

Esophageal Reflux
Updated: 08/26/2004

ABSTRACTS

More pathophysiologically oriented treatment of GORD?

Boeckxstaens GE, Tytgat GN.

Lancet. 2002 Apr 13; 359(9314):1267-8.

Vitamin intake and risk of subtypes of esophageal cancer in Germany.

Bollschweiler E, Wolfgarten E, Nowroth T, et al.

J Cancer Res Clin Oncol. 2002 Oct; 128(10):575-80.

PURPOSE: The incidence of adenocarcinoma of the esophagus is increasing in most Western industrialized nations especially in white males. The impact of vitamins on the development of squamous cell carcinoma (SCC) and adenocarcinoma (AC) of the esophagus has not been elucidated. The goal of this pilot-study was to analyze the influence of daily vitamin consumption on the frequency of esophageal carcinoma in Germany. **METHODS:** Ninety-nine patients (males) with esophageal carcinoma (52 with SCC and 47 with AC) were compared to a control group of 50 randomly selected males from the Cologne area. Using a computer program to record the data, patients and controls were questioned in detail about their dietary habits. The interaction between known risk factors and the influence of vitamins on esophageal tumor risk were analyzed using logistic regression analysis. **RESULTS:** The univariate analysis showed a significant risk reduction with increased intake of beta-carotene, vitamin C, vitamin E, and folic acid for both AC and for SCC. The results of logistic regression analysis were compatible with the known risk factors for SCC (alcohol and tobacco) and for AC (obesity, tobacco, and alcohol) and showed a significant risk reduction with an intake of vitamin E greater than 13 mg/day (RR=0.13, 95% CI=0.1-0.5, P=0.0004) and vitamin C greater than 100 mg/day (RR=0.33, 95% CI=0.11-0.92, P=0.034) for patients with SCC and similar results for patients with AC. **CONCLUSION:** Our data showed that low intake of vitamin C and E correlates significantly with the development of squamous cell carcinoma as well as adenocarcinoma of the esophagus in males. The relevance of interaction of vitamins with other dietary factors, alcohol, and tobacco are topics of current research

Epidemiologic trends in esophageal and gastric cancer in the United States.

Brown LM, Devesa SS.

Surg Oncol Clin N Am. 2002 Apr; 11(2):235-56.

Use of tobacco, moderate to heavy alcohol ingestion, infrequent consumption of raw fruits and vegetables, and low income accounted for more [figure: see text] than 98% of the SCE rates among both African American and white men and for 99% of the excess incidence among African Americans compared to whites in a case-control study in three areas of the United States [14]. Thus, it is likely that declines in the prevalence of smoking and drinking, especially among men, and increased intake of fresh fruits and vegetables may have contributed to the downward incidence and mortality rate trends reported for SCE. In addition, it seems plausible that obesity, GERD, and possibly reductions in H. pylori prevalence have contributed to the upward trends in ACE rates. Reductions in smoking, improved diet, and reductions in H. pylori prevalence probably have contributed to the consistent reductions observed for NGA. Contributing factors are less clear for the rising incidence rates of GCA during the 1970s and 1980s. These incidence rates have not continued to rise in recent years

Adenocarcinoma of the esophagus and Barrett's esophagus: a population-based study.

Bytzer P, Christensen PB, Damkier P, et al.

Am J Gastroenterol. 1999 Jan; 94(1):86-91.

OBJECTIVE: We described incidence rates of esophageal adenocarcinoma in Denmark in a 20-yr period and determined the proportion of patients diagnosed with esophageal adenocarcinoma who had a previous diagnosis of Barrett's esophagus, making them potential candidates for endoscopic surveillance. **METHODS:** Rates of esophageal and gastric cancers were collected from the Danish Cancer registry for the period 1970-1991. The registry was used to identify all cases of esophageal adenocarcinoma in the period 1987-1992. Medical records were retrieved and details concerning previous diagnosis of reflux disease and Barrett's esophagus were recorded. **RESULTS:** The age- and gender-adjusted incidence of esophageal adenocarcinoma increased eightfold, from 0.3/10(5)/yr in 1970 to 2.3/10(5)/yr in 1990. This increase could not be explained by changes in classification or diagnostic routines. Medical data were retrieved for 524 of the 578 cases of esophageal adenocarcinoma reported during the period 1987-1992. A history of reflux symptoms or a diagnosis compatible with reflux was reported in 113 of 524 patients. A total of 119 patients (23%) had previously been investigated for dyspepsia or reflux symptoms, most often by endoscopy. A previous diagnosis of Barrett's esophagus was found in only 1.3% of the cancer patients. **CONCLUSIONS:** The rate of esophageal adenocarcinoma in Denmark has increased eightfold over a 20-yr period, and this increase is not explained by changes in classification or diagnostic routines. More than 98% of esophageal adenocarcinomas were found in patients who could not have entered endoscopic surveillance, as Barrett's esophagus had not been diagnosed before the cancer diagnosis. Endoscopic surveillance to detect dysplasia may be an option for the individual patient with Barrett's esophagus, but these screening programs are not likely to reduce the death rate from esophageal adenocarcinomas in the general population

Nutrient intakes and adenocarcinoma of the esophagus and distal stomach.

Chen H, Tucker KL, Graubard BI, et al.

Nutr Cancer. 2002; 42(1):33-40.

