Aspirin May Improve Survival With Non-Metastatic Colorectal Cancer

Aspirin Use and Survival After Diagnosis of Colorectal Cancer.
Chan AT, Ogino S, Fuchs CS::
JAMA 2009; 302 (August 12): 649-658

Analysis of participants who developed non-metastatic colorectal cancer suggests that regular aspirin use after cancer diagnosis is associated with a survival benefit.

**Background:** Many observational studies have noted a reduced colorectal cancer risk in aspirin users. However, the effect of aspirin on the prognosis of established colorectal cancer is unknown. Animal experiments suggest that nonsteroidal anti-inflammatory drugs (NSAIDs) with activity against the isoenzyme cyclooxygenase-2 (COX-2) inhibit tumor growth and metastases.

**Objective:** To assess the relationship between aspirin use and colorectal cancer survival after diagnosis.

**Design:** Data analysis from 2 large prospective observational cohorts.

**Participants:** 1279 subjects in the Nurses' Health Study and the Health Professionals' Follow-up Study who were diagnosed with non-metastatic colorectal cancer.

**Methods:** Health information based upon self-administered questionnaires was obtained as well as relevant medical records. Subjects were divided into 4 groups: (1) no regular aspirin use before or after cancer diagnosis; (2) regular aspirin use before and after cancer diagnosis; (3) regular aspirin use before, but not after cancer diagnosis; and (4) regular aspirin use only after cancer diagnosis. Tissue samples from 459 participants were assayed for COX-2 status.

**Results:** After a median follow-up of 11.8 years, there were 480 total deaths; 222 were due to colorectal cancer. The following major associations were found: (1) subjects who took aspirin after the cancer diagnosis had a significant 29% reduction in colorectal cancer mortality (multivariate hazard ratio [HR] 0.71; 95% CI, 0.53 to 0.95) and a significant 21% reduction in all-cause mortality (HR 0.79; 95% CI, 0.65 to 0.97); (2) aspirin use prior to cancer diagnosis was not associated with mortality; (3) the beneficial effect of aspirin use after a colorectal cancer diagnosis appeared to occur only in those with tumors that over-expressed COX-2 (HR 0.39; 95% CI, 0.20 to 0.76).

**Conclusions:** Aspirin taken after diagnosis may reduce the risk of cancer mortality and all-cause mortality in those with colorectal cancer over-expressing COX-2.

**Reviewer's Comments:** This study contains all the benefits and pitfalls of the genre. Pros include: large scale, prospective assessment of data prior to the development of the issue under consideration, and attempted corrections for potential confounding variables. Cons include: multiple comparisons, statistical manipulations, and findings of associations only, and the possibility that the findings represent mere chance. Observational cohorts must be taken for what they are: hypothesis-generating explorations of potential associations among relatively rare events involving a large number of subjects. There were only 1279 colorectal cancers during the 20-some years of observation of over 170,000 participants. The bottom line: aspirin taken after diagnosis may reduce the risk of cancer mortality and all-cause mortality in those with colorectal cancer over-expressing COX-2. These findings are supported by animal data and secondary analysis of one clinical trial. Should aspirin be recommended as part of colorectal cancer treatment? Definitely not. Should the proper randomized controlled trial be initiated? Probably yes.

Additional Keywords: None

Print Tag: Refer to original journal article
MicroRNA Aids in Colon Cancer Screening

Differential Expression of MicroRNAs in Plasma of Patients With Colorectal Cancer: A Potential Marker for Colorectal Cancer Screening.

Ng EKO, Chong WWS, et al.: Gut 2009; 58 (October): 1375-1381

MicroRNA-92 has potential as a useful plasma marker in the screening and detection of colorectal cancer.

**Objective:** To determine whether plasma microRNAs could distinguish between patients with and without colon cancer.

**Participants/Methods:** The study was conducted in 3 separate phases: the first included a search to find putative eligible microRNA markers in plasma and tissue from patients with colorectal cancer and healthy controls; the second phase validated markers on a small sample of colorectal cancer patients and controls; and the third phase involved a large-scale validation of colorectal cancer patients, healthy controls, and other gastrointestinal (GI) disease controls. Samples from 5 colon cancer patients and 5 controls were obtained in phase 1; 25 colon cancer and 20 control patients participated in phase 2; and 90 colon cancer patients, 50 healthy controls, 20 inflammatory bowel disease patients, and 20 gastric cancer patients participated in phase 3.

**Interventions:** RNA was extracted by standard methods from plasma and tissues; microRNA profiling was performed using polymerase chain reaction techniques.

**Results:** 5 of 95 microRNAs researched were upregulated in plasma and tissue. MicroRNA-17-3p and microRNA-92 were significantly increased in colon cancer patients ($P < 0.001$).

**Conclusions:** MicroRNA-92 has potential as a useful plasma marker in the screening and detection of colorectal cancer.

**Reviewer's Comments:** This preliminary study seeks to find and validate the "magic bullet" of screening tests for the detection of colorectal cancer using a noninvasive blood test. Other groups of disease controls (such as pancreatic cancer, ischemic colitis, etc) must be included before this test can be adopted; for example, one of the problems with the use of troponin for diagnosing acute myocardial infarction is that we now know troponin is released from cardiocytes for many reasons (sepsis, GI bleeding, myocarditis, etc) that are not indicative of acute coronary thrombosis secondary to plaque rupture. In addition, sensitivity and specificity are mediocre (particularly specificity) which may limit use of this test.

Additional Keywords: None

Print Tag: Refer to original journal article
Is Driving Safe for Patients With Cirrhosis?

Minimal Hepatic Encephalopathy Is Associated With Motor Vehicle Crashes: The Reality Beyond the Driving Test.

Bajaj JS, Saeian K, et al::
Hepatology 2009; 50 (October): 1175-1183

Patients with cirrhosis and abnormal minimum hepatic encephalopathy inhibitory control tests have higher automobile crash rates when compared to patients with normal results.

