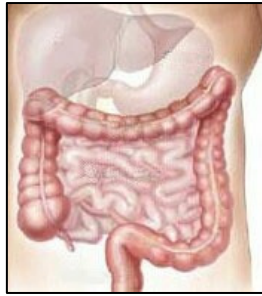


COLORECTAL CANCER RESEARCH Month Ending June 25, 2010



The following colorectal cancer research update extends from April 17 – June 25, 2010 inclusive and is intended for informational purposes only.

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DRUGS / SYSTEMIC THERAPIES

1. Statins Do Not Necessarily Lower Colon Cancer Risk (Apr. 19/10)

According to this study, statins do not lower the risk of colorectal cancer, and may even increase the chances of developing precancerous polyps. Statins are widely prescribed cholesterol-lowering drugs sold in a variety of generic forms and brand names, including Lipitor, Crestor and Zocor. Yet, researchers stressed that the results are "not conclusive," and that people taking statins to lower cholesterol and reduce their risk of heart attack should continue to take the drugs. Patients in this study taking statins for more than three years tended to develop more premalignant colon lesions. This finding needs to be followed up, but it should not raise alarm. For those who took statins for three years or longer, the chances of developing the adenomas were nearly 40% higher than those not on statins. Researchers claimed that the higher risk of colorectal polyp recurrence among a subgroup of statin users in this study may be due to chance and should not raise concerns. A similar previous study of polyp recurrence did not find higher risk among statin users and statin users should take solace from that. More information will be available through follow-up.

Bertagnolli, Monica, Cancer Prevention Research, online, April 19, 2010

2. Painkiller May Fight Colon Cancer (Apr. 22/10)

An investigational form of the drug naproxen blocks a molecular process that leads to the development of colorectal cancer. Naproxen is commonly known as Aleve, Anaprox, and Naprosyn. Though the drug has been tested only in the lab, and not on humans, it appears that the investigational form of naproxen may be more effective than standard naproxen in inhibiting colorectal tumour development. And an added benefit would be the reduced gastrointestinal toxicity of this novel type of naproxen. The new type of naproxen is known as NO-naproxen, and scientists are testing their finding in mice but do not yet have the results.

Fox Chase Cancer Center, news release, April 21, 2010

3. Phase III Clinical Trial Using Regorafenib to Treat Colorectal Cancer (May 7/10)

Regorafenib (BAY 73-4506) is closely related to the blockbuster therapy Nexavar, approved for primary liver cancer and renal cancer. It is a new cancer drug can that can be distinguished from Nexavar by only a single atom. Both are multikinase inhibitors that starve cancer tumors by blocking the growth of new blood vessels. Researchers will recruit about 690 patients with treatment-resistant metastatic colorectal cancer in a phase III study. The initiation of a Phase III clinical trial for regorafenib marks the

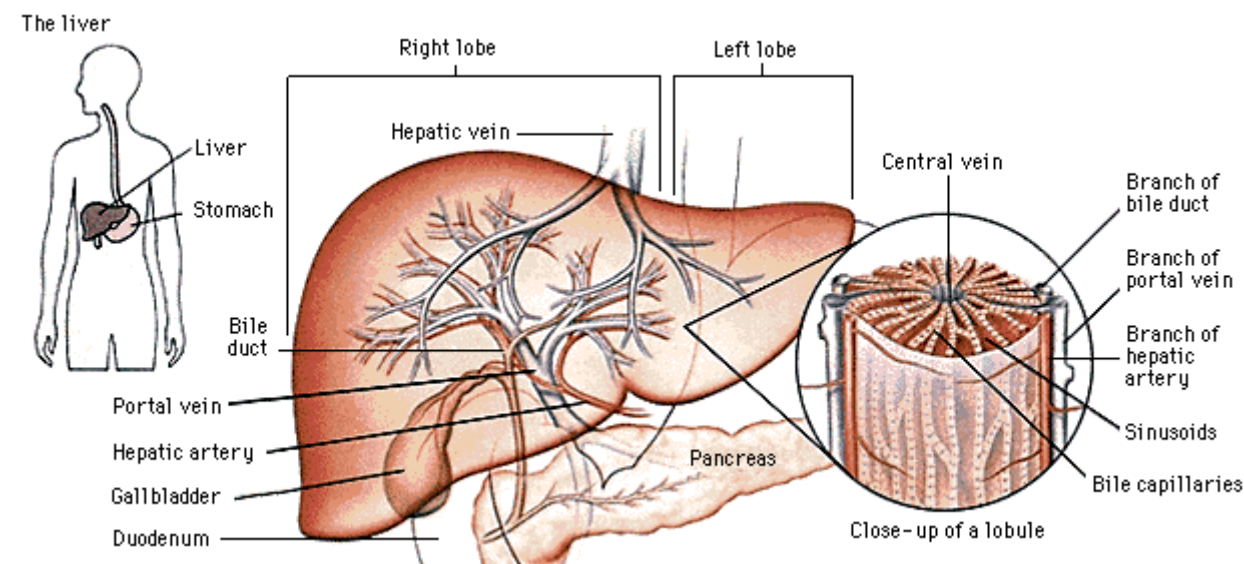
starting point for a potential new treatment option for colorectal cancer patients, and is an important milestone in the ongoing effort to meet the unmet needs of people affected by colorectal cancer. For those patients wishing to access the clinical trial details, please click here:

<http://clinicaltrials.gov/ct2/show/NCT01068769> . Study sites are limited to Boston, U.S.A.

<http://clinicaltrials.gov/ct2/show/NCT01068769>

4. Oxaliplatin-Induced Increase in the Size of the Spleen May Predict Liver Injury (May. 10/10)

Oxaliplatin-based regimens are widely used in patients with colorectal cancer in both the adjuvant and metastatic settings. Furthermore, oxaliplatin is increasingly being used before resection of liver metastases to facilitate a liver resection. In non-tumor-bearing portions of the liver, a high rate of sinusoidal injury has been found. Sinusoids (see image below) are very small blood vessels in the liver and sinusoidal dilatation is the enlargement of these very small vessels. Such high rates are not seen in patients not treated with chemotherapy or treated with other chemotherapy agents such as irinotecan or fluorouracil (5-FU). Increased morbidity, including a greater need for blood transfusions and longer hospitalization, has been associated with hepatic sinusoidal injury in these oxaliplatin-treated patients. The results of this study indicate that spleen size increased in 86% of patients treated with adjuvant folfox, better known as splenomegaly, when there is a 50% or greater increase in spleen size. Those patients treated with single agent 5FU had minimal changes in spleen size. And the increase in spleen size was significantly associated with the cumulative oxaliplatin dose. Furthermore, an increase in spleen size before resection of the liver **strongly correlated with a higher grade of hepatic sinusoidal injury**. Avastin which was also administered appeared to have a protective effect against sinusoidal injury. The strong correlation between oxaliplatin-induced increases in spleen size and development of hepatic sinusoidal injury suggests that spleen size may act as a potential biomarker for predicting the risk of hepatic sinusoidal injury. Researchers recommend that patients with splenomegaly after oxaliplatin therapy could be considered for preoperative percutaneous liver biopsy to assess the extent of hepatic sinusoidal injury. They could also undergo portal venous cannulation for evaluation of portal venous pressure or embolization to determine the regenerative capacity of the liver. The presence of sinusoidal injury could help determine the optimal extent and timing of liver resection.



The liver consists of four sections, or lobes. There are two main lobes--the right lobe, which is by far the larger, and the left lobe. Two small lobes lie behind the right lobe. Each lobe is made up of multisided units called lobules. Most livers have between 50,000 and 100,000 lobules. Each lobule consists of a central vein surrounded by tiny liver cells grouped in sheets or bundles. These cells perform the work of the liver. Cavities known as sinusoids separate the groups of cells within a lobule. The sinusoids give the liver a spongy texture and enable it to hold large amounts of blood. Source:

<http://library.thinkquest.org/28807/data/excr21.htm>

Overman, MJ, et al., Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. *J of Clinical Oncology*. 2010 Apr 20; DOI: 10.1200/JCO.2009.27.5701

5. Trying to Determine Which Patients Respond Best to Vectibix Therapy (May. 12/10)

Previous studies have reported that colorectal cancers with mutations in a gene known as KRAS do not respond well to drugs such as Vectibix (panitumumab). In an effort to expand these findings and further individualize colorectal cancer treatment, researchers evaluated several additional genes. Vectibix inhibits cancer cell growth and survival by targeting a protein known as the epidermal growth factor receptor (EGFR). Vectibix has been approved for the treatment of EGFR-expressing, metastatic colorectal cancer that has progressed on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Vectibix appears to benefit only those patients whose cancers do not contain a mutation in the gene known as KRAS. KRAS mutations occur in an estimated 40-50% of metastatic colorectal cancers and can be identified by testing a sample of tumor tissue. To explore

whether other genes also influence response to Vectibix, researchers evaluated information from a Phase III clinical trial. The study compared Vectibix to best supportive care among patients with metastatic colorectal cancer. Researchers tested samples of tumor tissue for KRAS mutations as well as mutations in NRAS, BRAF, PIK3CA, PTEN, AKT1, EGFR, beta-catenin (CINN1B), and TP53. Vectibix significantly improved progression-free survival among patients **without KRAS mutations** but did not benefit patients with KRAS mutations. The **NRAS** gene also influenced response to Vectibix. Patients with NRAS mutations did not appear to benefit from Vectibix. This study adds to a growing body of knowledge about which patients are most likely to respond to drugs such as Vectibix.

Peeters M et al. Use of massively parallel, next-generation sequencing to identify gene mutations beyond KRAS that predict response to panitumumab in a randomized, Phase III, monotherapy study of metastatic colorectal cancer (mCRC). Presented at the 101st annual meeting of the American Association for Cancer Research. Washington, DC, April 17-21, 2010. Abstract LBA 8791.

6. Sustained Avastin Aids Colon Cancer Patients (May 19/10)

Colorectal cancer patients benefited when they continued to include Avastin (bevacizumab – see image below) in their chemotherapy plan after their cancer got worse after initial treatment. They lived longer after beginning a second round of chemotherapy with Avastin than did other patients who received chemo without Avastin or those who didn't get any chemotherapy at all. The results are based on the ARIES study which observed patients after cancer progressed after either first or second line chemotherapy with Avastin. More than 1,000 patients were followed after their cancer progressed: either tumors began growing again or appeared in new locations.

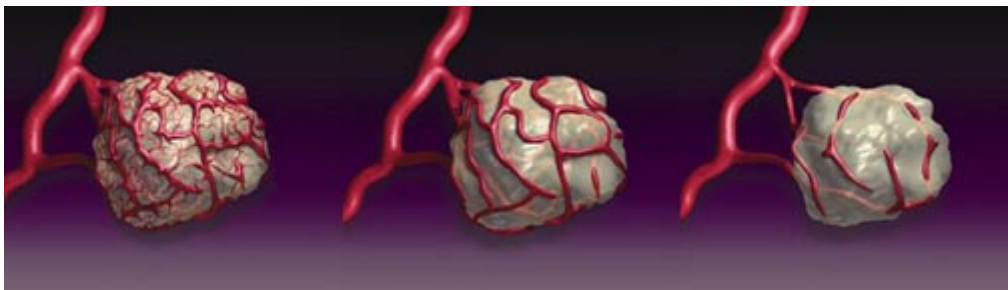
Median survival after the first disease progression was:

- 16.3 months for patients who continued an Avastin-based regimen
- 8.5 months for those who received a non-Avastin containing regimen
- 5.2 months for those who stopped therapy altogether

Side effects were similar to those seen in other clinical trials of Avastin.

- Gastrointestinal perforations (0.2%)
- Cardiovascular events caused by blood clots in arteries (1.9%)
- Bleeding (3.7%)

Updated information, including results for progression-free and overall survival, were reported at the 2010 ASCO meeting. The study confirms results of the BRiTE analysis, another observational study which also showed that continuing Avastin beyond cancer progression improved overall survival. While interesting, results from randomized studies are required to confirm that this difference is clinically significant. Currently [iBET \(Intergroup Bevacizumab Continuation Trial\)](#) is randomizing colorectal cancer patients in second-line therapy to continue with bevacizumab along with their chemotherapy or not. Randomized clinical trials can provide stronger evidence for treatment effectiveness than observational studies which may have bias in how a therapy is chosen for an individual patient.



Avastin's effects on colorectal tumours include the following:

- Reducing the tumor's blood supply by potentially causing existing small blood vessels in the tumor to die.
- Preventing the development of new blood vessels in the tumor.
- Facilitating the delivery of chemotherapy to the tumor cells by potentially making mature tumor vessels, which tend to be leaky, behave more like normal vessels.