We studied the relationship between nutrient intakes and adenocarcinoma of the esophagus and distal stomach among 124 esophageal adenocarcinoma cases, 124 distal stomach cancer cases, and 449 controls in a population-based case-control study in eastern Nebraska. The residual method was used to adjust nutrient intake quartiles or tertiles for energy intake. We observed significant inverse associations with risk of esophageal adenocarcinoma for dietary intakes of total vitamin A [highest vs. lowest quartile, multivariate odds ratio (OR) = 0.5, P for trend = 0.05], beta-cryptoxanthin (OR = 0.5, P = 0.05), riboflavin (OR = 0.5, P = 0.01), folate (OR = 0.5, P = 0.03), zinc (OR = 0.5, P = 0.05), dietary fiber (OR = 0.5, P = 0.05), protein (OR = 0.5, P = 0.02), and carbohydrate (OR = 0.4, P = 0.02). For distal stomach cancer, only vitamin C (OR = 0.6, P = 0.04), dietary fiber (OR = 0.4, P = 0.007), and carbohydrate (OR = 0.4, P = 0.004) were inversely associated with risk. Our analyses showed significant interaction between dietary fat intake, but not intakes of other nutrients, and respondent type for both cancer sites. Subgroup analyses among self-respondents revealed positive associations between saturated fat intake and risk of esophageal adenocarcinoma (OR = 1.0, 4.1, and 4.6 for intake tertiles, P for trend = 0.02) and risk of distal stomach cancer (OR = 1.0, 1.2, and 3.6, P = 0.03). However, no such associations were found among proxy respondents. Our data suggest that greater intake of dietary fiber, certain carotenoids, and vitamins may decrease the risk of esophageal adenocarcinoma, whereas greater intake of saturated fat may increase the risk of esophageal adenocarcinoma and distal stomach cancer

Up-regulation of tumor interleukin-8 expression by infiltrating macrophages: its correlation with tumor angiogenesis and patient survival in non-small cell lung cancer.

Chen JJ, Yao PL, Yuan A, Hong TM, Shun CT, Kuo ML, Lee YC, Yang PC.

Clin Cancer Res. 2003 Feb;9(2):729-37.

Institute of Biomedical Sciences and Molecular Biology, National Chung Hsing University, Taichung, Taiwan 402, Republic of China. **PURPOSE:** To evaluate the interaction between tumor-infiltrating macrophages and cancer cells and its effect on the expression of a potent angiogenic factor, interleukin-8 (IL-8), tumor angiogenesis, and patient outcome in non-small cell lung cancer (NSCLC). **EXPERIMENTAL DESIGN:** We measured tumor IL-8 mRNA expression (by real-time quantitative reverse transcription-PCR), intratumor microvessel counts, and tumor-infiltrating macrophage density (by immunohistochemical staining) in 35 NSCLC surgical specimens and correlated with the patient's clinical outcome. We then investigated the interaction between macrophages (cell line THP-1) and six different human cancer cell lines (four NSCLCs, one osteosarcoma, and one hepatoma) and its effect on IL-8 mRNA expression using a macrophage/cancer cell coculture system, IL-8 mRNA expression in lung cancer cells, and macrophages being measured separately after coculture in the presence or absence of six anti-inflammatory agents, i.e., pentoxifylline, aspirin, indomethacin, dexamethasone, celecoxib (a selective cyclooxygenase-2 inhibitor), and pyrrolidine dithiocarbamate, a specific nuclear factor kappaB (NF-kappaB) inhibitor. NF-kappaB transcriptional activity and protein levels were measured by reporter gene assay and Western blot. **RESULTS:** The tumor-infiltrating macrophage density correlated significantly and positively with tumor IL-8 mRNA expression and intratumor microvessel counts and significantly and negatively with patient survival. In addition, after cell-cell interaction in cancer cell:macrophage cocultures, marked IL-8 mRNA expression was induced in lung cancer cells (approximately 270-fold) and, to a lesser degree, in macrophages (4.5-fold). The increase in IL-8 mRNA expression correlated with the in vitro metastatic potential of the cancer cells. All six anti-inflammatory agents suppressed induction of IL-8 mRNA expression in lung cancer cells by >90%, four

(pentoxifylline, celecoxib, pyrrolidine dithiocarbamate, and dexamethasone) having a dose-dependent effect. NF-kappaB transcriptional regulation and protein levels were simultaneously increased in the nuclei of cancer cells in macrophage/cancer cell cocultures, this effect also being suppressed by all six anti-inflammatory agents. CONCLUSIONS: The interaction between infiltrating macrophages and cancer cells up-regulates IL-8 mRNA expression, especially in the cancer cells; this may contribute greatly to the increased tumor angiogenesis and adverse outcome in NSCLC patients with a high density of tumor-infiltrating macrophages. Anti-inflammatory agents can suppress the induction of IL-8 mRNA expression seen in lung cancer cells after coculture with macrophages, and this suppression is mediated, in part, through the NF-kappaB pathway.

Pharmacological characterization of the nitrergic innervation of the stomach.

Lefebvre RA.

Verh K Acad Geneesk Belg. 2002;64(3):151-66.

Heymans Institute of Pharmacology, Ghent University, De Pintelaan 185, B-9000 Gent. Proximal gastric relaxation is a vago-vagal reflex upon food intake. The efferent neurons involved at the level of the stomach are nonadrenergic noncholinergic. Deficient proximal gastric relaxation is observed in a portion of patients with functional dyspepsia, while exaggerated relaxation might contribute to the development of gastroesophageal reflux disease via triggering of transient lower esophageal sphincter relaxations. Nitric oxide (NO) is mediating, together with vasoactive intestinal polypeptide (VIP) as parallel cotransmitter, the nonadrenergic noncholinergic neurotransmission of the proximal stomach. Evidence for a sequential link between VIP as neurotransmitter and muscular NO generation was obtained when studied in isolated gastric smooth muscle cells; inducible NO synthase seems expressed. The endogenous gastric nitrergic neurotransmitter is not sensitive to superoxide anion generators and NO scavengers, that reduce the relaxation to exogenous NO. This is not due to the release of a nerve-derived hyperpolarizing factor in addition of NO, nor to binding to thiols, but Cu/Zn superoxide dismutase is involved in the protection of endogenous NO versus superoxide anions and scavenging. The release of NO from gastric nitrergic neurons is not sensitive to negative feedback but is inhibited via presynaptic alpha 2-adrenoceptors. Nitric oxide functionally antagonizes acetylcholine in the smooth muscle cells but does not influence the release of acetylcholine at the cholinergic varicosities. Stimulating or inhibiting the gastric nitrergic neurons might be a target for drug therapy in functional dyspepsia or gastro-esophageal reflux, respectively.

