COLORECTAL CANCER ASSOCIATION OF CANADA

COLORECTAL CANCER RESEARCH
Month Ending April 17, 2009

The following colorectal cancer research update extends from March 13 – April 17, 2009 inclusive and is intended for informational purposes only.

ENCOURAGING

Statistics Canada's Cancer Snapshot Tallies Cases (Mar. 18/09)

More Canadians are surviving cancer thanks to better detection and improved survival for breast, prostate and **colorectal cancers**, according to Statistics Canada. The agency's snapshot looked at cancer prevalence – how many people had had the disease in the decade prior to Jan. 1, 2005. The report claims that more Canadians are living with cancer than ever before and attributes the higher rates to cancer being detected more frequently in patients and improving survival rates. The study was the first of its kind in Canada and addressed a gap that needed to be filled.

www.cbc.ca/health/story/2009/03/18/cancer-prevalance.html

DRUGS

1. **Aspirin Helps Prevent Colorectal Adenomas** (Mar. 11/09)

Daily use of aspirin may reduce the risk of colorectal adenomas, especially advanced lesions, according to the results of a study published in the *Journal of the National Cancer* Institute. Individuals who have adenomas are at an increased risk of developing future adenomas and also colon cancer. As a result, these individuals are encouraged to undergo more stringent screening, such as colonoscopy, during which adenomas are removed to prevent the possibility that they may progress to cancer. In addition, researchers continue to evaluate the role of diet and other preventive factors that may help decrease the incidence of adenomas and colon cancer. Researchers performed a meta-analysis* on the data from all randomized, double-blind, placebo-controlled trials that have evaluated the use of aspirin for the prevention of colorectal adenomas. The data included four clinical trials with a total of 2,967 participants; these participants received 81-325 mg of aspirin per day. Among 2,698 participants who underwent colonoscopic follow-up after randomization, adenomas were found in 37% of those allocated to placebo and in **33%** of those allocated to any dose of aspirin (advanced lesions were found in 12% and **9%,** respectively). The researchers concluded that aspirin is effective for the prevention of colorectal adenomas in individuals with a history of these lesions.

*NB: A ***meta-analysis*** is a statistical procedure in which there is data gathered from two or more previous, related studies and then pooled together so as to produce a larger sample size from which to draw conclusions.

Cole BF, et al. Aspirin for the chemoprevention of colorectal adenomas: Meta-analysis of the randomized trials. Journal of the National Cancer Institute. 2009; 101:256-266.

2. **Vaccine to Prevent Colon Cancer Tested** (Mar. 20/09)

U.S. researchers are testing a vaccine to prevent colon cancer in those already at high risk for the disease. Unlike other anti-cancer vaccines that block viruses, this vaccine has been directed against a variant of a cell protein -- called MUC1. Colon cancer typically starts with an abnormal growth in the intestinal lining -- a polyp. Polyps that become cancerous are called adenomas. Adenomas produce MUC1 in excess. "By stimulating an immune response against the MUC1 protein in these precancerous growths, we may be able to draw the immune system's fire to attack and destroy the abnormal cells," principal investigator Dr. Robert Schoen of the University Of Pittsburgh School Of Medicine said in a statement. "That might not only prevent progression to cancer, but even polyp recurrence." A dozen people have received the experimental vaccine so far, and the researchers intend to enroll another 50 participants between 40 and 70 years old with a history of adenomas sized 1centimeter or more. After an initial dose of vaccine, the study participants get doses two and 10 weeks later. Blood samples at those time points as well as 12 weeks, 28 weeks and one year later will measure immune response.

www.cancercompass.com/cancer-news/1,15482,00.htm

3. Micromet Has Started A New Phase II Trial With Adecatumumab In Colorectal Cancer Patients (Mar. 23/09)

Micromet, Inc., a biopharmaceutical company developing novel, proprietary antibodies for the treatment of cancer, inflammation and autoimmune diseases, has announced the commencement of a randomized, controlled phase 2 trial of its human anti-EpCAM IgG1 antibody adecatumumab (MT201) for the treatment of patients with colorectal cancer (CRC) after complete resection of liver metastases. The trial has three arms comparing (i) single agent adecatumumab to (ii) combination chemotherapy (FOLFOX: 5-FU/Leucovorin plus Oxaliplatin), and to (iii) FOLFOX followed by adecatumumab. The primary endpoint will be the disease-free survival rate at one year. Apart from being the most highly and frequently expressed target antigen on colorectal cancer cells, **EpCAM** has recently been shown to drive tumor growth and to be expressed on colorectal cancer stem cells. The ability of adecatumumab to potentially control and eliminate newly developing metastases has been suggested in a recently reported Phase 2 trial of adecatumumab as monotherapy in metastatic breast cancer. In this trial, patients with high levels of EpCAM expression developed significantly fewer new lesions as compared to patients with low levels of EpCAM. Numerous published clinical and preclinical data suggest that therapies targeting EpCAM such as adecatumumab could prove to be highly effective anti-cancer therapeutics. The promise of adecatumumab to eliminate minimal residual disease in colorectal cancer patients and thereby to potentially improve cure rates in these patients at high risk of relapse will be explored.

www.cancercompass.com/cancer-news/1,15490,00.htm

4. Adjuvant Therapy of Hepatic Arterial Infusion (HAI) with Floxuridine and Dexamethasone Plus Systemic Folfox in Resected Liver Patients (Mar. 2409)

The purpose of this study was to determine the maximum tolerated dose of systemic folfox that could be administered with hepatic arterial infusion (HAI) of floxuridine (FUDR) and dexamethasone in the adjuvant setting after hepatic resection. Thirty-five patients with resected liver metastases were entered into a phase I trial using HAI/FUDR/Dex with escalating doses of Folfox. Systemic chemotherapy was delivered on days 15 and 29 with the doses of oxaliplatin escalated from 85 to 100 mg/m^2 and the 5-FU 48-h continuous infusion doses from 1000 to 2000 mg/m^2. The Leucovorin dose was fixed at 400 mg/m^2. Dose-limiting toxic effects were diarrhea, 8.5%, and elevated bilirubin, 8.5%. With a median follow-up of 43 months, the 4-year survival and progression-free survival were 88% and 50%, respectively. Adjuvant therapy after liver resection with HAI FUDR/Dex plus systemic folfox at 85 mg/m^2 and 5-FU by continuous infusion at 2000 g/m^2 with LV at 400 mg/m^2 is feasible and appears effective. Researchers concluded that randomized studies comparing this particular regimen to systemic FOLFOX are suggested.

