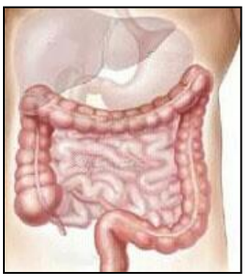
COLORECTAL CANCER RESEARCH

Month Ending January 14th, 2011



The following colorectal cancer research update extends from December 18th, 2010 – January 14th, 2011 inclusive and is intended for informational purposes only.

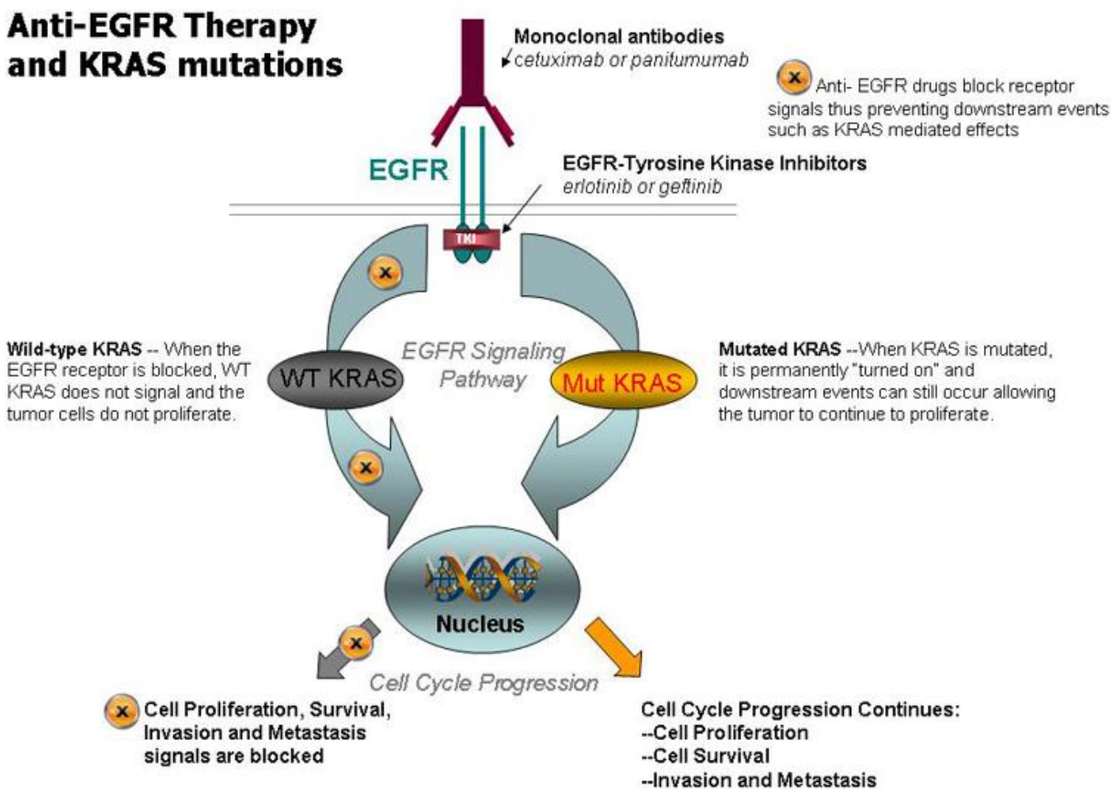
CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Testing for Kras Mutation is Helpful for Advanced Colorectal Cancer (Jan. 4/11)

Up to 80% of colorectal cancer patients are diagnosed with advanced disease. Often, monoclonal antibodies that target the epidermal growth factor receptor (EGFR), such as erbitux and vectibix, are used alone or in combination with chemotherapy to improve overall and progression-free survival in patients with advanced colorectal cancer. While these treatments have been proven effective, they also are expensive and can cause serious adverse effects. In addition, they do not benefit all patients. Researchers believe that mutations in certain genes be associated with resistance to anti-EGFR antibody therapy (such as erbitux and vectibix). Among them, Kristen-RAS (KRAS), a member of the rat sarcoma virus (ras) gene family of oncogenes (cancer genes), is particularly suspect. Researchers reviewed published data to determine whether KRAS mutation status affects success of anti-EGFR-based treatments for patients with advanced CRC and whether KRAS status predicts clinical outcomes in these patients. They found that KRAS mutations were consistently associated with reduced overall and

progression-free survival and increased anti-EGFR treatment failure. The authors conclude that patients whose tumors test positive for KRAS mutation should not be treated with anti-EGFR agents.



Source: http://www.exigon.com/dxps/Pages/kras-test.aspx

Dahabreh, IJ, et al., Systematic review: anti-epidermal growth factor receptor treatment effect modification by kras mutations in advanced colorectal cancer. Annals of Internal Med 2011; 154: pp. 37-49

2. Phase III Trial for Davanat Begins (Jan. 10/11)

The design of a phase III trial to test the cancer treatment **Davanat** is under way by Pro-Pharmaceuticals. The trial will see the drug co-administered with standard chemotherapy in patients with advanced colorectal cancer. The study will look at increased survival rates as a primary endpoint, as well as the reduction of serious side effects from chemotherapy. Davanat is a carbohydrate polymer composed of mannose and galactose. DAVANAT's mechanism of action is based on interacting with lectins on the cell surface. Lectins are a large and important super family of animal proteins which bind tightly, and very specifically, to particular sugar residues of glycoproteins. DAVANAT targets specific lectin receptors (galectins) that are over-expressed on cancer cells. Current research indicates that galectins affect cell development and play important roles in cancer, including tumor cell survival, angiogenesis (the formation of new tumour blood vessels) and tumor metastasis. Davanat works to target and interfere with Galectin receptors on cancer cells, which play an important role in tumor cell survival and its spread, giving the tumor the ability to evade the immune system. Data from a Phase II trial for the drug showed that it extended median survival by 46% compared with the best standard of care as determined by the patients' physicians. Researchers are highly encouraged by the findings of their previous clinical studies, which suggest that DAVANAT may be an effective anti-cancer agent that also reduces side effects such as mucositis. The company expects to receive approval for Davanat in South America later this year

http://news.drugs-expert.com/colorectal-cancer-news/pro-pharmaceuticals-to-begin-davanat-phase-iii-development-program-following-fda-approval/