**Background:** Minimum hepatic encephalopathy (MHE) is present in up to 80% of those with cirrhosis and associated with impaired attention, visuomotor coordination, psychomotor speed, and response inhibition. MHE can be assessed by both standard psychomotor tests (SPT) and computerized inhibitory control tests (ICT). Although those with MHE have impaired driving skills, the association with motor vehicle crashes is unclear.

**Objective:** To determine the association of MHE with crashes and traffic violations over the preceding year and on 1-year follow-up.

**Design:** Prospective study.

**Participants:** Subjects aged 18 to 65 years with cirrhosis from 2 academic medical centers.

**Methods:** Subjects were administered a battery of 4 SPT: (1) number connection test (NCT) A and B; (2) digital symbol test (DST); and (3) block design test along with ICT. Impaired psychomotor performance was defined as 2 standard deviations of control on any 2 SPT or >5 lures on the MHE ICT. Crashes and traffic violations were assessed by both self-report and records from the department of transportation (DOT) and compared to those with abnormal SPT and MHE ICT.

**Results:** 167 subjects (mean age 53 years and model for end-stage liver disease score 11) were included. Impaired psychomotor testing was present in 55% by SPT and 58% by ICT. A significantly higher proportion with abnormal MHE ICT experienced crashes in the preceding year compared to those without MHE ICT by both self-report (17% vs 0%, \( P = 0.0004 \)) and DOT records (17% vs 3%, \( P = 0.004 \)) with a relative risk (RR) of 5.5. SPT could not differentiate between crashes and traffic violations. More subjects with crashes had MHE by ICT than SPT by self-report (100% vs 50%, \( P = 0.03 \)) and DOT records (89% vs 44%, \( P = 0.01 \)) with excellent correlation between crashes and traffic violations by self-report and DOT records (kappa of 0.90 and 0.80). Those with MHE by ICT also had significantly higher future crashes/violations compared to those with normal ICT (22% vs 7%, \( P = 0.03 \)) while abnormal SPT was not associated with future crashes or traffic violations.

**Conclusions:** Patients with cirrhosis and abnormal MHE ICT have higher crash rates over the preceding year and on prospective follow-up when compared to patients with normal ICT. Also, ICT, but not SPT, was associated with both prior and future crashes and violations.

**Reviewer's Comments:** We are often asked by patients with cirrhosis or their families if it is safe to drive. These data strongly suggest that the MHE ICT is an excellent way to assess who is at risk for crashes and traffic violations. While assessment of MHE by ICT may not be practical in routine clinical practice, these data do open up opportunities for research. While we do not know if treating MHE will impact these outcomes, we do await the results of ongoing studies from these investigators on this important societal dilemma.

Additional Keywords: None

Print Tag: Refer to original journal article
Induction dosing with 360 µg per week of PEG α-2a for 12 weeks followed by standard dosing does not improve sustained virologic response rates over standard 48-week dosing.

**Background:** Because standard dose peginterferon (PEG) and ribavirin (RVN) have sustained virologic response (SVR) rates of 40% to 50% in those with genotype (GT) 1, more effective strategies are needed. Several studies have looked at whether intensified therapy with higher doses of PEG will improve SVR. However, these studies were often underpowered and have had mixed results.

**Objective:** To determine if high-dose PEG α-2a for the first 12 weeks can increase SVR compared to standard dose PEG combined with weight-based RVN in the treatment of patients with hepatitis C virus (HCV).

**Design:** Prospective, multicenter, multinational, randomized open label study.

**Participants:** 896 HCV treatment naïve GT1 subjects from Australia, New Zealand, Thailand, Argentina, Mexico, and Canada.

**Methods:** Subjects were randomized to 360 µg (high dose group, n=448) or 180 µg (standard group, n=448) of PEG α-2a weekly for 12 weeks followed by 36 weeks of 180 µg PEG α-2a weekly plus 1000 to 1200 mg RVN per day. Virologic response was assessed by HCV RNA (detection limit 15 IU/ml) at weeks 4, 8, 12, 24, and 48 (end of therapy) and at 24 weeks after therapy (SVR). Dose reductions were performed by protocol and growth factors were discouraged but permitted. Primary end point was SVR. Secondary end points were rapid virological response (RVR) and complete early virological response (EVR).

**Results:** Mean age of the cohort was 43 years, 82% were Caucasian, 69% were male, and 15% had advanced fibrosis. Although rates of RVR (36% vs 26%, \( P =0.007 \)) and EVR (74% vs 62%, \( P \))

**Conclusions:** Induction dosing with 360 µg per week of PEG α-2a for 12 weeks followed by standard dosing does not improve SVR rates over standard 48-week dosing.

**Reviewer’s Comments:** This large, well done study shows us that although high-induction dose PEG interferon combined with 1000 to 1200 mg per day RVN improves RVR and EVR, it does not improve SVR. Hopefully, the availability of novel oral antiviral therapies within the next few years will offer hope to those with poor predictors of response.

Additional Keywords: None

Print Tag: Refer to original journal article
At experienced intestinal transplant centers, 90% of patients are surviving at least one year.

**Objective:** To outline current state-of-the-art concepts with regard to small intestinal transplantation.

**Design:** Current concepts review.

**Methods:** Data were collected on 1031 adults and 733 children in the Intestinal Transplant Registry. Indications for transplant, surgical procedures, immunology of transplantation complications, postoperative outcome, and future trends were discussed.

**Results:** Total parenteral nutrition is the first-line treatment for short bowel syndrome, but long-term problems (including sepsis, thrombosis, liver disease, renal stones, and dehydration) can occur in 20% to 40% of patients within 5 years of therapy. Patients who have had complications of total parenteral nutrition are ideal candidates for intestinal transplantation. The decision to undergo intestinal transplant for improvement in quality of life in patients who have not had complications of total parenteral nutrition remains controversial. Transplants that involve only donor jejunoileum are referred to as isolated intestinal transplants; however, transplants that involve other organs (stomach, liver, duodenum, biliary tree, etc.) are referred to as multivisceral transplants. Ileostomy is usually created post-transplant, which can serve as access to the intestinal mucosa for biopsies to monitor rejection. Once graft function stabilizes, the ileostomy may be reversed. Tacrolimus augmented with low-dose steroids, with or without sirolimus, help to provide chronic immunosuppression. Graft rejection and infection are common complications of intestinal transplant and it is important to distinguish between them via biopsy and culture (a pathologist experienced with post-transplant biopsy interpretation is key). The most commonly seen symptom of rejection is diarrhea. At experienced centers, 1-year survival post-transplant >90%.