Kemeny, N, et al., Phase I Trial of adjuvant hepatic arterial infusion (HAI) with floxuridine (FUDR) and dexamethasone plus systemic oxaliplatin, 5FU and leucovorin in patients with resected liver mets from colorectal cancer. Annals of Oncology. Advance Access. Published online Feb. 20/09. doi: 10.1093/annonc/mdn769.

5. The Role of UFT in Metastatic Colorectal Cancer (Mar. 25/09)

5-Fluorouracil (5-FU) has been the most widely used chemotherapeutic agent for metastatic colorectal cancer (mCRC) and 5-FU combination therapy improves efficacy compared with monotherapy. The oral fluoropyrimidine **UFT (tegafur-uracil)** with leucovorin (LV) improves tolerability and has replaced 5-FU in many regimens. The efficacy and tolerability of UFT with LV in the first-line treatment of mCRC has been demonstrated in a number of phase II studies. In two phase III studies, UFT with Leucovorin has been shown to have comparable efficacy and improved tolerability versus intravenous bolus 5-FU, with very few cases of hand-foot syndrome (HFS) that is often seen with Xeloda therapy (capecitabine). Indirect comparisons of UFT and capecitabine suggest that they are comparable in terms of survival. In first-line treatment, UFT in combination with oxaliplatin (TEGAFOX) or irinotecan (TEGAFIRI) is effective and well tolerated, with similar efficacy and tolerability to the corresponding 5-FU- and capecitabine-based combinations, but with a lower incidence of Hand and Foot Syndrome. Alternating cycles of TEGAFOX and TEGAFIRI are effective and well tolerated, and the combination of TEGAFIRI and the targeted monoclonal antibody cetuximab (erbitux) has shown promising activity, similar to that of FOLFIRI plus cetuximab. After reviewing the role of Tegafur/Uracil in metastatic colorectal cancer, researchers concluded that UFT can be considered a reasonable replacement for intravenous 5-FU in the first- and second-line treatment of patients with mCRC.

Bennouna Jaafar, et al., The Role of UFT in Metastatic Colorectal Cancer. Oncology. Vol. 76, No. 5, 2009. pp 301-310.

6. Avastin Protects Patients with Liver Mets from Liver Damage (April 3/09)

Avastin (bevacizumab) protected patients with liver mets from one type of liver damage from chemotherapy before surgery to remove liver tumors. However, it had no effect on response rate to chemo with folfox or Xelox. Avastin reduced the severity of sinusoidal obstruction syndrome, a condition where veins in the liver become blocked. It had no effect on two other kinds of liver damage that are sometimes associated with chemotherapy before liver surgery: hepatic steatosis where fat builds up in liver cells and fibrosis, an accumulation of scar tissue.

Klinger, M, et al., Bevacizumab protects against sinusoidal obstruction syndrome and does not increase response rate in neoadjuvant Xelox/Folfox therapy of colorectal cancer liver metastases. European J of Surgical Oncology. Vol 35, Issue 5, May 2009, pp 515-520.

7. Comparing Folfox to 5FU/Leucovorin in Treating Advanced Colorectal Cancer (Apr. 8/09)

In a meta-analysis to evaluate the efficacy and safety of fluorouracil (FU)/leucovorin (LV)/oxaliplatin, (folfox) compared to FU/LV in treating advanced colorectal cancer, it was shown that folfox offers better efficacy (by way of response rate and progression free survival) than FU/LV in treatment of advanced colorectal cancer. Incidence of grade ¾ toxicities such as neutropenia (low white blood cell counts), thrombocytopenia (low platelet counts), vomiting, neurological toxicity, is significantly higher in the folfox group than in the FU/LV group but these are manageable or reversible.

Chen, Mian Ling, et al., A meta-analysis of chemotherapy regimen Fluorouracil/Leucovorin/Oxaliplatin Compared with Fluorouracil/Leucovorin in treating advanced colorectal cancer. Surgical Oncology. Published Ahead of Print. Doi: 10.1016/j.suronc.2009.02.015

8. Erbitux Plus Folfiri Reduces Time to Recurrence as First-Line Therapy in mCRC (Apr. 9/09)

The addition of Erbitux® (cetuximab) to FOLFIRI chemotherapy reduces the risk of disease progression in patients with metastatic colorectal cancer, according to the results of a study published in the *New England Journal of Medicine*. Epidermal growth factor receptor (EGFR), a protein commonly found in colorectal cancer, is associated with a poor prognosis. Erbitux is a type of therapy known as a monoclonal antibody, which specifically targets the EGFR receptor site and causes cell death. By targeting EGFR, the spread of cancer can be reduced or delayed. Researchers affiliated with the CRYSTAL trial evaluated the efficacy of Erbitux plus FOLFIRI as first-line treatment for metastatic colorectal cancer. The study included 599 patients who were treated with Erbitux plus FOLFIRI and 599 patients who were treated with FOLFIRI alone. The results indicated that Erbitux was associated with a **15%** reduction in the risk of progression, which was statistically significant. Progression-free survival was 8.9 months for the Erbitux group and 8.0 months for the control group. The complete and partial response rate was **47%** for the Erbitux group and 39% for the control group, which was also statistically significant. The difference in overall survival between the two groups was not statistically significant: 20 months for the Erbitux group and 19 months for the control group. The researchers concluded that the addition of Erbitux to FOLFIRI as first-line treatment reduced the risk of progression of metastatic colorectal cancer; and researchers noted that the benefit was limited to patients with wild-type KRAS status (no mutation in the Kras gene).

