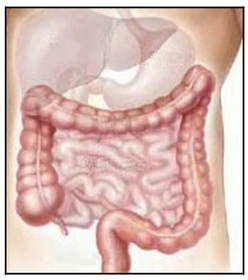
Colorectal Cancer Association of Canada

COLORECTAL CANCER RESEARCH

Month Ending May 15th, 2011



The following colorectal cancer research update extends from April 9th, 2011 – May 15th, 2011 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. FDA Approves Fusilev (Apr. 12/11)

The use of FUSILEV® (levoleucovorin) in combination with 5-fluorouracil in the palliative treatment of patients with advanced metastatic colorectal cancer has been approved by the FDA in the U.S. The NCCN Guidelines in the United States already recommend levoleucovorin in the treatment of colorectal cancer patients, but the manufacturer could not promote FUSILEV for this indication until now. FUSILEV

is a novel folate analog (which means it is a synthetic version of folic acid – a B vitamin – used in the in the treatment of malignant cell growths. FUSILEV is indicated for use in combination with 5-fluorouracil in the palliative treatment of patients with advanced metastatic colorectal cancer

http://finance.yahoo.com/news/FDA-Approves-FUSILEV-for-Use-bw-3662992486.html?x=0&.v=1

2. Reintroduction of Oxaliplatin in the Treatment of Metastatic Colorectal Cancer (Apr. 11/11)

Oxaliplatin-based chemotherapy is an effective first-line treatment option for patients with metastatic colorectal cancer (mCRC), which, in combination with targeted therapies (such as avastin and erbitux) and a sequential treatment approach using all active agents, has extended median overall survival to 2 years and beyond. Prolonged survival brings into focus the burden of treatment, in terms of associated toxicities and quality of life, and attention is now being paid to lowering the toxicity burden for patients receiving chemotherapy for mCRC without compromising efficacy. The use of oxaliplatin can lead to the development of sensory neuropathy (consisting of numbness and tingling in the hands, fingers and feet), which commonly limits the dose and/or duration of treatment that can be administered. According to the researchers, temporary withdrawal of oxaliplatin (more commonly referred to as "*treatment holidays"*) has been shown to be an effective strategy for the management of this adverse effect. Data from randomized controlled trials indicate that a formalized stop-and-go approach to the delivery of oxaliplatin does **not** compromise efficacy, and indeed for some patients may prove beneficial by allowing them to continue treatment for longer periods. This study presents a critical review of the evidence ***to support the utility of treatment interruption and reintroduction of oxaliplatin for the long-term management of mCRC.***

Grothey, Alex, et al., Reintroduction of oxaliplatin: a viable approach to the long-term management of metastatic colorectal cancer. Oncology 2010; 79: pp. 389-399

3. Pain Relievers May Lower Colorectal Cancer Risk (Apr. 10/11)

New research has contributed to evidence that the danger of developing rectal and colon cancers can be lessened by regularly using pain relievers, perhaps by up to 50%. This latest report by the National Cancer Institute also demonstrates that individuals at higher risk, such as those with a family history of colon cancer also gain benefit from the use of painkillers such as ibuprofen or aspirin. The latest research enhanced previous studies as it included greater numbers of individuals and also assessed exactly where in the colon the cancers developed.

Making use of details from over 300,000 individuals, the study assessed the frequency with which people took any of 19 painkillers, which included aspirin, ibuprofen and others. The decrease in cancer risk was variable, dependent upon how frequently individuals used the pain relievers and also the variety of cancer involved. In general, regular use of any of the painkillers showed a 20% decline in the danger of colorectal cancer over a 10 year period, and the more the drugs that were taken, the less likely was the diagnosis of colon or rectal cancer.

http://www.nlm.nih.gov/medlineplus/news/fullstory_110810.html

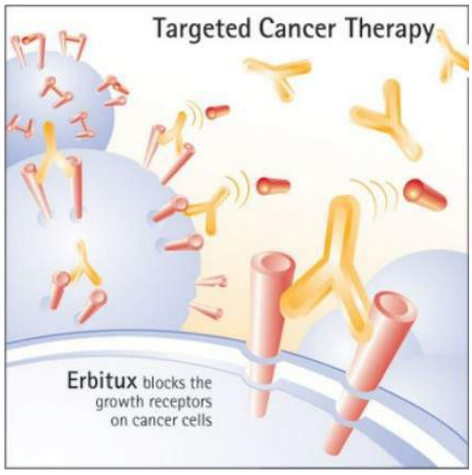
4. Erbitux in First Line Therapy for the Treatment of Metastatic Colorectal Cancer (Apr.19/11)