**Conclusions:** Intestinal transplantation is a viable method for maintaining gastrointestinal function especially in patients who have complications or failures of total parenteral nutrition.

**Reviewer's Comments:** A brief, but well-written overview of the field of small intestinal transplantation. Particularly useful were the illustrations depicting the surgical operations involved and the immunologic response to the donor allograft.

Additional Keywords: None

Print Tag: Refer to original journal article
**Mesalamine Toxicity Is Rare Cause of Eosinophilic Pneumonia**

*pulmonary manifestations of inflammatory bowel disease.*

Storch I, Sachar D, Katz S.:

Inflamm Bowel Dis 2003; 9 (March): 104-115

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Sulfasalazine-induced eosinophilic pneumonitis may be caused in some patients by allergic reaction to the sulfapyridine moiety and in others by reaction to mesalamine. Eosinophilic pneumonia is rare adverse effect of mesalamine therapy.

**Background:** A recent patient with ulcerative colitis (UC) developed a pneumonitis believed to be secondary to treatment with mesalamine. This subject is reviewed definitively (197 references). **Review:** Pulmonary disease has been associated with inflammatory bowel disease (IBD) much less frequently than with other organs. Incidental findings may be misinterpreted as direct associations. Very rare allergic reactions to sulfasalazine (SSAL) or its active moiety, mesalamine (5-ASA), represent the clearest cause of pulmonary disease in IBD patients. As of 2003, 47 cases of pulmonary dysfunction had been documented. The most common entity is eosinophilic pneumonia, which is defined as eosinophilic infiltration of the lungs with or without eosinophils in the peripheral blood. Also described are eosinophilic pleural effusions and fibrosing alveolitis. Side effects of SSAL and 5-ASA are idiosyncratic and not dose related. Most reactions occur within 2 to 6 months of starting the drug. However, 2 cases occurred within days of administration and 5 cases occurred after many years. The most common symptom is dyspnea (76%), fever (68%), and chest pain (65%). Peripheral eosinophilia is found in approximately 50%. Chest x-ray frequently reveals bilateral infiltrates or opacities. Recovery usually occurs within days or weeks of discontinuing the drug. Corticosteroids may hasten recovery. Definitive diagnosis requires recurrence of symptoms with drug rechallenge. Pneumonitis, as with drug-induced hepatitis caused by SSAL, may be secondary to an allergic reaction to either the sulfapyridine moiety or to 5-ASA.

**Reviewer's Comments:** Pulmonary disease, especially eosinophilic pneumonia secondary to treatment with SSAL or 5-ASA, is very rare, but may occur even after years of successful maintenance therapy. Drug rechallenge to confirm or disprove the diagnosis may be justified if the medication is required to control colitis. Many pulmonary reactions to SSAL may be due to allergy to sulfa, in which case mesalamine should be effective and well tolerated.

Additional Keywords: None

Print Tag: Refer to original journal article
In patients with moderate to severe ulcerative colitis, there was a 41% decrease in colectomies when treated with infliximab over a year.

**Background:** A significant number of patients with moderate to severe ulcerative colitis (UC) ultimately fail conventional medical therapy with aminosalicylates, immunomodulators and corticosteroids. Colectomy with ileoanal pouch anastomosis is considered curative; however pouchitis, bowel obstruction, erectile dysfunction or other complications may occur. Hence, though surgery may save lives and improve the quality of life, it is still considered by many as a medical failure.

**Objective:** To compare colectomy rates in patients with moderate to severe UC who were randomized to receive infliximab or placebo.

**Design:** Randomized, double-blind placebo controlled trial. **Patients:** 728 outpatients with moderate to severe UC.

**Methods:** Moderate to severe UC is defined by a Mayo Clinic Score of 6 to 12 points despite concurrent therapies with corticosteroids and/or 6-mercaptopurine/azathioprine and/or aminosalicylates. Patients were participants in the Active Ulcerative Colitis Trials (ACT 1 and ACT 2), which were trials evaluating induction and maintenance infliximab therapy (5 or 10 mg/kg IV) in moderate to severe UC. Colectomy and hospitalization data through week 54 were analyzed.

**Results:** Of patients, 630 had complete follow-up through 54 weeks. The cumulative incidence of colectomy through 54 weeks was 17% (36 of 244) in the placebo group compared to 10% (46 of 484) in the combined infliximab groups ($P = 0.02$), representing only an absolute risk reduction of 7%; this represents a hazard ratio of 0.59 or a 41% reduction in the risk of colectomy for the combined infliximab group compared to placebo. Prevention of colectomy appeared dose related with a cumulative colectomy rate for 5 mg/kg of 12% (28 of 242; $P = 0.166$) and for 10 mg/kg a rate of 8% (18 of 242; $P = 0.007$).

**Conclusions:** Infliximab induction therapy at 0, 2, and 6 weeks followed by maintenance infusions every 8 weeks in outpatients with moderate to severe UC reduces the cumulative incidence of colectomy at 54 weeks by 41%.

**Reviewer's Comments:** Over the course of a year, the benefits of infliximab therapy in patients with moderate to severe UC greatly outweigh the risks. Patients treated with infliximab are more likely to experience clinical response and clinical remission and are less likely to require colectomy. Of dosing amounts, 10 mg/kg appears more effective than 5 mg/kg. Short-term incidence of serious side effects (infection, malignancy) appears to be low; however, this may change with long-term follow-up, which may take decades.

Additional Keywords: None

Print Tag: Refer to original journal article
The use of anti-tumor necrosis factor agents with immunomodulators is associated with a slight increase in the risk of non-Hodgkin's lymphoma.