Deglycyrrhizinated liquorice in aphthous ulcers.

Das SK, Das V, Gulati AK, et al.

J Assoc Physicians India. 1989 Oct; 37(10):647.

Twenty patients with aphthous ulcers were advised deglycyrrhizinated liquorice (DGL) mouth wash and were followed for two weeks. Fifteen patients experienced 50-75% improvement within one day followed by complete healing of the ulcers by third day

Role of macronutrients, vitamins and minerals in the aetiology of squamous-cell carcinoma of the oesophagus.

Franceschi S, Bidoli E, Negri E, et al.

Int J Cancer. 2000 Jun 1; 86(5):626-31.

Between 1992 and 1997 we conducted a case-control study of oesophageal cancer in 3 areas of northern Italy. Cases were 304 patients (29 women), ages 39-77 years (median age 60 years), with a first incident squamous-cell carcinoma (SCC) of the oesophagus. Controls were 743 patients (150 women), ages 35-77 years (median age 60 years), admitted for acute illnesses, unrelated to tobacco and alcohol, to major hospitals of the areas under surveillance. We derived estimates of daily dietary intake of 6 macronutrients, cholesterol, and 20 micronutrients or minerals from a validated food-frequency questionnaire, including 78 food groups and recipes and 15 questions on individual eating patterns. After allowance for age, gender, area of residence, education, body mass index, physical activity, smoking habit, alcohol consumption and energy intake, most micronutrients were inversely associated with oesophageal SCC risk. Highly significant associations emerged for monounsaturated fatty acids [odds ratio (OR) in highest vs. lowest intake quintile = 0.5]; carotene (OR = 0.3); lutein + zeaxanthin (OR = 0.4); vitamin C (OR = 0.4); and niacin (OR = 0.5). Only retinol appeared to be positively related to risk (OR = 1.9). The effect of the above nutrients, expressed as ORs, appeared to be similar in non-smokers and smokers, and non/light drinkers and heavy drinkers

Screening for esophageal adenocarcinoma: an evidence-based approach.

Gerson LB, Triadafilopoulos G.

Adenocarcinoma of the esophagus and the gastroesophageal junction is the twentieth most common malignancy in the United States. In developed countries, the incidence of esophageal adenocarcinoma is increasing 5% to 10% per year. Despite the use of endoscopy for earlier detection, mortality from esophageal adenocarcinoma has not declined. Using an evidence-based approach, we review screening methods for esophageal adenocarcinoma, including the use of a symptom questionnaire, identification of patients with a family history of Barrett's esophagus, peroral or transnasal endoscopy, barium swallow, fecal occult blood testing, and brush and balloon cytology. Screening has not been shown to reduce rate of progression of Barrett's esophagus to esophageal cancer. Many treatment options for dysplastic Barrett's esophagus or early carcinoma appear effective, but long-term follow-up data are not available. There is currently insufficient evidence supporting population-based screening for Barrett's esophagus. Several risk factors, including severe reflux symptoms, male sex, and obesity, may identify patients with gastroesophageal reflux disease who are at the greatest risk of the development of cancer

Effect of acute and chronic administration of the GABA B agonist baclofen on 24 hour pH metry and symptoms in control subjects and in patients with gastro-oesophageal reflux disease.

Ciccaglione AF, Marzio L.

Gut. 2003 Apr;52(4):464-70.

University G d' Annunzio, Chieti-Pescara, Italy. **BACKGROUND AND AIMS:** The gamma-aminobutyric acid (GABA(B)) agonist baclofen has been shown to reduce reflux episodes during the first three postprandial hours in patients with gastro-oesophageal reflux disease (GORD) and in normal controls. The aim of the study was to assess the effect of acute (one day) and chronic (four weeks) administration of baclofen on 24 hour pH metry and symptoms in GORD patients and normal controls. **PATIENTS AND METHODS:** Acute study: 28 patients with GORD with none or mild oesophagitis at endoscopy and 15 controls underwent oesophageal and gastric 48 hour pH metry in which baclofen or placebo was given for 24 hours in a double blinded manner. Chronic study: 16 GORD patients received baclofen (10 mg four times daily) or placebo for four weeks. Twenty four hour oesophageal pH metry and reflux symptom scores were evaluated before and at the end of treatment. **RESULTS:** Acute study: the number of reflux episodes and per cent time with pH <4 was significantly lower after baclofen in GORD patients and controls ($p < 0.003$; $p < 0.0007$). Gastric pH increased significantly in GORD patients and controls ($p < 0.001$; $p < 0.05$). Chronic study: four weeks after initial administration of baclofen, the number of reflux episodes and percentage of time with pH <4 significantly decreased in all GORD patients ($p < 0.003$; $p < 0.02$). Symptom scores significantly improved after treatment with baclofen ($p < 0.0007$). **CONCLUSIONS:** The GABA(B) agonist baclofen reduces 24 hour gastro-oesophageal reflux and increases gastric pH in GORD patients and controls. When given for one month to GORD patients, baclofen reduces oesophageal acid refluxes and significantly improves symptoms. Baclofen may be useful in the therapy of GORD.

Esophageal cancer. Facts, figures, and screening.

Glenn TF.

Gastroenterol Nurs. 2001 Nov; 24(6):271-3.

Over the last 25 years, the incidence of adenocarcinoma of the esophagus has increased 350%, faster than any other malignancy in the western world. This increase is largely due to gastroesophageal reflux disease and Barrett's esophagus. While the current incidence of esophageal cancer is relatively low in comparison to other cancers in the United States, this may rapidly change. A cost-effective screening technique is needed for populations at risk for adenocarcinoma of the esophagus. Using unsedated esophagoscopy, gastroenterology nurses may be in the best position to coordinate and perform esophageal cancer screening for the U.S. population. This article provides an overview of esophageal cancer, including types, etiology, symptoms, and diagnosis. In addition to an overview of esophageal cancer, this article provides a look at non-physician, unsedated esophagoscopy as a future direction for esophageal cancer screening.