Source: <http://www.gene.com/gene/products/information/oncology/avastin/vegf-angiogenesis-cancer.html>

Cohn, et al., 2010 ASCO Annual Meeting; Abstract #3596, Clinical outcomes in bevacizumab-treated patients with metastatic colorectal cancer. Results from ARIES observational cohort study (OCS) and confirmation of BRiTE data on bevacizumab beyond progression.

7. Colon Cancer Drug Boosts Survival in Patients (May 20/10)

An experimental colorectal cancer drug being developed by Keryx Biopharmaceuticals Inc showed it improved overall survival and slowed cancer progression in patients with advanced colorectal cancer, according to a summary of final data from a mid-stage study. Researchers said the drug KRX-0401, also known as perifosine, was well tolerated and showed "promising activity" over chemotherapy as a second

or third-choice drug for patients with colorectal cancer that has spread. The study was presented at the 2010 American Society of Clinical Oncology (ASCO) in Chicago. The study looked at the safety and effectiveness of perifosine in combination with chemotherapy drug capecitabine (xeloda) in 38 patients with advanced colorectal cancer. All of the patients had already failed to improve on one or two other treatments. Of the 35 patients evaluated, 20% who received the perifosine combination responded to treatment, compared to 7% who got chemotherapy plus a dummy pill. Patients in the treatment group lived 18 months, compared with 11 months among those who got chemotherapy plus a placebo. The drug, being developed jointly with Canadian drug maker Aeterna Zentaris, blocks the activation of Akt, a new pathway thought to be linked with cell death and survival. High levels of activated Akt are seen frequently in many types of cancer, and are often a sign of poor prognosis.

Richards, DA, et al., Final results of a randomized phase II study of perifosine in combination with capecitabine versus placebo plus capecitabine in patients with second or third line metastatic colorectal cancer. ASCO, Abstract #3531

8. **Patients with Unresectable Liver Tumours Can Access Clinical Trial** (May 29/10)

Patients with liver tumors, including those that have spread from colorectal cancer, can enroll in a clinical trial at the National Institutes of Health Clinical Center in Bethesda. The trial will test the effectiveness of infusing the drug **melphalan** through the artery that feeds the liver. Colorectal cancer patients with liver metastases are eligible for the trial if they have already had chemotherapy including irinotecan or oxaliplatin. Limited cancer outside of the liver is acceptable if the most serious problem is within the liver itself. Treatment involves placing catheters in both the hepatic artery and hepatic vein. Melphalan is pumped through the hepatic artery for approximately 15 to 30 minutes and the liver bathed in the chemo drug (*hepatic perfusion*). The infusion will be repeated every 3 to 8 weeks up to 4 times. The trial and its treatment takes place at the NIH Clinical Center in Bethesda, MD, just outside of Washington, DC. There is no cost for care received at the NIH Clinical Center. Travel expenses and reasonable costs for meals and lodging are also paid to trial participants. Patients with primary liver cancer, neuroendocrine tumors, or liver metastases that have spread from other gastrointestinal cancers are also eligible for the trial.

For more information, you may contact:

- Itzhak Avital, MD
- Principal investigator
- Phone: 301-402-0083
- Fax: 301-496-0734
- avitali@mail.nih.gov

Or referrals may be forwarded to:

- Carole Webb, RN
- Research Nurse
- Phone: 301-451-6940
- Webbcc@mail.nih.gov

NCI-04-C-0273: A Phase II Study of Hepatic Arterial Infusion of Melphalan With Venous Filtration via Peripheral Hepatic Perfusion for Unresectable primary and Metastatic Cancers of the Liver

9. **Adding Avastin to Xeloda With Or Without Mitomycin C** (June 4/10)

This study sought to determine if adding avastin to xeloda with or without mitomycin C would improve progression free survival (time before disease got worse) in patients with metastatic colorectal cancer. 471 previously untreated unresectable metastatic colorectal cancer patients were randomly assigned to three groups and the following results were achieved:

- Xeloda : 5.7 months progression free survival
- Xeloda + avastin: 8.5 months progression free survival
- Xeloda + Avastin + Mitomycin C: 8.4 months progression free survival

Researchers concluded that adding avastin to xeloda with or without mitomycin significantly improved progression free survival without major additional toxicity or impairment of quality of life.

Tebbutt, NC, et al., Capecitabine, bevacizumab and mitomycin in first line treatment of metastatic colorectal cancer. J of Clinical Oncology. Early release published ahead of print. 10.1200/JCO.2009.27.7723

10. **Erbix Does Not Improve Survival in Stage III Colon Cancer with Normal KRAS** (Jun. 6/10)

The addition of Erbitux (cetuximab) to standard adjuvant chemotherapy in patients with stage III colon cancer who have normal *KRAS* gene activity does not improve survival, according to the results of a Phase III study presented at the 2010 annual meeting of the American Society of Clinical Oncology. Stage III colon cancer refers to cancer that has spread to lymph nodes surrounding the colon but not to

other parts of the body. Erbitux is a targeted therapy that inhibits growth of the cancer by binding to a portion of the epidermal growth factor receptor (EGFR), a protein located on the surface of many cancer cells. Among patients with metastatic colorectal cancer, response to Erbitux appears to vary by whether or not the tumor contains a mutation in a gene known as *KRAS*. Erbitux does not appear to benefit patients with *KRAS* gene mutations, but has been found to benefit patients with normal *KRAS*. This benefit among patients with metastatic colorectal cancer and normal *KRAS* prompted interest in the role of Erbitux among patients with earlier-stage colorectal cancer and normal *KRAS*. The Phase III study involved 1,760 patients with stage III colon cancer and normal *KRAS* who were randomized to receive either the chemotherapy regimen FOLFOX alone or FOLFOX plus Erbitux. After a median follow-up of 15.9 months, the results indicated that the three-year disease-free survival was similar between the two groups. The FOLFOX group had slightly better overall survival (87.3%) compared with the FOLFOX plus Erbitux group (82.1%). Patients who received the combination of Erbitux and FOLFOX experienced a significantly higher rate of moderate to severe side effects and as a result, fewer patients in this group were able to complete the full course of treatment. The researchers concluded that although Erbitux has previously been shown to improve survival in patients with metastatic colon cancer with normal *KRAS* gene activity, the same does not appear to be true in stage III colon cancer. Furthermore, the treatment was associated with significantly more side effects.

Alberts SR, et al. Adjuvant mFOLFOX6 with or without cetuximab (Cmab) in KRAS wild-type (WT) patients (pts) with resected stage III colon cancer (CC): Results from NCCTG Intergroup phase III trial N0147. Presented at 2010 ASCO. June 4-8, 2010. Chicago, IL. Abstract CRA 3507

11. **Xelox as First Line Treatment for Metastatic Colorectal Cancer** (Apr. 12/10)

This study tried to determine if the efficacy and safety of xeloda plus oxaliplatin (xelox) was equivalent to 5FU plus oxaliplatin (FUOX) in the first line treatment of metastatic colorectal cancer. A meta analysis (a search of trials whose results were compiled) of randomized controlled trials was carried out and it was determined that capox was equivalent to fuox in terms of tumour response rate, progression free survival and overall survival in the first line treatment for patients with metastatic colorectal cancer.

Zhao, G, et al., Capecitabine/oxaliplatin as first line treatment for metastatic colorectal cancer: a meta analysis. Colorectal Disease. Volume 12, Issue 7, pp. 615-623.

12. **Defective Mismatch Repair may be Predictive Marker for Lack of Efficacy to FU-Based Adjuvant Therapy in Colon Cancer** (Jun. 15/10)

The standard of care for stage III and some stage II colorectal cancer (CRC) tumors is adjuvant therapy with fluorouracil (FU) plus levamisole or leukovorin. Approximately 15% of CRCs exhibit defective DNA mismatch repair (dMMR), which may be measured by the presence of microsatellite instability (MSI) or by the loss of proteins produced by MMR genes, such as *MLH1* and *MSH2*. Mismatch repair refers to a system within the cell for correcting errors in the genetic material called DNA that works by detecting and replacing parts of the DNA (called bases) that are wrongly paired (mismatched bases). The system repairs the mismatch. When there is a mismatch in the DNA, a mismatch correction enzyme goes to that strand of DNA and removes a segment of the strand containing the mismatched base. The gap in the strand is then filled through the action of the enzyme DNA polymerase. Microsatellites are repeated sequences of DNA. Although the length of these microsatellites is highly variable from person to person, each individual has microsatellites of a set length. Microsatellite instability is a change that occurs in the DNA of certain cancer cells in which the number of repeats of microsatellites is different than the number of repeats that was in the DNA before the cancer. Mutations in mismatch repair (MMR) genes cause MSI in some colon tumors. See image and description below. According to this study, **patients with CRC and defective mismatch repair status do not benefit from FU-based therapy**. Researchers are recommending that mismatch repair status be determined for patients with stage II CRC.

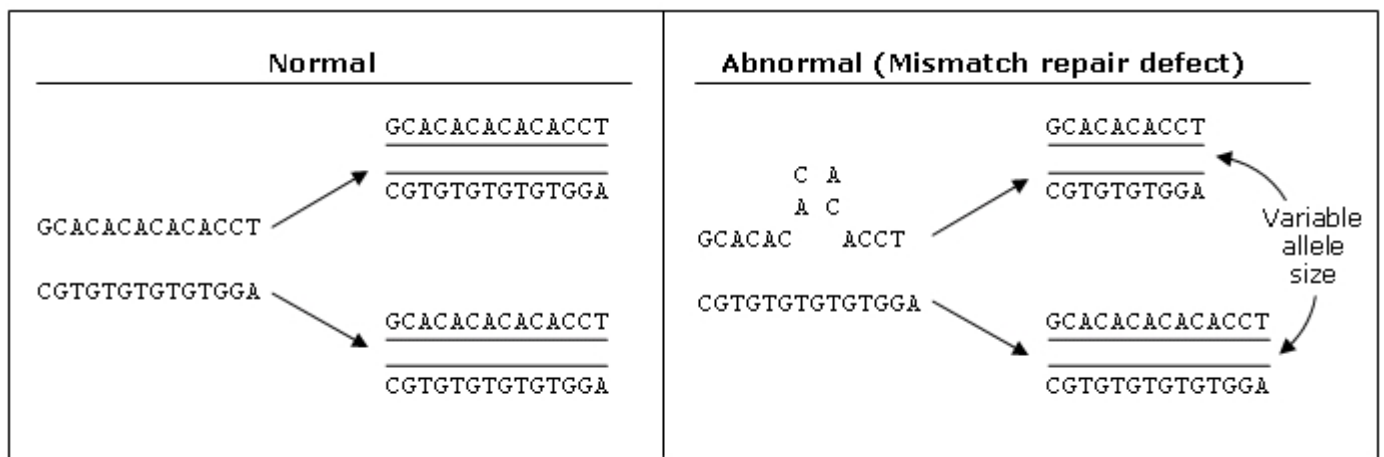
Microsatellite Instability:

The normal length of microsatellites in an individual's cells is set at birth, although lengths vary from one person to another. However, during the many divisions cells undergo in a person's lifetime, mistakes can be made duplicating DNA which don't get repaired, so microsatellites change in length in some tissues (as depicted in the diagram above). The presence of abnormally short or long microsatellites indicates that genes that should be repairing DNA are mutated and aren't doing their job. Mutations in DNA repair genes can lead to a particular form of colorectal cancer linked to microsatellite instability. About 1 in 6 or 7 (15%) colorectal cancers are microsatellite instable. Some people are born with mutations in DNA repair genes, as in Lynch syndrome. Others acquire mutations during their lives. Here are the classifications of Microsatellite Instability:

Microsatellite Instability High Tumours: Contain changes in 2 or more regions of the DNA (genetic material) of the tumour

Microsatellite Instability Low Tumours: Contain changes in one region of the DNA of the tumour.

Microsatellite Instability Stable Tumours: Contain no changes in the DNA of the tumour]



Adapted from Gruber SB, Kohlmann W (2003) The genetics of hereditary nonpolyposis Colorectal cancer. *J Natl Comp Cancer Net* 1:137-44

Sargent, DJ, et al., Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *J Clin Oncol.* 2010. Ahead of print. Accessed online.

