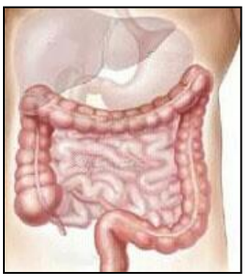
COLORECTAL CANCER RESEARCH

Month Ending November 19th, 2010



The following colorectal cancer research update extends from October 16 – November 19, 2010 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Xeloda For Metastatic Colorectal Cancer (Oct. 14/10)

The objectives of this study were to investigate the efficacy and safety profile of capecitabine-based chemotherapy in the treatment of MCRC, more commonly referred to as xeloda. Capecitabine is an oral chemotherapeutic agent and it was compared to its infusional version called 5Fluorouracil or 5FU. Treatment with capecitabine chemotherapy was associated with a significantly prolonged progression-free survival (time before the cancer got worse), whereas overall survival was not statistically significant. Patients in both capecitabine and 5-fluorouracil groups had equal 1-, 2-, and 3-year survival. The results also demonstrate that the response rate of capecitabine-based chemotherapy was comparable to 5-fluorouracil-based chemotherapy. When comparing single-agent capecitabine against 5-fluorouracil/leucovorin, our results showed an overall response in favor of the capecitabine arm. When toxicity was evaluated, a statistically significant benefit with capecitabine-based therapy was seen, especially for grade 3/4 neutropenia (diminished white blood cell count). Investigators concluded that capecitabine-based chemotherapy demonstrated a significantly superior progression-free survival, equivalent overall survival, and comparable response rate with 5-fluorouracil-based chemotherapy. These observations support the use of capecitabine-based chemotherapy in the treatment of MCRC as a first-line or as a neoadjuvant modality.

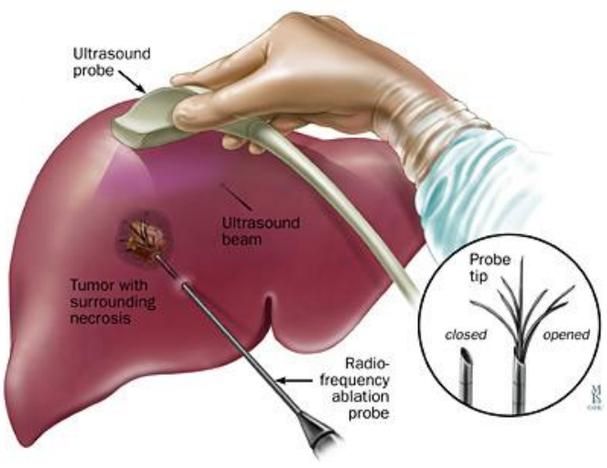
Ling, Wei, et al., Capecitabine based chemotherapy for metastatic colorectal cancer. J of Cancer Research and Clinical Oncology. DOI: 10.1007/s00432-010-0954-0

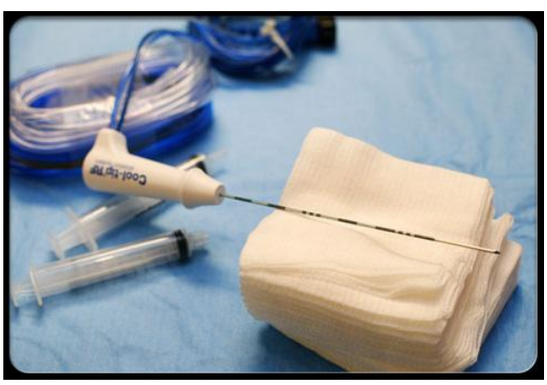
2. Treatment of Colorectal Cancer with Unresectable Synchronous Liver-Only Mets Using Combined Therapies (Oct. 16/10)

Resection + radiofrequency ablation (RFA – see description below) + hepatic artery infusion (HAI – see description below) + systemic chemotherapy for patients with unresectable synchronous liver-only metastases from colorectal cancer are now being utilized to address colorectal cancer that has spread to the liver only. Investigators compared the outcomes of 42 patients who underwent resection + RFA + HAI + systemic chemotherapy (RRHS) with that of 43 patients who underwent resection + RFA + systemic chemotherapy (RRS). The overall survival, the survival free of hepatic recurrence and the median survival in the RRHS group **were all significantly higher** than those in RRS group at 4 years. The rates of adverse effects were similar in the two groups**.** Investigators concluded that **f**or patients with unresectable synchronous liver-only metastases from colorectal cancer, RRHS not only decreases but also postpones hepatic recurrence and therefore improves overall survival at 4 years, as compared with RRS.

Radiofrequency Ablation:

Radiofrequency ablation or RFA is a technique that makes use of a "heating" probe to destroy tumors within the liver. A thin probe is placed within the tumor, typically under ultrasound guidance. After deploying the tip array, an electrical current is applied, generating heat (80-100 degrees Celsius) that destroys the tumor. RFA is generally indicated for small tumors within the liver and can be applied with minimal side effects. The advantage of this technique is that it can be used either in the operating room with an open or laparoscopic approach, or directly through the skin (percutaneous)

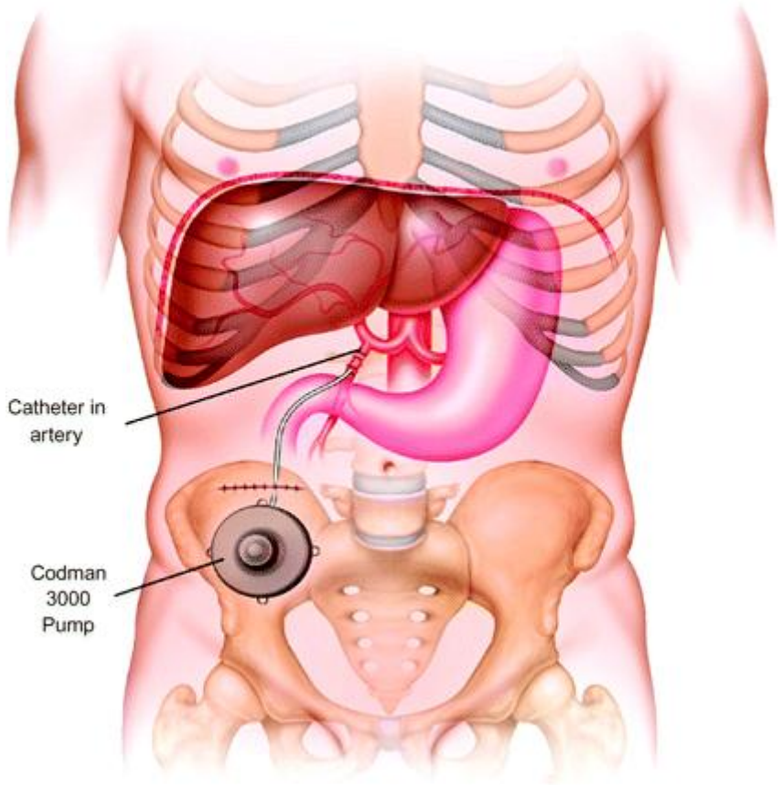




Source: http://www.hopkins-gi.org/GDL_Disease.aspx?CurrentUDV=31&GDL_Cat_ID=AF793A59-B736-42CB-9E1F-E79D2B9FC358&GDL_Disease_ID=A349F0EC-5C87-4A52-9F2E-69AFDB80C3D1

Hepatic Artery Infusion

The placement of a hepatic artery infusion pump into the blood supply of the liver allows chemotherapy medication to be delivered directly into the liver (See illustration below). The placement of a pump into the hepatic artery after liver resection has allowed for additional chemotherapy to be delivered after surgery for up to six months..



Source: ***http://www.sjmcmd.org/CancerInstitute.aspx?id=3976***

Cui, Yunlong, et al., Treatment of Colorectal cancer with unresectable synchronous liver-only metastases with combined therapeutic modalities. J of Gastrointestinal Surgery. DOI: 10.1007/s11605-010-1357-x .

3. Statin Drugs May Help Prevent Colon Cancer (Oct. 18/10)

According to the results of this study, statin drugs may lower the risk of colon cancer by as much as 12%. The longer people took the highly popular cholesterol-lowering pills, the lower their risk of later developing colon cancer. Many researchers have found that statin drugs, which include Pfizer Inc's Lipitor and AstraZeneca Plc's Crestor, have effects far beyond lowering cholesterol and reducing the risk of heart disease. According to the lead investigator, observational studies have suggested that long-term use of statins is associated with reduced risk of several cancers, including breast, prostate, lung, pancreas and liver. The findings suggest that randomized controlled trials designed to test the hypothesis that statins reduce the risk of colorectal cancer are warranted. The team did what is known as a meta-analysis, combining the findings of 22 scientific studies with more than 2.5 million volunteers. Overall, patients who took statins had a 12% lower risk of being diagnosed with colon cancer than people who did not take the drugs, they found. Statins are not risk-free. In May, British researchers reported that patients taking them have higher risks of liver dysfunction, kidney failure, muscle weakness and cataracts. And U.S. health officials have been watching data that suggests some statins such as Merck & Co's blockbuster drug Vytorin may actually raise the risk of cancer.

Samadder, Jewel, et al., American College of Gastroenterology (ACG) 2010 Annual Scientific Meeting and Postgraduate Course: Poster abstract P1217. Presented October 19, 2010.

4. Aspirin Reduces Colorectal Cancer Risk (Nov. 210)

Twenty-year follow-up data from over 14,000 individuals indicate that daily doses of 75 mg or more of aspirin taken for five or more years reduces the long-term incidence and mortality of colorectal cancer. Some studies have suggested that use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen may help protect against colorectal cancer. These studies, however, haven't determined the lowest possible effective dose for colorectal cancer prevention or how long aspirin or other NSAIDs must be used to have a protective effect. The current study evaluated patient data from four randomized trials in order to determine the preventive effect of aspirin on colorectal cancer over 20 years. Patients enrolled in these trials were randomized to either receive aspirin or not to receive aspirin. Average duration of scheduled treatment was six years. Death certificate and cancer registry data from over 14,000 patients were analyzed to determine colorectal cancer incidence and mortality in addition to assessing the effects of aspirin dose and duration of treatment.

- Patients who received aspirin were less likely to develop colon cancer during 20 years of follow-up "with a latent period of 7-8 years between aspirin intake and its preventive effect."
- Patients taking aspirin for five years or more appeared to benefit the most with a 70% reduction in risk of developing proximal colon cancer, which is in the upper bowel.
- Doses of aspirin above 75 mg daily did not demonstrate an improvement in risk reduction of developing colorectal cancer; however, doses of 30 mg daily appeared to be less effective.