3. New U.S. Phase I Study Involving Reolysin Opens (Jan. 10/11)

Oncolytics Biotech Inc. announced that a U.S. Phase I study of REOLYSIN in combination with FOLFIRI [Folinic Acid (leucovorin) + Fluorouracil (5-FU) + Irinotecan] in patients with oxaliplatin refractory/intolerant ***Kras* mutant colorectal cancer** (REO 022) is now open to enrollment. The principal investigator is Dr. Sanjay Goel of the Montefiore Medical Center at The Albert Einstein College of Medicine in New York. Investigators are focusing their clinical program increasingly to look at patients with ***Kras* mutant cancers** by either pre-screening patients for *Kras* status, as in the case of this study, or by selecting indications with widespread *Kras* involvement, such as the ongoing Phase II study in advanced pancreatic cancer (REO 017). The crc trial is a Phase I dose escalation study with three dose levels, comprising groups of three to six patients, to determine a maximum tolerated dose and dose-limiting toxicities with the combination of REOLYSIN and FOLFIRI. FOLFIRI will be administered on the first day of a two week (14-day) cycle, while REOLYSIN will be administered on days one through five of a four week (28-day) cycle. Eligible patients include those with confirmed cancer of the colon or rectum with *Kras* mutation and measurable disease. They must have progressed on or within 190 days after last

dose of oxaliplatin regimen as front-line therapy in the metastatic setting or be intolerant to oxaliplatin. The study is expected to enroll 12 to 20 patients. The rationale for conducting the study is based on signals of efficacy seen in a range of preclinical and clinical work with REOLYSIN. This includes a National Cancer Institute screen of seven colorectal cancer cell lines (four with ras mutations), all of which were susceptible to REOLYSIN; preclinical research into the efficacy of REOLYSIN in combination with various chemotherapeutic agents in colorectal cancer cell lines; observation of CEA responses and stable disease in colorectal patients in a phase I study of REOLYSIN as a monotherapy; and interim results from a translational study with REOLYSIN as a monotherapy that is currently ongoing, which showed evidence of viral replication and tumour cell death in four of six patients with metastatic colorectal cancer analyzed to date, two of which had confirmed *Kras* mutations in codon 12.

http://newswire.ca/en/releases/archive/January2011/10/c9269.html

4. Evaluating Systemic Therapy for Peritoneal Mets Using PSDSS (Dec. 24/11)

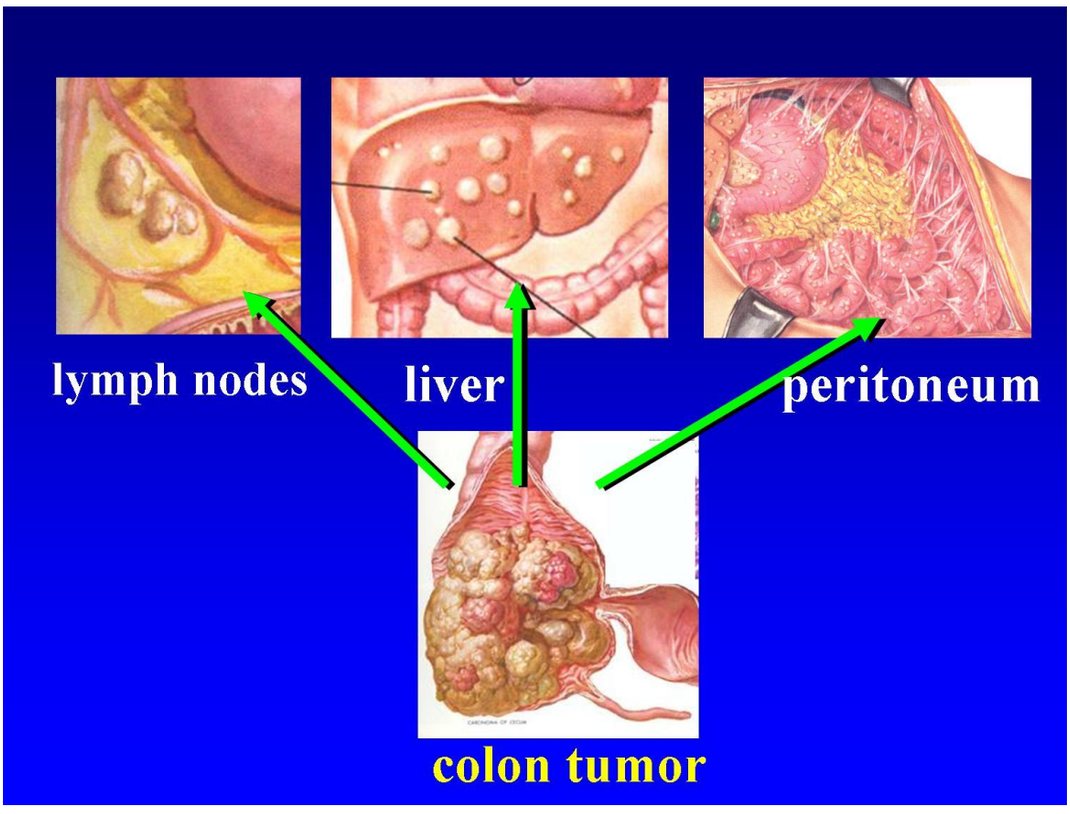
In this study, researchers evaluated the long-term survival of patients with peritoneal carcinomatosis (PC – or colorectal metastases to the peritoneum) treated with systemic chemotherapy regimens, and the impact of the retrospective **Peritoneal Surface Disease Severity Score (PSDSS)** on outcomes. The peritoneum is a transparent membrane that lines the abdominal cavity. The PSDSS classifies PC patients based on clinically relevant factors. One hundred sixty-seven consecutive patients treated with PC from colorectal cancer between years 1987-2006 were identified from a prospective institutional database. These patients either received no chemotherapy, 5-FU/Leucovorin or Oxaliplatin/Irinotecan-based chemotherapy. Stratification was made according to the retrospective PSDSS that classifies PC patients based on 3 clinically relevant factors. The three most important prognostic indicators used were; clinical symptoms, extent of carcinomatosis based on the tumor burden and tumor histopathology. Each of these three categories was classified into three sub-categories based on the severity of each factor:

i. **Clinical Symptoms**; none, mild (weight loss < 10% of body weight, mild abdominal pain, asymptomatic ascites) or severe (weight loss ≥ 10% of body weight, unremitting pain, bowel obstruction, symptomatic ascites).

ii. **Extent of Carcinomatosis Intraoperatively**; limited, moderate or extensive.