13. Adding Erbitux to First Line Chemotherapy Helps Advanced Colorectal Cancer Patients (Jun. 16/10)

According to a pooled analysis of two large randomized clinical trials comparing chemotherapy alone to chemotherapy plus Erbitux (cetuximab), the addition of erbitux to chemotherapy helps people with metastatic colorectal cancer. However, benefits depend on whether or not patient tumors have mutations of two genes, KRAS and BRAF. Previous studies have shown that only patients with normal or *wild type* KRAS get any benefit from EGFR inhibitors such as Erbitux or Vectibix (panitumumab) so a combined analysis of the CRYSTAL and OPUS studies looked only at outcomes in KRAS wild type tumors. In addition, the research team studied the effect of mutations to BRAF. They found that adding Erbitux to initial chemotherapy improved overall survival time, time until cancers got worse (*progression-free survival*), the percent of tumors that shrank with treatment (*overall response rate*) for tumors with wild-type KRAS. The best outcomes were in patients who had both wild-type KRAS and wild-type BRAF. Overall, benefits were smaller for both chemotherapy and chemotherapy plus Erbitux when BRAF was mutated. But even in patients with BRAF mutations, adding Erbitux appeared to help. The pooled analysis of KRAS wild type patients showed:

- Adding Erbitux to chemotherapy added four months to median survival time for the entire group of KRAS wild-type patients. With chemo alone, median overall survival was 19.5 months while it improved to 23.5 months with chemo and Erbitux.
- Progression-free survival was 7.6 months with chemo alone and 9.6 months with the combination of chemo and Erbitux.
- 38.5% of chemo only patients had tumors shrink at some point during their treatment compared to 57.3% of patients who also received Erbitux.

When just patients with *both* wild type KRAS and wild type BRAF were reviewed:

- Overall survival time was 21.1 months with chemo alone and 24.8 months with chemo plus Erbitux.
- Progression-free survival was 7.7 months with chemo and 10.9 months with the combination of chemo and Erbitux.
- Overall response rate was 40.9% for chemo and 60.7% for chemo and Erbitux.

Prognosis appeared to be poorer when KRAS wild type patients had mutated BRAF, but the researchers noted that there were too few BRAF mutated tumors to make the results statistically significant. However, adding Erbitux did improve outcomes. In those patients:

- Median overall survival was 9.9 months with chemo and 14.1 months with the addition of Erbitux.
- Progression-free survival was 3.7 months versus 7.1 months.
- Overall response was 13.2% for chemo alone and 21.9% with Erbitux and chemo.

Researchers concluded that this analysis confirms that the addition of cetuximab to chemotherapy first line in patients with KRAS wild type tumors achieves a statistically significant improvement in overall response rate, progression-free survival, and overall survival compared with chemotherapy alone. The best outcome was observed in patients with KRAS wild type/BRAF wild type tumors (90% of KRAS wild type patients). BRAF mutation status does not appear to be a strong predictive biomarker for the addition of cetuximab to chemotherapy but the sample size may be too small to be reliable.

Bokemeyer, C et al., 2010 ASCO, Abstract # 3506. *Cetuximab with chemotherapy as first line treatment for metastatic colorectal cancer.*

14. **Chemotherapy Benefits Young Patients and Those Over Fifty Equally Well in Stage II and III Colon Cancer** (Jun. 16/10)

According to this study, young patients with stage II or III colon cancer get equal benefit from chemotherapy as older patients, and they have similar side effects. Five years after treatment, 67% of patients under the age of fifty hadn't had their cancer spread beyond the colon (*recurrence-free interval*), the same percentage that applied to patients who were fifty or over. Overall survival and disease-free survival were somewhat better for young patients because they had fewer other reasons for dying. Overall and disease-free survivals reflect patients who are alive five years after beginning treatment. Neither includes people who have died from any cause, including their cancer. Researchers analyzed information from 33,574 individual colon cancer patients who took part in 24 different randomized Phase III clinical trials.

- 1,758 or 5.2% were under age 40
- 5,817 or 17.3% were under age 50
- 299 or 0.9% were under age 30

Comparing outcomes at 5 years:

- Overall survival was 75% for those younger than 40, 76% for those under 50, and 71% for those 50 and over.
- Disease free survival was 68% for patients under 40, 68% for those under 50, and 61% for 50 and over.
- Five year recurrence-free intervals were experienced by 68% under 40, 67% under 50, and 67% 50 and older.

There were no clinically meaningful differences in serious side effects between younger and older patients. Researchers concluded that among patients on chemotherapy, young (age 30-50) stage II and III colon cancer patients had similar recurrence-free interval and adjuvant chemotherapy benefit as older patients, with no clinically meaningful differences in adverse events. Young patients have improved overall survival and disease-free survival, likely primarily due to fewer competing causes of death. Adjuvant chemotherapy is beneficial for colon cancer patients aged 30-50 who meet typical chemotherapy eligibility criteria.

Sargent et al., 2010 ASCO Meeting, Abstract #3523: Benefits and adverse events in younger versus older patients receiving adjuvant chemotherapy for colon cancer: Findings from the 33,574 Patient ACCENT dataset.

15. **Young Advanced Colorectal Cancer Patients Do Just as Well as Older Patients Receiving Chemo** (Jun. 16/10)

When colorectal cancer spreads to other parts of the body, young people, under 50 who get chemotherapy, benefit as much as those who are older, according to this study. With drug combinations, there is no difference between those under 50 and those who are 50 and older in responding to chemotherapy, how long it takes before cancer gets worse, or in survival time. Although colorectal cancer is primarily diagnosed in older people — the median age at diagnosis is 70 — about 10% of colon and rectal cancers are diagnosed under the age of 50. While common wisdom was that younger patients had worse outcomes, a review of information from 9 randomized Phase III clinical trials testing first-line chemotherapy for metastatic colorectal cancer found this wasn't true. When a single drug was used, patients younger than 50 had shorter time before their cancer got worse (*progression-free survival*), but response to chemotherapy and overall survival time remained the same as patients who were fifty and older. With combination treatments:

- Median progression free survival was 7.2 months for patients under 50 and 8.4 months for those fifty and older.
- Overall survival was 16.3 months for under 50 and 14.8 months for older patients.
- 54% of younger patients had tumors shrink with chemotherapy compared to 51% of patients fifty and older.

None of these small differences were statistically significant. Younger patients did have more severe nausea, with 10% experiencing grade 3 or worse nausea with chemo compared to 7% of older patients, but they had less severe diarrhea (11% versus 14%) and less incidence of low white cell counts (16% vs 23%). Nearly 6,300 patients were included in the review with 793 under age 50 (13%) with 188 under 40 (3%). Researchers concluded that young advanced colorectal cancer patients are proportionally represented in phase III studies. Young age is modestly associated with poorer progression-free survival but not overall survival or response rate in treated advanced colorectal cancer patients, and young patients have more nausea but less diarrhea and neutropenias with chemotherapy in general. Young versus older patients derive the same benefits from combination chemotherapy. Based on this data, in the absence of a clinical trial, standard combination chemotherapy approaches are appropriate for young advanced colorectal cancer patients.

Blanke, et al., 2010 ASCO Meeting. Abstract #3520. Impact of young age on efficacy and safety in advanced colorectal cancer: a pooled analysis examining 6286 patients from nine first line phase III chemotherapy trials.

16. Neoadjuvant Chemoradiation Helps Rectal Cancer Patients (Jun. 15/10)

Combined neoadjuvant (before surgery) chemotherapy and radiation may allow patients with early rectal cancer to safely undergo less extensive surgery, according to preliminary results of this study. In the single-arm study among 84 patients with ultrasound-staged T2N0 rectal cancer, 43% had a pathologic complete response (pCR). Of the 77 patients who went on to local excision, 99% had negative margins at the time of surgery. If this approach proves to have good disease control in the long term, it may allow patients with early rectal cancer to have surgery that spares their rectum. Researchers maintained that they need to follow the patients long term to assess the risk of local recurrence and even the risk of distant metastasis but were encouraged with the results.

Garcia-Aguilar, J, et al., 2010 ASCO Meeting, Abstract #3510. Neoadjuvant Chemoradiation achieves pathologic complete responses in rectal cancer.

17. Hedgehog Adds No Benefit When Administered to Advanced Colorectal Cancer Patients (Jun. 18/10)

According to these study results, adding the Hedgehog inhibitor GDC-0449 to standard chemotherapy failed to increase the time before advanced colorectal cancer got worse. Researchers compared *progression-free survival* between patients who received either FOLFOX or FOLFIRI chemotherapy with Avastin and a group who received the same chemo regimen with GDC-0449. There was no difference. GDC-0449 was being developed by Genentech in collaboration with Curis. Hopes for the new treatment were raised at 2010 ASCO where reports showed no increased side effects with the new combination. Researchers thought that blocking the Hedgehog gene on the surface of cancer cells would stop a series of signaling events in a pathway inside the cell leading to cell death and lengthening the time until cancer began to grow again. Hedgehog is involved in embryonic development, particularly in growth of limbs. It was first observed in fruit flies where mutations led to many spiky extra legs making the curled up fly look like a hedgehog.

<http://phx.corporate-ir.net/phoenix.zhtml?c=123198&p=irol-newsArticle&ID=1438731&highlight=target=>

18. Avastin Helps Patients Maintain Chemo Effectiveness (Apr. 6/10)

Stopping XELOX chemotherapy combined with Avastin after six treatments and continuing with Avastin alone until colorectal cancer gets worse appears to be not detrimental, according to a study reported at the 2010 Annual Meeting of the American Society of Clinical Oncology in Chicago. Many patients have to stop oxaliplatin chemotherapy before getting its maximum effectiveness because of *peripheral neuropathy* — tingling, numbness, or pain in their hands and feet. Xeloda (capecitabine) can cause painful skin redness and cracking on the hands and feet or *hand-foot syndrome*, which can also affect time on chemotherapy. Giving only six treatments of Avastin (bevacizumab) plus XELOX chemotherapy and then stopping XELOX and using only Avastin until cancer progressed was as effective for the initial or first-line treatment of colorectal cancer as continuing XELOX. XELOX combines Xeloda (capecitabine) with oxaliplatin. In addition, the strategy reduced both severe peripheral neuropathy and hand-foot syndrome. In the MACRO study, 480 patients who had not received previous chemotherapy for metastatic colorectal cancer were randomly assigned to receive either:

- XELOX and Avastin until their cancer progressed or side effects made it impossible for them to continue treatment or
- Six treatments (18 weeks) of XELOX and Avastin followed by Avastin alone until progression.

After a median follow-up of 16 months, there were no significant differences in response rate, progression-free survival, or overall survival time.

- Median progression-free survival was 11.0 months when XELOX continued and 10.3 months when XELOX was dropped and Avastin continued as a single agent.
- Median overall survival was 25.3 months with continuous XELOX and 20.7 months continuing Avastin alone.
- Overall response rate was 60% for the continuing strategy and 57% for Avastin as a single agent after XELOX was stopped.

Severe grade three or worse side effects were

- Diarrhea: 11% in continuing strategy and 13% when Avastin was used alone.
- Hand-foot syndrome: 12% versus 6%.
- Neuropathy: 24% versus 7%

The researchers also pointed out that about 1 in 10 patients in both arms of the trial were able to have successful surgery to remove metastatic tumors. They concluded that Bevacizumab (BEV) as a maintenance therapy following induction XELOX-BEV was not inferior to continuation XELOX-BEV. This study suggests that maintenance therapy with single agent bevacizumab is an appropriate option

following induction XELOX-BEV in patients with metastatic colorectal cancer. Further studies evaluating single agent bevacizumab after standard chemotherapy in metastatic colorectal cancer are warranted.

Tabernero, et al., 1010 ASCO Meeting, Abstract #3501. Phase III study of first line xelox plus bevacizumab for 6 cycles followed by xelox plus bev or single agent Bev as maintenance therapy in patients with metastatic colorectal cancer: The MACRO trial.

SURGICAL THERAPIES

19. New Research Generated Out of Memorial Sloan Kettering Cancer Center (Jun. 1/10)

Liver resection is the goal of treatment strategies for liver-confined metastatic colorectal cancer. However, after resection the majority of patients will experience recurrence. Chemotherapy seems to improve outcomes compared with surgery alone. Researchers reviewed the data of the role of adjuvant chemotherapy after resection of liver-confined metastatic colorectal cancer. Optimal regimens and sequencing of chemotherapies when liver resection is an option were unclear. Some suggest that resectable liver metastases, in the absence of high-risk features, should begin with surgery and consideration given to adjuvant chemotherapy after surgery. If high-risk features are present, most physicians prefer a short course of systemic preoperative chemotherapy. Perioperative therapy and regional therapy with hepatic arterial infusion (HAI) both increase disease-free survival (DFS) when compared with surgery alone. In unresectable disease, consideration should be given to systemic chemotherapy with or without a biologic agent or HAI with systemic therapy. If the disease becomes resectable, adjuvant treatment should follow surgery. Adjuvant chemotherapy is usually FOLFOX, but HAI combined with systemic chemotherapy is also an option according to the researchers. The role of adjuvant treatment post-liver resection should not be viewed in isolation but rather in the context of prior treatment, surgical preference, and individual patient characteristics. Perioperative therapy and regional therapy have both shown an increase in DFS and the researchers concluded: "Conducting randomized trials examining the role of adjuvant chemotherapy has been difficult because of rapidly changing chemotherapies."