Influence of spontaneous sleep positions on nighttime recumbent reflux in patients with gastroesophageal reflux disease.

Khoury RM, Camacho-Lobato L, Katz PO, Mohiuddin MA, Castell DO.

Am J Gastroenterol. 1999 Aug;94(8):2069-73.

OBJECTIVE: Body position has been shown to influence postprandial and fasting gastroesophageal reflux (GER) in patients and normal volunteers when they are assigned to lie in a prescribed position. No published studies have evaluated the effect of spontaneous sleeping positions on recumbent reflux in patients with GER. **METHODS:** Ten patients, three female and seven male (mean age 47.6 yr, range 30-67 yr) with abnormal recumbent esophageal pH <4 on 24-h pH-metry participated. A

standardized high fat dinner (6 PM) and a bedtime snack (10 PM) were administered to all patients. GER during spontaneous sleep positions was assessed with a single channel pH probe placed 5 cm above the lower esophageal sphincter (LES) and with a position sensor taped to the sternum. Data were recorded with a portable digital data logger (Microdigitrapper-S, Synectics Medical) and analyzed for recumbent percent time pH <4 and esophageal acid clearance time in each of four sleeping positions. Time elapsed between change in sleeping position and GER episodes was also calculated. RESULTS: Right lateral decubitus was associated with greater percent time pH <4 ($p < 0.003$) and longer esophageal acid clearance ($p < 0.05$) compared to the left, supine, and prone. GER episodes were more frequent in the supine position ($p < 0.04$) and occurred within 1 min after change in sleeping position 28% of the time. CONCLUSIONS: The left lateral decubitus position is preferred in patients with nocturnal GER. Measures to aid patients in sleeping in this position should be developed.

Mitogenic and antiapoptotic role of constitutive NF-kappaB/Rel activity in pancreatic cancer.

Liptay S, Weber CK, Ludwig L, et al.

Int J Cancer. 2003 Jul 20; 105(6):735-46.

The transcription factor NF-kappaB/Rel was found to be constitutively activated in human pancreatic cancer. RelA is present in the nucleus in primary human pancreatic cancer samples as well as in pancreatic cancer cell lines. NF-kappaB/Rel-binding activity consists of NF-kappaB1(p50) and RelA(p65). Constitutive NF-kappaB/Rel activity correlates with IkappaB kinase (IKK) activity and can be blocked by dominant negative mutants of IKKbeta and to a lesser extent by IKKalpha. Constitutive NF-kappaB/Rel activity and the transactivation potential of RelA(p65) can be inhibited by dominant negative mutant Ras, the PI3 kinase inhibitor LY294002, or dominant negative mutant Akt kinase. Transfection of a dominant negative mutant epidermal growth factor receptor (EGF-R), EGF-R kinase inhibitor Tyrphostin and LY 294002 blocked IKK activity and NF-kappaB-dependent transcription. Inhibition of constitutive IKK or NF-kappaB/Rel activity increased the number of apoptotic cells. Stably expressing a nondegradable form of IkappaBalpha inhibited anchorage-dependent and -independent proliferation in MiaPaCa2 and Panc1 cells. Our data demonstrate that an EGF-R/Ras/PI3 kinase/Akt/IKK-dependent pathway contributes to constitutive NF-kappaB/Rel activity in pancreatic cancer. Inhibition of NF-kappaB/Rel activity reveals a mitogenic and antiapoptotic role for NF-kappaB/Rel in pancreatic cancer

Prospective study of serum selenium levels and incident esophageal and gastric cancers.

Mark SD, Qiao YL, Dawsey SM, et al.

J Natl Cancer Inst. 2000 Nov 1; 92(21):1753-63.

BACKGROUND: From March 1986 through May 1991, we conducted a randomized nutritional intervention trial, the General Population Trial, in Linxian, China, a region with epidemic rates of squamous esophageal and adenomatous gastric cardia cancers. We found that participants who received selenium, beta-carotene, and vitamin E had significantly lower cancer mortality rates than those who did not. In the current study, we examined the relationship between selenium levels measured in pretrial (1985) sera from participants and the subsequent risk of developing squamous esophageal, gastric cardia, and gastric non-cardia cancers during the trial. METHODS: This study was designed and analyzed in accord with a stratified case-cohort sampling scheme, with the six strata defined by sex and three age categories. We measured serum selenium levels in 590 case subjects with esophageal cancer, 402 with gastric cardia cancers, and 87 with gastric non-cardia cancers as well as in 1062 control subjects. Relative risks (RRs), absolute risks, and population attributable risk for cancers were estimated on the basis of the Cox proportional hazards models. All statistical tests are two-sided. RESULTS: We found highly significant inverse associations of serum selenium levels with the incidence of esophageal (P: for trend <10⁻⁴) and gastric cardia (P: for trend <10⁻⁶) cancers. The RR and 95% confidence interval (CI) for comparison of highest to lowest quartile of serum selenium was 0.56 (95% CI = "0.44-0.71") for esophageal cancer and 0.47 (95% CI = "0.33-0.65") for gastric cardia cancer. The population proportion of these cancers that is attributable to low selenium levels was 26.4% (95% CI = "14.45-38.36"). We found no evidence for a gradient of serum selenium associated with incidence of gastric non-cardia cancer (P: for trend = ".96"), with an RR of 1.07 (95% CI = "0.55-2.08") for the highest to lowest quartile of serum selenium. CONCLUSIONS: Our study supports findings from previous prospective studies and randomized trials that variations in selenium levels affect the incidence of certain cancers. In the United States, where intervention trials of selenium are in the planning stages, consideration should be given to including populations at high risk for squamous esophageal and gastric cardia cancers

Nutrient intake and risk of subtypes of esophageal and gastric cancer.