**Background:** There is concern that patients with Crohn's Disease (CD) treated with anti-tumor necrosis factor (TNF) may be at increased risk for non-Hodgkin's lymphoma (NHL).

**Objective:** To compare the rate of NHL in CD patients who have received anti-TNF with a population-based registry of patients not exposed to anti-TNF, and to a population of CD patients treated with immunomodulators (IM).

**Design:** Meta-analysis. **Patients:** 8905 CD patients treated with anti-TNF derived from 26 studies and followed for 21,178 patient-years.

**Methods:** Study criteria included randomized controlled trials, cohort studies, or case series reporting on anti-TNF therapy in adult CD patients. Standardized incidence ratios (SIR) were calculated by comparing the observed pooled rate of NHL with the expected rate of NHL among subjects not exposed to anti-TNF agents. This was derived from the Surveillance Epidemiology and End Results (SEER) cancer registry. Expected rate of NHL in CD patients treated with IM alone was obtained by meta-analysis.

**Results:** Among anti-TNF treated patients, 13 cases of NHL were reported (6.1 per 10,000 patient years). Of these, at least 9 were taking concomitant IM therapy, 1 had a history of IM therapy, in 2 the use or non-use of IM was not reported, and only 1 patient had clearly not been exposed to IM therapy. The expected rate of NHL in patients not receiving anti-TNF derived from the SEER registry was only 1.9 per 10,000 patient years. Anti-TNF treated patients had a significantly increased risk of NHL (SIR, 3.23) compared to those not treated with anti-TNF. In CD patients taking IM alone, the risk of NHL was 4 per 10,000 patient years (SIR, 1.7).

**Conclusions:** The use of anti-TNF agents with IM is associated with a slight increase in the risk of NHL.

**Reviewer's Comments:** Almost all CD patients who developed NHL after treatment with anti-TNF agents had either been treated previously or concomitantly with IM. There did not appear to be enough CD patients treated with anti-TNF but never treated with IM to convincingly give a SIR for NHL in patients treated with anti-TNF alone. The rate of NHL in CD patients treated with anti-TNF and IM is very small when compared to the clinical quality of life benefits. Whether or not IM should be withdrawn from patients treated with anti-TNF agents is controversial.
Objective: To retrospectively evaluate a group of patients with celiac disease (CD) on a gluten-free diet (GFD) to determine the onset of both malignant and non-malignant complications.

Design: Retrospective analysis.

Participants: 549 patients with CD seen between 1993 and 2006.

Methods: 251 (45.7%) had classical CD (ie, diarrhea, abdominal pain, weight loss, and malabsorption syndrome). Of patients, 262 (47.7%) had subclinical disease (ie, gluten-sensitive enteropathy with extraintestinal symptoms such as iron-deficiency anemia, alopecia, recurrent abortion, etc) and no gastrointestinal symptoms. The remaining 36 (6.6%) had the silent form of the disease found in screening high-risk groups such as first-degree relatives of patients with CD, insulin dependent diabetes mellitus, etc. Mean time the patients were on a gluten-free diet was 7.13 years (range 1 to 15 years). Almost 70.0% of patients were believed to be fully compliant with the GFD, while 20.4% reported

Results: Of patients, 18 (3.3%) developed complications while following a GFD. Of complications, 7 were malignant and the remaining 11 non-malignant. Of patients with complications, 14 (5.6%) were in the classical CD group, while only 4 (1.5%) patients with subclinical CD had complications. None of the patients with asymptomatic CD had complications. In the classical CD group, complications occurred after a mean of 6.5 years of following a GFD while those in the subclinical group developed complications after a mean time of 3.3 years. Of patients in the CD group with complications, 6 were not fully compliant with GFD, compared to 2 non-compliant patients in the subclinical group having complications.

Conclusions: Complications of CD occur in

Reviewer's Comments: This study found that a relatively small number of patients with CD develop complications of their disease whether they have classical or subclinical disease and complications seem to occur whether or not a GFD is rigidly adhered to. Patients with asymptomatic disease were found to not be at risk for complications. If the results of this study are confirmed, advising patients with subclinical or asymptomatic disease to rigidly follow a GFD might not be appropriate.

Additional Keywords: None

Print Tag: Refer to original journal article
Alcoholic Drinks May Decrease Risk of Barrett's Esophagus

Alcohol Types and Sociodemographic Characteristics as Risk Factors for Barrett's Esophagus.
Kubo A, Levin TR, et al:
Gastroenterology 2009; 136 (March): 806-815

Compared to a control population, an inverse relationship was noted between wine consumption and Barrett's esophagus whereas no similar association could be found for beer or liquor.

**Background:** During the past 3 decades, incidence of adenocarcinoma of esophagus has increased by 500%, which is more than any other cancer. Although it is well known that squamous cell cancer of the esophagus is related to alcohol consumption, no such association has been made with adenocarcinoma. It has been found that white males are most frequently diagnosed with adenocarcinoma suggesting that some environmental or lifestyle factor might be responsible for this increase.

**Objective:** To appraise the association between Barrett's esophagus and alcohol use, alcohol type, sociodemographic profiles, and other lifestyle factors.

**Design:** Case control study drawn from the Kaiser Permanente Northern California membership.

**Participants:** 320 new cases of Barrett's esophagus diagnosed between 2002 and 2005.

**Methods:** Participants were matched to persons with gastrointestinal reflux disease (GERD; n=316) and to population controls (n=317).

**Results:** The amount of alcohol consumed was not significantly associated with the risk of Barrett's esophagus, although stratification by beverage type showed an inverse relationship for wine drinkers (>7 glasses per week) compared to nondrinkers (odds ratio 0.44; 95% CI, 0.20 to 0.99; multivariate analysis). In controls, those who preferred wine were more likely to have college degrees and regularly take vitamin supplements than those who preferred beer or liquor, although adjustment for these factors or GERD symptoms did not eliminate the inverse association between wine consumption and Barrett's esophagus. It was found that education status was significantly inversely associated with the risk of Barrett's esophagus.