Power, DG, et al., Role of adjuvant therapy after resection of colorectal cancer liver metastases. J of Clin Onc. 2010; 28 (13): pp. 2300-2309

20. Liver Surgery Can Boost Colorectal Cancer Survival (Jun.2/10)

Patients with colorectal cancer that has spread to the liver and who are eligible for surgery, are around 40% more likely to survive if they undergo an operation to remove the liver disease. A new study from the National Cancer Intelligence Network (NCIN) shows that liver resection - removing the cancerous part of the liver and a small part of **healthy tissue around it** - can boost five year survival up to more than four in ten (46%). Not all patients with stage four of the disease are eligible for the treatment but in those where the surgery is possible this study suggests outcomes can be significantly improved. Smaller trials have shown that this technique is effective, but this is the first time researchers have been able to say just how successful it is on a national scale. This surgery is very skilled and should be undertaken by expert surgeons working in specialist liver units.

Morris, Eva, et al., The Surgical management and outcomes of colorectal cancer liver metastases, British J of Surgery; June 2010. Vol. 97, Issue S4.

21. Survival and Resection of Pulmonary Mets (Jun. 2/10)

Few patients with lung metastases from colorectal cancer (CRC) are candidates for surgical therapy with a curative intent, and it is currently impossible to identify those who may benefit the most from thoracotomy (surgical resection of the lungs). The aim of this study was to determine the impact of various parameters on survival after surgical removal of pulmonary mets originating from colorectal cancer. Researchers performed a retrospective analysis of 40 consecutive patients (median age 63.5 [range 33-82] years) who underwent resection of pulmonary metastases from CRC from 1996 to 2009. Median follow-up was 33 (range 4-139) months. Twenty-four (60%) patients did not have previous liver metastases before undergoing lung surgery. Median disease-free interval between primary colorectal tumor and development of lung metastases was 32.5 months. 3- and 5-year overall survival after thoracotomy was 70.1% and 43.4%, respectively. The following parameters were correlated with tumor recurrence after thoracotomy; a history of previous liver metastases; and lung surgery other than wedge resection. Prior resection of liver metastases was also correlated with an increased risk of death. Median survival after thoracotomy was 87 (range 34-139) months in the group of patients without liver metastases versus 40 (range 28-51) months in patients who had undergone prior. Researchers concluded that the main parameter associated with poor outcome after lung resection of CRC metastases is a history of liver metastases.

Ulrich, Landes, et al., Predicting Survival After pulmonary metastasectomy for colorectal cancer: previous liver metastases matter. BMC Surgery 2010, 10:17.

22. Radical Resection Superior for Early Stage Colorectal Cancer

(Jun. 6/10)

At the May 2010 Digestive Disease Week Meeting, a group of Mayo Clinic researchers presented a study demonstrating that radical resection is far superior for people with stage T1 colorectal cancer. Stage T1 means that the tumor has not broken through the wall of the colon or rectum to spread to other areas of the body, but it has spread into the muscle wall of the colon or rectum. The tumor is no longer solely on the surface or lining of the colon or rectum as is the case with T0. The researchers studied 519 people who had been diagnosed with either stage T0 or T1 colon or rectal cancer. Some of them were treated with local excision of their tumor, while others underwent radical resection. For people with stage T0 colorectal cancer (early noninvasive intramucosal (NIIM)), the 5 year survival rate was the same, regardless of whether they had local surgery or radical resection for their tumors. But for people with T1 colorectal cancer, those who had local surgery were more than 4 times more likely to have a recurrence of their cancer than people treated with radical resection. Recurrence was even more likely for tumors located in the rectum. A local excision is when the surgeon removes tissue limited to the immediate area of the tumor. A radical resection is more extensive. In this case, the surgeon will remove the tumor, plus one to two inches of healthy tissue on either side of the tumor. Some types of radical resections also involve removing the blood and lymph supply to the colon or section of the colon that is being removed.

De Groen, Petrus, et al., Digestive Diseases Week (DDW) 2010: Abstract 230. Presented may 2, 2010.

23. Examining the Optimal Number of Lymph Nodes In Stage II Colorectal Cancer Surgery (Jun. 7/10)

Lymph node status is the most important prognostic factor for colorectal cancer. The number of lymph nodes that should be examined during surgery has been controversial. The image below depicts the lymph nodes that are associated with the colon. The aims of this study were to assess the impact of the number of lymph nodes examined during colorectal surgery on survival of patients with stage II colorectal cancer and to determine the optimal number of lymph nodes that should be examined. The study included 664 patients who underwent resection for stage II colorectal cancer. The median number of lymph nodes examined was 12 (range: 1 to 58). The 5-year disease free survival rate was significantly higher for patients with **12 or more lymph nodes** examined compared to those with less than 12 lymph nodes examined. The significant difference in 5-year disease free survival persisted if the dividing number increased progressively from 12 to 23. However, the difference in survival was most significant for the number 21. The 5-year disease free survival of patients with 21 or more lymph nodes examined was 80% whereas that of patients with less than 21 lymph nodes examined was 60%. Upon further analysis, 21 or more lymph nodes examined was a factor that independently influenced survival. The 5-year disease free survival also increased progressively with the number of lymph nodes examined up to the number 21. After the number 21, the survival rate did not increase further. It was likely that **21 was the optimal number**, at and above which the chance of lymph node metastasis was minimal. Researchers concluded that the number of lymph nodes examined in colorectal cancer specimen significantly influences survival. It is recommended that **at least 21 lymph nodes** should be examined for accurate diagnosis of stage II colorectal cancer.

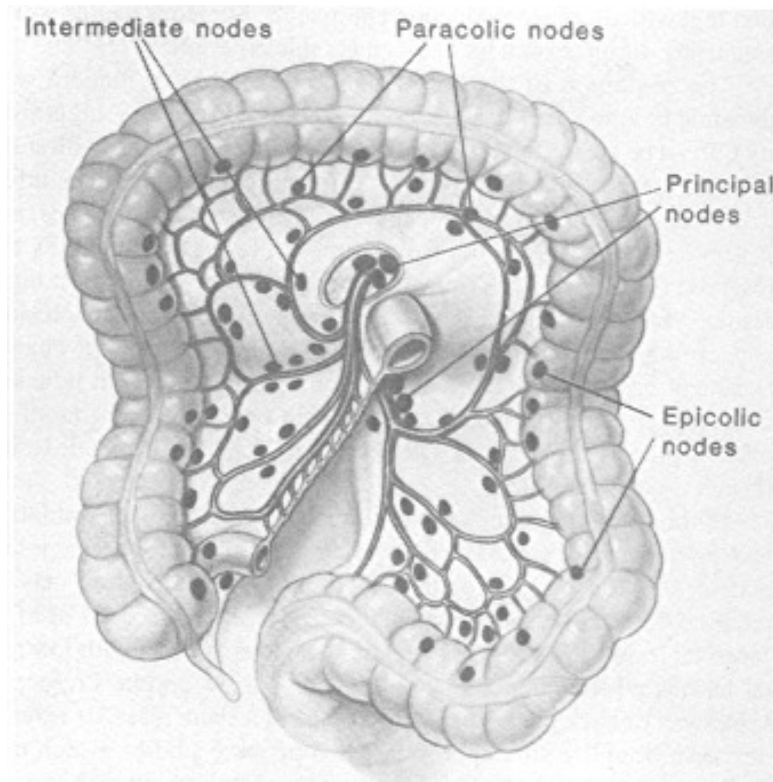


Diagram Showing Lymph Nodes Associated With Colon Surgery: The epicolic, paracolic, intermediate, and principal lymph node groups accompanying the vessels of the colon.

Source: <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=cmed&part=A24990>

RADIATION / INTERVENTIONAL RADIOLOGY

24. FDG-PET/CT Plays a Definite Role in Detecting Colorectal Cancer Recurrences (May 5/10)

The use of combined positron emission tomography and computed tomography (PET/CT) can confirm a suspected colorectal cancer recurrence at an early stage, helping significantly in treatment planning and improved targeted patient care, according to a study that was presented at the ARRS 2010 Annual Meeting in San Diego, CA. PET/CT is a type of nuclear medicine imaging that uses traces of radioactive material to diagnose or treat many types of cancers. With modern surgical techniques and advanced chemotherapy, growing subsets of patients with colorectal cancer recurrences are being considered for treatment with curative intent. Therefore, accurate re-staging and early detection of recurrence is important. The study included 71 patients with suspected colorectal recurrence. Fifty-one patients had a suspected local recurrence based upon conventional CT or MR and 20 patients had a suspected recurrence based upon an elevated carcinoembryonic antigen (CEA) test with unremarkable conventional imaging. All 71 patients underwent a PET/CT scan to confirm/disconfirm recurrence. PET/CT accurately confirmed a recurrence in 40/71 patients. This shows that PET/CT has a definite role in the management of patients with recurrent colorectal cancer in addition to conventional imaging and the CEA test.

<http://www.medicalnewstoday.com/articles/187578.php>

25. Effectiveness of PET for Predicting Chemo Response in Colorectal Cancer Liver Mets (May 17/10)

Chemotherapeutic agents may be able to convert unresectable colorectal liver metastasis to resectable disease, therefore changing the surgical options of a patient. The role of positron emission tomography (PET) for patients undergoing chemotherapy was explored in this study. From May 1, 2006, through August 31, 2008, data for 224 consecutive patients were entered into a prospective database for evaluation of hepatic metastasis of colorectal cancer. One hundred thirty-eight patients underwent PET and conventional imaging (a combination of computed tomography, magnetic resonance imaging, and ultrasonography). Researchers tried to determine the accuracy of PET scans to detect residual viable colorectal cancer liver metastases after a significant response to systemic chemotherapy. Patients with biopsy-proven disease underwent hepatic resection (120 patients [87.0%]), radiofrequency ablation (2 [1.4%]), or resection with radiofrequency ablation (7 [5.1%]). Nine patients (6.5%) had inoperable disease that was found during the time of surgery. When performed within 4 weeks of chemotherapy, PET had a negative predictive value of 13.3% and a positive predictive value of 94.3%. The sensitivity was 89.9%, the specificity was 22.2%, and the accuracy was 85.5%. Researchers concluded that positron emission tomography within 4 weeks of chemotherapy is not a useful test for evaluation of colorectal hepatic metastases. The high rate of false-negative results is likely due to metabolic inhibition caused by chemotherapeutic drugs. They recommend that physicians not use PET in patients recently completing chemotherapy; rather, they should undergo the appropriate oncologic hepatic operation based on the high probability of viable malignant disease.

Glazer, Evan S, et al., Effectiveness of positron emission tomography for predicting chemotherapy response in colorectal cancer liver metastases. Archives of Surgery. Vol. 145, No. 4, April 2010: pp. 340-345

26. PET & CT Colonography May Be Useful in Detecting Polyps and Colorectal Cancer (Jun. 1/10)

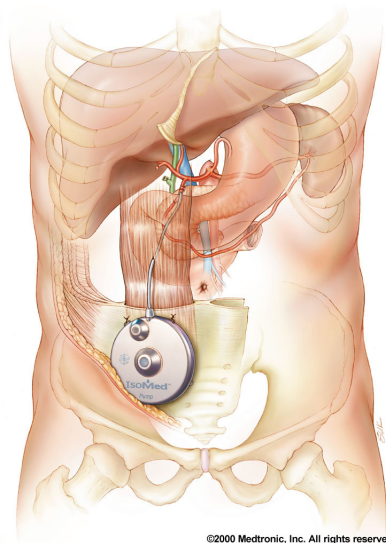
This study shows that positron emission tomography (PET) -- a molecular imaging technique -- combined with computer tomography (CT) colonography may provide a suitable alternative for detecting polyps and cancer in the colon. This particular imaging method may be especially desirable for patients because it does not require sedation or bowel preparation. One of the first indications of colorectal cancer is often the presence of polyps, which are abnormal tissue growths on the inner lining of the colon or large intestine. If these polyps are detected non-invasively and without the use of bowel preparation and sedatives, investigation can be much easier on patients who would otherwise undergo colonoscopies. CT colonography (CTC) is an imaging technique that presents a promising, less invasive alternative to colonoscopy. The CTC scan provides images of the lining of the bowel, which has been gently distended with gas, without the need for sedatives. One potentially major advantage of CTC over colonoscopy is its ability to visualize the large bowel -- without the patient having to take strong laxatives. PET scanning produces images of the uptake of blood sugar (glucose) by body tissues. Because cancerous cells tend to take up more blood sugar than normal tissue, these concentrations provide clear evidence of any abnormalities. This study researched the effectiveness of using a combination of CTC and PET scans without any bowel preparation to detect significant abnormalities in the colon. Although other work has demonstrated that combined PET CTC is technically feasible, most have required patients to undergo complete bowel preparation and only a small number of patients have been studied. The current study is the largest to date investigating combined PET CTC in patients without any bowel preparation. 56 patients agreed to undergo a one-hour CTC and PET scan about two weeks before their scheduled colonoscopy. This was done without the use of laxatives. Patients were also asked to complete a questionnaire to see how they tolerated the tests and which ones they preferred. The colonoscopy

results were then compared with the CTC scan on its own and with the CTC and PET scans combined. The study found that the combined PET CTC scans detected all the important larger polyps found by the invasive colonoscopy technique. In addition, most patients found the combined scan technique more comfortable and preferred it to colonoscopy.