Van Cutsem , et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. New England Journal of Medicine. 2009; 360: 1408-1417.

SURGICAL

9. Surgical vs. Non-surgical Management of Primary Tumour in Patients with Incurable Disease (Mar. 16/09)

This study reviewed and compared the outcomes of patients with incurable bowel cancer managed by resection and non-resection strategies over a 7-year period. 154 patients had surgically incurable bowel cancer. Survival was compared between patients managed by resection of primary, non-resectional intervention and those managed with supportive care only. The median survival of each group was as follows: resected patients 11 months, non-resectional intervention 7 months and supportive care alone 2 months. The overall operative mortality for the resection group was 16%. Researchers concluded that in an unselected bowel

cancer population surgical resection of the primary tumour in patients presenting with incurable disease does not improve survival and is associated with a high risk of post-operative mortality.

Evans MD., et al., Outcomes of resection and non-resection strategies in management of patients with advanced colorectal cancer. World J of Surgical Oncology. 2009; 2:28. doi:10.1186/1477-7819-7-28

10. Laparoscopic Monitored Colonoscopic Polypectomy: Long-Term Follow-up (Mar. 16/09)

Colonoscopy is widely used to remove benign polyps. However, a variety of "difficult polyps" are not accessible for colonoscopic removal because of their size, broad base, or difficult location (impossible to see the polyp's base, polyps behind mucosal folds or in tortuous colonic segments). The aim of this study was to evaluate the long-term follow-up and oncologic safety of laparoscopically monitored colonoscopic polypectomy **(LMCP)**. From May 1990 to January 2008, all the patients undergoing LMCP were analyzed and then followed up with colonoscopic studies at 6 months, 1 year, and every year thereafter. A total of 209 polyps were removed in 160 patients: 82 men (51%) and 78 women (49%). During a mean follow-up of 63.37 months and median follow-up of 65 months, there has been no recurrence. Long-term follow-up demonstrated that a combined endoscopic-laparoscopic approach is safe and effective. Malignant lesions identified during LMCP can be treated laparoscopically during the same operation, avoiding the need of a second procedure, with good long-term oncologic outcome.

Franklin, Morris, et al., Laparoscopic Monitored Colonoscopic Polypectomy: Long-Term Follow-Up. World J of Surgery. On-line Edition March 12, 2009. Doi: 10.1007/s00268-009-9967-8

RADIATION / INTERVENTIONAL RADIOLOGY

11. Therasphere Therapy Shows Promise in Treatment of Liver Mets (Mar.18/09)

Among patients with colorectal cancer that has spread to the liver, treatment of the liver with Therasphere® (yttrium-90 glass microspheres) appears to provide stability of disease. These results were published in the journal *Cancer*. When colorectal cancer metastasizes (spreads to other parts of the body), it often spreads to the liver. In some cases, these liver metastases can be surgically removed. In other cases, however, surgery is not an option and other approaches to treatment are required. Liver-directed therapies that may be considered include conformal radiation therapy, radiofrequency ablation, transarterial chemoembolization, and radioembolization with Therasphere. Therasphere delivers radiation directly to the area of the liver that contains the cancer. Microscopic glass beads that contain a radioactive material are delivered through a catheter into the hepatic artery. The beads become trapped in the blood vessels that feed the tumor and deliver radiation to the tumor. To explore the safety and efficacy of Therasphere among patients with colorectal cancer that has spread to the liver, researchers conducted a study among 72 patients with liver metastases that could not be surgically removed. In 60% of the patients, the liver was the only site of metastasis. Study participants each received an average of two Therasphere treatments.

- Side effects of treatment included fatigue (61%), nausea (21%), and abdominal pain (25%).
- 40% of patients experienced a reduction in the extent of cancer within the liver.
- Cancer progression in the liver occurred a median of 15.4 months after first treatment.

Therasphere may eventually expand the treatment options available to patients with liver metastases. The researchers note that further research is warranted, including studies that test Therasphere in combination with systemic therapy.

Mulcahy MF, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. Cancer [early online publication]. March 6, 2009.

12. Stereotactic Radiation Therapy (SRT) for Liver Mets (Mar.30/09)

Stereotactic radiation is a specialized type of external beam radiation therapy that used focused radiation beams to target a well-defined tumor. With stereotactic treatments, radiation oncologists use detailed imaging, computerized three dimensional treatment planning and precise treatment set-up to deliver the radiation dose with extreme accuracy. Stereotactic radiotherapy (SRT) delivers high doses of radiation to a carefully targeted area of the body. Its goal is to destroy cancer cells while leaving healthy tissue unharmed. Radiation oncologists at Princess Margaret Hospital at the University of Toronto used SRT to treat 68 patients with cancer that had spread to their liver, 40 of whom had colorectal cancer. Patients, who were **not eligible for surgery or additional chemotherapy,** had six radiotherapy treatments over two weeks. No patients in the trial developed radiation-induced liver disease. Some patients experienced pain, changes in liver enzymes, nausea, and fatigue, but overall serious side effects were limited. About half of the patients (49%) had tumors shrink (respond) after treatment including 4 complete and 29 partial responses. 56 patients did have their cancer recur — 8 in the tumor treated with SRT, 22 in other parts of their liver, and 34 in areas of the body outside the liver. Median survival time for all patients was 17.6 months, and median time before cancer got worse (*progressed)* was 3.6 months. 63% of colorectal cancer patients lived at least a year after treatment. Mark Lee and his colleagues at the University of Toronto concluded: Individualized six-fraction liver metastases SRT is safe, with sustained local control observed in the majority of patients.