The researchers concluded that 75 mg daily (or more) of aspirin taken for five years or more reduced the long-term risk of developing and dying from colorectal cancer. Individuals may wish to speak with their physician regarding the risks and benefits of daily aspirin use for reducing the risk of colorectal cancer

Rothwell, PM, et al., Long term effect of aspirin on colorectal cancer incidence and mortality: 20 year follow up of five randomized trials. The Lancet (early online publication). October 22, 2010.

5. New Insights on Anti-EGFR Therapy Candidacy (Oct. 26/10)

Although colorectal cancer patients with mutations in the *KRAS* gene tend not to respond to anti-egfr therapy drugs such as Erbitux® (cetuximab), responsiveness may vary by the specific type of *KRAS* mutation, according to the results of this study. For patients with colorectal cancer, a test of the *KRAS* gene should be strongly considered before beginning treatment with epidermal growth factor receptor (EGFR) inhibitors such as Vectibix® (panitumumab) and Erbitux® (cetuximab). Vectibix and Erbitux are targeted therapies that inhibit growth of the cancer by binding to a portion of the EGFR, a protein located on the surface of many cancer cells. An estimated 40-50% of colorectal cancers contain a mutation in the *KRAS* gene. Colorectal cancers that contain a *KRAS* mutation are unlikely to respond to EGFR inhibitors. However, researchers recently conducted a study to determine whether patients with certain *KRAS* gene mutations may still derive benefit from treatment with Erbitux. In this study researchers evaluated pooled data from 579 metastatic colorectal cancer patients with chemotherapy-refractory disease. In the subset of patients treated with Erbitux (either alone or in combination with chemotherapy), outcomes among patients with a *KRAS* mutation known **as the codon 13 mutation** were compared with outcomes among patients with other *KRAS* mutations.

- Overall survival was **7.6 months among patients with the *KRAS* codon 13 mutation and 5.7 months among patients with other *KRAS* mutations.**
- Progression-free survival was **4.0 months among patients with the *KRAS* 13 codon** mutation and 1.9 months among patients with other *KRAS* mutations.

The researchers concluded that Erbitux treatment was associated with a survival benefit in chemotherapy-refractory colorectal cancer **patients with the *KRAS* 13 codon mutation** compared with patients with other *KRAS* mutations (Codon 12). Prospective trials evaluating the role of Erbitux in patients with this specific *KRAS* mutation may be warranted. Approximately 5% of patients with metastatic colorectal cancer have this particular KRAS mutation. While some experts may quibble with the study's methodology -- pooling data from several already-completed trials -- this may be the only way that enough patients with this relatively rare (codon 13) mutation could be collected for a legitimate analysis.

DeRoock, et al., Association of kras p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab. JAMA. 2010; 304 (16): pp. 1812-1820

6. Administering Avastin and CAPOX vs. CAPOX alone in Patients Who Have Received A Radical Resection For Their Liver Mets (Oct. 28/10)

Approximately 50% of patients with colorectal cancer develop hepatic (liver) metastases. Radical resection is the most effective treatment for patients with colorectal liver metastases offering five year survival rates between 36-60%. Unfortunately only 20% of patients are resectable at time of diagnosis. Radiofrequency ablation is an alternative treatment option for irresectable colorectal liver metastases with reported 5 year survival rates of 18-30%. Most patients will develop local or distant recurrences after surgery, possibly due to the outgrowth of micro-metastases present at the time of liver surgery. This study examined how an improved disease free survival for patients after resection or resection combined with RFA of colorectal liver metastases could be achieved by adding the angiogenesis inhibitor bevacizumab (avastin) to an adjuvant regimen of CAPOX (capecitabine plus oxaliplatin). Patients were assessed no more than 8 weeks before surgery with CEA measurement and CT scanning of the chest and abdomen. Patients were randomized after resection or resection combined with RFA to receive CAPOX and Bevacizumab or CAPOX alone. Adjuvant treatment (post surgical treatment) was initiated between 4 and 8 weeks after resection or resection in combination with RFA. In both arms patients were assessed for recurrence/new occurrence of colorectal cancer by chest CT, abdominal CT and CEA measurement. Patients were assessed after surgery but before randomization, thereafter every three months after surgery in the first two years and every 6 months until 5 years after surgery. In case of a confirmed recurrence/appearance of new colorectal cancer, patients were treated with surgery or any subsequent line of chemotherapy and were followed for survival until the end of study follow up period as well. The primary endpoint was disease free survival. Secondary endpoints were overall survival, safety and quality of life. This study was designed to demonstrate a disease free survival benefit by adding bevacizumab to an adjuvant regime of CAPOX in patients with colorectal liver metastases undergoing a radical resection

or resection in combination with RFA, but the findings are not yet complete and will be reported on as soon as they become available. The study is referred to as the Hepatica study.

Snoeren, Nikol, et al. A randomized two arm phase III study in patients post radical resection of liver metastases of colorectal cancer to investigate bevacizumab in combination with capecitabine plus oxaliplatin (CAPOX) vs. CAPOX alone as adjuvant treatment. BMC Cancer 1010. 10: 545

7. Irinotecan Toxicity Reduced (Nov. 3/10)

U.S. researchers believe they have discovered a way to stop severe side effects caused by a drug commonly used to treat patients with colon cancer. The pre-clinical findings involve the chemotherapy drug Irinotecan, or CPT-11, which can cause severe diarrhea, resulting in lower dosages and reducing the drug's effectiveness. Colon cancer is treatable, especially if caught early. And CPT-11 is one of the major chemotherapy agents used to treat it. Researchers wanted to alleviate the suffering by reducing the toxicity of the drug and making treatment more effective. The research is unique because it targets the specific enzyme in the bacteria of the digestive system that causes the gastric side effects — but without damaging the other beneficial microbes needed to keep intestines healthy. The researchers' intervention, which would be administered orally at the time of treatment, will require several more years of research and approvals to bring to market. Approximately 10% of colon cancer patients treated with Irinotecan experience severe side effects. When the drug was introduced about 10 years ago, up to 30% suffered severe diarrhea, but physicians have improved management and dosages as they have become more familiar with it. Eliminating the side effects could benefit those patients. However, it wouldn't necessarily mean dosages could be increased across the board because all cancer drugs have toxicity that produces other side effects every time dosages are raised, such as reduction in white blood cells that fight infection. But the researchers used a clever approach to the problem by targeting the culprit enzyme, unlike traditional methods such as antibiotics or activated charcoal used to absorb toxins in the digestive

Wallace, Bret, et al., Alleviating Cancer Drug Toxicity by Inhibiting a Bacterial Enzyme. Science. November 5, 2010. Vol. 330, No. 6005, pp. 831-835

8. NSAID Use on Survival After Diagnosis of Colorectal Cancer (Nov. 3/10)

Non-steroidal anti-inflammatory drug (NSAID) use decreases both the incidence of colorectal cancer and recurrence of adenomas among patients with prior colorectal neoplasia. However, few studies have investigated the association between NSAID use and colorectal cancer-specific survival. The role of prediagnostic NSAID use was therefore examined in this study in relation to colorectal cancer-specific survival. Cases were aged 20–74 and diagnosed from 1997 to 2002. Detailed information on history of NSAID use, including type, frequency and duration, was collected through an interviewer-administered questionnaire. Follow-up for mortality was also completed. The main outcome measure was death due to colorectal cancer after diagnosis. NSAID use prior to colorectal cancer diagnosis was associated with an ~20% lower rate of colorectal cancer mortality after diagnosis compared with never use. This relationship appeared to be duration dependent, with longer reported use prior to diagnosis associated with lower rates of colorectal cancer mortality among cases. The most pronounced reductions in mortality were observed among cases diagnosed with proximal (right side of the colon disease), whereas no association was observed between NSAID use prior to diagnosis and colorectal cancer-specific mortality among cases diagnosed with distal (left side of the colon) or rectal disease. The findings suggest that regular use of NSAIDs prior to diagnosis is associated with improved colorectal cancer survival, particularly among cases diagnosed with proximal disease and in longer term NSAID users.

Coghill, Anna, et al., prediagnostic non-steroidal anti-inflammatory drug use and survival after diagnosis of colorectal cancer. GUT. DOI: 10.1136/gut.2010.221143

9. Gout Drug Promising for Colorectal Cancer (Nov. 8/10)

This small study suggests that taking allopurinol, a drug that has been used to treat gout for more than 20 years, may reduce colorectal tumor growth and lower the risk for colorectal cancer. Italian researchers compared three treatment groups with precancerous colorectal polyps. For up to six weeks, patients took either a placebo, 100 milligrams of allopurinol, or 300 milligrams of allopurinol, an oral drug that reduces levels of uric acid in the body. To measure effectiveness, researchers looked at levels of a colorectal cancer biomarker called **Ki67** in the tissue of colorectal polyps. Among people who took a placebo, Ki67 levels increased by 70%, but they increased by 12% among people taking 300 milligrams of allopurinol and by 6% among people taking 100 milligrams of the drug. Study researcher presented the study results at the Ninth Annual American Association for Cancer Research Frontiers in Cancer Prevention Research Conference held in Philadelphia. "In the era of very expensive targeted therapy in oncology, it is important to search for cheap agents that could be active in cancer prevention and thus have huge public health implications," research investigator DeCensi said in a statement. Colorectal cancer tumors have high levels of reactive oxygen metabolites, which are critical for tumor growth. Allopurinol, sold under the brand names Lopurin and Zyloprim, reduced reactive oxygen metabolite activity. Earlier research had also shown that gout patients taking allopurinol had a lowered risk for colorectal cancer.

http://www.aacr.org/home/public--media/aacr-in-the-news.aspx?d=2156

10. Administering Avastin + Folfiri in Chemo-refractory Patients with Metastatic Colorectal Cancer (Nov. 9/10)

The optimal chemotherapeutic regimen suitable for metastatic colorectal cancer (mCRC) patients previously treated with 5-fluorouracil (5FU), oxaliplatin, irinotecan and biotherapies remains an unresolved issue. The aim of this study was to evaluate the activity of bevacizumab (avastin) combined with FOLFIRI-3 in mCRC after failure of prior chemotherapy including fluoropyrimidine, irinotecan and oxaliplatin. Patients were treated with bevacizumab in combination with FOLFIRI-3 every 14 days. Forty-nine consecutive patients were treated. Four hundred and twenty four cycles of chemotherapy were delivered. Median follow-up was 11 months. Eleven patients (22.4%) had an objective partial response and 26 (53.1%) were stabilized. Median progression-free survival (PFS) and overall survival (OS) were 7 and 13 months respectively. CEA change at 2 months predicted improved overall survival. This study suggests that bevacizumab combined with FOLFIRI3 may be active in mCRC patients after failure of all classical lines of chemotherapy offering them a viable option.