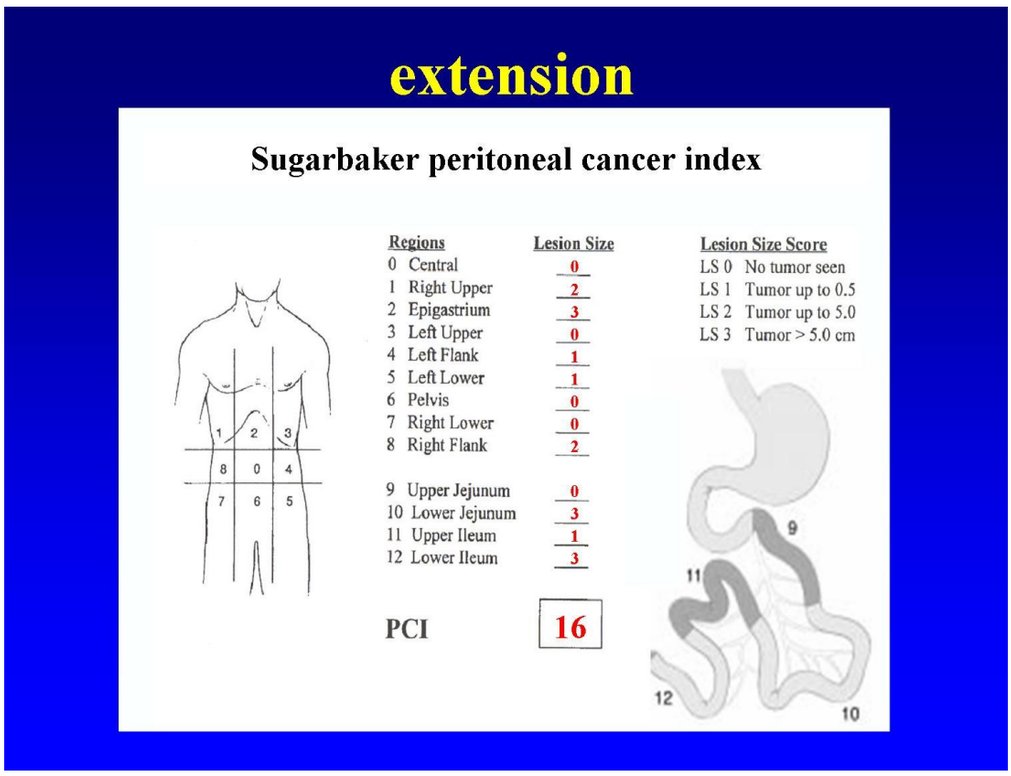
iii. **Tumor Histopathology** of the primary tumor; well to moderately differentiated without positive lymph node, moderately differentiated with positive lymph nodes or poorly differentiated and/or signet ring

Investigators noted that median survival was 5 months for patients who had no chemotherapy, 11 months for patients treated with 5 FU/LV, and 12 months for patients treated with Oxaliplatin/Irinotecan-based chemotherapy. Survival differed between patients treated with chemotherapy compared to those patients who did not receive chemotherapy. PSDSS staging was identified as an independent predictor for survival. A trend towards improved outcomes is demonstrated from treatment of patients with PC from colorectal cancer using modern systemic chemotherapy. Researchers concluded that the PSDSS appears to be a useful tool in patient selection and prognostication in PC of colorectal origin.



A Colon Tumor Can Travel To Distant Organs, Not the Least of which Are the Liver and the Peritoneum

Source: ***http://www.drmulier.com/3%20en%20pat%20info%20hipec.html***



The surgeon measures the amount of cancer in 13 different regions of the abdomen and gives each region a score from 1 to 3. These scores are added to a global score (Sugarbaker Peritoneal Cancer Index). This scoring has a double aim. In case of peritoneal cancer by a bowel tumor, it allows to avoid a meaningless operation: when the score is higher than 20, the chances of improving survival by performing the HIPEC procedure are very small and the intervention is stopped. In addition, the score allows an estimation of the prognosis. The lower the score, the better the prospects.

Source: ***http://www.drmulier.com/3%20en%20pat%20info%20hipec.html***

OW Pelz, Joerg, et al., Evaluation of Best Supportive Care and systemic chemotherapy as treatment stratified according to the retrospective peritoneal surface disease severity score (psdss) for peritoneal carcinomatosis of colorectal origin. BMC Cancer. 2010, 10:689

SURGICAL THERAPIES

5. Longer Intervals Between Neoadjuvant Chemoradiation and Rectal Cancer Surgery

(Dec.24/10)

The aim of this study was to determine the effect of a longer interval between neoadjuvant chemoradiation (chemoradiation given before rectal surgery) and surgery on surgical complications and cancer outcomes. A colorectal cancer database was queried for clinical stage II and III rectal cancer patients undergoing neoadjuvant chemoradiation followed by rectal surgery between 1997 and 2007. The neoadjuvant regimen consisted of a long course external beam radiation and 5-fluorouracil chemotherapy. Patients with inflammatory bowel disease, hereditary cancer, extracolonic malignancy, urgent surgery, or non-validated treatment dates were excluded. Patients were divided into two groups according to the interval between chemoradiation and surgery (<8 and ≥8 weeks). Surgical complications and oncologic outcomes were compared. One hundred seventy-seven patients were included. Groups were comparable with respect to demographics, tumor, and treatment characteristics. Surgical complications were not affected by the interval between chemoradiation and surgery. Patients undergoing surgery ≥8 weeks after chemoradiation experienced a significant improvement in pathologic complete response rate (30.8% vs. 16.5%) and had decreased 3-year local recurrence rate (1.2% vs. 10.5%). A longer interval correlated with less local recurrence, although statistical significance was not reached. Investigators concluded that an interval between chemoradiation and surgery ≥8 weeks is safe and is associated with a higher rate of pathologic complete response and decreased local recurrence.

Geisler, Daniel, et al., Neoadjuvant therapy for rectal cancer: the impact of longer interval between chemoradiation and surgery. J of Gastrointestinal Surgery. Doi: 10.1007/s11605-010-1197-8

6. Delaying Chemo After Surgery is Not Beneficial (Dec. 29/10)

According to the results of this study, waiting more than 2 months for adjuvant therapy (chemo after surgical removal of the primary tumour), doubles the risk that patients will die. When adjuvant chemotherapy was delayed more than 60 days past surgery, patients were more likely to die within five years. However, there wasn't a significant decrease in relapse-free survival. Doctors at the Sylvester Comprehensive Cancer Center at the University of Miami in Florida reviewed information on 186 stage II and III patients, 49 (26%) of whom started chemotherapy more than 60 days after their surgery. Thirty percent of those cases were system-related: late referrals or insurance issues, for instance. The relative

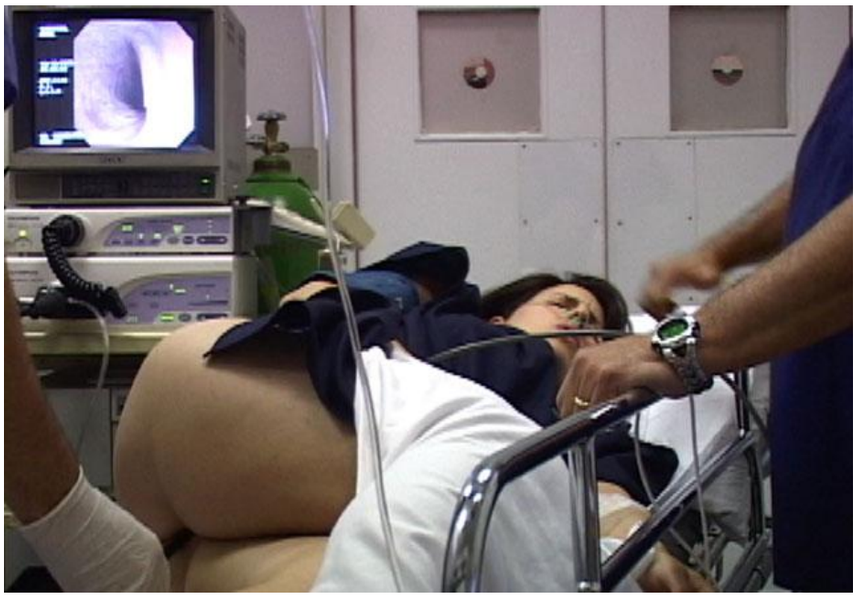
risk of dying within five years (*overall survival)* was 2.17 — a little over double that of patients who began their chemo earlier. Recurrence-free survival favored patients with earlier chemo, but wasn't statistically significant. Researchers concluded that adjuvant chemotherapy delay >60 days after surgical resection of colon cancer is associated with worse overall survival.