***Lee et al.*, Phase I Study of Individualized Stereotactic Body Radiotherapy of Liver Metastases. *Journal of Clinical Oncology,* Volume 20, Number 10, April 1, 2009.**

SCREENING

13. Updates in Colorectal Cancer Screening Guidelines from the American College of Gastroenterology (Mar. 18/09)

The American College of Gastroenterology has updated the colorectal cancer screening recommendations which have not been updated since 2000. The guidelines recommend that colonoscopy, beginning at age 50 and performed every 10 years, is the "preferred" screening test for colorectal cancer. They recommend that physicians first offer this test alone rather than a menu of options. However, if patients are not willing to have a colonoscopy, they support offering:

- Preferably. a **cancer prevention test**: Either flexible Sigmoidoscopy every 5 to 10 years or CT colonography every 5 years.
- A test primarily for **cancer detection**: Preferred test is fecal immunohistochemical test for blood (FIT).

They further recommend that African Americans begin testing at 45 rather than 50. Changes from the 2000 Guidelines include the following:

- Screening tests are divided into cancer prevention and cancer detection tests (ie colonoscopy and Sigmoidoscopy vs. FIT). Cancer **prevention** tests are preferred over tests that primarily detect colorectal cancer.
- Screening is recommended for African Americans beginning at age **45.**
- CT colonography every 5 years replaces double contrast barium enema as the radiology screening alternative when patients decline colonoscopy.
- **FIT** (fecal immunohistochemical testing) replaces older guaiac-based fecal occult blood testing (FOBT). FIT is the preferred cancer detection test.
- Annual Hemoccult SENSA and fecal DNA testing every three years are alternative cancer detection tests.
- A family history of only small tubular adenomas in first-degree relatives (parents, children, siblings) is not considered to increase the risk of colorectal cancer.
- Individuals with a single first-degree relative with colorectal cancer or advanced adenomas diagnosed at age **60 or older** can be screened like average risk people, whereby screening with colonoscopy can start at **age 50** and every **10 years** thereafter. If diagnosed at age **< 60,** screening can commence at **age 40** and every **5 years** thereafter.

The Guidelines also include guidelines for screening patients with a family history of colorectal cancer, familial adenomatous polyposis (FAP), and hereditary non-polyposis colon cancer (HNPCC).

OTHERS

14. Effective Prep is Certain to Clean Right Side of Colon for Colonoscopy (Mar.14/09)

Researchers have found an effective preparation to be certain to clean the right side of the colon in preparation for colonoscopy. **Pico-Salax** plus **Ducolax** (bisacodyl) tablets on both days before colonoscopy cleaned the right side of the colon more completely than either Pico-Salax alone or Fleet Phospho-Soda (oral sodium phosphate). All patients were encouraged to drink 3 to 4 liters of Gatorade or clear liquids. Patients tolerated both of the Pico-Salax regimens better than the oral sodium phosphate and monitoring during the exams found them safer than oral sodium phosphate. Pico-Salax combines a packet containing sodium Pico sulfate, magnesium oxide, and citric acid to form a magnesium citrate purgative. Pico-Salax is available in Canada and Europe, but not in the United States. Oral sodium phosphate is only available by prescription in the US.

Hookey, Lawrence, et al., Pico-Salax Plus Two-Day Bisacodyl is superior to pico-salax alone or oral sodium phosphate for colon cleansing before colonoscopy. The American J of Gastroenterology. March 2009, 104: 703-709.

15. Mutation in PIK3CA Gene Found in Tumor Leads to Poor Outcome (Mar. 19/09)

Stage I through III colon cancer patients whose colorectal tumors had a mutation in the PIK3CA gene, were more likely to die of colon cancer than patients with normal or *wild-type* PIK3CA. About 1 in 5 patients had that mutation in tumor tissue. Patients with a PIK3CA mutation were more than twice as likely to die from colon cancer. This was especially true in KRAS wild-type tumors (no mutation in that gene) where a PIK3CA mutation increased risk of death almost four times. However, in KRAS mutated tumors, the presence of PIK3CA made little difference in cancer-specific survival. Five years after surgery, 9 out of 10 patients whose tumors didn't have PIK3CA mutations had not died of colon cancer compared to a little more than 8 out of 10 (84%) with mutated PIK3CA.

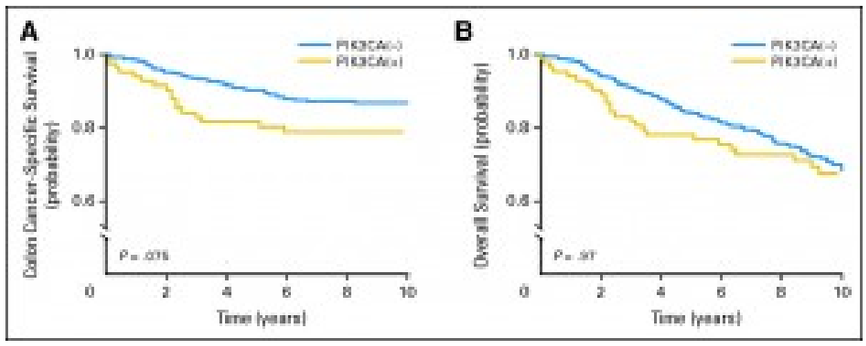

Image from Journal of Clinical Oncology, v. 27, No 9 (March 20), pp 1477-1484

Yellow Line Represents the Mutated PIK3CA

PIK3CA mutations activate a pathway in cancer cells that leads to cell division, cell survival, invasion of other tissues, and the development of new blood vessels. Studies in colon cancer cells have found drugs that block PIK3 also have anti-tumor activity. Shugi Ogino and colleagues at Dana Farber Cancer Institute in Boston concluded, "Among patients who undergo a curative resection of colon cancer, *PIK3CA* mutation is associated with shorter cancer-specific survival. The adverse effect of *PIK3CA* mutation may be potentially limited to patients with *KRAS* wild-type tumors."