**Conclusions:** This study found that there are associations between alcohol types, socioeconomic status, and the risk of Barrett's esophagus. Although the choice of alcoholic beverages was associated with several factors, multiple adjustments (including for GERD) did not eliminate the relationship between alcohol and Barrett's esophagus.

**Reviewer's Comments:** Compared to a control population, an inverse relationship was noted between wine consumption and Barrett's esophagus whereas no similar association could be found for beer or liquor. In addition it was found that although the choice of alcoholic beverages was related to other demographic and health seeking behavior factors (such as vitamin use); adjustments for these factors did not eliminate the inverse association observed between wine consumption and Barrett's esophagus. If the results of this study are confirmed by other investigators, we will be able to encourage patients to drink modest amounts of wine to decrease their risk of Barrett's esophagus. This could be a major advance in preventive medicine.

Additional Keywords: None

Print Tag: Refer to original journal article
Background: Many chronic diseases, especially diabetes, coronary heart disease, stroke, and cancer, are thought to be modifiable by lifestyle modification, including not smoking, undergoing physical activity, avoiding obesity, and adhering to healthy dietary principles. While this is not new information, most previous investigations have focused on only a single lifestyle factor, rather than multiple.

Objective: To analyze the association(s) among multiple lifestyle factors and the development of chronic disease.

Design: Prospective observational cohort.

Participants: 23,153 eligible German participants aged 35 to 65 years, who were free of the chronic diseases of interest at baseline.

Methods: Data were collected from the European Prospective Investigation in Cancer and Nutrition (EPIC), a multicenter, pan-European prospective observational cohort. Participants underwent an initial structured interview and periodic follow-up questionnaires. They were analyzed with respect to the following 4 defined healthy lifestyle factors: (1) no history of smoking; (2) body mass index

Results: Mean and median follow-up was about 8 years. Of participants,

Conclusions: Adherence to these 4 healthy lifestyle factors can have a strong impact on the prevention of chronic disease.

Reviewer’s Comments: This is the type of data which drives public policy. It is assumed that behavioral modification will have individual clinical benefit. This may very well be true, but the inherent flaw in this logic is the confusion of association with causality -- that because lifestyle factors are associated with health outcomes, it is assumed that they cause the outcomes. It is further assumed that early adoption of healthy lifestyle factors, or changes to the factors which already exist, will alter outcomes; however, this faith remains a faith without proof. I try to follow these healthy behaviors, but I think we should be humble in our preaching, with the realization that we may always be wrong.

Additional Keywords: None

Print Tag: Refer to original journal article
Analysis of a large, prospective observational cohort finds that red and processed meat intake is associated with increased all-cause, cardiovascular disease, and cancer mortality, while white meat intake is inversely associated.

**Background:** Although it is thought that high intake of red meat is associated with increased mortality, many prior studies have examined vegetarians and did not factor in other lifestyle factors, such as smoking, physical activity, or body weight.

**Objective:** To assess potential risk factors of red, processed, and white meat intake on all-cause, cardiovascular disease, and cancer mortality.

**Design:** Prospective large-scale observational cohort.

**Participants:** 322,263 men and 223,390 women aged 50 to 71 years at baseline.

**Methods:** Participants were members of the National Institutes of Health-AARP (formerly known as American Association of Retired Persons) Diet and Health Study, an analytic cohort of volunteers from 6 states and 2 cities. Subjects completed a baseline questionnaire asking about demographics, lifestyle factors, and food frequency. Quintiles of red, processed, and white meat consumption were calculated. Cox proportional hazards regression models were used to calculate multivariable hazard ratios (HR). Morality information was determined by linkage to national death databases.

**Results:** During 10 years of follow-up, there were 47,976 male deaths and 23,276 female deaths. Men and women in the highest quintiles of both red and processed meat as compared with the lowest quintile had significantly elevated risks for all-cause mortality. For men, red meat consumption had a HR of 1.31 (95% CI, 1.27 to 1.35), while processed meat had a HR of 1.16 (95% CI, 1.12 to 1.20). For women, red meat HR was 1.36 (95% CI, 1.30 to 1.43), and processed meat HR was 1.25 (95% CI, 1.20 to 1.31). Similar elevated associated risks were seen in both men and women for cardiovascular disease, cancer, and other causes of mortality. White meat intake, comparing highest with lowest quintile, in both men and women, was inversely associated with various mortality risks. Smoking may still be an important confounding variable.

**Conclusions:** Red and processed meat intake is associated with modest increases in all-cause, cardiovascular, and cancer mortality.

**Reviewer's Comments:** This is at least the fifth publication this year from the same cohort -- the others looked at pancreatic cancer risks and at dairy and calcium intake and associated cancer risks. Dipping in the same pool too often increases the possibility of finding chance associations only. Additionally, the author of an American College of Physicians (ACP) Journal Club review expresses concern regarding underestimating potential lifestyle associations with intake of red meat -- smoking, physical activity, body weight, calorie intake, and educational status -- suggesting a "healthy cohort" effect rather than a specific meat effect. The ACP review also points out that the associated risk of death from other causes (suicide, injury, diabetes, dementia, etc) is actually higher than that from the outcomes under question, weakening any biologically plausible explanations and increasing the chance of statistical flukes. Nonetheless, when taken for what it is (a large scale, prospective observational cohort searching for associations), the findings support those from other similar observations.

Additional Keywords: None

Print Tag: Refer to original journal article
Increasing Dietary Fat May Increase Pancreatic Cancer Risk

*Dietary Fatty Acids and Pancreatic Cancer in the NIH-AARP Diet and Health Study.*

Thiébaut ACM, Jiao L, et al.:

*J Natl Cancer Inst* 2009; 101 (July 15): 1001-1011

Increased intake of total, saturated, and monounsaturated fat, predominately of animal origin, was associated with increased risk for pancreatic cancer.

**Background:** Some observational studies of various types have linked dietary fat intake to pancreatic cancer risk. Since early detection and therapy of pancreatic cancer are problematic, modification of risk factors may provide the current best chance to reduce the burden of disease.