Bayraktar, Ulas Darda, et al., Does delay of adjuvant chemotherapy impact survival in patients with resected stage II and III colon adenocarcinoma? Cancer. December 2010. Doi: 10.1002/cncr.25720

SCREENING

7. Research Highlights Benefits of Colonoscopies (Jan. 3/11)

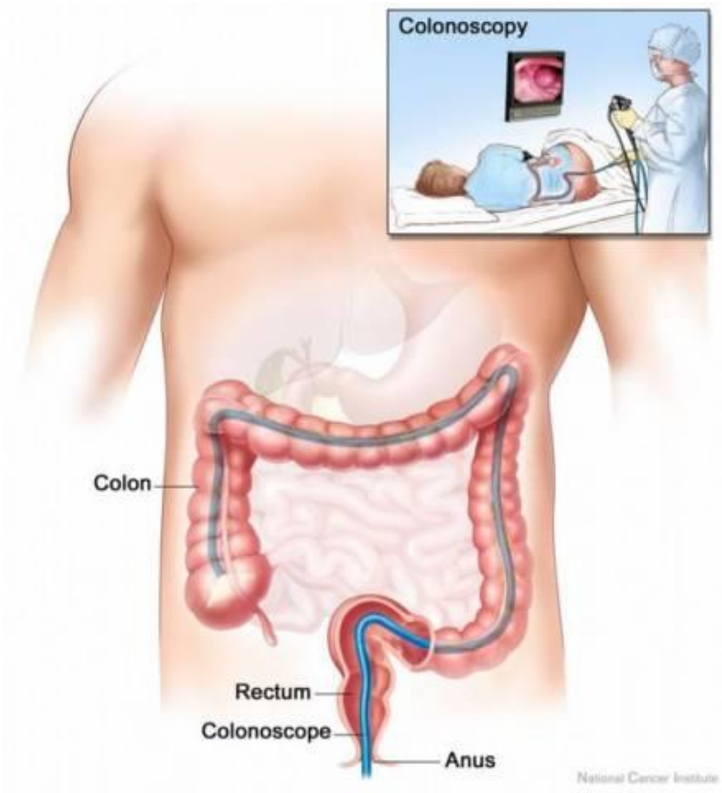
It is considered one of the most effective cancer screening and prevention exams, but recent studies have raised concerns that a colonoscopy may not be useful for detecting certain colorectal cancers. Now a new study from Germany offers strong evidence that the test **can** prevent colorectal cancers located throughout the colon -- not just those easiest to reach with the fiberoptic imaging scope. Experts say the findings should reassure patients that a colonoscopy saves lives by detecting and removing precancerous polyps throughout the colon before they can become malignant. This study tells us that when done well, colonoscopy is effective in both the left and right side of the colon. Colonoscopy involves a flexible fiberoptic scope with a video camera, which is threaded through the large intestine to search for and remove polyps before they become malignant (See illustrations below).



The Colonoscopy Procedure

Source: http://www.brinathurston.com/colonkaraoke.html

Widely performed in the U.S., Canada and Europe, it is considered the most effective screening tool for colorectal cancer. It is used to visualize the entire large intestine, including the section farthest away from the rectum. But several recent studies from Canada have raised doubts about the effectiveness of colonoscopy in this area, known as the right side of the colon. In one study, researchers in Ontario failed to find evidence that colonoscopy screening reduced deaths from right-sided colorectal cancers, although a survival benefit was seen in patients with left-sided cancers. In another study, researchers from the University of Manitoba found that colorectal cancers occurring on the right side of the colon appeared to be missed during colonoscopy far more often than cancers occurring on the left side.



The Colonoscopy Procedure

Source: http://www.bowelandkeyholeclinic.com/article.asp?article=14

In the newly published study, investigators from the German Cancer Research Center compared the colonoscopy histories of close to 1,700 colorectal patients living in southwest Germany with 1,900 people without cancer matched for age, sex, and place of residence. Study participants were asked whether they had had a colonoscopy during the previous 10 years, and patient medical records were analyzed. After taking into account known colorectal cancer risk factors, colonoscopy screening within the previous decade was associated with a 77% overall reduction in colorectal cancer risk. The risk reduction was 84% and 56%, respectively, for left-sided and right-sided cancers. In patients younger than age 60, however, screening was associated with a 26% reduction in risk in right-sided cancer, which was not statistically significant. The reduction in risk was seen for all cancer stages and for both men and women. While it is not as easy for patients in the U.S. to know if they are getting a high-quality colonoscopy, researchers say every patient should ask two key questions when they schedule their exam:

- What is the polyp detection rate of the practitioner performing my colonoscopy?
- Can I see documentation that my colonoscopy will cover my entire colon?

Polyps occur in approximately 25% of men and 15% of women aged 50 and over who have the exam. A rate much lower than this may indicate a less than thorough examiner. Likewise, asking for evidence that the colonoscopy covered the entire colon, which may include a photograph of the point of the large intestine furthest from the rectum, known as the cecum, could lead to a more thorough exam. Patients can help make colonoscopy better by demanding evidence that the doctor performing the exam has followed these quality measures.

Brenner, Hermann, et al., Protection from colorectal cancer after colonoscopy – a population based, case-control study. Annals of Internal Medicine. January 4, 2011. 154: 24

8. High Endoscopy Completion Rates Tied to Fewer Missed Colorectal Cancers (Jan. 4/11)

Patients whose colonoscopies were performed by endoscopists with high completion rates were less likely to receive a diagnosis of colorectal cancer 6-36 months later, compared with patients whose colonoscopies were done by endoscopists with lower completion rates. This study drew on five databases comprising virtually all residents of Ontario. Patients were included in the analysis if they had colorectal cancer (CRC) diagnosed in 2000-2005 and had had a colonoscopy 6-36 months prior to diagnosis. Polypectomy (removal of polyps) rate was the proportion of colonoscopies associated with a code indicating removal of a polyp larger than 3 mm over the same 2-year period, and completion rate was the proportion of colonoscopies performed by the relevant endoscopist that were complete to the cecum. Overall, more than 34,000 patients were diagnosed with CRC during the study period, and 14,064 met the study criteria. Of these, 1,260 (9.0%) were considered to have a post-colonoscopy colorectal cancer (PCCRC), defined as a “CRC within 3 years following a colonoscopy in which the cancer was not detected,” wrote the authors. After controlling for patient and endoscopy factors, patients undergoing colonoscopy performed by an endoscopist with a completion rate of 95% or greater were less

likely to have a PCCRC than if performed by an endoscopist with a less than 80% completion rate for proximal (right sided) and distal (left sided) cancers. Polypectomy rate was also associated with PCCRCs, at least in the proximal colon.