Ogino, Shugi, et al., PIK3CA Mutation is associated with poor prognosis among patients with curatively resected colon cancer. J of Clinical Oncology. Vol 27, No9 (March 20), 2009: pp 1477-1484.

16. Study Finds that Blood Transfusions Make Cancer Spread Faster in Mice (Mar. 20/09)

Researchers at Denver Hospital are maintaining that blood transfusions can make cancer spread faster. According to the study, cancerous tumours grew 4 times as fast in mice that

received blood transfusions compared with mice that received a manufactured substitute for red blood cells. The mice used in the research had pancreatic cancer, one of the most aggressive types. But lead investigator Barnett said the findings could affect treatment for all kinds of cancer. Even though doctors have suspected for years that blood transfusions aren't ideal for cancer patients, as many as 80% of people who have surgery to treat pancreatic cancer receive blood transfusions, according to researchers. Doctors have known since the 1970s that receiving a blood transfusion can weaken a person's immunity. Donated blood can be stored for up to 42 days before it's pumped into someone's body, and as it sits, cells break down, Barnett said. It's unclear exactly why donated blood makes tumors grow faster, but researchers suspect it has to do with a weakening of the immune system after a transfusion. The research gives a boost to polymerized hemoglobin, a blood substitute marketed under the name PolyHeme. PolyHeme, developed by a lab in Evanston, is a solution of chemically modified human blood that is compatible with all blood types and has a shelf life of about one year. The hope is this will turn out to be safer and then this could be given instead of blood," Barnett said. Further research is necessary before recommending a switch to PolyHeme, he said. Barnett is continuing to investigate why certain blood types and blood donated by man, seem to make tumors grow faster.

www.cancercompass.com/cancer-news/1,15484,00.htm

17. Colorectal Cancer Risk Increased with Endometrial Cancer (Mar. 25/09)

These study results concluded that endometrial cancer is associated with an elevated risk of colorectal cancer, but not breast cancer. In the study, the incidence rate of colorectal cancer in women with endometrial cancer was 0.7% - low but significantly higher than the 0.2% rate seen in the general population, according to lead investigator from the University of British Columbia. The results also indicate that screening rates for colorectal cancer, as well as breast cancer, were roughly twice as high in women with endometrial cancer than in other women. Although colorectal cancer was more likely to develop in study patients than in the general population, breast cancer was not. Screening rates for breast and colorectal cancer in the study group were 64% and 30%, respectively, compared with rates of 31% and 15% in the general population.

Kwon, Janice, et al., Secondary Cancer Prevention During Follow-Up for Endometrial Cancer. Obstetrics & Gynecology. April 2009. Vol 113; Issue 4: pp.790-795.

18. Loss of Tumour Mismatch Repair (MMR) Function is Predictive of Improved Outcome with Adjuvant Folfiri (Apr. 13/09)

Mismatch repair refers to the system within the cell for correcting errors in DNA that works by detecting and replacing bases in the DNA 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 called DNA polymerase. Tumours are classified as either MMR **deficient** (loss of tumour mismatch repair function) or MMR **competent** (possessing tumour mismatch repair function). Some past studies have shown a lack of benefit of 5FU adjuvant (post surgical) chemo in patients with mismatch repair deficient colorectal cancer. Instead, only mismatch repair competent tumours displayed a benefit to 5FU adjuvant chemo.

This study provides evidence that loss of tumour mismatch repair (MMR) function **(deficient)** may predict improved outcome in stage III patients treated with the folfiri (fluorouracil, leucovorin, and irinotecan) regimen as compared with those receiving fluorouracil and leucovorin only. Stage III patients were randomly assigned to receive either postoperative weekly FU/LV or weekly Folfiri. Overall survival was the end point to be measured. Patients whose tumours were MMR-**deficient** and treated with **folfiri** showed improved 5-year overall survival vs. those patients with mismatch repair intact tumours (competent). This relationship was **NOT** observed among patients treated with the FU/LV regimen. Instead, longer disease free survival was observed in the folfiri group with MMR-deficient tumours vs. those receiving FU/LV. Researchers concluded that loss of tumour MMR function (deficient) may predict improved outcome in patients treated with the folfiri regimen as compared with those receiving FU/LV.

Bertagnolli, Monica, et al., Microsatellite Instability Predicts Improved Response to adjuvant Therapy with Irinotecan, Fluorouracil, and Leucovorin in Stage III Colon Cancer: Cancer and Leukemia Group B Protocol 89803. J of Clinical Oncology. Vol 27, No 11 (April 10), 2009: pp 1814-1821.

NUTRITION

19. Evidence Shows that DHA Suppresses Colon tumor Cell Growth (Mar. 14/09)

The role of n-3 and n-6 PUFAs (polyunsaturated fatty acids) in colorectal cancer cell growth has not been well studied. It is known that PGE2 (Prostaglandin E2) generated from AA (Arachidonic Acid), is an important factor in the tumorigenesis of colorectal cancer. However, previous in vitro observations have led to uncertainty regarding a differential role of omega-3 and omega-6 PUFAs for growth of tumor cells, as some findings are contradictory, and most studies have not addressed the effect of a changed n-3/n-6 PUFA ratio on cell growth. A research article published on March 7, 2009 in the *World Journal of Gastroenterology* addresses this problem. This study demonstrated that the n-3 PUFA DHA (Docosahexaenoic Acid) can directly suppress AA- as well as PGE2-induced colon cancer cell growth. These results add evidence to the argument that the ratio of n-6/n-3 PUFA (and in particular the ratio of AA versus DHA) may be a critical determinant of proliferation and tumor growth in the colon, and that DHA supplementation can suppress tumor cell growth, even in the presence of high AA- and PGE2 levels. These results suggest that supplementation of DHA may be a powerful tool to counteract AA- and PGE2-promoted colon cancer cell growth that is associated with the predominant Western diet.