Taylor, S.A., et al., Nonlaxative PET/CT Colonography: Feasibility, Acceptability, and Pilot Performance in Patients at Higher Risk of Colonic Neoplasia. Journal of Nuclear Medicine, 2010; 51 (6): 854 DOI: [10.2967/jnumed.109.072728](https://doi.org/10.2967/jnumed.109.072728)

27. Administering Hepatic Arterial Infusion using Raltitrexed and Oxaliplatin for Liver Mets (Jun. 8/10)

The aim of this study was to evaluate the efficacy and safety of combined hepatic arterial infusion (HAI – see image below), which is a combination of raltitrexed and oxaliplatin, in refractory colorectal cancer with only liver metastases. Seventeen consecutive patients with unresectable metastatic colorectal cancer, after the failure of two lines of systemic chemotherapy, were treated with HAI raltitrexed followed by oxaliplatin every 3 weeks between January 2006 and January 2009. All patients presented with the metastatic disease limited to the liver and had failed at least two lines of chemotherapy, which contained oxaliplatin, irinotecan and a fluoropyrimidine. The median number of cycles was six (range 1-15). Researchers observed three complete responses and eight partial responses among assessable patients. The median time to progression was 10.5 months and the median survival time was 27.5 months. Toxicity included grade 3-4 neutropenia (in 17%), grade 3-4 thrombopenia (in 17%), and grade 2 abdominal pain (in 47%). Researchers concluded that the combination regimen of HAI raltitrexed and oxaliplatin is feasible and promising in patients who presented isolated hepatic metastases of colorectal cancer after failure of irinotecan and oxaliplatin treatment. They recommend that further evaluation of this combination is required.



Hepatic Arterial Infusion (HAI), usually an option for patients with metastatic colon cancer, is a therapy involving the delivery of chemotherapy drugs to the liver through a catheter into the main artery supplying the liver. 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 above). 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. Results of two randomized trials have shown significant improvement in disease-free survival.

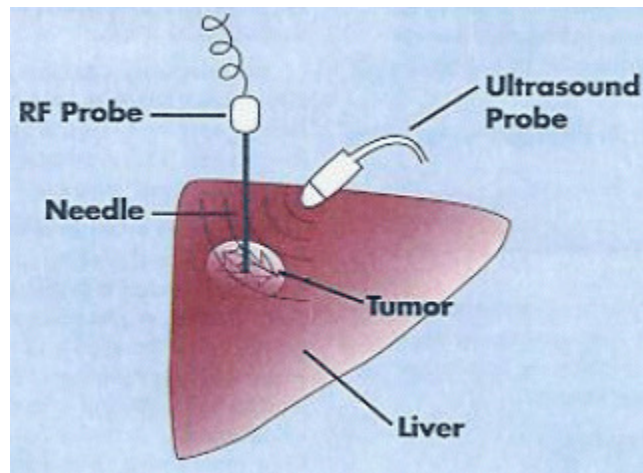
To view the report on these trials, visit <http://www.medtronic.com/neuro/hai/physician/overview.html>.

Khouri, C et al., Raltitrexed and oxaliplatin hepatic arterial infusion for advanced colorectal cancer: A retrospective study. Anti-Cancer Drugs, July 2010; Vol 21, Issue 6: pp. 656-661

28. Combining RFA and Chemo For Unresectable Colorectal Liver Mets (Jun. 10/10)

In patients with unresectable CRC liver mets there is an increasing tendency to combine systemic chemotherapy (CT) with local tumour destruction by RFA (radiofrequency ablation). However, the benefit of this combined treatment has not yet been demonstrated. This randomized phase II study (ClinicalTrials.gov NCT00043004) evaluated the benefits of adding RFA to systemic CT in patients with ≤ 9 unresectable CRC liver mets and no extrahepatic disease. Between 2002 and 2007, 119 patients were randomized between CT alone (59) or RFA plus CT (60). In both arms, CT consisted of 6 months FOLFOX plus, since October 2005, bevacizumab or better known as avastin. Baseline characteristics were similar between arms: 60% had ≥ 4 LM, 51 patients (85%) received CT in the RFA + CT arm and 59 (all) in the CT arm. The median number of CT cycles for patients who started CT was 10 in both arms. Toxicity profiles for CT were comparable between both groups. At a median follow up of 4.4 years, the 30-months Overall Survival rate was 61.7% in the RFA +CT arm and 57.6% in the CT arm. In eligible patients (RFA + CT; 57 pts, CT; 58 pts) these figures were 64.9% and 56.9% respectively. The median PFS was 16.8 months in the RFA + CT arm and 9.9 months in the CT arm. The number of patients with first recurrence at the RFA site only was 5 (9%). 4 more patients (7%) had a first recurrence at a RFA site in combination with a recurrence elsewhere in the liver. This was the first study that prospectively investigated the efficacy of RFA in combination with CT. The primary endpoint (30-months OS > 38%) was met, but also 30 months OS in the CT arm was much higher than 38%. Since the study design does

not allow a formal comparison between treatment arms, and longer follow-up is needed to assess overall survival, researchers maintain the benefit in overall survival of adding RFA to CT is uncertain.



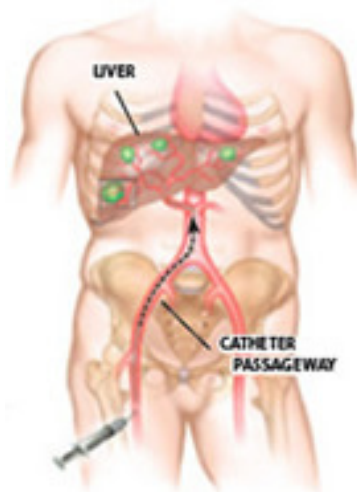
Radiofrequency ablation is performed on small liver tumors. A small needle is placed directly into the center of the tumor. This specially designed needle is connected to a radiofrequency generator, which heats the needle tip, killing the tumor. It is possible to have more than one tumor heated during the procedure. It takes approximately 30 minutes per tumor. The procedure destroys the tumor only, sparing healthy liver tissue.

Source: <http://www.uphs.upenn.edu/radiology/patient/services/ir/info/radio.html>

Ruers, T, et al., ASCO 2010 Meeting. Abstract #3526. Final results of the EORTC intergroup randomized study 40004 evaluating the benefit of radiofrequency ablation combined with chemotherapy for unresectable colorectal liver metastases.

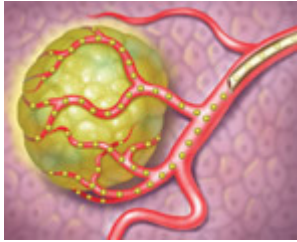
29. Comparing 5FU Infusion Alone or With Yttrium-90 Microspheres For The Treatment of Liver Mets (Jun.24/10)

Liver metastases are a major cause of mortality among patients with advanced colorectal cancer. Hepatic intra-arterial injection of the β -emitting isotope **yttrium-90 (^{90}Y)** bound to resin microspheres (known as radioembolization – see image and description below) delivers therapeutic radiation doses to liver metastases with minimal damage to adjacent tissues. Researchers conducted a prospective, multicenter, randomized phase III trial in patients with unresectable, chemotherapy-refractory (a term commonly used to describe a situation where the disease is no longer controlled by current therapy therefore amounting to disease progression) liver-limited metastatic CRC (mCRC) comparing arm A (fluorouracil [FU] protracted intravenous infusion 300 mg/m² days 1 through 14 every 3 weeks) and arm B (radioembolization plus intravenous FU 225 mg/m² days 1 through 14 then 300 mg/m² days 1 through 14 every 3 weeks) until liver progression. The researchers' objective was to measure time to liver progression (TTLP). Cross-over to radioembolization was permitted after progression in arm A. Forty-six patients were randomly assigned and 44 were eligible for analysis. Median follow-up was 24.8 months. Median TTLP was 2.1 and 5.5 months in arms A and B, respectively. Median time to tumor progression (TTP) was **2.1 and 4.5 months**, respectively. Grade 3 or 4 toxicities were recorded in six patients after FU monotherapy and in one patient after radioembolization plus FU treatment. Twenty-five of 44 patients received further treatment after progression, including 10 patients in arm A who received radioembolization. Median overall survival was **7.3 and 10.0 months** in arms A and B, respectively. Researchers concluded that radioembolization with ^{90}Y -resin microspheres plus FU is well tolerated and significantly improves TTLP and TTP compared with FU alone. This procedure is a valid therapeutic option for chemotherapy-refractory liver-limited mCRC.



SIR-Spheres microspheres are an innovative means of treating liver cancer or liver mets. In cases where it is not possible to surgically remove the liver tumors, SIR-Spheres microspheres can be used to deliver targeted, internal radiation therapy directly to the tumor.

This technique uses millions of tiny polymer beads or microspheres which contain a radioactive element called yttrium-90. SIR-Spheres microspheres are very small, approximately 32 microns in size, and are about one-third the diameter of a strand of hair. SIRT is usually administered as an outpatient procedure by a specially trained physician known as an interventional radiologist. A small catheter is guided into the liver and the SIR-Spheres microspheres are infused through the catheter.



The microspheres with the radioactive yttrium-90 are carried by the bloodstream directly to the tumors in the liver where they preferentially lodge in the small vessels feeding the tumor and deliver their dose of radiation. Unlike conventional external beam radiation, which can only be applied to limited areas of the body, SIR-Spheres microspheres selectively irradiate the tumors and therefore have the ability to deliver more potent doses of radiation directly to the cancer cells over a longer period of time.

Source: <http://www.iconradiology.com/oncology-radiology-liver-tumor-portland-oregon.htm>

Hendlisz, A, et al., Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J of Clinical Onc.* Published online ahead of print June 21, 2010. DOI: 10.1200/JCO.2010.28.5643

SCREENING

30. One Flexible Sigmoidoscopy Can Reduce Colorectal Cancer Deaths (Apr. 30/10)

According to the results of this study, one flexible sigmoidoscopy screening between the ages of 55 and 64 reduced both colorectal cancer diagnoses and deaths during a randomized clinical trial in the United Kingdom. After following 170,000 people for more than 11 years, deaths from colorectal cancer were 43% lower among those who had a flexible sigmoidoscopy screening. Diagnosis of colorectal cancer was reduced by 33%. This is the first prospective clinical trial that actually proved that examining the rectum and colon with a scope could reduce colorectal cancer deaths. Participants in the trial had indicated their willingness to be part of a randomized trial and were assigned either to a control group or to receive a single flexible sigmoidoscopy exam. Twice as many people were in the control group as in the sigmoidoscopy group. Participants were only people of average risk. Those with previous colorectal cancer, polyps, inflammatory bowel disease, or family history were not included. Enrollment in the trial began in 1996 with a goal of following patients for 15 years. During a median 11 years of follow-up, there were 1,818 cases of colon or rectal cancer in the control group compared to 706 in the sigmoidoscopy group. Among those who didn't have sigmoidoscopy, 538 people died of colorectal cancer and 189 died who did have the exam. There was some selection bias — patients chose to enter the trial themselves but not whether they would get a sigmoidoscopy. After researchers adjusted for that bias, incidence of cancer was about a third less (33%) for those who received sigmoidoscopy and deaths were reduced by 43%. Lead investigator pointed out that most people develop polyps in their 50's and cancer later in life. About two-thirds of colon cancers are found in the distal colon, the part of the colon that can be reached by the sigmoidoscope. The exams did not require sedation. Preparation was a single phosphate enema which participants administered at home about an hour before leaving for their appointment. Dr. Atkins and her colleagues concluded: Flexible sigmoidoscopy is a safe and practical test and, when offered only once between ages 55 and 64 years, confers a substantial and long-lasting benefit.