**Objective:** To analyze associations between dietary fat intake and pancreatic cancer risk, and to analyze food sources of dietary fat and potential associations with pancreatic cancer risk.

**Design:** Prospective, large scale observational cohort.

**Participants:** Eligible participants in the National Institutes of Health-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study, initiated in 1995.

**Methods:** A Food Frequency Questionnaire (FFQ) was mailed to 3.5 million AARP members aged 50 to 71 years residing in 6 states and 2 metropolitan areas. Two 24-hour dietary recall surveys were also obtained in some. Nutrient intakes were calculated based upon U.S. Department of Agriculture databases, and pancreatic cancer data were collected from state cancer registries. Cox proportional hazards regression models were used to calculate hazard ratios (HR).

**Results:** 525,473 participants met eligibility criteria. During a mean follow-up of 6.3 years, 1337 cases of pancreatic cancer were diagnosed. Comparing the highest quintile of fat consumption with the lowest quintile, risk of pancreatic cancer in men was 53% increased and in women was 23% increased. Combining data for men and women and after multivariable analysis, risks were significantly increased for total fat (HR 1.23; 95% CI, 1.03 to 1.46), saturated fat (HR 1.36; 95% CI, 1.14 to 1.62), and monounsaturated fat (HR 1.22; 95% CI, 1.02 to 1.46), but not polyunsaturated fat. Association for increased pancreatic cancer risk was strongest for saturated fat from animal sources, particularly red meat and dairy products (HR 1.43; 95% CI, 1.20 to 1.70). Associations with fat intake were independent of energy intake.

**Conclusions:** Increased risk of pancreatic cancer is associated with intake of total, saturated, and monounsaturated fats, particularly derived from red meat and dairy products.

**Reviewer's Comments:** As is always true with similar large scale prospective observational cohorts, statistical analysis is daunting, and findings only represent associations, not causality. The unproven assumption is that modification of total (or source of) fat intake will reduce the risk for pancreatic cancer. It is also possible that associations found are statistical flukes, especially since the same investigators studying the same cohort have found associations with lifestyle factors (reported by me in abstract in the August 30, 2009, Practical Reviews in Gastroenterology) and heavy alcohol intake (reported by me in abstract in this current Practical Reviews in Gastroenterology issue).

Additional Keywords: None

Print Tag: Refer to original journal article
A moderately increased risk for pancreatic cancer is associated with heavy alcohol use, especially liquor, although there may be residual confounding by cigarette smoking.

**Background:** Alcohol excess has been associated with a number of gastrointestinal tract cancers. However, evidence for an association between alcohol intake and pancreatic cancer remains equivocal, with many studies finding positive associations and others finding no association.

**Objective:** To determine if alcohol intake, especially after correction for cigarette smoking history, is associated with risk of pancreatic cancer.

**Design:** Prospective large scale observational cohort study.

**Participants:** Eligible participants in the National Institutes of Health-AARP (formerly the American Association of Retired Persons) Diet and Health Study, initiated in 1995.

**Methods:** A baseline health and Food Frequency Questionnaire (FFQ) was mailed to 3.5 million AARP members, aged 50 to 71 years, residing in 6 states and 2 metropolitan areas. Self-reported information was obtained on alcohol intake and other potentially confounding factors. Cancers were identified by state registries. Cox proportional hazards regression models were used to calculate relative risks (RR).

**Results:** 470,681 respondents met eligibility criteria. During a mean 7.3 years of follow-up, 1149 cases of exocrine pancreatic cancer developed. Compared with light drinkers, those who consumed ≥6 drinks per day had a significant increased risk for pancreatic cancer (RR 1.55; 95% CI, 1.13 to 2.13) while those who drank ≥3 drinks per day also had an increased risk (RR 1.45; 95% CI, 1.17 to 1.80). Increased risk was in men only and appeared to occur only in liquor drinkers, not wine or beer drinkers. Because there were relatively few heavy drinkers who never smoked, the authors could not eliminate the possibility that cigarette smoking was a confounding variable.

**Conclusions:** Heavy alcohol use appears to play a role in pancreatic cancer epidemiology, although cigarette smoking may have a confounding role.

**Reviewer's Comments:** As is always true with similar large scale prospective observational cohorts, the statistical analysis is daunting, and the findings only represent associations, not causality. These data confirm other evidence that support the role of alcohol, especially liquor, as an etiologic factor in pancreatic cancer risk. Because the authors have published 3 different studies, using the same observational cohort, in 3 different journals, finding different potential etiologic associations for pancreatic cancer, it is possible that some, or all, of their findings are due to chance. Further analysis in other prospective cohorts is necessary to confirm these findings.

Additional Keywords: None

Print Tag: Refer to original journal article
Can Sargramostim Induce Remission in Crohn’s Patients?

Steroid-Sparing Properties of Sargramostim in Patients With Corticosteroid-Dependent Crohn’s Disease: A Randomised, Double-Blind, Placebo-Controlled, Phase 2 Study.

Valentine JF, Fedorak RN, et al:
Gut 2009; 58 (October): 1354-1362

Sargramostim is superior to placebo in Crohn’s patients for induction of remission in steroid-dependent disease.

**Objective:** To determine if the recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF), sargramostim, is useful in inducing remission in steroid-dependent Crohn’s disease.

**Design:** Randomized, double-blind, placebo-controlled, phase 2, multicenter study.

**Participants:** 129 patients with active ileocolonic and colonic Crohn’s disease despite >3 months of therapy with 10 mg to 40 mg prednisone daily participated in the study.

**Methods:** 87 patients were randomized (at a 2:1 ratio) to receive sargramostim 6 µg/kg subcutaneously daily and 42 patients received placebo for up to 22 weeks. In weeks 1 to 4, patients received study drug plus steroids; in weeks 4 to 14, patients were tapered from steroids; and finally there was an observation period for 4 weeks where patient received study drug and ≤7.5 mg prednisone. Primary end point was a steroid-free remission (Crohn’s disease activity index).