Habbel P, et al., Docosahexaenoic Acid suppresses arachidonic acid-induced proliferation of LS-174T human colon carcinoma cells. World J Gastroenterology. 2009; 15 (9): 1079-1084.

20. Study Reveals Vegetarians Have Fewer Cancers But Higher Risk of Colorectal Cancer (Mar. 16/09)

UK researchers found that vegetarians had a lower overall cancer rate than meat eaters, but contrary to suggestions from other studies, they found a higher rate of colorectal cancer among the vegetarians than among the meat eaters. The results showed that:

- The standardized incidence ratio for all cancers for all participants was 72% (that is lower than the overall population).
- Compared with meat eaters in the cohort, and after adjusting for age, sex and smoking status, the vegetarians in the cohort showed an 11% lower incidence rate of all cancers.
- However, for colorectal cancer, vegetarians showed a 39%higher incidence rate compared with meat eaters.

The authors concluded that: "The overall cancer incidence rates of both the vegetarians and the nonvegetarians in this study are low compared with national rates." "Within the study, the incidence of all cancers combined was lower among vegetarians than among meat eaters, but the incidence of colorectal cancer was higher in vegetarians than in meat eaters," they added.

Key, Timothy, et al., Cancer Incidence in vegetarians: results from the European prospective Investigation into Cancer and nutrition (EPIC-OXFORD). American J of Clinical Nutrition. Online publication March 11, 2009. doi: 10.3945/ajcn.2009.26736M

21. Benefits of Italian Extra-Virgin Olive Oil Reduced at 6 Months of Storage (Mar.18/09)

The health benefits of extra-virgin olive oil may include preventing conditions related to coronary disease, stroke and certain types of cancers such as colorectal cancer. The protective role of virgin olive oil is the result of components that act as antioxidants. Researchers at the University of Foggia in Italy analyzed several varieties of extra-virgin olive oil produced from groves in the Italian countryside at production and during storage. After three months of storage, the antioxidant activity in the oils remained unchanged. However, antioxidants decreased by about 40% for almost all of the oils after six months.

Bajand, A, et al., Changes in phenolic content and antioxidant activity of Italian extra virgin olive oils during storage. J of Food Science. Vol 74, Issue 2. pp 177-183.

22. A Low GI Meal Promotes Satiety (Mar. 18/09)

Eating a meal with a low GI (glycemic index) increases gut hormone production which leads to suppression of appetite and the feeling of fullness. This research examined the effects of a low versus high GI meal on levels of gut hormones. This is the first study to provide clues as to how

a low GI meal produces satiety. GI (Glycemic Index) is a ranking assigned to carbohydrates according to their effect on the body's blood sugar levels. A low GI meal takes longer to digest and releases sugar into the bloodstream more slowly than a high GI meal. High GI foods include white bread, croissants and cornflakes and are assigned glycemic index values from 51-100, whereas granary bread, milk and most fruit and vegetables are all classed as low GI foods and assigned GI values from 1-50. A low GI diet is known to cause reduced appetite but the mechanisms behind this have so far remained unknown. To address this, researchers looked at the effects of a single low versus high GI meal on gut hormone levels in twelve healthy volunteers. Each participant ate an identical medium GI meal for dinner, fasted overnight, and was given either a low (46) or high (66) GI meal for breakfast. Blood samples were then taken every 30 minutes for 150 minutes, and levels of the gut hormone glucagon-like peptide 1 (GLP-1) and insulin measured. GLP-1 is a hormone produced by the gut that has been shown to cause a feeling of fullness and suppression of appetite. Volunteers who ate a low GI breakfast had 20% higher blood plasma levels of GLP-1 and 38% lower levels of insulin, compared to those who had consumed a high GI breakfast. These results show for the first time that eating a low GI meal increases GLP-1 production and suggest a physiological mechanism as to why a low GI meal makes you feel fuller than a high GI meal.

www.medicalnewstoday.com/articles/142501.php

23. Trans Fats Increase Colon Cancer Risk (Mar. 19/09)

Researchers have found that higher consumption of trans fatty acids can increase a person's risk of precancerous colorectal tumors by 86% and their results provide additional support to recommendations to limit trans fatty acid consumption. While consumption of trans fats increased the risk of developing adenoma, it did not appear to affect the number, size or location of the tumors. Trans fats are a particular type of fat that occurs naturally only in very trace amounts in meat and dairy products. The bulk of trans fats in the modern diet are synthetically produced by the partial hydrogenation of vegetable oils. Unlike other fats, trans fats have no nutritional value to the human body. Nevertheless, they have come to be widely used in restaurants and packaged foods, because they hold flavor longer and have a greater shelf life than non-hydrogenated oils. The current study is not the first to link trans fats to colorectal cancer, which affects thousands of new people per year. Prior research has linked markers of trans fat consumption to an elevated colorectal cancer risk.