Atkins, Wendy, et al., Once only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomized controlled trial. *The Lancet*; Vol. 375, Issue 9726: pp. 1624-1633.

31. No Colorectal Cancer Detected After Ten Years of a Negative Colonoscopy (May 1/10)

No participants in a study of the German colonoscopy screening program who had a clear colonoscopy developed colorectal cancer almost twelve years after their exam. Advanced adenomas were also reduced significantly. Scientists at the German Cancer Research Center in Heidelberg compared a group of 553 people who had a negative screening colonoscopy to another group of 2701 who didn't receive a colonoscopy. After an average of 11.9 years, there were no colorectal cancers diagnosed in people with a negative colonoscopy compared to 8.4 in the group that weren't screened. Advanced adenomas — polyps most likely to become cancerous — were more than 52% lower 11 to 15 years later. Even after 16 years, risk of finding an advanced adenoma was reduced by more than 47%. Statutory health insurance in Germany has offered free screening colonoscopies to people over 55 since 2002. Since that time over 1.8 million colonoscopy screenings have been done reaching about 40% of German women and 30% of men. Researchers recommend that the low risk of CRC and advanced adenomas after a negative colonoscopy supports suggestions that screening intervals be extended to ≥ 10 years.

Brenner, Hermann, et al., Low Risk of colorectal cancer and advanced adenomas more than ten years after negative colonoscopy. *Gastroenterology*; Vol. 138, Issue 3: pp. 870-876

32. DNA Stool Test Under Development (May 4/10)

DNA stool testing is more likely to find early stage cancers and precancerous growths than current tests, according to Mayo Clinic Researchers. Noninvasive stool DNA testing can detect two types of colorectal precancers and could play a larger role in colon cancer prevention. Compared with widely used fecal blood tests, stool DNA testing has higher detection rates for curable stage colorectal cancer and for common precancerous polyps (adenomas). The first study found that stool DNA testing detected 5 out of 5 cases of colon cancer and 4 out of 5 cases of a precancerous lesion called dysplasia in 10 patients with inflammatory bowel disease. In the second study, the researchers found that stool DNA testing had a success rate of 71% in detecting serrated colorectal polyps, compared to a 7% detection rate with fecal blood tests. Serrated colorectal polyps, which are believed to be the forerunner in about 30% of colon cancer cases, can be difficult to detect using most types of colorectal cancer screening. Unlike common polyps, they tend to be flat and the same color as the colon lining.

Mayo Clinic, news release, May 3, 2010.

33. Using One Day Colonoscopy Prep (May 24/10)

New research is now pointing the way to an easier preparation for colon cancer screening. The randomized study compared colonoscopy results of 116 patients. Half of those screened prepared for their test with medications taken the day before and the day of the procedure. The other half of the group prepared for the screening by taking medications only on the day of the test. **The researchers reported that the two ways of preparing for an afternoon colonoscopy were equal.** The most important thing when preparing for a colonoscopy test is to make sure the colon is completely empty. All stool must be out of the colon in order for the doctor to get a clear view. A clear view allows for better detection of changes in the colon that can lead to cancer and for catching cancer itself in the early stages, when it is most curable. If scheduled for an afternoon colonoscopy, ask the doctor or nurse if you need to take the laxative medication to clear your colon the night before. You can ask if taking this medication the morning of your procedure is an option. When discussing these options, you can mention the study showing that same day medication is effective.

Kastenber, David, et al., Efficacy of morning only compared with split dose polyethylene glycol electrolyte solution for afternoon colonoscopy: a randomized controlled single blind study. Am J Gastroenterol. Advance online publication 20 April 2010. Doi: 10.1038/ajg.2010.160

34. More Choices Increase CRC Screening Use (May 8/10)

When people were offered a personal choice of either FOBT or colonoscopy screening by their primary care provider, more people actually completed the test they chose than if only one option had been offered. In a study of 1,000 ethnically and racially diverse people, the lowest percentage had a colonoscopy when that was the only test offered. More completed fecal occult blood testing if it was the single choice. Overall 65% of the 1,000 patients studied were screened after their doctor recommended testing. Primary care providers randomly recommended patients be screened for colorectal cancer by:

- Colonoscopy alone
- FOBT alone
- Their choice of colonoscopy or FOBT

In order to make colonoscopy easier, barriers to having the exam were reduced by:

- Reducing or eliminating the patient's cost for colonoscopy.
- Providing information about the test and preparation for it in the language the patient preferred.
- Providing rides to and from the exam.
- Having an *open access* system with no more than 2 weeks between test recommendation and the scheduled procedure date.

While two out of three participants in the study had a recommended test:

- 38.4% had a colonoscopy when it was the only recommendation.
- 67.1% completed an FOBT when only FOBT was recommended.
- 70.0% completed screening when they were given a choice between FOBT or colonoscopy.

During a follow-up survey, health beliefs that interfered with having a colonoscopy included

- Fear of test results.
- Fear of cancer treatment.
- Concern that they wouldn't be able to do the necessary prep.

Researchers concluded: Recommendation of colonoscopy alone results in lower adherence to any colorectal cancer screening test compared with recommendation for fecal occult blood test alone or choice of FOBT or colonoscopy.

Inadomi, et al., Digestive Disease Week, Abstract #124. Method of Recommendation for Colorectal Cancer Screening Strategies Impacts Adherence.

35. Physicians Not Performing CRC Screening Correctly (May 12/10)

FOBT screening saves lives but only when it is performed correctly. Three out of four primary care doctors did a fecal occult blood test once during an office visit, a method that is ineffective in finding cancer or preventing death from colorectal cancer. One out of four used the in-office test exclusively. Less than half of doctors had a system in place to be sure that home tests were completed and returned. The 2006–2007 National Survey of Primary Care Physicians Recommendations and Practices for Cancer Screening conducted by the National Cancer Institute in collaboration with CDC and the Agency for Healthcare Research and Quality surveyed a sample of primary care doctors about their recommendations for colorectal cancer screening. Family physicians, general practitioners, obstetrician-gynecologists, and internists were included. Over 90% of surveyed doctors said that they used an FOBT for colorectal screening at least once a month. Of those 24.8% performed the test only in their offices, 52.9% used both office and home tests. Three out of five doctors used a test that is no longer recommended because of its low sensitivity. A single in-office test during a rectal exam will miss 95% of cancers and advanced polyps. In other practices that reduced the value of fecal occult blood tests:

- Almost 1 in 5 doctors (17.8%) repeated a positive FOBT rather than refer a patient for colonoscopy immediately.
- Of those doctors who repeated FOBT, nearly a third (28.8%) stopped follow-up evaluation if the second FOBT was negative.
- Most doctors (61.1%) were using the least sensitive test, a standard guaiac test, which is no longer recommended. Only 22% used the higher sensitivity guaiac test and 8.9% used a fecal immunohistochemical test which is more sensitive and doesn't require patients to follow a special diet or refrain from certain medications before the test. 14.7% didn't know what test they used.
- Only 44.3% had a system in place — chart reminders, telephone calls, or mailings — to follow up on FOBTs that weren't returned.
- 62.2% of doctors had no system in place to be sure that patients referred for follow-up evaluation of a positive test actually got that testing.

Researchers claimed that while FOBT done appropriately is an important screening option, in-office FOBT may be worse than no screening at all because it misses 95% of cases of advanced neoplasia, giving many patients a false sense of reassurance. The researchers concluded: Although FOBT is an important option for colorectal cancer screening, our study suggests that its potential to save lives is not currently being realized because many physicians are continuing to use inappropriate implementation methods. Intensified efforts to inform physicians of recommended technique and promote the use of systems for tracking test completion and follow-up are needed.

Nadel, Marion, et al., Fecal occult blood testing beliefs and practices of U.S. primary care physicians: serious deviations from evidence-based recommendations. J of General Internal Medicine. Online first April 10, 2010. Open Access.

36. Rates of Adenoma Detection Linked to Risk of Interval Colorectal Cancer (Jun.6/10)

Endoscopists who detect tumors or polyps (adenomas) at a higher rate during colonoscopy screening for colorectal cancer tend to produce a lower risk for interval cancer among their patients, according to this study. During a colonoscopy, a lighted tube with an attached camera is inserted into the rectum and through the colon. Colonoscopy is performed by an endoscopist, a healthcare professional who specializes in such procedures. Interval cancers are cancers that develop in the period between screening colonoscopy and follow-up, or surveillance, colonoscopy. A factor that may influence a patient's risk of developing an interval cancer is the endoscopist's rate of detection of adenomas during screening colonoscopy. To evaluate whether the rate at which an endoscopist detects adenomas can predict a patient's risk of interval colorectal cancer, researchers evaluated information from about 186 endoscopists and 45,000 patients who had undergone colonoscopy screening. Adenoma detection rate was calculated for each endoscopist, and was defined as the proportion of screened subjects in whom at least one adenoma was identified.

- 42 interval cancers were identified.
- The endoscopist's rate of adenoma detection during screening colonoscopy was significantly associated with the risk of interval cancers: patients undergoing colonoscopy performed by an endoscopist with a detection rate of more than 20% had a significantly lower risk of interval cancers compared with patients whose endoscopists had a detection rate **of less than 20%**.

It appears that an endoscopist's rate of detection of adenomas during screening colonoscopy may be a measure of colonoscopy quality. Endoscopists who have a higher rate of adenoma detection tend to produce a lower risk for interval cancers among their patients.

PSYCHO-SOCIAL

37. Using Physical Therapy to Improve Fatigue in Hospice Patients (May 28/10)

According to this study, dying cancer patients had less fatigue and their physical symptoms improved when they had physical therapy (PT) three times a week. Control group patients who were not included in the PT program had both physical symptoms and quality of life get worse, even over two weeks of observation. Patients in the study were part of a hospice program in Poland. Researchers maintained: "Our analysis showed that, on average, after 3 weeks of kinesitherapy, a significant decrease of the intensity of fatigue was observed, while in the control group, it increased after 2 weeks of observation. The obtained results provide evidence that a planned set of exercises decreases cancer-related fatigue effectively".

Buss, Tomasz, et al., Kinesitherapy alleviates fatigue in terminal hospice cancer patients – an experimental, controlled study. Supportive Care in Cancer, Vol 18, No. 6, June 2010. pp 743-749

38. Depression & Metastatic Cancer (Jun.6/10)

A substantial number of patients with metastatic cancer may suffer from depression which tends to persist and grow more severe toward the end of life, according to the results of this study. While cancer and other serious illnesses are risk factors for depression, little research has been performed to evaluate the severity and duration of depression among patients with advanced cancer. In an effort to establish the risk factors and progression of depressive symptoms in this group, researchers from Canada conducted a study among 365 patients with metastatic gastrointestinal or lung cancer. At the beginning of the study, patients were evaluated in terms of physical distress, self-esteem, attachment security, spiritual wellbeing, social support, hopelessness, and depression. Then, at two-month intervals, patients were reevaluated in terms of physical distress, social support, hopelessness, and depression. Thirty-five percent of patients reported at least mild depressive symptoms and 16% experienced moderate to severe depression. This depression persisted in up to one-third of subjects. Moderate to severe depression was three times more common in the final three months of life than it was at least one year prior to death. Risk factors for depression included younger age; pre-existing antidepressant use; lower self-esteem and spiritual wellbeing; and a higher degree of attachment anxiety, hopelessness, and physical burden of illness. The researchers commented that "the combination of greater physical suffering and psychosocial vulnerability put individuals at greatest risk for depression." The researchers concluded that depression is relatively common among patients with advanced cancer and grows stronger with closer proximity to death. They recommend an integrated approach that addresses the emotional and physical distress in this patient population.