Ghiringhelli, Francois, et al., Bevacizumab plus folfiri-3 in chemotherapy-refractory patients with metastatic colorectal cancer in the era of biotherapies. Investigational New Drugs. DOI: 10.1007/s10637-010-9575-3

11. Calcium and Magnesium Infusions Are Helpful in Reducing Oxaliplatin Side Effects (Nov. 16/10)

Infusions of calcium and magnesium can reduce numbness and tingling caused by oxaliplatin without affecting survival, according to a recent study in the Netherlands. And of noteworthy importance is the fact that the infusions did not affect treatment efficacy. Most colorectal cancer patients being treated with oxaliplatin chemotherapy experience some ***sensory peripheral neuropathy*** that may vary from mild tingling in their hands and feet to pain and difficulty walking. Although peripheral neuropathy usually gets better within a few months after treatment ends, it can last years for some patients. Sometimes patients need to stop oxaliplatin treatments before they get full advantage from them because of this troublesome side effect. Researchers evaluated how infusions of calcium and magnesium during oxaliplatin chemotherapy affected patients enrolled in a randomized clinical trial (CAIRO 2) that tested adding Erbitux to a combination of CAPOX (Xeloda® and oxaliplatin) and Avastin. Patients were not randomized to get calcium/magnesium (Ca/Mg) infusions, but about 3 out of 4 got at least one infusion during their first treatment cycle. The impact on peripheral neurotoxicity was as follows:

- All grades of neurotoxicity were 85% in the group of patients that got Ca/Mg infusions versus 92% in those who didn't.
- Grades 2 or greater neurotoxicity occurred in 40% of patients receiving Ca/Mg versus 45% of those who didn't.

And the impact on treatment efficacy was as follows:

- Tumors shrank (*response rate)* in 43% of those getting Ca/Mg compared to 50% of those who didn't.
- Median time before cancer got worse (*progression-free survival)* was 10.1 months in the Ca/Mg group and 10.7 months in those without it.
- Median time until death was 10.1 months in the Ca/Mg group and 10.7 months in the group that didn't receive the protective treatment.

Investigators concluded that in this largest retrospective analysis to date they observed that Ca/Mg infusions significantly reduced all grade oxaliplatin-related neurotoxicity and Ca/Mg infusions did not affect the clinical efficacy of treatment. Patients receiving oxaliplatin therapy may wish to dialogue with their physicians about magnesium/calcium infusions.

Knijn, N, et al., The effect of prophylactic calcium and magnesium infusions on the incidence of neurotoxicity and clinical outcome of oxaliplatin-based systemic treatment in advanced colorectal cancer patients. European J of Cancer. Online edition November 8, 2010

12. Irinotecan or Oxaliplatin as First Line Therapy for the Treatment of Advanced Colorectal Cancer (Nov. 18/10)

This study sought to compare the clinical efficacy and toxicity of irinotecan combined with 5-fluorouracil and leucovorin with those of oxaliplatin combined with 5-fluorouracil and leucovorin as first-line therapy for advanced colorectal cancer. A literature search was performed using keywords "irinotecan", "oxaliplatin" and "colorectal cancer" on all randomized controlled trails reported on irinotecan versus oxaliplatin combined with 5-fluorouracil and leucovorin as first-line therapy for advanced colorectal cancer. 7 clinical studies with 2095 participants of advanced colorectal cancer were included in this meta analysis (pooling of studies). The baseline characteristics of irinotecan group were similar to those of oxaliplatin group. The **response rate of oxaliplatin group was higher** than that of irinotecan group and the median **overall survival of oxaliplatin group was longer** by 2.04 months than that of irinotecan group. In the comparison of grade 3–4 toxicity between the two groups, the incidences of nausea, emesis (vomiting), diarrhea and alopecia (hair loss) in irinotecan group were higher than those in oxaliplatin group, respectively. However, the incidence of neurotoxicity, neutropenia (lowered white blood cells) and thrombocytopenia (low platelet count) in irinotecan group were lower than those in oxaliplatin group respectively. Investigators concluded that both irinotecan and oxaliplatin combined with 5-fluorouracil and leucovorin were effective in the first-line therapy of advanced colorectal cancer. However, the combined regimen of oxaliplatin plus 5-fluorouracil and leucovorin is more efficacious.

Irinotecan trended to result in more gastrointestinal tract reactions than oxaliplatin did, but the myelosuppression and neurotoxicity were more frequent in oxaliplatin regimen than irinotecan regimen.

Xiao-bo, Liang et al., Irinotecan or oxaliplatin combined with 5-fluorouracil and leucovorin as first line therapy for advanced colorectal cancer: a meta analysis. Chinese Medical Journal. 2010, Vol. 123, No. 22: pp. 3314-3318

SURGICAL THERAPIES

13. Repeated Liver Resection for Recurrence of Colorectal Cancer Mets (Oct. 16/10)

Resection of liver metastases is accepted as the preferred treatment for diverse tumours, implying a survival improvement. Metastases often recur after the first hepatectomy and, very few would be potentially resectable. The current study consisted of a retrospective study of 18 patients undergoing repeated hepatectomies (two or more liver resections in the same patient) due to metastases of colorectal cancer between 1988 and 2006. Thirteen men and five women, mean age 57.55 years, participated. In all patients, repeated liver resection was performed due to recurrence of the metastases. Complication rate after the first hepatectomy was 11.1% and after the second 16.6%. Mortality rate was 11.1% after second hepatectomy, and there was no mortality after the third hepatectomy. Three- and 5-year survival after colectomy (primary surgery of the colorectum) was 88.9% and 77.8%, respectively; after first hepatectomy 3- and 5-year survival was 88.9% and 61.1%, respectively; after second hepatectomy, 3- and 5-year survival was 83.3% and 61.1% respectively; and 3-year survival after third hepatectomy was 67%. The investigators concluded that repeated resections by expert surgeons for recurrent liver metastases can be safely performed, with low morbidity and mortality rates similar to first hepatectomies. Repeated resections of liver metastases of colorectal cancer improve global survival.

Illustration of the sequential parts of a Liver Resection:

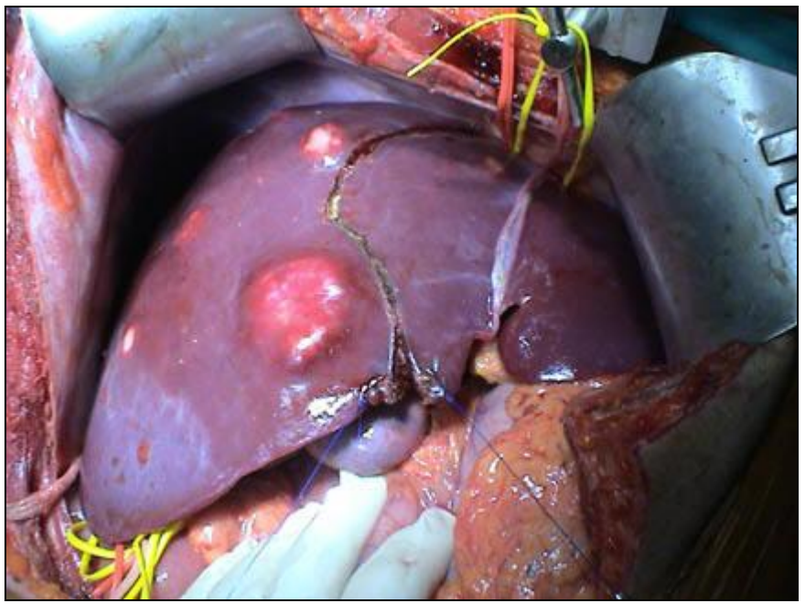


Figure 1: Showing the metastatic tumours of the liver originating from colorectal cancer.

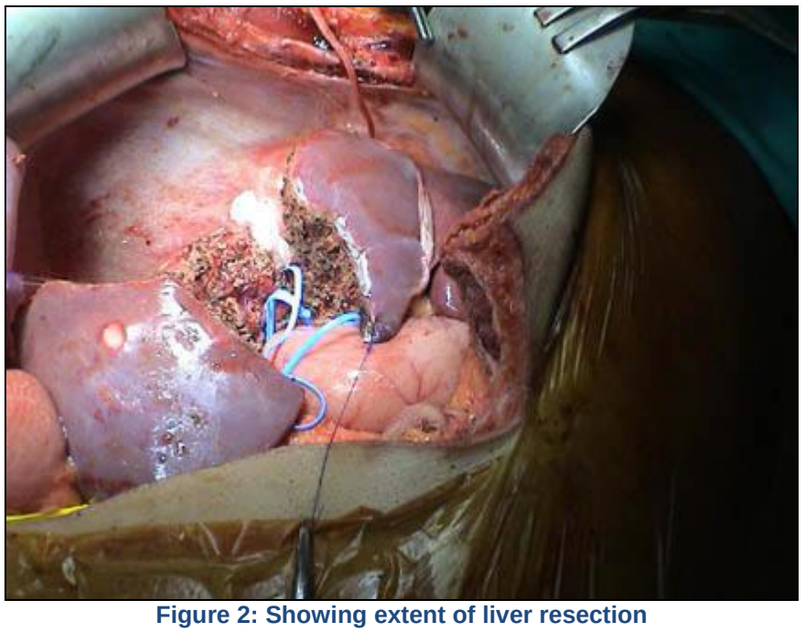


Figure 2: Showing extent of liver resection

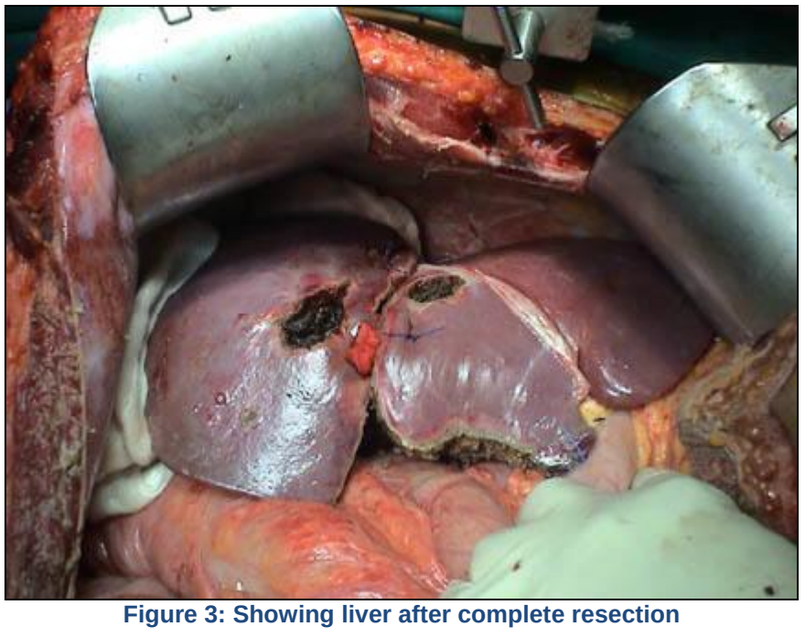


Figure 3: Showing liver after complete resection

Source: http://www.akspublication.com/paper06_jan-jun2008.htm

Ruiz-Tovar, Jaime, et al., Repeated Liver resection for recurrence of colorectal cancer metastases. Clin and Translational Oncology. Vol. 12, No. 9: pp. 634-638