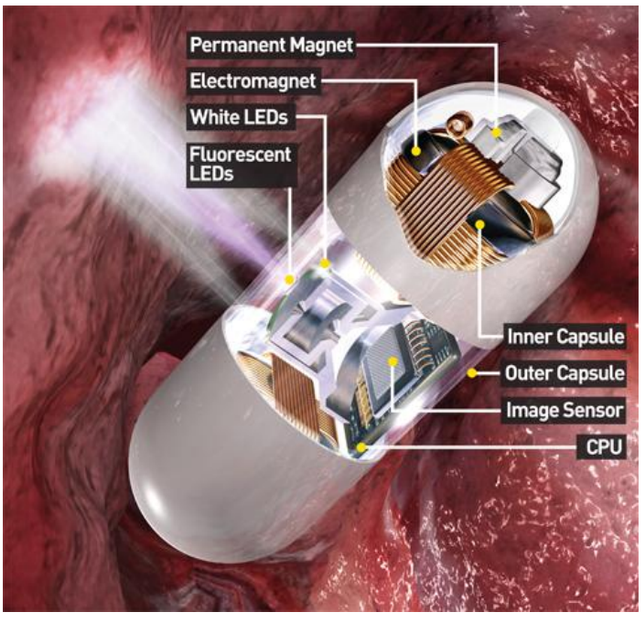
Baxter, Nancy, et al., Analysis of administrative data finds endoscopist quality measures associated with post-colonoscopy colorectal cancer. Gastroenterology. Vol. 140, Issue 1: pp. 65-72

9. Update Provided on PillCam Colon 2 (Jan. 5/11)

Given Imaging, a world leader in specialty GI products and pioneer of capsule endoscopy, announced the start of a study in the United States for PillCam® COLON 2 capsule endoscopy. The PillCam COLON 2 video capsule is equipped with two miniature color video cameras (one on each end), a battery and an LED light source; it measures 11 mm X 31 mm. PillCam COLON 2 is designed to transmit up to 35 frames per second for approximately 10 hours to a recording device worn by the patient. Data are transferred from the device to a computer that uses RAPID software to compile the video data and enable the physician to review and report the results of the PillCam study.

Depicting the actual size of a PillCam

Source: http://prevention-of-health.com/english/colon.html



Cross Section of the PillCam

Source: http://marty4650.blogspot.com/2010/09/amazing-pill-cam.html

The risks of PillCam® capsule endoscopy include capsule retention, aspiration, or skin irritation. PillCam COLON 2 capsule endoscopy has additional risks, including those associated with the drug products used to prepare the patient for the procedure, which are currently used for colonoscopy, and to move the capsule through the patient's digestive tract faster. It may also present other risks that are unknown, but which the clinical studies are designed to detect. Medical, endoscopic, or surgical intervention may be necessary to address any of these complications, should they occur. Please consult your physician or refer to www.givenimaging.com for detailed information. Additional information about this clinical trial can be found at www.clinicaltrials.gov. This study will enroll up to 50 patients to confirm the optimal procedures and logistics to be used in a larger trial to help support the Company's planned submission to the U.S. Food and Drug Administration (FDA). The expense and complexity of the upcoming pivotal study, combined with the large number of patients to be enrolled, are the driving factors in conducting a smaller trial to confirm procedures and logistics, which they believe will enable a more efficient completion of the larger trial. They conducted a controlled European launch of PillCam COLON 2 in 2010. Based on the device's initial success, they plan to expand their sales and marketing efforts in Europe in 2011 and launch this product in Canada and several Latin American countries. To date, approximately 2,000 PillCam COLON 2 capsules have been used in non-U.S. markets both in clinical trials and in clinical practice. The PillCam COLON 2 video capsule is designed to visualize the colon. Given plans to seek FDA clearance to market PillCam COLON 2 for colorectal cancer screening in patients who are unwilling to undergo standard colonoscopy.

http://www.msnbc.msn.com/id/40922573/ns/business-press_releases/

PSCHYCOSOCIAL

10. Quality of Life of Patients Undergoing Screening (Jan. 4/11)

Screening for colorectal cancer can potentially bring enormous health benefits. Nevertheless, the negative effects of screening methods can reduce screening participation and thereby hinder the desired

effects on individual and societal health. At present, there is no generally agreed method to either assess the perception and satisfaction of patients screened or the outcome of the screening procedures in colorectal cancer in terms of quality of life. In this study the authors inform about the past development and present availability of instruments to measure health-related Quality of Life (HRQOL) and review the few studies within which such instruments have been used in screening campaigns. Researchers claim that prevention is certainly an important part of the management of diseases, but the assessment of the perception and the quality of life of patients undergoing a screening test is essential to make sure that population adhere to calls for screening. Until now, this type of evaluation has only been used sporadically, mainly applying traditional generic instruments or non-validated questionnaire constructs. Researchers, therefore, suggested the creation of a specific instrument for the assessment of HRQOL in colorectal cancer screening. These results will be discussed in an upcoming issue of *Value in Health*, the official journal of the International Society for Pharmacoeconomics and outcomes Research. *Value in Health* publishes papers, concepts, and ideas that advance the field of pharmacoeconomics and outcomes research and help health care leaders to make decisions that are solidly evidence-based. The journal is published bi-monthly and has a regular readership of over 5,000 clinicians, decision-makers, and researchers worldwide.

Pizzo, Elena, et al., Screenee perception and health-related quality of life in colorectal cancer screening: a review. Periodicals. Vol. 14, Issue 1: pp. 152-159 (Jan. 2011)

OTHER

11. Canadian Colorectal Cancer Survival Rates Among the Highest (Dec. 22/10)

Survival rates for colorectal, breast, lung, and ovarian cancers are higher in Australia, Canada, and Sweden than Denmark and the United Kingdom and are intermediate in Norway, according to this study. Investigators evaluated data from population-based cancer registries in 12 jurisdictions in six countries for 2.4 million adults diagnosed with primary colorectal, lung, breast, or ovarian cancer between 1995 and 2007, with follow-up through Dec. 31, 2007. Between 1995 and 2007, the investigators found that relative survival improved for primary **colorectal**, lung, breast, and ovarian cancers in all jurisdictions. Survival was higher in Australia, Canada, and Sweden, intermediate in Norway, and lower in Denmark, England, Northern Ireland, and Wales, especially during the first year after diagnosis and for patients aged 65 years and older. The international range narrowed for patients aged 65 years and older with colorectal cancer by 2 – 6% at one year and by 2 – 3% at five years. "Differences in individual, health-system, and clinical factors -- such as public awareness of cancer, diagnostic delay, stage, comorbidity, and access to optimal treatment -- are all potential explanations for the overall differences in relative survival," the authors write.