Mayne ST, Risch HA, Dubrow R, et al.

Cancer Epidemiol Biomarkers Prev. 2001 Oct; 10(10):1055-62.

Incidence rates for adenocarcinoma of the esophagus and gastric cardia have been rising rapidly. We examined nutrient intake

as a risk factor for esophageal and gastric cancers in a population-based case-control study in Connecticut, New Jersey, and western Washington state. Interviews were completed for cases with histologically confirmed esophageal adenocarcinoma (n = 282), adenocarcinoma of the gastric cardia (n = 255), esophageal squamous cell carcinoma (n = 206), and noncardia gastric adenocarcinoma (n = 352), along with population controls (n = 687). Associations between nutrient intake and risk of cancer were estimated by adjusted odds ratios (ORs), comparing the 75th versus the 25th percentile of intake. The following nutrients were significantly inversely associated with risk of all four tumor types: fiber, beta-carotene, folate, and vitamins C and B6. In contrast, dietary cholesterol, animal protein, and vitamin B12 were significantly positively associated with risk of all four tumor types. Dietary fat [OR, 2.18; 95% confidence interval (CI), 1.27-3.76] was significantly associated with risk of esophageal adenocarcinoma only. Dietary nitrite (OR, 1.65; 95% CI, 1.26-2.16) was associated with noncardia gastric cancer only. Vitamin C supplement use was associated with a significantly lower risk for noncardia gastric cancer (OR, 0.60; 95% CI, 0.41-0.88). Higher intake of nutrients found primarily in plant-based foods was associated with a reduced risk of adenocarcinomas of the esophagus and gastric cardia, whereas higher intake of nutrients found primarily in foods of animal origin was associated with an increased risk

Pathophysiological effects of long-term acid suppression in man.

McCloy RF, Arnold R, Bardhan KD, et al.

Dig Dis Sci. 1995 Feb; 40(2 Suppl):96S-120S.

A critical evaluation has been made of the available evidence in man of the effects of prolonged low acid states on the structure and function of the stomach. Various human models have been examined. 1. Ageing does not affect acid output from the normal male stomach, and there may be an increase in women. With progressive atrophy of the corpus mucosa, which is more frequent and rapid in patients with gastric ulcer, there is an associated loss of secretory function. Chronic gastritis and atrophy are the most important age-related changes, which in many cultures are hypothesized to develop via a prior *Helicobacter pylori*-related gastritis. However, *H. pylori* colonization of the mucosa decreases with increasing grades of gastric atrophy probably because intestinal metaplasia provides a hostile environment. Atrophy and intestinal metaplasia are associated with precancerous lesions and gastric cancer. Apparent hyperplasia of the gastric argyrophil endocrine cells is a common and spontaneous phenomenon in patients with atrophic gastritis, which in part may be related to the preferential loss of nonendocrine cells. 2. Pernicious anemia is associated with a complete lack of acid production, marked hypergastrinemia, and endocrine cell hyperplasia in the majority of patients. ECL-cell carcinoids and gastric cancer occur with a prevalence of 3-7%, and endoscopic surveillance in routine clinical practice is not warranted. 3. Gastric ECL-cell carcinoids are rare events that have been described in association with two diseases in man, pernicious anemia and Zollinger-Ellison syndrome as part of multiple endocrine neoplasia syndrome type I, and usually relate to marked hypergastrinemia and the presence of chronic atrophic gastritis with gastric antibodies or a genetic defect rather than the presence or absence of acid. Regression or disappearance of ECL-cell carcinoids, either spontaneously or after removal of the gastrin drive, has been recorded. Lymph node, and rarely hepatic, metastases are documented but death in these cases has been anecdotal. 4. Therapy with H₂ antagonists may result in up to a twofold rise in serum gastrin levels but in man no endocrine cell hyperplasia has been recorded. However, the data for H₂ antagonists on these aspects are very limited. There is no drug-related risk of gastric or esophageal cancer, although the incidence of the latter may be raised. Long-term treatment with omeprazole is associated with a two- to fourfold increase in gastrin levels over baseline values in one third of patients and apparent endocrine cell hyperplasia in 7% of cases overall.(ABSTRACT TRUNCATED AT 400 WORDS)

Gastrin stimulates receptor-mediated proliferation of human esophageal adenocarcinoma cells.

Moore TC, Jepeal LI, Boylan MO, Singh SK, Boyd N, Beer DG, Chang AJ, Wolfe MM.

Regul Pept. 2004 Aug 15;120(1-3):195-203.

Section of Gastroenterology, Boston University School of Medicine and Boston Medical Center, 650 Albany Street, EBRC Fifth Floor, MA 02118, USA. The prevalence of esophageal adenocarcinoma in the setting of Barrett's metaplasia continues to increase in Western nations at a rate greater than any other cancer. The trophic properties of gastrin have been documented in gastric, pancreatic and colon cancer cell lines, suggesting a potential role for this regulatory peptide in the growth of these malignancies. The aims of these studies were to identify and characterize the presence of functional cholecystokinin type-2 (gastrin) receptors on the membranes of human esophageal adenocarcinoma cells. Reverse transcriptase-polymerase chain reaction (RT-PCR) demonstrated the presence of cholecystokinin type-2 receptor transcripts in human esophageal adenocarcinoma cell lines. Competitive binding assays revealed specific binding of gastrin in SEG-1 cells (IC₅₀ of 2.4 x 10⁻⁸ M). This finding was confirmed by laser scanning confocal microscopy through internalization of rhodamine green labeled gastrin heptapeptide in SEG-1 cells. Gastrin caused a dose-dependent increase in proliferation of SEG-1 cells when compared to controls. This effect was abolished by co-incubation with L365,260, a CCK-2-specific receptor antagonist. Gastrin-induced phosphorylation of the p44 and p42 mitogen-activated protein kinases was demonstrated by Western blot analysis. In conclusion, the studied human esophageal adenocarcinoma cell lines possess cholecystokinin type-2 (gastrin) receptors.