14. Survival and Recurrence After Surgery for Distal Rectal Cancer. (Nov. 2/10)

Treatment of distal rectal cancer (very low rectal cancer) remains challenging and includes proctectomy and colo-anal anastomosis (CAA – where the anus is attached to the colon) or abdominoperineal resection (APR - the surgical removal of the anus, rectum, and sigmoid colon, resulting in the need for a permanent colostomy). The purpose of this study was to evaluate long-term survival and local recurrence outcomes in patients treated for distal rectal cancer. A retrospective study of 304 patients treated for distal rectal cancer with radical resection from 1993 to 2003 was performed. Patients were grouped by procedure (CAA or APR). The median tumor distance from the anal verge was 2. Margins were negative in all but four patients. The 5-year overall survival rate was 82%. Older age, advanced pathologic stage, presence of lymphovascular or perineural invasion, earlier treatment period, and APR surgery type were associated with worse survival. The 5-year local recurrence rate was 5.3% after CAA and 7.9% after APR. The researchers concluded that low rates of local recurrence and good overall survival can be achieved after treatment of distal rectal cancer with stage-appropriate chemoradiation and proctectomy with CAA or APR. Sphincter preservation can be achieved even with distal margins less than 2 cm.

Silberfein, EJ, et al., Long term survival and recurrence outcomes following surgery for distal rectal cancer. Annals Surg Oncol. 2010 Nov. 1; 17(11): pp. 2863-2869

15. Chemo + Radiation Does Not Improve Survival in Patients with Resectable Rectal Cancer (Nov. 3/10)

Two previously published systematic reviews showed that radiotherapy (RT) reduces the risk of local recurrence in patients with resectable rectal cancer, though the data on survival are still equivocal. This study sought to assess the effects of chemotherapy combined concomitantly with radiotherapy (CRT) on the increase of overall survival, and on the prevention of local recurrence and distant metastases. Studies were included if they were randomized controlled trials (RCTs) comparing preoperative or postoperative CRT to preoperative or postoperative RT alone, and if they included patients with resectable rectal adenocarcinoma without metastases. Thirteen RCTs, seven of preoperative CRT vs. preoperative RT (2787 patients), four of postoperative CRT vs. postoperative RT (726 patients) and two of postoperative CRT vs. preoperative RT (1400 patients), were analyzed. Preoperative CRT compared to preoperative RT alone significantly reduced the 5-year local recurrence rate. No increase was observed in 5-year overall survival rate, and in the occurrence of distant metastases. Instead, postoperative CRT did not reduce local recurrence, distant metastases and overall mortality. By pooling data on postoperative CRT vs. preoperative RT, a significant reduction of local recurrence was found for the preoperative approach, though no difference was found in distant metastases rates and overall survival. Finally, the risk of mortality related to toxic events was significantly higher when adding chemotherapy to radiotherapy. Researchers concluded that in patients with resectable rectal cancer, **CRT does not increase overall survival, despite the fact that preoperative CRT significantly reduces the risk of the local recurrence**. No reduction in the distant metastases rate was found. Toxicity-related mortality was significantly increased by the concomitant approach, emphasizing the need for safer treatment combinations.

Fiorica, F, et al., Can chemotherapy concomitantly delivered with radiotherapy improve survival of patients with resectable rectal cancer? A meta-analysis of literature data. Cancer Treat Rev. 2010 Nov. 1; 36 (7): pp. 539-549

16. Comparing Quality of Life After Laparoscopic and Open Colorectal Surgery (Nov. 3/10)

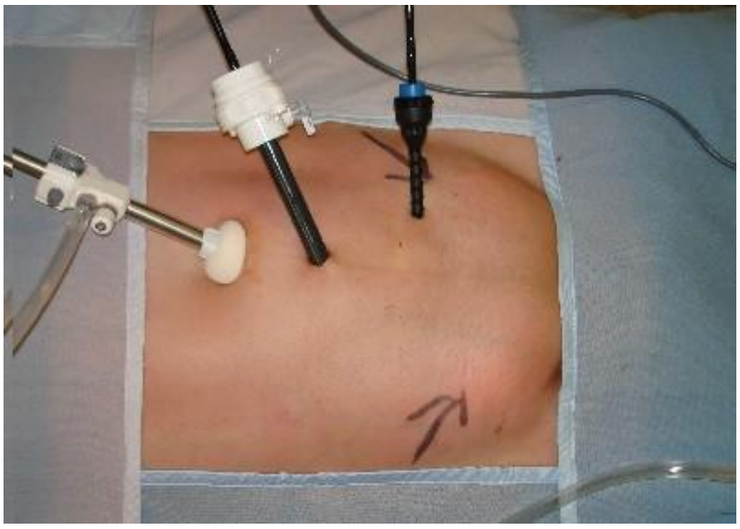
This study was a systematic review of the available evidence on quality of life in patients after laparoscopic or open colorectal surgery. A systematic review was performed of all randomized clinical trials (RCTs) that compared laparoscopic with open colorectal surgery. Primary endpoint was quality of life after laparoscopic and open colorectal surgery, as assessed by validated questionnaires. The search resulted in nine RCTs that included 2263 patients. Short- and long-term results of these RCTs were described in 13 articles. Postoperative follow-up ranged from 2 d to 6.7 years. Four RCTs did not show any difference in quality of life between laparoscopic or open colorectal surgery. The remaining five studies reported a better quality of life in favor of the laparoscopic group on a few quality of life scales at time points ranging from 1 wk to 2 years after surgery. In conclusion, investigators maintained that based on presently available high-level evidence, this systematic review showed no clinically relevant differences in postoperative quality of life between laparoscopic and open colorectal surgery.

Bartels, SA, et al., Quality of life after laparoscopic and open colorectal surgery: a systematic review . World J Gastroenterol. 2010 October. 16 (40): pp.5035-5041

17. Keyhole Surgery Deemed Safe and Effective (Nov. 17/10)

A new research by University of Leeds has suggested that laparoscopic or 'keyhole' surgery is a safe, effective way of removing bowel tumours and should be offered to all patients undergoing surgery for colorectal cancer. The study involved approximately 400 patients with colon cancer and another 400 with rectal cancer. Initial results from the study, published previously, showed that keyhole surgery was as safe as open surgery for colorectal cancer and that in the short term the cancer was no more likely to return. However, some surgeons were concerned that the minimally invasive technique would not be as good at removing all cancer cells from tissue around the tumour and that after a few years, the cancer would simply recur. This risk was thought to be highest for patients with rectal cancer. These latest findings show that this is not the case and that in the hands of an experienced surgeon, the chance of colorectal cancer recurring does not depend on the surgical method. "There is still a body of surgeons who are skeptical about laparoscopic colorectal cancer surgery and particularly laparoscopic rectal surgery. These long-term follow-up results should now help to convince any remaining skeptics that the minimally invasive technique is safe and effective for most patients with colorectal cancer," said lead author of the paper, David Jayne, senior lecturer in surgery at the University of Leeds. "Where suitable, laparoscopic surgery should now be offered to all patients with colorectal cancer so that they can benefit from the recognized advantages, such as quicker recovery, shorter hospital stay and earlier return to normal function," he added.

Laparoscopic Surgery:



Laparoscopic surgery is often referred to as 'keyhole surgery'. Very small cuts are made in the patient's abdomen and a fine telescope (a laparoscope) and other specialized instruments are inserted through these cuts. ***Source: http://www.cheltenhamvascularunit.co.uk/laphernia.html***

Jayne, D.G., et al., Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer. **British Journal of Surgery*, 2010; 97 (11): 1638*** DOI: 10.1002/bjs.7160

RADIATION/INTERVENTIONAL RADIOLOGY

18. Radiation Before Surgery Prevents CRC Recurrence (Oct. 25/10)

Patients with cancer found in the rectum who receive one week of radiation therapy before surgery have a 50% reduction in chance that their cancer will return after 10 years, according to a large, randomized study that was presented at the plenary session, Nov. 1, 2010, at the 52nd Annual Meeting of the American Society for Radiation Oncology (ASTRO). Researchers believe that this short course of

radiation will open a new window of opportunities in the treatment of rectal cancer. Cancer coming back to its original tumor site and surrounding area, called a local recurrence, is a major problem in the treatment of rectal cancer patients. The mesorectum is the fatty tissue near the rectum that contains blood vessels and lymph nodes. When rectal cancer recurs, it is often in these lymph nodes. Therefore, a better surgical technique called total mesorectal excision (TME) was introduced worldwide. It removes the entire mesorectum and lymph nodes and is most successful when all of the tumor and surrounding area is removed and no cancer cells remain. In this study, it was demonstrated that preoperative radiotherapy is still beneficial in these optimally operated patients. The study involved more than 1,800 rectal cancer patients who were eligible for total mesorectal excision surgery and whose disease had spread outside of its original location but not to other parts of the body. Patients were randomly selected to receive short-term radiation before surgery or surgery alone. Researchers wanted to examine the effectiveness of adding radiation to TME surgery to control local recurrence among these patients. Findings show that patients who underwent radiation before surgery had a significant decrease (6%) in their chances of local recurrence after 10 years of treatment, compared to those who did not have radiation (11%). Investigators concluded that their study suggests that tumors in the middle rectum and stage III rectal cancer patients will most greatly benefit from receiving radiation before surgery."