Vinikoor, LC, et al., Consumption of trans-fatty acid and its association with colorectal adenomas. American J of Epidemiology. Vol 168, Issue 3, pp.289-297; doi:10.1093/aje/kwn134

24. Type I Diabetes & Outcomes of Colorectal Cancer (Mar.19/09)

Patients with diabetes mellitus or Type I Diabetes appear to have an increased risk of colorectal cancer. However, there is limited information on the outcome for diabetic patients diagnosed with this type of cancer. The health records of 1,194 patients treated for colorectal adenocarcinoma from 1980 - 2004 were reviewed. Diabetes status and prognostic factors were registered. Researchers wished to measure cancer specific survival and overall survival. After a curative resection of their primary tumor, the estimated 5-year cancer specific survival in 97 diabetic patients was 73% and 79% in 1097 non-diabetic patients (not significant). The estimated overall 5-year survival in patients treated with curative intent was 46% in diabetic patients and 65% in non-diabetic patients. The diabetic patients were significantly older and more frequently had cardiac diseases. Researchers concluded that diabetes mellitus did not affect the short-term survival or the cancer specific survival of patients. A shorter overall survival was associated with cardiac diseases and higher age.

Jullumstro, Eivind, et al., Diabetes mellitus and outcomes of colorectal cancer. Acta Oncologica. Vol 48, Issue 3, April 2009, pp.361-367.

25. Licorice Compound Offers New Cancer Prevention Strategy (Mar. 23/09)

Researchers have discovered that a chemical component of licorice may offer a new approach to preventing colorectal cancer without the adverse side effects of other preventive therapies. In this study, evidence shows that inhibiting the enzyme 11?-hydroxysteroid dehydrogenase type 2 (11?HSD2) - either by treatment with a natural compound found in licorice or by silencing the 11?HSD2 gene - prevents colorectal cancer progression in mice predisposed to the disease. One promising target for chemoprevention is the enzyme cyclooxygenase 2 (COX-2), which promotes colorectal cancer progression via the action of the enzyme's inflammatory products, the prostaglandins. Inhibiting this enzyme - with non-steroidal anti-inflammatory drugs (NSAIDs)

like ibuprofen or with selective COX-2 inhibitors like Vioxx or Celebrex - reduces the number and size of colon polyps in mice and in patients with an inherited predisposition to colon cancer. However, both types of drugs cause serious adverse side effects that limit their utility for chemoprevention. Previous studies have found that by inhibiting 11?HSD2 in the kidney suppresses COX-2 expression in that organ, and the researchers in this study sought to determine if the same could be true of the colon, seeing that the colon is one of the only other organs with high expression of 11?HSD2; suggesting that this enzyme might play a role in colorectal cancer progression. Researchers, therefore, inhibited 11?HSD2 with glycyrrhizic acid, the main sweet-tasting component of licorice, and by silencing the gene for 11?HSD2. Both treatments inhibited the production of prostaglandin E2 (an inflammatory molecule produced by the COX-2 enzyme) and **prevented the development of colon polyps (adenomas) and tumor growth and metastasis.** Because 11?HSD2 is highly expressed only in kidney and colon, blocking the enzyme produces effects specific to those tissues - unlike NSAIDs, selective COX-2 inhibitors, and steroid treatments that can prevent cancer progression but also cause serious side effects like gastrointestinal irritation, cardiovascular events, and immunosuppression, respectively. Licorice has been used as a nutraceutical for thousands of years for ailments ranging from coughs to constipation. But even licorice is not without side effects; long-term consumption can lead to low blood potassium and increases in blood pressure - side effects linked to the inhibition of 11?HSD2.

www.scienceblog.com/cms/licorice-compound-offers-new-cancer-prevention-srategy-19731.html

26. Whole Grains Lower Risk of Colorectal Cancer (Mar. 23/09)

This study evaluated the effectiveness of whole grain consumption in preventing colorectal cancer. A systematic review of 11 cohort studies was performed (meta-analysis). The age group of the patients was between 25 and 76 years. The period of study varied from 6 to 16 years, where 7,745 persons developed colorectal cancer during the follow-up period. After analyzing the stats of patients who developed colorectal cancer during the follow-up period, researchers concluded that consumption of whole grains were inversely associated with the risk of developing colorectal cancer.

Haas, P, et al., Effectiveness of whole grain consumption in the prevention of colorectal cancer: Meta-analysis of cohort studies. International J of Food Sciences and Nutrition. March 21, 2009. doi: 10.1080/09637480802183380

27. Red Meat Raises Death Risk (Mar. 23/09)

People who eat more red or processed meat have a higher risk of death from all causes including **cancer**, while a higher consumption of white meat reduces such risks. Over the study period, 47,976 men and 23,276 women died. The one fifth of men and women who ate the most red meat -- a median of 62.5 grams per 1,000 calories per day -- had a higher mortality rate than the one fifth who consumed the least -- 9.8 grams per thousand calories, according to the report. A similar rate held true for consumers of processed meat. Comparatively, the top fifth of white meat consumers had a slightly lower risk for death than those who ate the least white meat. "For overall mortality, 11% of deaths in men and 16% of deaths in women could be prevented if people decreased their red meat consumption to the level of intake in the first quintile," wrote the authors led by Rashmi Sinha of NIH's National Cancer Institute. "The impact on cardiovascular disease mortality was an 11% decrease in men and a 21% decrease in women if the red meat consumption was decreased to the amount consumed by individuals in the first quintile." Cancer-causing compounds are known to form during high-temperature cooking of meat, the report stated, and meat is a major source of saturated fat, which has been linked to certain cancers. Lower meat consumption has been linked to reductions in risk factors for heart disease, including lower cholesterol levels and blood pressure. "These results complement the recommendations by the American Institute for Cancer Research and the World Cancer Research Fund to reduce red and processed meat intake to decrease cancer incidence," the authors wrote.

