus and on spatial memory were evaluated in two experiments. Results show that pregnenolone sulfate enhanced acetylcholine release by more than 50% of baseline and improved recognition memory of a familiar environment. Therefore, our results suggest that the septo-hippocampal pathway could be involved in the promnesic properties of this neurosteroid.

Brain Res. 2002 Oct 4;951(2):237-42

Molecular mechanism of pregnenolone sulfate action at NR1/NR2B receptors.

NMDA receptors are highly expressed in the CNS and are involved in excitatory synaptic transmission and synaptic plasticity as well as excitotoxicity. They have several binding sites for allosteric modulators, including neurosteroids, endogenous compounds synthesized by the nervous tissue and expected to act locally. Whole-cell patch-clamp recording from human embryonic kidney 293 cells expressing NR1-1a/NR2B receptors revealed that neurosteroid pregnenolone sulfate (PS) (300 microm), when applied to resting NMDA receptors, potentiates the amplitude of subsequent responses to 1 mM glutamate fivefold and slows their deactivation twofold. The same concentration of PS, when applied during NMDA receptor activation by 1 mM glutamate, has only a small effect. The association and dissociation rate constants of PS binding and unbinding from resting NMDA receptors are estimated to be $3.3 \pm 2.0 \text{ mM}^{-1}\text{sec}^{-1}$ and $0.12 \pm 0.02 \text{ sec}^{-1}$, respectively, corresponding to an apparent affinity $K(d)$ of 37 microm. The results of experiments indicate that the molecular mechanism of PS potentiation of NMDA receptor responses is attributable to an increase in the peak channel open probability ($P(o)$). Responses to glutamate recorded in the continuous presence of PS exhibit marked time-dependent decline. Our results indicate that the decline is induced by a change of the NMDA receptor affinity for PS after receptor activation. These results suggest that the PS is a modulator of NMDA receptor $P(o)$, the effectiveness of which is lowered by glutamate binding. This modulation may have important consequences for the neuronal excitability.

J Neurosci. 2004 Nov 17;24(46):10318-25

Effect of neurosteroids on the retinal gabaergic system and electroretinographic activity in the golden hamster.

Abstract It has been established that neurosteroids can either inhibit or enhance GABA(A) receptor activity. Although GABA is the main inhibitory neurotransmitter in the mammalian retina, the effects of neurosteroids on retinal GABAergic activity have not been investigated. The aim of this work was to study the neurochemical and electroretinographic effects of neurosteroids in the golden hamster. On one hand, pregnenolone sulfate inhibited and allotetrahydrodeoxycorticosterone increased GABA-induced $[(36)\text{Cl}]^{-}$ uptake in neurosynaptosomes. On the other hand, in whole retinas, pregnenolone sulfate increased, whereas allotetrahydrodeoxycorticosterone decreased high potassium-induced $[(3)\text{H}]\text{GABA}$ release. The effect of both neurosteroids on GABA release was $\text{Ca}(2+)$ -dependent, as in its absence release was not altered. The intravitreal injection of pregnenolone sulfate or vigabatrin (an irreversible inhibitor of GABA degradation) significantly decreased scotopic b-wave amplitude, whereas the opposite effect was evident when bicuculline or allotetrahydrodeoxycorticosterone were injected. A protein with a molecular weight close to that of hamster adrenal cytochrome P450 side-chain cleavage (P450_{scc}) was detected in the hamster retina. P450_{scc}-like immunoreactivity was localized in the inner nuclear and the ganglion cell layers. These results indicate that neurosteroids significantly modulate retinal GABAergic neurotransmission and electroretinographic activity. In addition, the selective localization of P450_{scc} suggests that neurosteroid biosynthesis might occur only in some layers of the hamster retina.

J Neurochem. 2005 Jul 11

Hypercholesterolemia treatment: a new hypothesis or just an accident?

A new hypothesis concerning the association of low levels of steroid hormones and hypercholesterolemia is proposed. This study presents data that concurrent restoration to youthful levels of multiple normally found steroid hormones is able to normalize or improve serum total cholesterol (TC). We evaluated 20 patients with hypercholesterolemia who received hormonorestorative therapy (HT) with natural hormones. Hundred percent of patients responded. Mean serum TC was 263.5 mg/dL before and 187.9 mg/dL after treatment. Serum TC dropped below 200 mg/dL in 60.0%. No morbidity or mortality related to HT was observed. In patients characterized by hypercholesterolemia and sub-youthful serum steroidal hormones, our findings support the hypothesis that hypercholesterolemia is a compensatory mechanism for life-cycle related down-regulation of steroid hormones, and that broadband steroid hormone restoration is associated with a substantial drop in serum TC in many patients.

Med Hypotheses. 2002 Dec;59(6):751-6

CSF neuroactive steroids in affective disorders: pregnenolone, progesterone, and DBI.

Recently several steroid compounds have been discovered to act as neuromodulators in diverse central nervous system (CNS) functions. We wondered if neuroactive steroids might be involved in affective illness or in the mode of action of mood-regulating medications such as carbamazepine. Levels of the neuroactive steroids pregnenolone and progesterone, as well as the neuropeptide diazepam binding inhibitor (DBI) (known to promote steroidogenesis), were analyzed from cerebrospinal fluid (CSF) obtained by lumbar puncture (LP) from 27 medication-free subjects with affective illness and 10 healthy volunteers. Mood-disordered subjects who were clinically depressed at the time of the LP had lower CSF pregnenolone ($n = 9$, 0.16 ng/ml) compared with euthymic volunteers ($n = 10$, 0.35 ng/ml; $p < 0.01$). In addition, pregnenolone was lower in all affectively ill subjects ($n = 26$, 0.21 ng/ml), regardless of mood state on the LP day, than healthy volunteers ($p < 0.05$). No differences were found for progesterone or DBI levels by mood state or diagnosis. Progesterone, pregnenolone, and DBI did not change significantly or consistently in affectively ill subjects after treatment with carbamazepine. CSF pregnenolone is decreased in subjects with affective illness, particularly during episodes of active depression. Further research into the role of neuroactive steroids in mood regulation is warranted.

Biol Psychiatry. 1994 May 15;35(10):775-80

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