http://www.astro.org/Publications/

19. Whole Liver Radiotherapy for Advanced Liver Metastases (Nov. 1/10)

This study investigated whether whole-liver radiotherapy (RT) is beneficial in end-stage colorectal cancer with massive liver metastases and severe hepatic dysfunction. Between June 2004 and July 2008, 10 colorectal cancer patients, who exhibited a replacement of over three quarters of their normal liver by metastatic tumors and were experiencing severe liver dysfunction after having undergone chemotherapy, underwent whole-liver RT. RT was administered using computed tomography-based three-dimensional planning. Improvement in liver function tests, defined as a decrease in the levels within 1 month after RT, symptom palliation, toxicity, and overall survival were analyzed retrospectively. Liver function test levels of alkaline phosphatase, total bilirubin, aspartate transaminase, and alanine transaminase improved in 8, 6, 9, and all 10 patients, respectively, and the median reduction rates were 42%, 68%, 50%, and 57%, respectively. Serum carcinoembryonic antigen (CEA – cancer biomarker) level decreased after RT in three of four assessable patients. For all patients, pain levels decreased and acute toxicity consisted of nausea/vomiting. Further chemotherapy became possible in four of 10 patients. Although limited by small case number, this study demonstrated a possible role of whole-liver RT in improving hepatic dysfunction and delaying mortality from hepatic failure for end-stage colorectal cancer patients with massive liver metastases. Investigators maintain that further studies should be followed to confirm these findings.

Yeo, Seung Gu, et al., whole liver radiotherapy for end stage colorectal cancer patients with massive liver metastases and advanced hepatic dysfunction. Radiation Oncology 2010, 5:97.

20. Whole Brain Radiation Following Surgery or Radiosurgery (Nov. 16/10)

Results from this randomized Phase III study indicate that whole-brain radiation therapy (WBRT) following removal of one to three brain metastases with surgery or radiosurgery does not improve overall survival or duration of functional independence but does reduce recurrence of brain metastases. One common site for various types of cancer to spread is the brain. For decades, WBRT has been the standard treatment for patients with brain metastases. However, researchers have developed more precise delivery of radiation to the site(s) of cancer so that more radiation can be delivered to the cancer and healthy surrounding tissue may be spared from the side effects of radiation. Stereotactic radiosurgery (SRS) involves the precise three-dimensional delivery of radiation directly to the cancer. In recent years, SRS combined with WBRT has shown a survival benefit over WBRT alone. The risks and benefits of adding WBRT to either SRS or surgical removal of brain metastases are unclear; studies are ongoing. In the current Phase III randomized study, researchers evaluated whether patients with brain metastases who had undergone either SRS or complete surgical resection of their brain metastases would benefit from the addition of WBRT. Specifically, researchers were interested in determining whether or not WBRT would improve the duration of cognitive function by improving the control of recurrent disease in the brain. Patients enrolled in this study had one to three brain metastases from any solid tumor except for small cell lung cancer and were considered to have a performance status of 0-2, which includes the following:

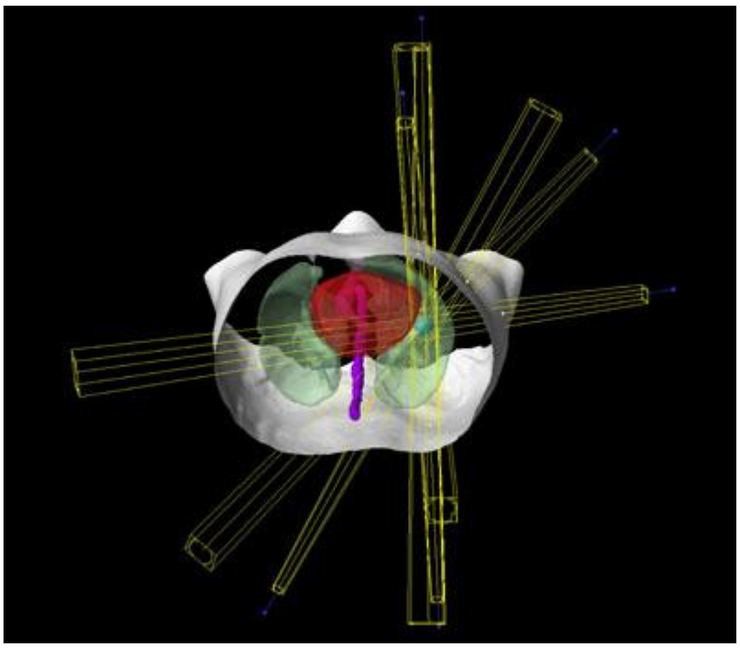
- Asymptomatic and fully able to carry on normal activities (performance status 0)
- Symptomatic and able to continue light activities, restricted from strenuous activities (performance status 1)
- Symptomatic and unable to work but out of bed more than half of the time (performance status 2)

Following removal of brain metastases by either SRS or surgery, 359 patients were randomized to receive WBRT or observation only and were monitored to determine how long it took for a patient's performance status to deteriorate past status 2.

- For patients randomized to the observation arm, the median time to a performance status greater than 2 was 10.0 months.

- For patients randomized to the WBRT arm, the median time to a performance status greater than 2 was 9.5 months.
- Overall survival was similar in both arms of the study.
- WBRT reduced the recurrence rate of brain metastases from nearly 80% to approximately 50%.
- Death due to progression of brain metastases occurred in 44% of patients in the observation arm and 28% of patients in the WBRT arm.

The researchers concluded that WBRT following SRS or surgical removal of one to three brain metastases **did not improve overall survival or duration of time before performance status deterioration**; however, **WBRT did impact death due to brain metastases as well as brain metastases recurrences.**



Example of the employment of SBRT.

Source: www.reviewpost5.phpzila.net

Kocher M, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: Results of the EORTC 22952-26001 Study. 0*Journal of Clinical Oncology *[early online publication]. November 1, 2010.

SCREENING

21. CRC Screening Guidelines Not Adhered to By Physicians (Oct. 15/10)

According to the results of this study, only one in five primary care doctors in the U.S. follows all the guidelines for colorectal cancer screening. Of the remaining doctors studied, approximately 40% followed guidelines for ***some* tests**; the remaining 40% didn't follow any screening guidelines. The survey of nearly 1,300 primary care physicians showed that many either overuse or underuse screening tests. Most doctors did recommend initial screening at age 50, and many followed suggested intervals for a specific test. But only 19% followed guidelines for every type test. The guidelines are complicated by the fact that there are four different types of routine screening (fecal or stool tests, colonoscopy, sigmoidoscopy, or barium enema), each with different recommended intervals, and several different organizations have suggested guidelines. The good news: more people are getting screened. The challenge is for doctors to stay updated with the latest recommendations, and for patients to ask for screening. The study authors recommend the following to patients:

- *Routine screening guidelines only apply if you have no symptoms or risk factors.* If you have a family history of colon or rectal cancer, or a history of ulcerative colitis or Crohn's disease, you will likely need more frequent screening, or to start before age 50.
- Because they detect cancer but not precancerous lesions, annual fecal (stool) tests must be done faithfully every year. For colonoscopies, you must do careful pre-test preparation for the most accurate results.
- Don't wait until the next scheduled screening if you develop symptoms (e.g., changed bowel habits or stools, unexplained abdominal symptoms, fatigue, rectal bleeding or dark stools).

Yabroff, KR et al . Are physicians' recommendations for colorectal cancer screening guideline-consistent? Journal of General Internal Medicine; DOI 10.1007/s11606-010-1516-5 , 2010

22. Reduction in Colorectal Cancer After Colonoscopy Varies By Site of the Cancer (Oct. 16/10)

Colonoscopies may significantly reduce the risk of dying from colorectal cancer, though the benefits appear limited to reducing mortality from distal, not proximal, colorectal cancer, according to research published in the October issue of *Gastroenterology.* University of Manitoba researchers in Winnipeg, Canada examined data for 30,461 individuals who had a colonoscopy between 1987 and 2007, followed until March 2008, death, or migration from the province, to determine the prevalence of CRC mortality in people who had had a colonoscopy compared with the general population. The researchers found an overall reduction in death from CRC of 29%; death from distal CRC dropped by 47%, but there was **no reduction in mortality from proximal CRC**. The authors write: In Manitoba, colonoscopies significantly reduce mortality from CRC, but the benefit is not uniform for colorectal tumors that arise in different areas of the colon.

Diagram Illustrating the Parts of the Distal Colon or left side of the colon (which include the rectum, sigmoid colon and descending colon up to the splenic flexure).

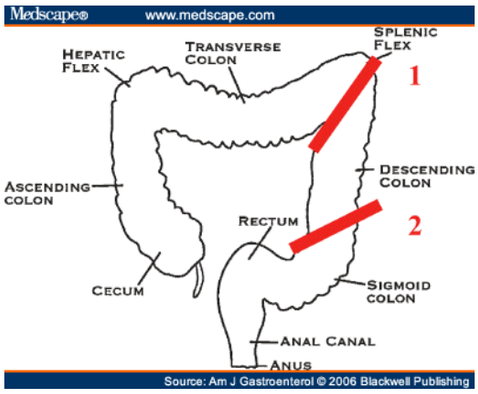
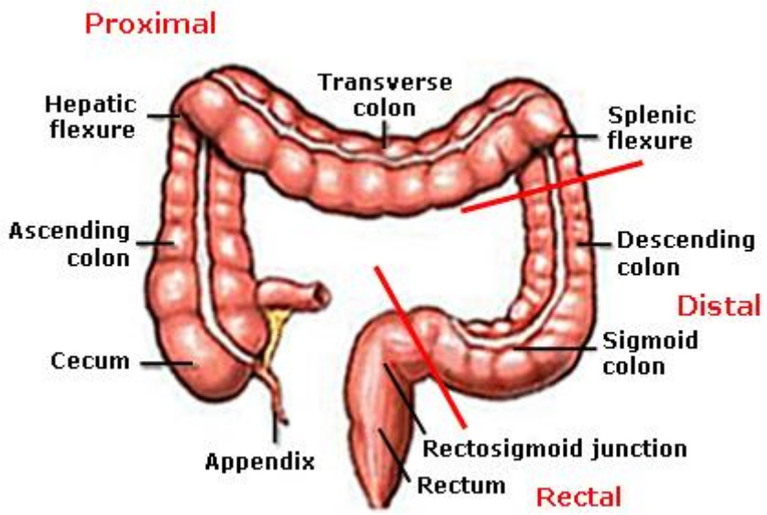