Coleman, MP, et al., Cancer Survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Benchmarking Partnership): an analysis of population-based cancer registry data. The Lancet, Vo. 377, Issue 9760, pp. 127-138

12. Mutation Identification Helpful in Treating Colorectal Cancer (Dec.23/10)

The fight against colorectal cancer is always a race against the clock. Early diagnosis and the identification of the particular type of the disease involved are crucial to the prospects of a successful cure. Because there are different molecular pathways to colorectal cancer, it has become increasingly clear in recent years that information about the type of cancer in question can be found in the patient's genetic pattern. However, the variety of the changes or mutations in the genome is extensive and the methods available up to now often only enabled a limited interpretation. Scientists from the Max Planck Institute for Molecular Genetics in Berlin have now developed an efficient analytical strategy: with the help of targeted DNA sequencing and bioinformatics, they can identify the mutation patterns behind a colorectal cancer case in a single step. The instability of so-called **microsatellites**, small sequences of DNA that frequently repeat themselves, is a characteristic attribute that enables the differentiation of varying types of colorectal cancer.

Microsatellite instability

Microsatellites are short, repetitive DNA sequences that are scattered throughout the genome. Microsatellite instability (MSI), is a marked difference in the number of repeated sequences between tumor and normal tissue. MSI is a hallmark of hereditary nonpolyposis colorectal cancer (HNPCC) tumors, and it is caused by errors in DNA replication due to mutations in DNA repair genes.

Source: ***http://www.mindupbioresearch.com/biomarkers.html***

As soon as the DNA repair system fails to function correctly, these microsatellites become unstable. In current cancer diagnosis, the first step involves the examination of the patient's genome for **instable microsatellites**. If these are found, it may be assumed that the repair mechanisms are defective; in the next step, an attempt is made to analyze the repair gene and establish which mutations have triggered the disease. This step-by-step diagnosis is tedious and expensive, and its application was limited up to now. Investigators succeeded in transferring the tools for the diagnosis of colorectal cancer research to the new sequencing technologies and thereby combining several steps in the diagnostic process. The targeted sequencing of the building blocks of the informative tumour genome (exome) makes it possible to ascertain, in a single step, whether the microsatellites are unstable, and which mutations promote the development of the disease. The scientists used next generation sequencing with the highest throughput - the very latest gene sequencing method - along with bioinformatics analysis methods. The latter examine the functional relevance of the tumour mutations using special computer programs - the software uses and collates the extensive information about genes and their functions available on publicly accessible databases. A combination of two classification algorithms (PolyPhen and MutationTaster) was used. If both algorithms classify a mutation as "dangerous", it is included in the list of candidates for subsequent analysis by oncologists. In the recently published study, the Berlin-based scientists examined the tumour tissue of colorectal cancer patients with different microsatellite statuses. They sequenced a total of six cancer tumour genomes. Around 50,000 small nucleotide mutations could be identified for each tissue. Rigorous bioinformatics analysis enabled the researchers to filter out the functionally significant mutations: 358 mutations in tumours with unstable microsatellites and 45 in tumours with stable microsatellites. ***Hence, it became clear that tumours with unstable microsatellites have approximately eight times more functionally relevant mutations than tumours with stable microsatellites.*** At the same time, the scientists were able to identify several mutations in already known tumour-relevant genes, the BRAF and KRAS genes, including the damaged repair gene, and TP53, a gene known as the "guardian of the genome" as it can usually prevent the growth of a tumour. In addition to the known mutations, changes in the BMPR1A gene in two patients were also demonstrated and functionally characterized. This gene is already known to play a role in juvenile polyposis syndrome, a disease of childhood and young adulthood accompanied by extensive polyp formation in the gastrointestinal tract, which can form a preliminary stage of colorectal cancer. The mutations of the gene described in the study show effects on signal transmission within the cancer cell. The scientists firmly believe that their new analytical strategy not only helps to win time in the fight against the cancer, but also represents an important step in the direction of personalized medicine. Among other things, their analyses provided information about genes that respond to certain drugs and about the mutated target genes of drugs. "Because we identify the molecular causes in addition to the raised mutation rate, we also establish the basis for individually tailored treatments," explain the investigators. "Our combination of gene sequencing and bioinformatics analysis could become the gold standard for individualized cancer treatments in the future."

13. IBD and PSC Patients At Risk for Colorectal Cancer (Jan. 4/11)

Inflammatory bowel disease (IBD – see explanation below) and primary sclerosing cholangitis (PSC – see explanation appearing below) tend to occur together. It's thought that the percentage of people with PSC that also have IBD could be as high as 90%.
People at higher risk for PSC include men and those who have ulcerative colitis throughout their colon (pancolitis). People who have both diseases are recommended to get a yearly colonoscopy. The results of this study provide some evidence that this constant monitoring could be beneficial. Those who have both IBD and PSC are also at a higher risk for colon cancer. The retrospective study looked at the records of 54 patients with both diseases and colon cancer. The data showed that the colon cancer was diagnosed in the first 2 years with similar frequency as it was 8 to 10 years after the double diagnosis. The authors concluded that this validates yearly colonoscopies for those who have both IBD and PSC.

Inflammatory Bowel Disease:

Ulcerative colitis and Crohn's disease are incurable chronic diseases of the intestinal tract. The two diseases are often grouped together as inflammatory bowel disease (IBD) because of their similar symptoms. Crohn's disease and ulcerative colitis have similar symptoms, but are different in the manner in which they affect the digestive tract. Each disease also has different surgical options, and may be treated with a spectrum of diverse medications. The most common symptoms of IBD include, but are not limited to:

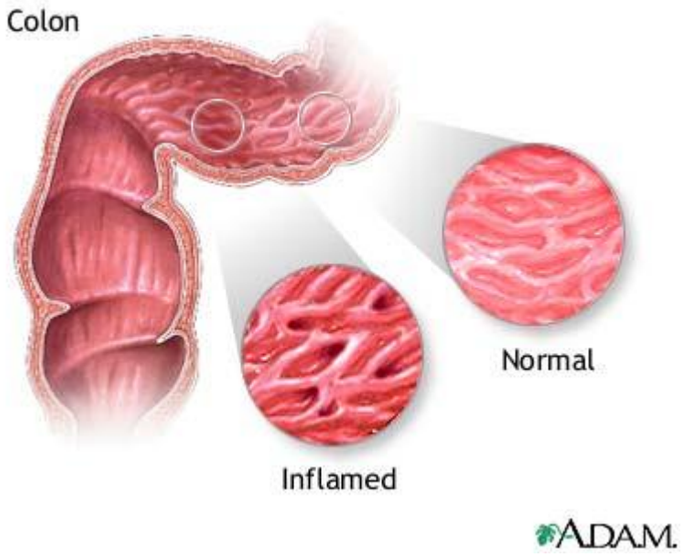
- Abdominal pain
- Weight loss Fever
- Rectal bleeding
- Skin and eye irritations
- Diarrhea

Crohn's disease can affect the small and large intestine as well as other organs in the digestive tract. Unlike ulcerative colitis, which only affects the inner layer, Crohn's disease commonly involves all layers of the intestinal wall. Some complications that can occur in Crohn's disease include:

- Strictures - a narrowing of part of the intestine.
- Fistulas - abnormal tunnels that connect two organs.
- Fissures - cracks in the anal skin.