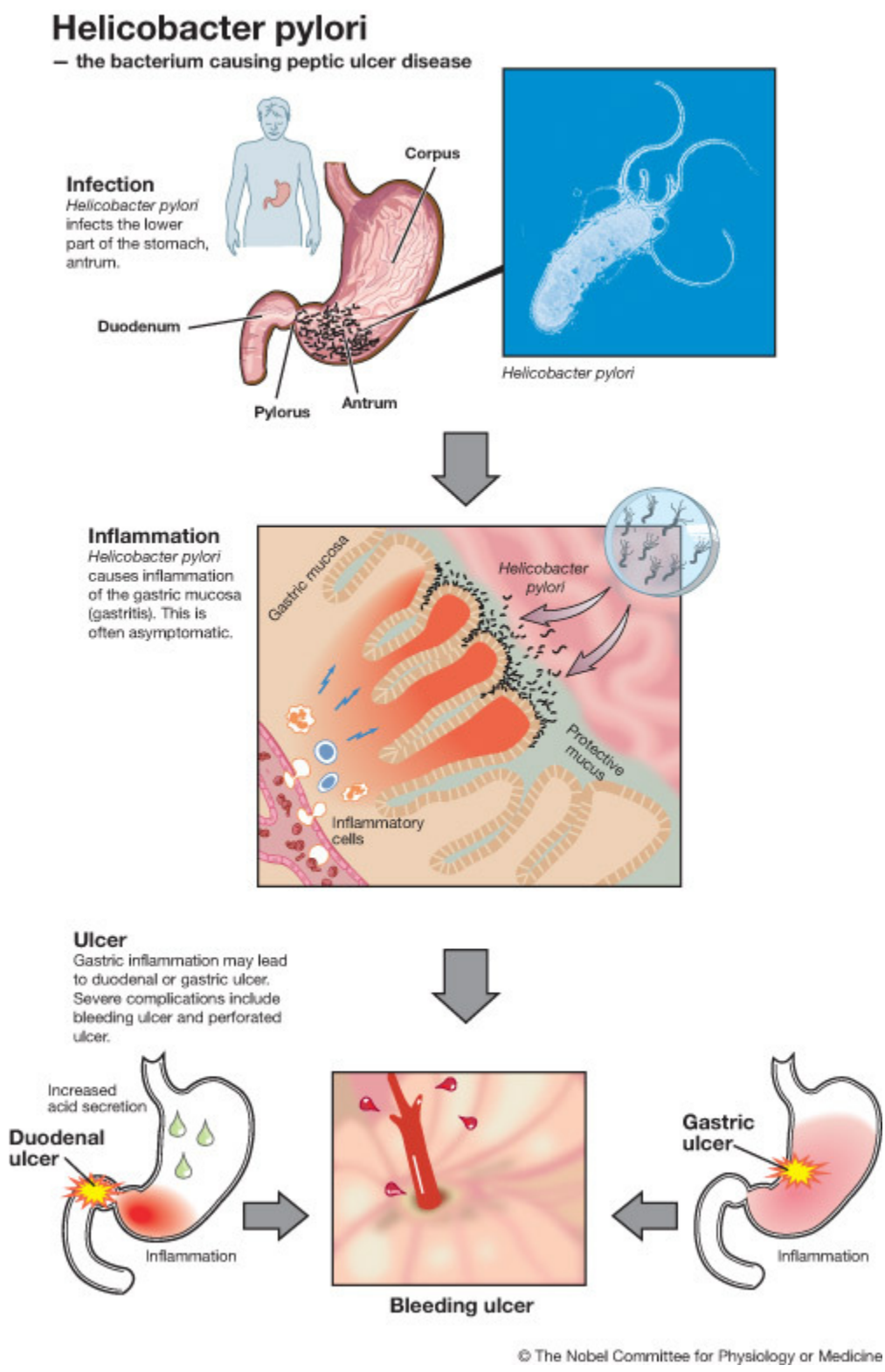
Lo, C, et al., Longitudinal study of depressive symptoms in patients with metastatic gastrointestinal and lung cancer. J of Clin Onc. Published early online: May 17, 2010

OTHER

39. Colorectal Cancer Risk Linked to Stomach Bacterium and Inflammation (Apr. 19/10)

A chronic stomach infection or high levels of inflammation may place a person at risk for colon cancer — or serve as an early warning sign of the disease — according to two studies. In the first study, researchers analyzed the medical records of 1,262 blacks over age 40 who had undergone a colonoscopy to check for polyps in the colon and also had an gastroscopy to assess stomach health. The endoscopies revealed that about one-third of the patients had a stomach infection of *Helicobacter pylori*, a common bacterium known to cause low-grade inflammation, ulcers and possibly even stomach cancer (see image below). The researchers found that 43% of patients in the study who harbored *H. pylori* also had colorectal polyps, compared with 34% of those not infected with *H. pylori*. Polyps can be precancerous and are routinely removed during colonoscopy. *H. pylori* infection increases the body's manufacture of a hormone called **gastrin**, which can have a pro-growth effect on cells that, if unchecked, could lead to cancerous growth. Researchers speculated that *H. pylori* infection may also trigger production of inflammation-causing cells that produce free radicals, unstable reactive oxygen species that can cause cancer-inducing mutations. Researchers recommended that the presence of *H. pylori* in the colon and specifically in polyps should be tested to clarify the microbe's role in colon cancer. In the other study, researchers compared blood levels of C-reactive protein (CRP) in 209 Chinese women who had colon cancer and 279 women without it who matched the cancer patients in other respects. CRP is a marker of inflammation in the body. When researchers ranked CRP levels for all the women, those with levels in the highest one-fourth were more than twice as likely to have colon cancer as were those with CRP levels that ranked in the lowest one-fourth. Even if CRP levels and cancer are associated, this study doesn't establish a cause-and-effect relationship, according to study author. In the study, women

with more advanced colon cancer had higher CRP levels which suggests that the cancer itself might be spurring this inflammatory protein. High CRP levels might therefore be a warning sign of early colon cancer in some people. Many common cancers arise in cells that line the insides of organs, such as the lung and colon. This is the barrier from the outside world, and these areas carry huge amounts of bacterial flora. These are sites in which the immune inflammatory response is going to try to control that flora — and there is always going to be collateral damage. If that damage includes changes to the cells' genes and disturbs their growth cycle, such cells can turn malignant.



Source: http://nobelprize.org/nobel_prizes/medicine/laureates/2005/press.html

Zahaf, M et al., *Helicobacter pylori* increases the risk of colorectal polyps in African Americans. Abstract #2713, American Association for Cancer Research 101st Annual Meeting, 2010.

Yang, M et al., Blood C-reactive protein levels and colon cancer risk. Abstract #2791, Amer Assoc for Cancer Research 101st Annual Meeting, 2010.

40. **Colitis-Associated Cancer Suppressed by Immune Sensors** (Apr. 19/10)

Particular components of inflammasomes -- protein complexes needed for generating immune responses to pathogens and cellular damage -- lessen the severity of colitis and colitis-associated colon cancer in mice, according to this study. Compared to healthy humans, patients with ulcerative colitis, a form of inflammatory bowel disease, have a higher risk of developing colorectal cancer. As the inflammasome is typically associated with activation of the immune system, researchers suspected that mice lacking inflammasome components would be more resistant to colitis and associated colorectal cancer. Unexpectedly, mice lacking some but not all inflammasome components developed more severe colitis

and larger tumor burdens in the colon. Additional work is needed to determine how specific inflammasome components protect against colitis in mice, and whether inflammasomes play similar roles in humans.

Allen, Irving C. et al., *The NLRP3 inflammasome functions as a negative regulator of tumorigenesis during colitis-associated cancer*. *J Exp Med*, April 12, 2010 DOI: [10.1084/jem.20100050](https://doi.org/10.1084/jem.20100050)

41. Lower Use of Diagnostic Testing Increases CRC Mortality in African Americans (Apr. 21/10)

The higher incidence and mortality from colorectal cancer among African Americans compared with Whites may be due to differences in health care utilization rather than differences in susceptibility to cancer, according to this study. Despite an overall decrease in colorectal cancer incidence and death in recent decades, disease rates in African Americans have remained high compared with Whites. Incidence rates of colorectal cancer are almost 20% higher among African Americans, and death rates are 50% higher. These racial disparities raise two major questions: Are African Americans genetically predisposed to greater risk for the disease? Or are differences in healthcare access and utilization of services responsible? To explore the possible causes of racial disparity in colorectal cancer incidence and mortality, researchers evaluated colorectal cancer screening outcomes and follow-up diagnostic testing among 57,561 White patients and 3,011 African-American patients. All patients underwent screening for colorectal cancer with flexible sigmoidoscopy (FSG).

- Among the patients who had abnormal results with FSG screening, more White patients than African-American patients (72% versus 63%) had a follow-up diagnostic colonoscopy within one year of the FSG screening.
- Rates of FSG-detected colorectal abnormalities did not differ significantly by race.

The researchers concluded that, given the disparities observed between Whites and African Americans in follow-up testing but not in rates of colorectal abnormalities, it appears that use of healthcare services—and not biological differences—may explain the higher rates of colorectal cancer incidence and mortality among African Americans. Further understanding and resolution of racial disparities in healthcare access and utilization are an important step in reducing disease rates; such measures can make way for effective, widespread screening and treatment of abnormalities.

Laiyemo AO, et al. *Race and Colorectal Cancer Disparities: Health-Care Utilization vs Different Cancer Susceptibilities*. *Journal of the National Cancer Institute* [early online publication]. March 31, 2010.

42. Older Stage III Colon Cancer Patients Should Be Treated According to Evidence-based Recommendations (Apr.21/10)

The treatment of Stage III colon cancer does not always follow evidence-based recommendations, especially for older patients, according to the results of this observational study. Stage III colon cancer refers to cancer that has spread through the wall of the colon to nearby lymph nodes but is not detected elsewhere in the body. Although patients with Stage III colon cancer may have their cancers completely removed by surgery, they benefit from the addition of chemotherapy and/or radiation (adjuvant therapy) to kill any remaining cells in the body that may go undetected. Randomized trials have clearly demonstrated that adjuvant chemotherapy improves survival in patients with Stage III colon cancer by approximately 30%. Several previous studies have shown that elderly patients benefit from adjuvant chemotherapy to the same degree as younger patients but are less likely to actually receive this therapy. Studies have consistently shown that age is not a predictor of relapse or overall survival in patients receiving adjuvant chemotherapy for Stage II-III colon cancer. Although elderly patients with colon cancer appear to benefit from adjuvant therapy, there is still concern about side effects and quality-of-life issues. Optimally treating patients with other health conditions is an additional challenge in the older population. These are the main reasons given for not administering adjuvant therapy to elderly patients with colon cancer. The current study evaluated data on 675 patients with Stage III colon cancer who had undergone surgery to remove their cancer. The study included patients throughout the United States in a variety of settings including hospitals, university medical centers, and private practice. Of the 675 patients, 202 were 75 years of age or older and 473 were under the age of 75.

- 50% of patients 75 years of age or older received adjuvant chemotherapy compared with 87% of younger patients.
- 14% of older patients received oxaliplatin in the adjuvant regimen compared with 44% of younger patients.
- Older patients received a shorter course of adjuvant chemotherapy than younger patients.
- Patients receiving adjuvant chemotherapy had more adverse events than non-treated patients.
- Late adverse events were lower in older patients than in younger patients, which may have been due to less intensive adjuvant therapy.

Researchers maintain that studies have shown that the treatment of Stage III colon cancer with adjuvant chemotherapy improves overall survival and recurrence rates. Treatment plans that follow evidence-based recommendations are crucial to improve outcomes in both the elderly and younger Stage III colon cancer population. Elderly patients with colon cancer eligible for adjuvant therapy should speak with their physician regarding their individual risks and benefits of adjuvant therapy.

43. **Early Circulating Tumour Cells May Predict Disease Free and Overall Survival in Advanced CRC Patients Treated with Chemo & Targeted Therapies** (May 18/10)

According to this study, circulating tumor cell levels measured before and during treatment predicted survival in patients with advanced colorectal cancer being treated with chemotherapy and targeted agents. **Circulating tumor cells** (CTCs) are cells that have detached from a primary tumor and circulate in the bloodstream. CTCs may constitute *seeds* for subsequent growth of additional tumors (metastasis) in different tissues. In the treatment of advanced colorectal cancer (ACC), there is a growing need for early predictive markers of response to therapy, including therapy using targeted agents, to avoid unnecessary treatment in patients unlikely to respond. KRAS mutation status is one marker used to predict response to inhibitors of epidermal growth factor receptor such as erbitux and vectibix, but markers with broader applicability would be useful. In this study, researchers evaluated the prognostic and predictive role of prediagnostic levels of circulating tumor cells (CTCs) in patients with ACC treated in the Dutch CAIRO2 trial. The study randomized 755 patients to receive first-line treatment with capecitabine, oxaliplatin, and bevacizumab, with or without weekly cetuximab. Low CTC count was defined as <3 CTCs/7.5 mL of blood, and high CTC count was ≥3 CTCs/7.5 mL. In total, 467 patients were assessable for CTC analysis, equally distributed between the two study arms. Median follow-up was 16.8 months. Median progression-free survival (PFS) was **2.4 months longer in patients with low vs high baseline CTC levels** (10.5 months vs 8.1 months, respectively). Median **overall survival (OS) was also longer in patients with low baseline CTCs** (22.0 months vs 13.7 months). Researchers concluded the correlation between low baseline CTC and significantly improved PFS and OS was observed in each treatment arm.