Diagram Illustrating the Proximal Colon or right side of the colon (including the cecum, ascending colon, hepatic flexure and transverse colon)



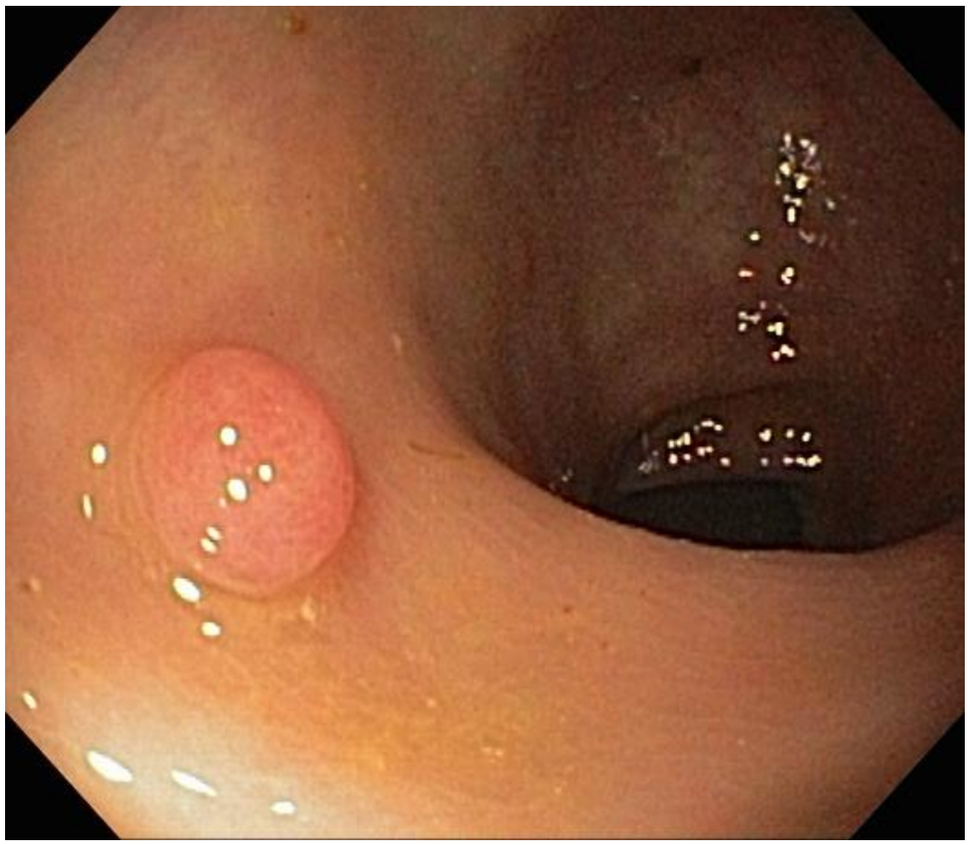
Source: http://www.cancercare.on.ca/cms/one.aspx?portalId=1377&pageId=67772

Singh, Harminder, et al., the reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. Gastroenterology. Vol. 139, Issue 4, pp. 1128-1137

23. Colonoscopy Technique Catches More Polyps in Proximal Colon (Oct. 18/10)

Precancerous growths in the colon known as **sessile serrated adenomas (SSA)** are found in approximately 1% of colonoscopy exams. A sessile serrated adenoma is a premalignant flat lesion in the colon thought to lead to colorectal cancer through the "serrated pathway". From among those patients who underwent colonoscopy with a biopsy of abnormal tissue, researchers identified approximately 41% who had non-hyperplastic polyps, those which are not benign. Of this group, approximately 5% had sessile serrated adenomas categorized as either low or high dysplasia, reflecting the degree of cellular abnormality. See illustration of sessile serrated adenoma below:

Sessile Serrated Polyp



A sessile serrated adenoma, abbreviated SSA, is a premalignant flat (or sessile) lesion of the colon, predominantly seen in the cecum and ascending colon.

Source: ***http://en.wikipedia.org/wiki/File:Sessile_serrated_adenoma_endo.jpg***

The interval for the progression from SSA to SSA with low-grade dysplasia can be estimated to be approximately seven years, and the further progression to high-grade dysplasia can be estimated at an additional four years, according to researchers. These polyps appear to advance at a slower rate than conventional adenomas. An endoscopic technique known as **retroflexion**, when used in the right side of the colon, may increase the diagnostic yield of polyps, including large adenomas (larger than 10 millimeters) and serrated lesions, particularly in men, older patients and those with polyps found on forward examination according to this study. In retroflexion, the tip of the colonoscope is in a deflected position to better visualize the proximal side (right side of the colon – see figure above) of the colon's anatomy. Colonoscopy has a significant miss rate for the smallest adenomas, but retroflexion in the right side of the colon could reduce the miss rate associated with lesions on the proximal sides of the folds and flexures in the colon. In the study, of a total of 1000 patients who underwent colonoscopy, retroflexion in the right side of the colon was successful in 945 patients. The colonoscopists in the study identified 500 polyps in 287 patients on forward examination of the right colon, as the colonoscope passed through, and an additional 68 polyps in 58 patients on retroflexion of the scope. Importantly, 41% of the patients who had polyps identified on retroflexion had **negative exams** on forward examination. The risk of identifying a polyp on retroflexion was three times more likely among those who had a polyp detected on forward view compared to those patients who were negative on forward examination. While the presence of a polyp on forward view predicted the detection of polyps in retroflexion in this study, the analysis revealed that older age and male gender were significant predictors of finding polyps on retroflexion after a negative forward exam.

Diagram Illustrating the Colonoscopy Procedure:

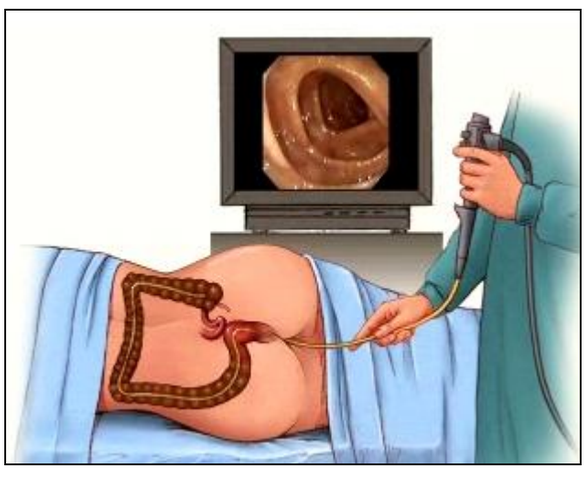
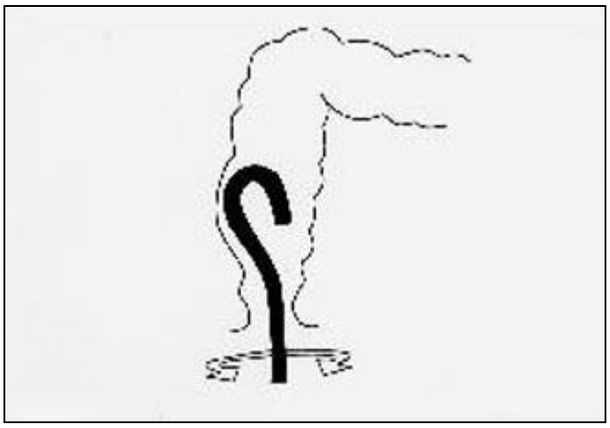


Diagram Illustrating Retroflexion Colonoscopy in the Distal Rectum:



Retro-flexion is necessary to obtain a view of the distal rectum, upper anal canal and proximal colon.

Source: ***http://www.healthhype.com/colonoscopy-preparation-procedure-pictures-risks-cost.html***

Source: ***http://www.rcsed.ac.uk/journal/vol47_2/4720010.html***

http://www.sciencedaily.com/releases/2010/10/101018092235.htm

24. Advanced Cancer Patients Continue Screening (Oct. 22/10)

The findings of this study concluded that a significant proportion of patients with advanced cancers continue to undergo cancer screening, even though screening is unlikely to benefit these patients. Cancer screening can detect disease in its early stages, before it causes symptoms. For many people, treatment at these early stages is more likely to be effective than treatment at more-advanced stages. In this way, cancer screening is credited with a substantial decline in deaths from cancer. For people with advanced cancer, however, the benefit of screening is questionable. Many of these patients have a limited life expectancy, making it unlikely that they would live long enough for an early-stage cancer to affect their survival. In such cases, screening without a known benefit may subject patients to risks of subsequent testing, biopsies, and psychological distress. To evaluate the frequency of screening among patients with advanced cancer, researchers assessed 87,736 fee-for-service Medicare enrollees in the U.S. Patients were aged 65 years or older and had been diagnosed with advanced lung, colorectal, pancreatic, grastroesophageal, or breast cancer between 1998 and 2003. These patients were matched by age, sex, and race with 87,307 Medicare enrollees who did not have cancer. Patients with cancer were followed until death or December 31, 2007, whichever came first. Screening tests evaluated included mammography, Pap test, PSA test, and lower gastrointestinal endoscopy such as colonoscopy.

- Among women with an advanced cancer diagnosis, 8.9% received at least one screening mammogram compared with 22% of women without cancer.
- 5.8% of women with advanced cancer received a Pap test compared with 12.5% of women without cancer.
- 15% of men with an advanced cancer diagnosis received a PSA test compared with 27.2% of men without cancer.
- Among all patients, 1.7% with advanced diagnoses received lower gastrointestinal endoscopy compared with 4.7% of those without cancer.
- Patients with advanced cancer who had a recent history of screening were more likely to undergo screening following diagnosis.
- Other factors associated with a high probability of screening were higher socioeconomic status and being married.

The researchers conclude that even though patients with advanced cancer are unlikely to benefit from screening, many of these patients continue to undergo screening. They suggest that efforts to encourage cancer screening have resulted in such “deeply engrained habits” that patients and healthcare providers maintain screening schedules among patients with advanced cancer, for whom benefit is questionable.

Sima CS, et al., Cancer screening among patients with advanced cancer.* JAMA. *2010;304(14):1584-1591. doi:10.1001/jama.2010.1449.