Several types of surgery can be used to treat the symptoms and complications of Crohn's disease, yet none are a cure. The most common is the resection, during which surgeons remove a diseased piece of the intestine and reconnect the two cut ends. Surgeons use stricturplasty to open up narrowed sections of the intestine by making an incision lengthwise along the stricture and closing it in the opposite direction. A colostomy, removal of part of the large intestine, or an ileostomy, removal of the entire large intestine, are other surgical procedures.

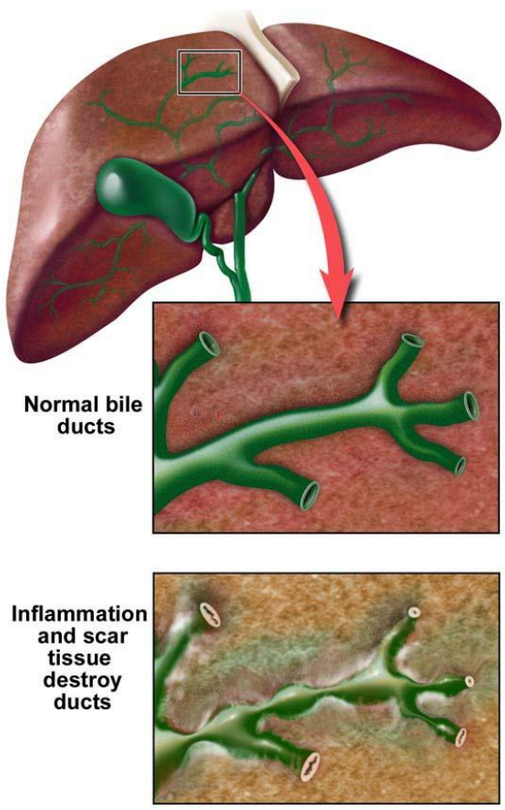
In ulcerative colitis, the inner lining of the large intestine (colon) and rectum are inflamed. The disease does not affect the small intestine. A serious complication of ulcerative colitis is toxic mega colon, the collection of gases in the colon causing it to inflate. There are several surgical options for the ulcerative colitis patient. Surgery for ulcerative colitis always involves removal of the entire colon, or a colectomy. With no colon, an alternative method of collecting stool must be utilized. In an ileostomy, the end of the small intestine is connected to an opening (stoma) in the abdomen where stool is collected in an ostomy appliance worn on the outside of the abdomen. Fashioning a pouch from the small intestine to collect waste, and connecting it to the rectum creates an ileoanal anastomosis (j-pouch).



Source: http://healthforworld.blogspot.com/2008/11/inflammatory-bowel-disease.html

PSC:

Primary sclerosing cholangitis (PSC) is a disease of the liver that causes inflammation and narrowing of the bile ducts inside and outside of the liver (see image below). It's not certain what causes PSC, although it is most likely autoimmune. PSC is not thought to be directly inherited, but it is thought to have a genetic component. Bile is necessary for the digestion of fat and to carry waste out of the liver. PSC causes the bile ducts to narrow from scarring and inflammation, and bile begins to accumulate in the liver, which damages it. This damage eventually leads to scar formation and cirrhosis, which prevents the liver from performing its important functions. Several years of PSC can lead to a cancerous tumor of the bile ducts called cholangiocarcinoma, which occurs in 10 to 15% of patients. PSC does progress slowly in most cases, but it can also be unpredictable. People with PSC can receive treatment to relieve symptoms and help them lead an active life, but the condition can be life threatening.



Source: http://www.procto-med.com/primary-sclerosing-cholangitis-psc/

Thackeray EW, et al.. Colon neoplasms develop early in the course of inflammatory bowel disease and primary sclerosing cholangitis. **Clin Gastroenterol Hepatol *1 Jan 2011 9:52-56. 4 Jan 2011.***

NUTRITION & HEALTHY LIFESTYLE

14. High Levels of Blood Folate Linked to Tumor Suppressors (Dec. 22/10)

According to the results of this study, people with higher levels of folate in their red blood cells were more likely to have two tumor-suppressing genes shut down by methylation, a chemical off switch for genes. DNA hypermethylation is found in a variety of cancers and diseases of aging, such as heart disease. Methyl groups attach to genes at sites called CpG islands and protrude like tags or book marks from the promoter region, preventing gene expression. The new finding is that having high levels of folate in the blood, as observed in a sensitive measure of red blood cell (RBC) folate, is related to higher levels of DNA methylation. **Folate** is a naturally occurring B-vitamin that plays a role in DNA creation, repair and function as well as red blood cell production. Pregnant women who have a folate deficiency are at elevated risk of giving birth to a child with neural tube defects, which are caused by the failure of the spinal cord or brain to fully close during development. Folate is found in green, leafy vegetables, fruits, dried beans and peas. Since 1998, its synthetic version, folic acid, has been added to breads, cereals, flours, pastas, rice and other grain products under order from the U.S. Food and Drug Administration. This has driven down the rate of neural tube defects in the United States. Folate also is taken as a dietary supplement. The recommended daily requirement is 400 micrograms for adult men and women and an additional 400 for women capable of becoming pregnant. Folate's effect on cancer, once thought to be mainly preventive, has become less clear in recent years, with scientists finding cancer-promoting aspects of folate intake in colorectal, prostate and other cancers. In this study, the research team analyzed the association between folate blood levels and dietary and lifestyle factors on DNA methylation in normal colorectal tissue. They enrolled 781 patients from a parent clinical trial that compared folate to aspirin in the prevention of precancerous colorectal polyps. They gathered demographic, lifestyle and dietary information and compared methylation of two tumor-suppressing genes between the first colonoscopy and one three years later. The genes, ERα and SFRP1, are expressed in normal colorectal tissue but silenced by methylation in colon cancer. The two genes also have been found to be methylated in breast, prostate and lung tumors. Age was strongly associated with increased methylation -- a finding that confirmed longstanding research. Methylation levels also varied between the rectum and right colon and among different ethnic groups for each gene. Neither folate nor aspirin treatment were significantly associated with methylation levels. ***However, RBC folate was associated with methylation of both genes with significant differences emerging between the top quarter of patients with the highest RBC folate count and the bottom quarter with the lowest***. RBC folate levels closely reflect long-term folate intake. "These differences were not trivial, they were the equivalent of 10 years of extra aging for those with high RBC folate counts," researchers maintain. "…it may be worrisome that taking extra folate over the long term might lead to more DNA methylation, which then might lead to extra diseases including potentially an increased chance of developing cancer and other diseases of aging". The lead researcher states: "The data for folate supplementation right now are very ambiguous and I personally think people taking folate should think twice about it". "Also, these findings, added to other data, should trigger a rethinking of the U.S. position that everyone should be taking extra folate."