Tol, J et al., *Circulating tumour Cells early predict progression free and overall survival in advanced colorectal cancer patients treated with chemotherapy and targeted agents. Ann Oncol. 2010 May; Vol. 21, Issue 5: pp. 1006-1012*

NUTRITION & HEALTHY LIFESTYLE

44. **Low Levels of Vitamin B6 May Increase Risk of CRC** (Apr. 21/10)

Individuals with low blood levels of an active form of vitamin B6 or low dietary intake of vitamin B6 may have an increased risk of developing colorectal cancer according to the results of this study. Vitamin B6 is a water-soluble vitamin that performs a wide variety of functions in the body. Foods that contain vitamin B6 include fortified cereals, beans, meat, poultry, fish, and some fruits and vegetables. Pyridoxal 5'-phosphate (PLP) is the principal active form of vitamin B6 and can be measured in blood. Although few people have clinical signs of vitamin B deficiency, many older people have low blood levels of vitamin B6. Some previous studies have suggested that higher levels of vitamin B6 may reduce the risk of colorectal cancer. To further explore the relationship between vitamin B6 and risk of colorectal cancer, researchers conducted a combined analysis of nine previous studies of vitamin B6 intake and four previous studies of blood PLP levels.

- Overall, individuals with the highest intake of vitamin B6 were 10% less likely to develop colorectal cancer than individuals with the lowest intake of vitamin B6. This result was not statistically significant, however, suggesting that it could have occurred by chance alone. One study appeared to have an inordinate effect on these results, and when this study was excluded a statistically significant 20% reduction in risk was observed among individuals with the highest vitamin B6 intake.
- Higher blood PLP levels were also linked with a reduction in risk of colorectal cancer. Each 100-pmol/mL increase in blood PLP reduced the risk of colorectal cancer by 49%.

The results of this analysis suggest that higher blood PLP and higher dietary intake of vitamin B6 may reduce the risk of colorectal cancer.

Larsson SC, et al., *Vitamin B6 and risk of colorectal cancer: a meta-analysis of prospective studies. JAMA. 2010;303:1077-1083.*

45. **Omega 3s Can Protect Against Colon Cancer** (May 5/10)

The healthy fats known as omega-3s already have numerous benefits, from allergy control to stroke prevention. Now there's one more: colon cancer protection. There are two types, DHA and EPA. The DHA form made news all by itself recently when studies demonstrated its importance for brain and eyesight; it also has been shown to inhibit growth of cancerous colon cells. But now EPA is getting its due. Researchers have been studying people with an inherited condition that makes colorectal cancer almost a sure thing. Taking EPA daily for six months substantially reduced their precancerous colon polyps. Results like this have been found with the drug celecoxib, but that may cause heart problems when used for a long time. Omega-3s, on the other hand, protect the heart. If at high risk for colon cancer, check with the doctor about taking extra EPA. (In the study, people took 2 grams a day.) Keep in mind that certain drugs interact with EPA, and high doses cause bleeding in some people; again, talk to

the doctor. While it's easy to find both DHA and EPA in fish-oil supplements, that's not where we get our omega-3s. We get them from the same source fish do: algae (pills, in our case). Algae omega-3s are high in DHA, but some DHA converts to EPA (not vice versa).

<http://www.theprovince.com/health/taking+omega+Start/2997065/story.html>

46. **Coffees and Colas Do Not Increase Colon Cancer Risk** (May 7/10)

Coffee and tea are the most commonly consumed beverages worldwide, and consumption of sweetened soft drinks is increasing. Although polyphenols in coffee and tea have been thought to protect against colorectal cancer, all three beverages have been studied as potential risk factors. The association between the consumption of coffee, tea, and sweetened soft drinks and the risk of developing colorectal cancer was examined in this study of a pooled analysis of 13 prospective cohort studies conducted in North America and Europe. No statistically significant association was found between the risk of developing colorectal cancer and consumption of coffee or sweetened soft drinks, although a small positive association was found for higher tea consumption. The results were similar regardless of sex, smoking status, alcohol consumption, body mass index, physical activity, and tumor site. Drinking more than six 8-oz cups of coffee or 18 oz of sweetened soft drinks is not associated with a risk of colorectal cancer. The modest association with consumption of more than four 8-oz cups of non-herbal tea requires further study according to researchers. The association between colon cancer risk and coffee consumption was studied only in a European population, and thus, the lack of such an association cannot be generalized to other populations. Only 2% of the population consumed more than four 8-oz cups of tea or 18 oz of soft drinks, and thus, the study may be underpowered to draw conclusions for high consumption levels. Addition of milk and sugar to coffee and tea and consumption of different types of tea or diet soft drinks were not directly measured in the studies and may result in unmeasured confounding.

Zhand, X, et al., Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: pooled analysis of prospective cohort studies. J of the National Cancer Institute. 2010; DOI: 1093/jnci/djq107

47. **Barbecuing Promotes Production of Carcinogens** (May 18/10)

Barbecue is one of summer's greatest pastimes. Grilling is touted as a great way to cook food, but only if done properly. For if done improperly, it can become chock-full of **carcinogens – cancer causing agents**. Carcinogens are formed when meat is cooked quickly at high temperatures on a grill (gas or charcoal). But high heat isn't the only factor -- when fat drips off meat into the flame or heating element and smoke generates, this splatter effect can also cause carcinogens. And there is research linking carcinogens found in grilled meat and colorectal adenoma risk. Colorectal adenomas are benign tumors and the starting point of most colon cancers, as well as a marker for colon cancer risk. Studies have also linked carcinogens found in grilled meats to higher risk of breast cancer, stomach cancer, and pancreatic cancer. Adhering to these recommendations may decrease the carcinogen-forming compounds when barbecuing:

- Cook low and slow (lower temp, longer time).
- Put distance between heat and meat (raise the grill rack if you can).
- Trim the fat (fat burns).
- Cook meat partially before grilling.
- During grilling, flip meat frequently.
- Put foil on or under the grill to reduce splatter.

http://thestir.cafemom.com/healthy_living/103078/are_you_serving_carcinogens_with

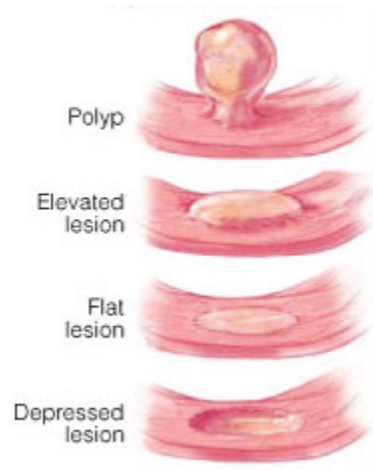
48. **Vitamin D Status Tied To Cancers** (May 19/10)

High vitamin D status appears to correlate to reduced risk of several cancers, **including colorectal cancer**, according to this study. Scientists from the European Institute of Oncology, Milan, performed a systematic review based on a meta-analysis of observational studies of serum 25-hydroxyvitamin D level and colorectal, breast and prostate cancer, and colonic adenoma. The team searched the scientific literature through December 2009 considering research reports written in any language. In the end, 35 independent studies were identified. The researchers noted a 10 ng/mL increase in serum 25-hydroxyvitamin D for colorectal cancer (2630 cases in 9 studies); for breast cancer (6175 cases in 10 studies); and for prostate cancer (3956 cases in 11 studies). Differences between cases and controls in the season of blood draw or in overweight/obesity or physical inactivity could not explain the results on colorectal and breast cancer. They concluded there was a consistent inverse relationship between serum 25-hydroxyvitamin D levels and colorectal cancer; however, no association was found for breast and prostate cancer.

<http://www.naturalproductsinsider.com/news/2010/05/vitamin-d-status-tied-to-cancers.aspx>

49. **Smoking Linked to Flat Adenomas** (Jun.21/10)

According to the results of this study, since smoking is associated with flat adenomas, smokers may require screening with high-definition colonoscopes to detect flat adenomas. Little is known regarding the risk factors for these flat lesions, which may account for over one-half of all adenomas detected with a high-definition colonoscope. The aim of this study was to investigate smoking as a risk factor for flat adenomas (see image below) in an average risk population undergoing screening colonoscopy. At a university hospital endoscopy center, 600 asymptomatic patients presenting for colorectal cancer (CRC) screening were screened with a high-definition (1080i signal) wide-angle (170° field of view) colonoscope. Participants also provided information regarding demographic factors, diabetes and other medical conditions, medications, family history of CRC, diet, and smoking history. The primary endpoint was polyp structure. After performing the analysis, smoking (heavy smokers vs nonsmokers) was associated with flat adenoma of any size, with flat adenoma 6 mm in diameter or greater, and with flat advanced adenomas. "Smoking was associated with flat adenomas in our population," the study authors write. "Our findings may explain the earlier onset of CRC in smokers as well as the advanced stage with which they present, when compared with nonsmokers. Smokers may require screening with high-definition colonoscopes to detect flat adenomas."



Flat lesions are more difficult to locate and more likely to be cancerous than the more familiar polyps with a knobby appearance

Source: <http://www.tabletprep.com/colon-cancer/index.aspx>

Anderson, Joseph, et al., *Association of smoking and flat adenomas: results from an asymptomatic population screened with a high-definition colonoscope. Gastrointest Endosc. 2010;71:1234-1240, 1241-1243.*

50. Pickled Meat Raises Colorectal Cancer Risk (Jun. 22/10)

Eating a lot of pickled red meat consumption has been linked with an increased risk of colorectal cancer in residents of Newfoundland and Labrador, according to this new study. The study assessed the association between the intakes of total red meat and pickled red meat and the risk of colorectal cancer in 1,204 residents of Newfoundland and Labrador. In Newfoundland and Labrador, pickled meat can be either homemade or purchased from farmer's market or supermarkets. While little has been written about the distinct dietary characteristics of Newfoundlanders and Labradorians, given the frequency and quantity of pickled meat consumption, Newfoundland and Labrador is probably matched by no other population in the world. Two common pickled meats in the provincial diet are trimmed naval beef and cured pork riblets. These meats include sodium nitrite as one of the preserving agents and it has been suggested that nitrite/nitrate compounds can be converted to carcinogenic compounds. It is generally believed that dietary habits are a major contributor to colorectal cancer and are at least responsible for 30% of colorectal cancer cases. However, little is known about how the effects of red meat intake on colorectal cancer vary across populations and the association between pickled meat and colorectal cancer has not been adequately examined. Researchers concluded that their study shows a positive association between the consumption of pickled meat and colorectal cancer and demonstrates that the level of consumption of pickled meat has a significant effect.

Wang, Peter, et al., *Pickled Meat consumption and colorectal cancer (CRC): a case control study in Newfoundland and Labrador, Canada. Cancer Causes Control; 2010 May 27. [Epub ahead of print]*

51. Healthy Diet May Cut Colorectal Cancer Risk (Jun.23/10)

Eating a diet rich in fruits and vegetables, low-fat dairy foods, and fish may reduce the risk of colorectal cancer, according to this new study. Although previous studies have produced conflicting findings about the effectiveness of such a diet, the new research found a benefit. Researchers found that eating a largely plant-based diet with higher intakes of fruits, vegetables, whole grains, nuts, seeds, vegetable oils, and low-fat dairy in women and fish in men was associated with a reduced risk of colorectal cancer. Eating in this healthful way reduced the risk of colon cancer by 65% in women and by 62% in men. Why fish was a part of the protective dietary pattern only in men and low-fat dairy only in women is not known at this time. Researchers evaluated the diets of 431 men and women with colorectal cancer and the diets of 726 healthy men and women who didn't have colon cancer. They categorized the participants

into a fruits-and-vegetables diet pattern and a meat-potatoes-refined grains pattern. In men, a third pattern -- a diet rich in alcohol and sweetened beverages -- was found. They also looked at how well participants followed the 2005 Dietary Guidelines for Americans and the MyPyramid recommendations, which suggest a diet rich in fruits, vegetables, and whole grains. In addition to finding the reduced risk of colorectal cancer for people eating the diet heavy in fruits and vegetables -- 62% reduced risk for men and 65% for women -- they found that the more closely men and women adhered to the Dietary Guidelines, the lower the cancer risk. Men and women with higher adherence to the guidelines had a lower risk of colorectal cancer, reducing it by 44% (men) and 56% (women). Researchers concluded that rather than focusing on a single food, nutrient, or other dietary component, focus on eating an overall plant-based diet that emphasizes fruits, vegetables, whole grains, nuts, seeds, and vegetable oil. The diet pattern associated with higher cancer risk in the study included greater intakes of red and processed meat, poultry, fried and white potatoes, high-fat dairy, sweets, salty snacks, butter, mayonnaise, gravy, pizza, and refined grains.

Miller, Paige, et al., Diet Index-Based and Empirically Derived Dietary Patterns Are Associated with Colorectal Cancer Risk. Journal of Nutrition, July 2010; vol 140: pp 1267-1273.