Receptors bind gastrin, resulting in increased proliferation in SEG-1 cells.

The Effect of Omeprazole on Serum Concentrations of Theophylline, Pepsinogens A and C, and Gastrin in Elderly Duodenal Ulcer Patients.

Pilotto A, Franceschi M, Lagni M, et al.

Am J Ther. 1995 Jan; 2(1):43-6.

With the aim of verifying the effect of omeprazole treatment on theophylline serum concentration in elderly peptic ulcer patients, we studied 10 male subjects aged >65 years (mean age = 75.2, range = 67--86) with chronic obstructive bronchopneumonia and endoscopically diagnosed duodenal ulcer in acute phase. All subjects were treated with a slow-release formulation of theophylline 200 mg b.i.d. plus omeprazole 20 mg daily for 4 weeks. In all subjects serum concentrations of azote, creatinine, theophylline were determined at the beginning and after 1 and 4 weeks; at the beginning and end of the study, pepsinogen group A (PGA), pepsinogen group C (PGC) and gastrin were measured. Statistical analysis was performed with the Student's t-test for paired data. The results showed no statistically significant differences after 1 and 4 weeks of omeprazole treatment in serum concentrations of theophylline (T(0) = 7.4, T(1 week) = 7.5, T(4 weeks) = 6.0, p = ns), azote (T(0) = 45.2, T(1 week) = 30.5, T(4 weeks) = 36.1, p = ns), creatinine (T(0) = 1.27, T(1 week) = 1.02, T(4 weeks) = 1.16, p = ns), PGA (T(0) = 99.5, T(4 weeks) = 126.2, p = ns), and PGC (T(0) = 10.6, T(4 weeks) = 12.1, p = ns); however serum gastrin increased from T(0) = 70.2 plus minus 13.2 to T(4 weeks) = 130.3 plus minus 18.3 (p < 0.0001). It was concluded that (1) serum concentration of theophylline is not affected by the concomitant omeprazole treatment lasting 1 month in elderly patients suffering from chronic obstructive bronchopneumonia and peptic ulcer, (2) modifications of dosages of theophylline and/or omeprazole are not necessary in the elderly with normal renal function, (3) the increase in fasting serum gastrin after 4 weeks of treatment may indicate that omeprazole 20 mg daily is efficacious in inhibiting gastric acid secretion in the elderly people

Nutrient intake and esophageal cancer in the Caspian littoral of Iran: a case-control study.

Siassi F, Pouransari Z, Ghadirian P.

Cancer Detect Prev. 2000; 24(3):295-303.

The purpose of this study was to investigate the possible contribution of different dietary nutrients in the development of esophageal cancer (EC) in the Caspian littoral of Iran. Forty-one cases and 145 members of their households were matched for age and gender with 40 non-blood-relative controls and 130 members of their households for their nutrient intake. A standard 24-hour dietary recall questionnaire was used to estimate the daily intake of energy, protein, P, Fe, Na, K, vitamins C and A, thiamin, riboflavin, and niacin. Dietary nutrient deficiency was defined as less than 75% of the World Health Organization human nutritional requirements, except for P, Na, and K, for which the United States Recommended Dietary Allowances were followed. The results indicate the following: (1) The mean daily intake of all nutrients, except for riboflavin, was significantly lower in cases than in control subjects (P < .05); (2) with the exception of protein, riboflavin, and phosphorus, significant correlation was observed between the pattern of nutrient intake and health status of the study subjects (P < .05); and (3) dietary deficiency of niacin and phosphorus was associated significantly with the risk of EC development among case and control households (P < .01-.001), indicating that persons living in case households with dietary deficiencies of these nutrients have more than twice the risk of developing EC tumors than those living in control households. In conclusion, apparently some nutrients, such as P and niacin, may play a role in the etiology of esophageal cancer, and the status of these nutrients may be used eventually as an epidemiologic predictive marker for EC in the Caspian littoral of Iran and perhaps other regions

H2-receptor antagonists may increase the risk of cardio-oesophageal adenocarcinoma: a case-control study.

Suleiman UL, Harrison M, Britton A, et al.

Eur J Cancer Prev. 2000 Jun; 9(3):185-91.

Adenocarcinoma of the lower oesophagus and the gastric cardia has shown a dramatic worldwide increase in incidence over the last 25 years, but the cause is unknown. A large number of drugs have been introduced over this period of time, and it has been suggested that drugs that relax the lower oesophageal sphincter (DRLOS) might be causative, and on the other hand that non-steroidal anti-inflammatory drugs (NSAIDs) may be protective. H2-receptor antagonists (H2RAs) may allow achlorhydric reflux to continue without symptoms, and it is postulated that such asymptomatic reflux is uncontrolled by the usual conservative measures and may lead to increased oesophageal damage. H2RAs were first marketed in 1970 and might be the cause of the observed increase of cardio-oesophageal adenocarcinoma (COA). In a case-control study, the records of 56 subjects who died of COA in the period 1 January 1990 to 31 December 1992 were compared with those of 56 age-/sex-matched controls who died of myocardial infarction. They were 28 females and 84 males, mean age 69.8 years. The NHS records containing the lifetime prescription history of each subject were retrieved from the health authority. Each prescription was recorded, omitting drugs

taken in the two years before diagnosis. Analysis was performed using conditional logistic regression. Other variables, including the use of antacids, steroids, smoking and alcohol, were also examined. Subjects dying of COA were more likely to have consumed H2RAs (relative risk (RR) 7.50, 95% CI 1.33-42.09, $P < 0.02$). On the other hand, they were less likely to have consumed NSAIDs (RR 0.16, 95% CI 0.03-0.93, $P < 0.04$) or DRLOS (RR 0.14, 95% CI 0.02-1.0, $P = "0.05$)." This study supports a protective effect from NSAIDs against COA, but the similar effect of DRLOS is related to the increased use of cardiac drugs in the control group. H2RAs appear to have a harmful effect, which may be related to the worldwide increase in COA. However, the trend may have been apparent before cimetidine was widely available, and it is possible that the cause is multifactorial

Prevention of esophageal cancer: the nutrition intervention trials in Linxian, China. Linxian Nutrition Intervention Trials Study Group.