Wallace, Kristin et al., Association between Folate Levels and CpG Island Hypermethylation in Normal Colorectal Mucosa. **Cancer Prevention Research*, December 2010 3:1552-1564 DOI: 10.1158/1940-6207.CAPR-***

15. A Healthy Lifestyle Leads to Less Colorectal Cancer (Dec. 22/10)

A Danish study of 55,000 middle-aged men and women monitored for an average of 10 years showed a clear association between healthy lifestyle and a lower risk of developing colorectal cancer. "Colorectal cancer is predominantly a disease of Westernized countries, indicating that components of a Western lifestyle may contribute to risk," researchers wrote in the journal. Yet only three prospective studies had been done—in which people without cancer were monitored over a period of time to see who developed colorectal cancer, and how lifestyle actions compared in those who did and didn't develop it. And the three previous studies used different lifestyle factors. This study was one of the first to study the impact of five basic healthy behaviors, rather than just one. The study reveals…that even modest differences in lifestyle might have a substantial impact on colorectal cancer risk. Using internationally accepted health recommendations, the study found that most Danes in the study followed 4 of the 5 healthy behaviors:

- 80% were physically active at least 30 minutes daily
- 76% had a waist circumference indicating recommended weight
- 64% were nonsmokers
- 59% drank alcohol within recommended limits (fewer than 7 drinks per week for women; fewer than 14 drinks per week for men).

But, only 2% followed dietary recommendations (eating at least 600 grams fruits and vegetables, eating less than 500 grams of red or processed meat per week and getting less than 30% of calories from fat.) "If all participants had followed merely one additional recommendation, we estimate that 13% of the cases of colorectal cancer (that ensued in the next 10 years) might have been prevented," the researchers said. "Furthermore, we estimate that 23% of the colorectal cancers in the cohort [studied] were associated with lack of adherence to the recommendations for the 5 lifestyle factors," they concluded.

Christensen, Jane, et al., Association of adherence to lifestyle recommendations and risk of colorectal cancer: a prospective Danish cohort study. BMJ. 2010; 341:c5504

16. Consistent Exercise Can Prevent Colorectal Cancer (Dec. 24/10)

According to the results of this study, consistent exercise is associated with a lower risk of dying from colon cancer. The study is among the first to show that physical activity can make the disease less deadly. Researchers examined data from the American Cancer Society Prevention Study II (CPS II) to look at whether changes in physical activity influenced either the incidence of colon cancer diagnosis or the risk of death from the disease. The CPS II study included more than 150,000 men and women. To determine how exercise affected colon cancer, the researchers compared their levels of physical activity between 1982 and 1997, and linked those activity levels both to the number of colon cancer diagnoses between 1998 and 2005, and to the number of colon cancer deaths that occurred between 1998 and 2006. It turned out that those who exercised consistently for at least 10 years had the lowest risk of colon cancer death. People who were consistently active over the course of their adulthood had a lower risk of death from colon cancer than those who were sedentary. People often wonder around the start of a new year whether exercise really will help them stay healthy or whether it's already too late. It's never too late to start exercising, but it's also never too early to start being active. That's the message researchers hope people will take away from this study. The benefits of starting an exercise program include not just preventing colon cancer and death from the disease, but also reduced risk of heart disease, diabetes and other cancers. Researchers say the greatest benefits seem to accrue in those who have exercised for the largest percentage of their lives. But it isn't necessary to run marathons or to work out for many hours every day. Going for a 30-minute walk every day can reduce your risk of a number of diseases. And in addition, the research has also shown that people feel better as a result of exercising, physically and mentally. Hence, they are able to function better. And physical activity can also be beneficial after a cancer diagnosis already has been made. There is evidence that being physically active can reduce the risk of recurrence and death following a cancer diagnosis. So even those who haven't been physically active can begin exercising after their diagnosis and see some real benefits as well.

Wolin, KY, et al., Change in physical activity and colon cancer incidence and mortality. Cancer Epidemiology, Biomarekrs & Prevention, Vol. 19 (12): pp. 3000-3004. Dec. 2010

17. Metabolic Syndrome Linked to Colorectal Cancer (Jan. 7/11)

Metabolic syndrome is defined by the presence of certain chronic disease risk factors. This includes:

- high blood pressure
- high triglycerides (fat in the blood)
- low HDL ("good") cholesterol
- insulin resistance or high blood sugar
- central obesity (carrying excess weight around the belly and upper body).

The connection between metabolic syndrome and risk of heart disease, diabetes, and stroke is well-know. New research now points to another potential pitfall of metabolic syndrome. It turns out metabolic syndrome also may increase the risk of certain types of cancer, including colon cancer. In this study, researchers collected information on body mass index (BMI), blood pressure, blood sugar levels, cholesterol, and triglycerides from 578,700 men and women. The group was followed for an average of 12 years, and the study authors looked at the connection between metabolic syndrome and risk of developing colon cancer. The worse a person's metabolic syndrome was, the more likely that person was to develop colon cancer during the 12 years of follow-up for the study. Men with the worst metabolic syndrome had 20% higher risk of colon cancer compared with men who did not have metabolic syndrome. For women, the increased colon cancer risk with metabolic syndrome was 14%. In addition to the overall severity of metabolic syndrome, certain factors that define the condition also increased colon cancer risk. For men, high body mass index (BMI), high blood pressure, and high triglycerides each significantly increased colon cancer risk. For women, a high BMI was most strongly linked with a higher risk of colon cancer. One of the most important ways to lessen the impact of metabolic syndrome on health is to lose weight. Simply losing 10% of your body weight, or about 20 pounds for a 200 pound person, will improve blood glucose levels, blood pressure, and blood lipids (fats in the blood, such as triglycerides).

Stocks, Tanja, et al., Metabolic factors and the risk of colorectal cancer in 580,000 men and women in the metabolic syndrome and cancer project. Cancer; First published online: 17 Dec. 2010. Doi: 10.1002/cncr.25772

18. Calcium Can Help with Polyps (Jan. 6/11)

Some studies show that taking calcium supplements can reduce colon cancer risk. Other studies don't show any protection from colon cancer with calcium at all. To try to resolve this question, researchers recently conducted a systematic review of all randomized clinical trials on calcium and colon cancer risk. They identified six, well-conducted randomized studies on calcium and colon cancer. Calcium supplements did not appear to reduce colon cancer risk overall, **but they did reduce risk in one group of people**. For people with a history of adenomas, calcium supplements significantly reduced the likelihood of being diagnosed with more adenomas in the future. Taking 1,200 to 2,000 mg of supplemental calcium per day reduced the risk of future adenomas by 20%. This is important because adenomas are a type of colon polyp that can lead to colon cancer if left untreated. Anything that can

reduce the growth of adenomas likely will reduce the risk of colon cancer as well. Talk to your doctor about whether you should take calcium before you do so. Some studies have suggested that too much calcium can harm health. Don't load up on this nutrient unless you know you can benefit from it.

Carroll, C, et al., Supplemental calcium in the chemoprevention of colorectal cancer: a systematic review and meta-analysis. Clin Ther. 2010 32(5): 789-803