**Results:** Sargramostim-treated patients underwent remission 18.6% of the time versus 4.9% in the placebo group ($P = 0.03$). Sargramostim-treated patients also had improvement in quality of life; however, they did have pain at the injection site, dyspnea, and musculoskeletal pain.

**Conclusions:** Sargramostim was more efficacious in inducing steroid-free remission in patients with Crohn’s disease who are steroid-dependent.

**Reviewer’s Comments:** The study had a high rate of patients discontinuing secondary to the forced steroid taper design of the study. It is still unclear whether sargramostim can induce a long-term steroid-free remission in Crohn’s patient. Further long-term studies (>6 months) should give more data in this regard.

Additional Keywords: None

Print Tag: Refer to original journal article
At present, aggressive screening of high-risk individuals in kindreds of familial pancreatic cancer is not justified.

**Objective:** To determine if a prospective screening program for pancreatic cancer could result in early detection of familial pancreatic cancer.

**Design:** Prospective, non-randomized non-blinded cohort study.

**Participants:** 76 high-risk asymptomatic individuals registered in the National German Familial Pancreatic Cancer Registry (FaPaCa).

**Methods:** High-risk patients were defined as: first-degree relatives of a patient with familial pancreatic cancer or melanoma pancreatic cancer syndrome, members of a familial pancreatic cancer family that carries a BRCA2 gene mutation, or member of a melanoma pancreatic cancer syndrome family independent of relationship degree. Between June 2002 and December 2007, patients were enrolled in the screening program for a total of 182 physician office visits. Patients underwent a physical exam, lab tests, abdominal magnetic resonance cholangiopancreatographic/magnetic resonance imaging (MRCP/MRI) and pancreatic endoscopic ultrasound (EUS). If abnormalities were detected, a fine-needle aspiration was performed by EUS. CEA, CA 19-9, CDKN2a and BRCA2 gene analyses were also performed.

**Results:** In 28 patients, abnormalities were detected on either EUS (n=25) or MRCP/MRI (n=12). Of these, 7 patients had fine-needle aspirations and 7 underwent pancreatic surgical exploration, of which 6 had limited pancreatic resection performed. Pathology findings included 3 serous cyst adenomas, 1 intraepithelial neoplasia (PanIN1) with lobular fibrosis, 1 PanIN2 and 1 PanIN1 with gastric type intraductal papillary mucinous neoplasm (IPMN).

**Conclusions:** Although EUS/MRI/MRCP detected early precursor pancreatic lesions, the overall yield of the screening program was low. Due to high expense, a screening program for the detection of pancreatic cancers in this group of asymptomatic family members of patients with pancreatic cancer cannot be recommended at present.

**Reviewer's Comments:** Detection of pancreatic cancer at an early stage even in kindreds of patients with family cancer syndromes remains problematic. Further work on non-invasive testing is clearly an active area of research by pancreatologists.

Additional Keywords: None

Print Tag: Refer to original journal article
Preventing First Variceal Bleed: Carvedilol Vs Band Ligation

Randomized Controlled Trial of Carvedilol Versus Variceal Band Ligation for the Prevention of the First Variceal Bleed.

Carvedilol, a non-selective beta blocker, may become an option for primary prophylaxis of the first esophageal variceal bleed in patients with cirrhosis.

Background: Prophylaxis of the first variceal bleed in patients with cirrhosis and large esophageal varices is usually undertaken with either a beta-blocker, such as propranolol or nadolol, or by variceal band ligation. Band ligation may be more effective than propranolol, but overall survival appears similar. Carvedilol, a non-selective beta-blocker, appears to lower portal pressures more effectively than propranolol and therefore might be a better agent for primary prophylaxis.

Objective: To compare efficacy of carvedilol versus variceal band ligation in the prophylaxis of the first variceal bleed in patients with cirrhosis.

Design: Multicenter Scottish study.

Participants: 77 patients randomized to carvedilol and 75 to band ligation.

Methods: Patients with cirrhosis and grade II or larger varices, no previous bleed, and who had not been previously treated with beta-blockers or nitrates were randomized to band ligation or carvedilol. Those assigned to band ligation had their first session after randomization followed by repeat ligation every 2 weeks until eradication, then a repeat endoscopy at 3- and 6-month intervals with rebanding as needed. Carvedilol was given in a dose of 6.25 mg daily and increased to 12.5 mg if systolic blood pressure was ≥90 mmHg after one week. The first variceal bleed, defined as hematemesis and/or melena with endoscopic findings of variceal bleeding or recent hemorrhage with a drop of hemoglobin of ≥2 g within 24 hours, was the primary end point which also included bleeding due to banding-induced ulceration. Secondary end points were overall mortality and bleeding-related death within 6 weeks of the first bleed.

Results: At baseline, groups were well-matched. Alcoholic liver disease was the main cause of cirrhosis (73%). Among patients in the carvedilol group, 32% discontinued treatment compared to 31% of patients in the banding group. Median time from randomization to initial ligation was 21 days and to eradication was 60 days. In the intention-to-treat analysis, 10% of patients in the carvedilol group had a variceal bleed compared to 23% in the band ligation group, a statistically significant difference (P =0.04). No difference in overall mortality or bleeding-related mortality was found.

Conclusions: Carvedilol is a treatment option for primary prophylaxis of the first variceal bleed in patients with cirrhosis and large esophageal varices

Reviewer’s Comments: Because nearly a third of patients discontinued their assigned treatment, ligation was often delayed and variceal eradication was unsuccessful in a large number of patients. Because hepatic venous pressure gradients were not measured, this study is seriously flawed. Nonetheless, if carvedilol can be shown to be more effective than the other non-selective beta-blockers and band ligation in a more tightly controlled and larger study, a role for it in the primary prophylaxis of the first variceal bleed will be established.

Additional Keywords: None

Print Tag: Refer to original journal article
Adjuvant chemotherapy in patients with T3N0M0 colon cancer without risk factors improves survival.

**Background:** At present it is not clear if patients with no known risk factors and T3N0M0 colon cancer benefit from receiving postoperative chemotherapy.