25. Stool DNA Test As a Colorectal Cancer Screening Tool (Nov. 11/10)

According to the findings of this study, an investigational stool DNA test may be effective as a screening tool for colorectal cancer. Cancers of the colon and rectum, sometimes referred to together as colorectal cancer, often begin with the development of an adenomatous polyp, which is a small tumor that grows in the colon. These polyps often take 10 to 15 years to transform into cancer. Because this development phase is so long, screening and early detection can play a crucial role in the prevention of colorectal cancer, as detection and removal of the polyps can prevent the development of the disease. When detected early, colorectal cancer is a highly curable disease. However, once the cancer has spread to

distant and/or several sites in the body, cure rates remain low. Colorectal cancer is currently the second leading cause of cancer deaths in the United States and Canada. Thus, screening measures to detect polyps or colorectal cancer early may significantly reduce the number of deaths caused by colorectal cancer annually. Screening procedures for colorectal cancer include the fecal occult blood test (FOBT), sigmoidoscopy, colonoscopy, and the double-contrast barium enema; however, the potential for earlier detection and higher cure rates may increase with the advent of more refined screening techniques. Due to the cost and invasive nature of some screening procedures, individuals are sometimes resistant to colorectal cancer screening. For example, fewer than 30% of eligible individuals have had a screening test for colorectal cancer compared with 70 to 80% of women undergoing screening for breast cancer and cervical cancer. Consequently, much research is aimed at developing patient-friendly but effective screening procedures. A newer type of test that's showing promise is a **stool DNA test**. Cells from the colon and rectum are shed in the stool, and stool DNA tests look for DNA changes that are characteristic of polyps or cancer. If the test suggests that polyps or cancer may be present, patients undergo colonoscopy for further evaluation. In the current study, stool samples from 678 individuals were tested with an investigational DNA test.

- The test detected 87% of earlier-stage cancers (Stage I-Stage III) and 69% of advanced cancers (Stage IV).
- The test detected 64% of precancerous adenomas greater than 1 cm.

Investigators claim that these results are promising. Additional studies are planned to determine the role of this strategy in colorectal cancer screening.

Ahlquist D, et al. Next generation stool DNA testing for detection of colorectal neoplasia. Early marker evaluation. Presented at the American Association for Cancer Research special conference on Colorectal Cancer: Biology to Therapy, Philadelphia, PA. October 27-30, 2010.

OTHER

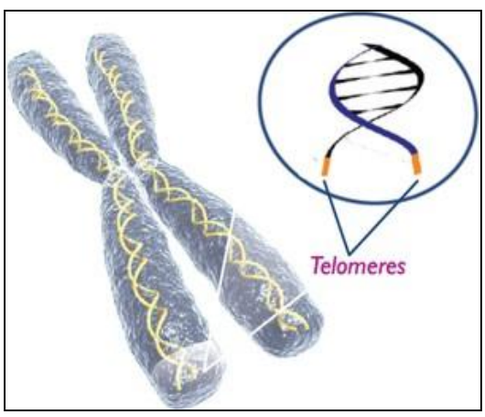
26. Prostate Cancer Can Increase Risk of Colorectal Cancer (Oct. 19/10)

According to the results of this study, men who have prostate cancer have a higher risk of developing colon cancer than men who don't have prostate cancer. Researchers at the University of Buffalo (UB) in New York state found in a study of more than 2,000 men that patients diagnosed with prostate cancer had significantly more abnormal colon polyps, known as adenomas, and advanced adenomas than men without prostate cancer. The study is the first to show that men with prostate cancer are at increased risk of developing colon cancer. The researchers reviewed the patient records, colonoscopy reports and pathology reports, as well as data on the prevalence of adenomas, advanced adenomas, cancerous adenomas and their location within the colon, in 2,011 men who had colonoscopies at the Veterans Affairs Medical Center in Buffalo. When the researchers compared the colonoscopy results from 188 men diagnosed with prostate cancer with the rest of the patients, they found that the prostate cancer patients had a significantly higher prevalence of abnormal polyps and advanced adenomas compared to the rest of the study sample. 48% of prostate cancer patients had adenomas, compared to 30.8% of the men without prostate cancer. More than 15% of prostate cancer patients had advanced adenomas compared to 10% of the men without prostate cancer. Researchers stressed the importance of men who have been diagnosed with prostate cancer having routine screening for colon cancer and called for larger studies to be done to determine if screening for colorectal cancer should begin earlier for prostate cancer patients than the currently recommended age of 50.

American College of Gastroenterology Meeting; San Antonio, Texas, USA: 15–20 October 2010
http://www.buffalo.edu/ubreporter/2010_10_21/prostate_colon_cancers

27. Telomere Length Affects Colorectal Cancer Risk (Oct. 29/10)

For the first time, researchers have found a link between length of telomeres and an increased risk for colorectal cancer. Telomeres are small strips of DNA that cover the ends of chromosomes -- they are similar to the plastic coverings on shoelace tips. See image below:



Source: http://www.spectracell.com/telomere-testing/

They prevent chromosome tips from fraying during cell division. If the telomeres shorten, then cells age. Shortened telomeres have been associated with an increased risk of cancer development. Researchers sought evidence of biological aging in people who develop colorectal cancer at a young age. The researchers hoped to determine what was causing these young patients to develop a disease that is typically associated with aging. They anticipated that they would see some people who had young-onset colon cancer and shorter telomeres compared to people of the same age group who did not have cancer. They were surprised, however, to find a group with longer telomeres. Even for people their age, their telomeres were longer than expected for healthy people. This suggests that there may be two different mechanisms that affect telomere length and that set up susceptibility to cancer. The researchers measured peripheral blood leukocyte DNA telomere length in 772 patients diagnosed with microsatellite stable colorectal cancer. Patients were younger than 60 years at diagnosis and had no history of chemo-radiotherapy. The researchers compared this group's telomere length with 1,660 nonrelated, age-matched, healthy controls. Patients with the longest telomeres -- those patients in the 95th percentile of telomere length -- were 30% more likely to develop colorectal cancer than those in the 50th percentile, the results showed. Overall, the individuals with the shortest and the longest telomere lengths were at an increased risk for colorectal cancer. These results indicate that there may be two distinct groups of colorectal cancer in young-onset patients. One that involves telomere shortening and this subset of young-onset of colorectal cancer patients may have accelerated aging. The other may be a distinct subgroup of patients with longer telomeres.

http://www.sciencecentric.com/news/10102913-telomere-length-affects-colorectal-cancer-risk.html

28. Large, Serrated Polyps Related To Greater Risk of CRC (Nov. 5/10)

In this study, researchers sought to determine the association between the presence of serrated colorectal polyps (see figure below) and colorectal cancer, based on evidence that serrated polyps have different malignant potential than traditional adenomas, according to the study's abstract. Researchers studied more than 10,000 subjects who underwent first-time colonoscopies. The data collected on the subjects includes, age, sex and the location, size and histology of polyps or tumors found at colonoscopy. Researchers concluded that the presence of large serrated polyps, which are defined as those that were at least 10 millimetres, is the highest risk factor for proximal (or right sided – see figure above) colorectal cancer.

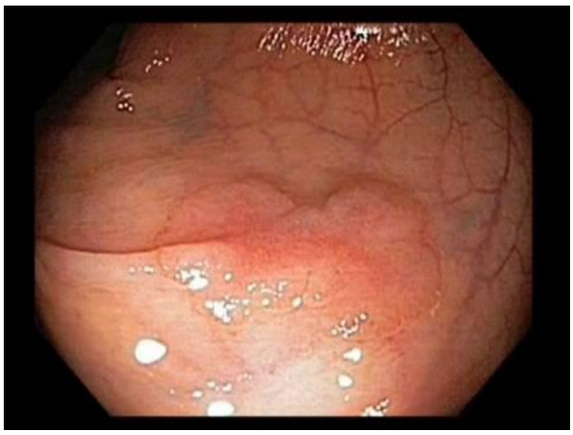


Photo of Flat Serrated Polyp of the Colon.

Source: http://newsblog.mayoclinic.org/2010/04/28/stool-dna-testing-could-play-expanded-role-in-colon-cancer-prevention/

Hiraoka, Sakiko, et al., The presence of large serrated polyps increases risk for colorectal cancer. Gastroenterology. Vol. 139, Issue 5: pp. 1503-1510

29. Prostate Cancer Treatment Increases Risk of Colorectal Cancer (Nov. 13/10)

Men taking androgen deprivation therapy (ADT) for prostate cancer may have an increased risk of colorectal cancer, according to the results of this study. Androgen deprivation therapy is a widely-prescribed treatment in men with prostate cancer, although its usage for low-risk disease remains controversial, given the adverse side effects, including osteoporosis, cardiovascular disease, diabetes and obesity; the last two are risk factors for colorectal cancer. To determine whether prostate cancer patients taking androgen deprivation therapy are at an increased risk of colon cancer, investigators did an observational study of men with prostate cancer. Specifically, they identified 107,859 men aged 67 years or older who were diagnosed with prostate cancer between 1993 and 2002, with follow-up through 2004. The men received the ADT either in the form of gonadotropin-releasing hormone (GnRH) agonists, or an orchiectomy (surgical removal of one or both testicles). The researchers found that there was a 30-40% relative increase in the rate of colorectal cancer among the men treated with ADT compared with those who were not. Furthermore, the longer the men took ADT, the greater their risk of developing

colorectal cancer. However, further study would be needed to determine the risk with treatment over longer periods than could be observed in this study. The authors write that the study results could have "important implications" for men with prostate cancer taking ADT, especially those with localized, slow-growing disease, for whom the duration of ADT is generally longer. In an accompanying editorial, Jennifer H. Lin, Ph.D., and Edward Giovannucci, M.D., of Brigham and Women's Hospital in Boston write that the study shows that an elevated risk of colorectal cancer may be an additional consideration in the decision to use ADT, especially given the side effects and their effect on quality of life.