Taylor PR, Li B, Dawsey SM, et al.

Cancer Res. 1994 Apr 1; 54(7 Suppl):2029s-31s.

In Linxian China, the esophageal/gastric cardia cancer mortality rates are among the highest in the world. There is suspicion that the population's chronic deficiencies of multiple micronutrients are etiologically involved. We conducted two randomized, placebo-controlled nutrition intervention trials to test the effects of vitamin and mineral supplements in lowering the rates of esophageal/gastric cancer. In the first trial, the dysplasia trial, 3318 adults with a cytological diagnosis of esophageal dysplasia received daily supplementation with 26 vitamins and minerals in doses typically 2-3 times the United States Recommended Daily Allowances, or placebos, for 6 years. The second trial, the general population trial, involved 29,584 adults and used a one-half replicate of a 2(4) factorial experimental design which tested the effects of four combinations of nutrients: A, retinol and zinc; B, riboflavin and niacin; C, vitamin C and molybdenum; and D, beta-carotene, vitamin E, and selenium. Doses for these daily supplements ranged from 1 to 2 times the United States Recommended Daily Allowances, and the different vitamin/mineral combinations or placebos were taken for a period of 5.25 years. As part of the general population trial, an end-of-intervention endoscopy survey was carried out in a small (1.3%) sample of subjects to see if supplementation affected the prevalence of dysplasia and early cancer. Herein we review the methods of these trials and the results of the endoscopic survey. Fifteen esophageal and 16 gastric cancers were identified in endoscopic biopsies from the 391 subjects evaluated from two villages, and nearly all were asymptomatic. No significant reductions in the prevalence of esophageal or gastric dysplasia or cancer were seen with any of the four supplement groups. However, the prevalence of gastric cancer among participants receiving retinol and zinc was 62% lower than those not receiving those supplements ($P = 0.09$), while participants receiving beta-carotene, vitamin E, and selenium had a 42% reduction in esophageal cancer prevalence (0.34). We have reported separately that cancer mortality over the entire 5.25-year period was significantly reduced among those receiving beta-carotene, vitamin E, and selenium. The findings from the overall trial and the endoscopic sample offer a hopeful sign and should encourage additional studies with these agents in larger numbers of subjects

Antioxidants and cancers of the esophagus and gastric cardia.

Terry P, Lagergren J, Ye W, et al.

Int J Cancer. 2000 Sep 1; 87(5):750-4.

Antioxidant vitamins have attracted considerable attention in previous studies of esophageal squamous-cell carcinoma, but dietary studies of adenocarcinoma of the esophagus and gastric cardia remain sparse. Treating these tumors as distinct diseases, we studied intakes of vitamin C, beta-carotene and alpha-tocopherol in a nationwide population-based case-control study in Sweden, with 185, 165, and 258 cases of esophageal adenocarcinoma, esophageal squamous-cell carcinoma, and gastric cardia adenocarcinoma, respectively, and 815 controls. Subjects with a high parallel intake of vitamin C, beta-carotene, and alpha-tocopherol showed a 40-50% decreased risk of both histological types of esophageal cancer compared with subjects with a low parallel intake. Antioxidant intake was not associated with the risk of gastric cardia adenocarcinoma. Separately, vitamin C and beta-carotene reduced the risk of esophageal cancers more than alpha-tocopherol. We found that antioxidant intake is associated with similar risk reductions for both main histological types of esophageal cancer. Our findings indicate that antioxidants do not explain the diverging incidence rates of the 2 histological types of esophageal cancer. Moreover, our data suggest that inverse associations with esophageal squamous-cell carcinoma and adenocarcinoma may be stronger among subjects under presumed higher oxidative stress due to smoking or gastroesophageal reflux, respectively. Our results may be relevant for the implementation of focused, cost-effective preventive measures

Gastrin and colorectal cancer: a prospective study.

Thorburn CM, Friedman GD, Dickinson CJ, et al.

Gastroenterology. 1998 Aug; 115(2):275-80.

BACKGROUND & AIMS: Gastrin is a putative promoter of colorectal carcinomas. The aim of this study was to evaluate the temporal relationship between gastrinemia and development of colorectal malignancy. **METHODS:** We conducted a nested case-control study among 128,992 subscribers to a health maintenance program who had participated in a multiphasic health checkup between 1964 and 1969. Serum had been frozen since the checkup and the cohort followed up for cancer. Of 1881 incident colorectal carcinoma cases, 250 were randomly selected; 1 control without cancer was matched to each case by age, sex, education, and date of serum collection. Stored sera were tested for *Helicobacter pylori* immunoglobulin G and for gastrin and glycine-extended gastrin. **RESULTS:** Verified cases included 166 colon cancers, 58 rectal cancers, and 9 with cancer in both locations. A mean of 15.3 years had elapsed between serum collection and diagnosis of cancer. Median gastrin levels were similar in cases and controls (41.7 vs. 40.7 pg/mL). However, a gastrin level above normal was associated with increased risk for colorectal malignancy (odds ratio, 3.9; 95% confidence interval, 1.5-9.8). If this association is causal, 8.6% of colorectal cancers could be attributed to high serum gastrin level. **CONCLUSIONS:** Hypergastrinemia is associated with an increased risk of colorectal carcinoma

Regulation and function of COX-2 gene expression in isolated gastric parietal cells.

Pausawasdi N, Ramamoorthy S, Crofford LJ, Askari FK, Todisco

Am J Physiol Gastrointest Liver Physiol. 2002 Jun;282(6):G1069-78.

Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan 47109-0682, USA. We examined expression, function, and regulation of the cyclooxygenase (COX)-2 gene in gastric parietal cells. COX-2-specific mRNA was isolated from purified (>95%) canine gastric parietal cells in primary culture and measured by Northern blots using a human COX-2 cDNA probe. Carbachol was the most potent inducer of COX-2 gene expression. Gastrin and histamine exhibited minor stimulatory effects. Carbachol-stimulated expression was inhibited by intracellular Ca(2+) chelator 1,2-bis(2-aminophenoxy) ethane-N,N,N',N'-tetraacetic acid-AM (90%), protein kinase C (PKC) inhibitor GF-109203X (48%), and p38 kinase inhibitor SB-203580 (48%). Nuclear factor (NF)-kappaB inhibitor 1-pyrrolidinedithiocarbonyl acid inhibited carbachol-stimulated expression by 80%. Similar results were observed in the presence of adenoviral vector Ad.dom.neg.lkappaB, which expresses a repressor of NF-kappaB. Addition of SB-203580 with Ad.dom.neg.lkappaB almost completely blocked carbachol stimulation of COX-2 gene expression. We examined the effect of carbachol on PGE(2) release by enzyme-linked immunoassay. Carbachol induced PGE(2) release. Ad.dom.neg.lkappaB, alone or with SB-203580, produced, respectively, partial (70%) and almost complete (>80%) inhibition of carbachol-stimulated PGE(2) production. Selective COX-2 inhibitor NS-398 blocked carbachol-stimulated PGE(2) release without affecting basal PGE(2) production. In contrast, indomethacin inhibited both basal and carbachol-stimulated PGE(2) release. Carbachol induces COX-2 gene expression in the parietal cells through signaling pathways that involve intracellular Ca(2+), PKC, p38 kinase, and activation of NF-kappaB. The functional significance of these effects seems to be stimulation of PGE(2) release.

Gastrin activates nuclear factor kappaB (NFkappaB) through a protein kinase C dependent pathway involving NFkappaB inducing kinase, inhibitor kappaB (IkappaB) kinase, and tumour necrosis factor receptor associated factor 6 (TRAF6) in MKN-28 cells transfected with gastrin receptor.

Ogasa M, Miyazaki Y, Hiraoka S, Kitamura S, Nagasawa Y, Kishida O, Miyazaki T, Kiyohara T, Shinomura Y, Matsuzawa Y.

Gut. 2003 Jun;52(6):813-9.

Department of Internal Medicine and Molecular Science, Graduate School of Medicine, Osaka University, Japan. **BACKGROUND:** We previously reported that gastrin induces expression of CXC chemokines through activation of nuclear factor kappaB (NFkappaB) in gastric epithelial cells that express gastrin receptor. **AIMS:** To clarify gastrin receptor mediated signals leading to activation of NFkappaB. **METHODS:** MKGR26 cells were created by transfecting gastrin receptor cDNA into MKN-28 cells. Degradation of inhibitor kappaB (IkappaB) and phosphorylation of protein kinase C (PKC)-delta were both detected by western blot analysis. NFkappaB activation was determined by luciferase assay and electrophoretic mobility shift analysis. **RESULTS:** Gastrin induced degradation of IkappaB-alpha and activation of NFkappaB, which was abolished by the selective gastrin receptor antagonist L-740,093 and the general PKC inhibitor GF109203X. Gastrin induced phosphorylation of PKC-delta, and its inhibitor rottlerin partially suppressed NFkappaB activation. However, the mitogen activated protein kinase (MAPK) kinase inhibitor PD98059, p38 MAPK inhibitor SB203580, and tyrphostin AG1478 had no effect on NFkappaB activation. Introduction of the dominant negative mutant of IkappaB kinase, of NFkappaB inducing kinase, and of tumour necrosis factor receptor associated factor 6 (TRAF6), but not that of TRAF2, inhibited gastrin induced activation of NFkappaB. **CONCLUSIONS:** Gastrin activates NFkappaB via a PKC dependent pathway which involves IkappaB kinase, NFkappaB inducing kinase, and TRAF6.

Clinical trial of deglydyrrhizinized liquorice in gastric ulcer.

Turpie AG, Runcie J, Thomson TJ.

Gut. 1969 Apr; 10(4):299-302.

Control of transient lower oesophageal sphincter relaxations and reflux by the GABA(B) agonist baclofen in patients with gastro-oesophageal reflux disease.

Zhang Q, Lehman A, et al.

Gut. 2002; 50(1):19-24.

Possible immunologic involvement of antioxidants in cancer prevention.

Zhang YH, Kramer TR, Taylor PR, et al.

Am J Clin Nutr. 1995 Dec; 62(6 Suppl):1477S-82S.

The people of Linxian County, China have one of the world's highest rates of esophageal cancer. Two intervention trials were conducted to determine whether supplementation with specific vitamins and minerals could lower mortality from or incidence of cancer in this population and whether supplementation with multiple vitamins and minerals would reduce esophageal and gastric cardia cancer in persons with esophageal dysplasia. About 30,000 general population (GP) subjects in the GP trial were randomly assigned to one of eight intervention groups according to a one-half replicate of a 2(4) factorial experimental design and were supplemented for 5.25 y with four combinations of micronutrients at doses from one to two times the US recommended dietary allowance (RDA). About 3000 subjects in whom dysplasia was diagnosed in the dysplasia trial were randomly assigned to groups receiving daily supplementation with 14 vitamins and 12 minerals at two to three times the US RDA or placebo for 6 y. Results of the dysplasia trial indicate that in individuals with esophageal dysplasia, micronutrient supplementation had little effect on T lymphocyte responses. In contrast, male participants in the GP trial who were supplemented with beta-carotene, vitamin E, and selenium showed significantly ($P < 0.05$) higher mitogenic responsiveness of T lymphocytes in vitro than those not receiving these micronutrients

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