**Objective:** To determine if patients with T3N0M0 colon cancer with no known risk factors benefit from chemotherapy.

**Design:** Retrospective analysis.

**Participants:** 247 patients with no known risk factors and pathologically confirmed T3N0M0 colon cancer seen from 1994 to 2004.

**Methods:** Patients were divided into 2 groups: those who received surgery alone and those who received adjuvant chemotherapy. None of the patients received preoperative chemotherapy or radiation therapy.

**Results:** Although there were no guidelines for the use of chemotherapy in T3N0M0 colon cancer, 198 (80.2%) patients received adjuvant chemotherapy. The remaining 49 (19.8%) had only surgery. Overall survival rate of patients was 92.8%. Those in the surgery plus adjuvant chemotherapy group had a survival of 94.2% whereas the group who had only surgery had a 5-year survival of 85.4% ($P=0.032$) as determined by multivariate analysis. In comparing various chemotherapeutic agents used (5-fluorouracil, capecitabine and uracil/tegafur) no difference in their therapeutic efficacy was found.

**Conclusions:** Adjuvant chemotherapy after surgery in T3N0M0 colon cancer without risk factors has been shown to prolong survival.

**Reviewer's Comments:** This is a nicely performed analysis of patients with T3N0M0 colon cancer demonstrating that chemotherapy improves survival. This should help in making the decision as to whether or not to offer chemotherapy in these patients with T3N0M0 lesions and no risk factors.

Additional Keywords: None

Print Tag: Refer to original journal article
Abdominal cocoon may explain unusual cases of recurrent partial small bowel obstruction.

**Background:** Abdominal cocoon (AC) is a rare condition characterized by total or partial encasement of the small bowel by a thick fibrous membrane.

**Objective:** To determine methods of diagnosis and treatment of abdominal cocoon.

**Design:** Retrospective analysis.

**Participants:** 24 cases seen at a hospital in China between January 1997 and September 2007.

**Methods:** Data, including clinical manifestations, auxiliary examination, diagnosis, and surgical results of AC patients were analyzed.

**Results:** 87.5% of patients with AC presented with symptoms of partial or complete small bowel obstruction and 54.2% of patients had an abdominal mass. The chief complaints of the affected patients were nausea, vomiting, abdominal pain, abdominal distention, constipation, and passage of gas. It should be noted that none of the patients affected by this condition had previous surgery. Of cases, 9 were male and 15 female; mean age was remarkably young at 34 years with a range of 15 to 57 years. Mean course of disease was 26 months. The shortest course was 3 days in a patient who presented with acute complete intestinal obstruction leading to surgery; the longest course was 18 years and was manifested by chronic and recurrent intestinal obstruction. Most patients were diagnosed as having AC at the time of surgery. Of cases, 3 were diagnosed by CT scan and 1 by barium enema. It was not clear how many patients had CT scans of the abdomen prior to surgery. In all cases, the surgical finding was that part of or all of the small intestine was encapsulated in a dense, white, fibrous, cocoon like membrane. The membrane was removed in all cases and adhesions were lysed and all patients had uneventful recoveries. No recurrences were noted during follow-up of 3 months to 9 years (mean of 37 months).

**Conclusions:** This rare disease presents with non-specific findings and in this study preoperative diagnosis was rarely made. Once diagnosed and treated the prognosis in this unusual condition seems quite good and it is encouraging that no recurrences of the disease were noted.

**Reviewer’s Comments:** Although this condition is rare it should be considered in any patient who has recurrent partial small bowel obstruction without a prior history of abdominal surgery. It is encouraging that surgical treatment yields excellent results and recurrences were not seen in this condition.

**Additional Keywords:** None

**Print Tag:** Refer to original journal article
Weight reduction through lifestyle intervention leads to improvements in the liver histology in nonalcoholic steatohepatitis.

**Background:** Nonalcoholic steatohepatitis (NASH) is a common problem that can lead to cirrhosis and liver failure. Unfortunately, there is no approved pharmacologic therapy. Because obesity is common in those with NASH, weight loss is often recommended. However, the efficacy of weight loss for the treatment of NASH has not been carefully evaluated.

**Objectives:** To determine the effect of a year-long weight reduction with lifestyle intervention using the combination of diet, exercise, and behavior modification education on clinical and histologic parameters of NASH.

**Design:** Prospective, randomized, single center study.

**Participants:** Overweight or obese subjects (body mass index [BMI] of 25 to 40) with biopsy-proven NASH.

**Methods:** Subjects were randomized 2:1 to receive intensive lifestyle intervention (LS) or structured education (controls). LS included weight loss strategies and weekly meeting for the first 6 months followed by monthly meetings focused on changing both eating and exercise habits with the goal of losing 7% to 10% body weight within the first 6 months and then maintaining this weight loss. Controls got basic information about healthy eating, exercise, and weight control and met every 12 weeks. All subjects were assigned a calorie goal-based diet. The physical activity intervention was mostly unsupervised with a particular emphasis on walking. After 48 weeks, subjects underwent a follow-up biopsy. Liver histology was assessed by the NASH activity score (NAS).

**Results:** Of 65 enrolled in screening, 31 were eligible for the trial. Mean age was 48, mean BMI was 34, and 71% were men. Those randomized to LS lost 9.2% of their weight compared to 0.2% in controls (P =0.003). More in the LS group had a reduction in NAS of ≥3 points or had a post-treatment NAS of ≤2 when compared to controls (72% vs 30%, respectively; P =0.03). NAS improved in the LS group (4.4 to 2.0) compared to controls (4.9 to 3.5). Percent weight reduction correlated with improvement in NAS (r =0.47, P =0.007). Compared to those that did not lose ≥7% of their weight, those that did had improvements in steatosis (P PP

**Conclusions:** Weight reduction through lifestyle intervention leads to improvements in the liver histology in NASH.

**Reviewer's Comments:** In addition to the benefits of weight reduction on insulin resistance, hypertension, and overall health, these data show that it can lead to improvements in the liver histology in NASH and therefore, weight reduction should be considered standard in all overweight or obese subjects with NASH.

Additional Keywords: None

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