www.cancercompass.com/cancer-news/1,15502,00.htm

28. Flax Prevents Colon Cancer (Apr. 5/09)

New research from South Dakota State University offers evidence that including flax in the diet may help prevent colorectal tumors or keep tumors from growing as quickly when they do form. Flaxseed contains a high percentage of alpha-linoleinic acid, omega-3 fatty acid, and lignans, a group of chemical compounds found in plants that act as antioxidants. The study was

conducted in a special strain of mice that develop spontaneous intestinal tumors due to a mutation in a gene. This study investigated the effects of cancer preventive agents on genetically predisposed individuals. Results indicated that mice on diets supplemented with flaxseed meal and flaxseed oil had, on average, 45% fewer tumors in the small intestine and the colon compared to the control group. Lead investigator concluded that dietary flaxseed oil and meal are effective chemopreventive agents against colon and intestinal tumor development in experimental animal models and that further studies are needed to establish the optimal amount of flaxseed that should be incorporated into human diets to get an anti-tumor benefit. Further studies are required to explore the possible mechanism of action by which flaxseed can help prevent colon cancer.

www.argusLeader.com/News

29. Fiber: The Beneficial Effects (Apr. 7/09)

It has long been known that eating a lot of fiber helps lower the risk of colon cancer. But exactly how that worked hasn't been known -- until now. Research at Medical College of Georgia published online this month in Cancer Research is focusing on a chemical fermented from fiber in the colon that works with a protein on the colon cell surface to kill cancer cells. But it turns out there is more of an interactive, symbiotic relationship between the bacteria and the host, and one way is through the breakdown of fiber by the bacteria into useful chemicals. One of those, called butyrate, is a natural inhibitor of histone deacetylase, a cancer-causing process. The idea is that the bacteria, using the fiber you take in the diet, produces this histone deacetylase inhibitor. The fiber and the bacteria together give you protection against colon cancer. It works in two different ways: Researchers found a transporter that carries the chemical into the cell to do its work; there is also a protein on the surface of the cells, g-protein-coupled receptor 109A, that starts a process that results in cancer-cell death when it is activated by butyrate. Researchers found human colon cancer cells manage to turn off both processes. The team is now breeding mice that lack both to test their theories. The study emphasized the need to get fiber in your diet -- if not for you, then for your bacteria. The bottom line is, we ought to keep our normal bacteria happy and healthy in order to get the beneficial effects from them.

www.cancercompass.com/cancer-news/1,15548,00.htm

30. Omega 3 Fatty Acids Prevent Muscle Loss in Cancer Patients (Apr. 11/09)

New research shows that omega 3 fatty acids prevent muscle loss in cancer patients who undergo major surgery. The study showed that patients who underwent surgery for esophageal cancer maintained muscle mass from omega 3 fatty acids administered before, immediately after, and for three weeks following surgery. According to lead investigator: An increasing number of patients are treated with chemotherapy alone or in combination with radiation therapy before they undergo surgery. The surgery is a serious operation lasting several hours and can take weeks to recover from surgery and up to six months to recover pre-illness quality of life. Weight loss is extremely common both before and especially after this type of surgery, and any approach that can preserve weight, in particular muscle weight and strength, may represent a real advance. The study showed that omega 3 fatty acids were superior for preventing muscle loss among the cancer patients who received 2.2 grams of purified EPA from omega 3 fatty acids in a nutritional supplement, compared to patients who received a similarly flavored supplement with the same amount of calories, protein, and micronutrients, but without omega 3 fatty acids. The cancer patients, given the omega 3 fatty acids before and after surgery maintained muscle mass, and all other aspects of body composition. The group who did not receive omega 3 fatty acids lost a significant amount of weight, with 68% experiencing ‘clinically severe’ weight loss after esophageal cancer surgery. The patients who were not given omega 3 fatty acids experienced weight loss comprising 100% loss of muscle mass. “Omega 3 enriched nutrition appears to prevent loss of muscle mass by reducing the amount of inflammatory markers in the blood” said Dr. Reynolds. He suggests that omega 3 fatty acids act to reduce metabolic stress typically seen after surgery. Cancer patients given omega 3 fatty acids also were less likely to develop fever, showing that omega 3 fatty acids reduce inflammation. The researchers expect the study results **can benefit anyone undergoing major surgery.** Throughout cancer care, many patients undergoing therapy nowadays have a combination of surgery, chemotherapy and radiation therapy, and studies addressing whether nutritional supplementation with omega 3 for the entire duration of treatment should be considered. Finally, researchers do not expect these findings are unique to cancer surgery, and similar benefits may

accrue to patients needing complex surgical care for non-cancer problems, for instance liver transplantation or major cardiac surgery.

www.emaxhealth.com/1020/51/30420/omega-3-fatty-acids-prevent-muscle-loss-cancer-patients

31. Colorectal Cancer and Coffee Ingestion (Apr. 13/09)

Coffee is not significantly associated with a decreased risk of colorectal cancer, contrary to the results of previous trials that found a possible protective effect of coffee against these cancers, according to the results of a review of studies published in the International Journal of Cancer. An inverse association between coffee consumption and the risk of colorectal cancer has been found in several case-control studies, but the association was not consistent in prospective cohort studies, which are designed differently, claimed the lead researcher. **Case-control studies** include patients with a disease or condition who are compared with "controls," healthy individuals matched up with the study group for factors such as age and sex to avoid bias. **Prospective cohort studies** are studies, in which the participants have a certain characteristic in common, such as a smoking habit or birth order, are identified and then followed forward in time; the final outcome is unknown to the researchers before the trial ends. The researchers conducted a systematic review of **prospective cohort studies** to examine the association between coffee consumption and colorectal cancer. They identified 12 studies that included a total of 646,848 participants and 5403 patients with colorectal cancer. The combined result of the studies, comparing high versus low coffee consumption categories, revealed no significant association between coffee consumption and colorectal cancer risk.

www.in.reuters.com/article/health/idINTRE53C4S920090413