Gillessen, Silke, et al., Risk of colorectal cancer in men on long-term androgen deprivation therapy for prostate cancer*. Journal of the National Cancer Institute*, 2010; DOI: 10.1093/jnci/djq419

30. Preventive Care and Surveillance is Higher Among CRC Survivors (Nov. 18/10)

Colorectal cancer survivors who participate in clinical trials have better routine preventive health care and cancer screening than the general population, and also have high rates of compliance with cancer surveillance, according to the results of this study. Researchers conducted a study to examine both routine preventive care and cancer surveillance in 708 long-term (five years or more) CRC survivors who had previously been enrolled in National Surgical Adjuvant Breast and Bowel Project (NSABP) adjuvant trials. The researchers found that NSABP patients were significantly more likely to have received recommended health interventions, including having a usual source of health care (97.7% versus 93.8%); getting a flu shot in the past 12 months (67.5 versus 44.3%); and having a Pap smear (67.3 versus 54.8%), mammogram (80.4 versus 70.7%), and prostate-specific antigen test (84.5 versus 74.5%) than patients in the cohort. For CRC surveillance, the NSABP cohort also showed high adherence to recommendations for **colonoscopy, carcinoembryonic antigen test**, and computed tomography scans. Investigators concluded that they demonstrated the feasibility of using clinical trials to identify, contact, and study long-term cancer survivors and the possibility of comparing them with the non-cancer general population. The complete findings of this study will be reported at a later date encompassing patient-reported outcomes of quality of life, function, and symptoms; this will offer a better understanding of how these health behaviors affect the experience of long-term cancer survivors.

Kunitake, Hiroko, et al., Routine preventive care and cancer surveillance in long-term survivors of colorectal cancer: results from national surgical adjuvant breast and bowel project protocol LTS-01. J of Clinical Oncology. Doi: JCO.2010.30.1903

NUTRITION & HEALTHY LIFESTYLE

31. Smoking Linked to Colorectal Cancer (Oct. 15/10)

The study is the first large population-based study in Canada that shows a clear relationship between colorectal cancer and smoking. The study's senior author said the team's research found cigarette smoking increased the risk of colorectal cancer among men and women, but it demonstrated a stronger **effect for males** than females. Globally, colorectal cancer is the third leading cause of death from cancer in males and the fourth leading cause of death from cancer in females. The study involved an investigation of 702 colorectal cancer cases, with participants recruited using the Newfoundland and Labrador Colorectal Cancer Registry. The results from this group were compared to a control group of 717 people, ages 20 to 74, who were randomly selected. It was noted in the research document that 258 of the 702 colorectal cancer patients are now deceased; including 143 who died before the actual survey was conducted, requiring responses from proxies.

http://www.bioportfolio.com/news/article/195767/Study-Links-Smoking-Colorectal-Cancer.html

32. C Reactive Protein and Colorectal Cancer (Oct. 15/10)

C reactive protein, or CRP, is a protein in the blood. Several things can affect blood CRP levels, but the key thing to remember is that higher-than-normal CRP levels point to inflammation in the body. And inflammation can put a person at greater risk for colon cancer CRP levels can vary from person to person and they can vary in an individual over time. CRP is a substance that changes in response to inflammation. The more inflammation a person has ongoing in his or her body, the higher the level of CRP. In this way, a person's blood level of c reactive protein is a non-specific measure of his or level of inflammation. CRP is considered non-specific, because many things can cause CRP levels to go up. This is because many things can cause inflammation. An infection, such as a cold or flu, can cause CRP levels to rise, for example. Cigarette smoking, obesity, and uncontrolled diabetes can increase inflammation, and CRP levels, too. Many people are familiar with acute inflammation, which is signaled by things such as a fever or swelling and pain. When we measure CRP we are looking for another form of inflammation: the chronic, low-grade inflammation that can go on in the body every day. To understand chronic inflammation, consider that every cell in your body conducts ongoing conversations with the cells around it. When inflammation is in balance, these conversations are similar to a pleasant, neighborly chat. This would be apparent with a low CRP level. When inflammation is out of control, cellular communication becomes nasty. It's more like a shouting match, and even may lead to pushing and shoving. Inflammation ratchets up the tone and volume of cellular conversations to damaging levels. When this is happening in the body, CRP levels will go up. And the damage caused by excessive inflammation has been linked to development of many chronic diseases, including colon cancer. This means that anything that can help bring inflammation under control, may be an effective way

to help lower colon cancer risk. This study suggests that people with a high CRP have up to a **36% increased risk of colon cancer** compared with those whose CRP levels are in the normal range. This CRP-colon cancer link was strongest in men. But even before this latest study, several others have pointed to a potential connection between CRP levels and colon cancer risk. The study concluded that CRP signals inflammation and inflammation may damage the cells in the colon, leading to increased risk of colon cancer.

Aleksandrova, Krasimira, et al., Circulating C-Reactive Protein concentrations and risks of colon and rectal cancer: a nested case control study within the European prospective investigation into cancer and nutrition. Amer J of Epidemiology. Vol. 172, Issue 4: pp. 407-418

33. No Link Between High Carb Diet And Colorectal Cancer (Nov. 3/10)

Chinese women who eat a traditional diet rich in white rice and other starchy foods that spur a surge in blood sugar do not seem to have an elevated risk of colon cancer, according to this new study. The findings add to the conflicting body of evidence as to whether foods with a high "glycemic index" are related to an increased risk of colon cancer. **Glycemic index, or GI**, refers to how rapidly a carbohydrate causes blood sugar to rise. High-GI foods, like white bread, white rice and potatoes, tend to make blood sugar levels rise quickly. With low-GI foods, such as lentils, soybeans, yogurt and many high-fiber grains, blood sugar levels also rise, but not as fast and not as high. A related concept, called the **glycemic load**, refers to both the GI and the amount of carbohydrates in a given food: a low-calorie piece of fruit, for instance, may have a relatively high GI, but still provide only a small glycemic load. The idea that a diet with a high glycemic load might contribute to colon cancer risk is based on human physiology: High blood sugar levels trigger release of the blood-sugar-controlling hormone insulin, which -- along with a related hormone called insulin-like growth factor 1 -- may stimulate the growth and spread of cancer cells. In line with that, a number of studies have found that people with type 2 diabetes, who have abnormally high blood sugar and insulin levels, get colon cancer more often than do people without diabetes. Hence, a diet heavy in high-GI foods could be a risk factor for colon cancer. But studies on the question have so far come to conflicting conclusions. For this new study, researchers followed 73,000 middle-aged and older Chinese women over a decade, looking at the association between reported diet habits and the risk of developing colon cancer. The women, who were cancer-free and between the ages of 40 and 70 at the study's start, completed detailed diet questionnaires that allowed the researchers to estimate the total glycemic load of their diets. Overall, 475 women were diagnosed with colon or rectal cancer during the 10 years the researchers studied them. When the researchers divided the study participants into five groups based on dietary glycemic load, they **found no evidence that the women's risk of colorectal cancer increased along with glycemic load**. Because rice was by far the greatest contributor to the women's glycemic load, the researchers also looked at the relationship between the number of rice servings a woman ate per day and her risk of colorectal cancer. Again, there was no apparent link, according to the investigators. The study has its limitations. Like any study that relies on diet questionnaires, it is prone to erroneous measurements. And while there was no association between glycemic load and colorectal cancer in this study group, the findings cannot disprove a possible role of high-GI diets in colon cancer development. However, the researchers point out that many of the studies that have found a GI-colon cancer link have been so-called case-control studies, where patients with colon cancer reported on past diet habits and were compared with a group of healthy individuals. Only limited conclusions can be drawn from that type of research. Prospective studies such as the current one, which follow initially healthy people over time, are considered a stronger design. And, as investigators noted, most similar studies from the U.S. and Europe have also found no association between high-GI diets and colon cancer. A majority of studies focused on women, but a couple included men as well.

Li, Hong-Lan, et al., Dietary glycemic load and risk of colorectal cancer in Chinese women. Amer J of Clinical Nutrition, online October 20, 2010.

34. High Vitamin B Levels Reduce Colorectal Cancer Risk (Nov. 3)

New research shows a correlation between higher levels of vitamins B2 (riboflavin) and B6 and a reduced risk of developing colorectal cancer. B-vitamins are essential for metabolism and have been linked to a reduced risk of colorectal cancer in previous studies. Since associations with the B-vitamin folate have been studied most often, researchers in the current study focused on potential associations of other B vitamins (B2, B6, and B12) and colorectal cancer. This European population-based study included subjects who were participants in the Prospective Investigation into Cancer and Nutrition (EPIC) cohort. The study included 1,365 adults diagnosed with colorectal cancer and 2,319 age and gender-matched control subjects. Blood samples were taken at enrollment and analyzed for vitamins B2, B6, and B12, as well as 8 variants of genes that relate to the function of these vitamins. After an average follow-up of 3.6 years, individuals whose vitamin B6 levels were among the top 20% of participants had a 32% lower risk of developing colorectal cancer when compared to those whose levels were in the lowest 20%. Among those whose vitamin B2 levels were highest, the risk was 29% lower than those whose levels were lowest. There were no significant associations for vitamin B12 and colorectal cancer. Vitamin levels were lower in smokers compared to nonsmokers, and the benefits for vitamin B6 were stronger in males who consumed ≥30 g (one ounce) of alcohol per day. This research is the first population-based study to indicate that vitamin B2 is inversely associated with colorectal cancer, and it supports previously suggested inverse associations of vitamin B6 with colorectal cancer.

Simone, JPM, et al., Vitamins B2, B6 and B12 and related genetic variants as predictors of colorectal cancer risk. Cancer Epidemiol Biomarkers Prev; 19(10): pp. 2549-61

35. Exercise Helpful During Cancer Treatment (Nov. 19/10)

Traditionally, people undergoing cancer treatments were told to rest and avoid exertion, to save their strength during treatment. But more experts now say that the best way to get through treatment, and possibly the best way to beat cancer, is to stay as physically active as possible. The American College of Sports Medicine has revised its national recommendations, saying that cancer patients and survivors should strive for the same goal as everyone–about 150 minutes a week of moderate aerobic exercise, along with resistance training and stretching. The panel does caution that workout regimens must be adapted to each person's condition and treatment. For example, some cancer treatments make bones more brittle, which will require exercise that place less stress on them. And immunosuppressed patients must avoid exercise in groups of people. But the expert panel cited research showing that aerobic activity reduces fatigue, and loss of both muscle and bone mass. Exercise also can calm fear and restore a sense of control. And the most important benefit, emerging evidence shows, may be a better chance of survival: Treatments can be more effective when the body can better withstand the effects of chemotherapy and radiation. Dr. Eleanor Walker, lead author of an ongoing study of exercise in cancer patients in Detroit, says her research is "potentially showing that even if you don't start your exercise training until you've received your diagnosis, it can still be of some help. And if you're in a healthier state before you get a [cancer] diagnosis, you're going to do better because your body is in better shape and you have reserves…"

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