This study provides an updated analysis of the Phase III CRYSTAL study which included the evaluation of overall survival (OS) according to KRAS mutation status in patients with metastatic colorectal cancer (mCRC). It found that the addition of Erbitux® (cetuximab) to standard chemotherapy (FOLFIRI) in patients with KRAS wild-type disease resulted in a significant improvement in OS of 3.5 months, compared with FOLFIRI alone. CRYSTAL is the only trial to date to demonstrate a significant overall survival benefit of a targeted therapy in combination with current standard chemotherapy (FOLFIRI) in 1st line treatment of mCRC. "CRYSTAL has proven to be a landmark study in colorectal cancer through the scientific knowledge it has delivered to the oncology community, helping to catapult the practice of personalized medicine forward." "It was rewarding for the results of CRYSTAL to not only show an improved response rate, but also improved overall survival". "CRYSTAL has proven to be a landmark study in colorectal cancer through the scientific knowledge it has delivered to the oncology community, helping to catapult the practice of personalized medicine forward." CRYSTAL is a multicenter, Phase III, randomized, controlled trial involving 1,198 patients and investigating the efficacy and safety of Erbitux in combination with FOLFIRI vs. FOLFIRI alone in the 1st line treatment of patients with mCRC. "CRYSTAL was the first Phase III trial to demonstrate the significance of the KRAS biomarker in 1st line mCRC. The

findings have since led to a critical shift towards more personalized management of this disease and, most importantly, to improved outcomes for patients. The top-line CRYSTAL results in patients with KRAS wild-type tumors (n=666) receiving Erbitux plus FOLFIRI are:

- Median OS was 23.5 months compared to 20.0 months in those receiving chemotherapy alone
- The risk of disease progression was reduced by 30.4%
- The likelihood of achieving a tumor response doubled overall

Erbitux® is a first-in-class and highly active monoclonal antibody targeting the epidermal growth factor receptor (EGFR). As a monoclonal antibody, the mode of action of Erbitux is distinct from standard non-selective chemotherapy treatments in that it specifically targets and binds to the EGFR.



This binding inhibits the activation of the receptor and the subsequent signal-transduction pathway, which results in reducing both the invasion of normal tissues by tumor cells and the spread of tumors to new sites. It is also believed to inhibit the ability of tumor cells to repair the damage caused by chemotherapy and radiotherapy and to inhibit the formation of new blood vessels inside tumors, which appears to lead to an overall suppression of tumor growth. The most commonly reported side effect with Erbitux is an acne-like skin rash that seems to be correlated with a good response to therapy. In approximately 5% of patients, hypersensitivity reactions may occur during treatment with Erbitux; about half of these reactions are severe

Van Cutsem, Eric, et al., Cetuximab Plus Irinotecan, Fluorouracil, and Leucovorin As First-Line Treatment for Metastatic Colorectal Cancer: Updated Analysis of Overall Survival According to Tumor* KRAS *and* BRAF *Mutation Status J Clin Oncol 2011 April. Doi: 10.1200/JCO.2010.33.5091

5. Zaltrap Extends Survival in Metastatic Colorectal Cancer (Apr.29/11)

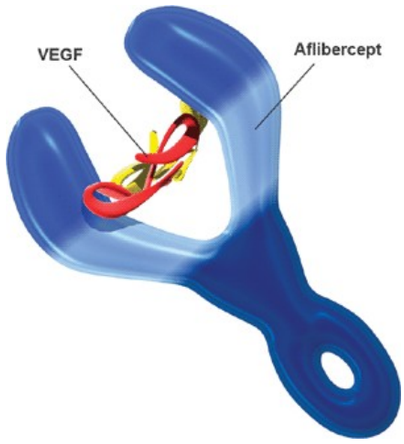
ZALTRAP® (otherwise known as aflibercept) added to survival time when given along with FOLFIRI to colorectal cancer patients who had already progressed on earlier oxaliplatin treatment. On April 26, 2011, the manufacturer announced positive results for the Phase III VELOUR trial, which compared ZALTRAP to a placebo during FOLFIRI chemotherapy. The VELOUR trial enrolled 1,226 people with colorectal cancer that had spread and who had already had their cancer get worse on an initial treatment with oxaliplatin. Patients came from the United States and throughout the world. They were randomly assigned to receive:

- FOLFIRI (irinotecan, leucovorin, and infusional 5-FU) plus ZALTRAP
- FOLFIRI plus a placebo

The primary outcome was overall survival time. Secondary outcomes included:

- Time before tumors grew or new tumors appeared (*progression free survival).*
- Percentage of patients whose tumors shrank while on treatment *(response rate).*
- Treatment side effects.
- Ability of treatment to provoke an immune system response *(immunogenicity).*

Aflibercept or ***VEGF trap*** is a specially developed protein that can block the development of new blood vessels as it circulates in the blood stream or in the spaces between blood vessels near tumors. It acts on two different vascular endothelial growth factors (VEGF) as well as placental growth factor (PIGF).



A representative of the manufacturer claimed: *We are pleased with the results of the ZALTRAP Phase III study in this group of patients. We are committed to bringing ZALTRAP to patients with advanced colorectal cancer and maximizing the therapeutic potential of this unique and exciting medicine*. Others added: *These findings are exciting given the limited second-line treatment options for patients with metastatic colorectal cancer. Based upon these positive findings, we plan to submit regulatory applications for marketing approval to the U.S. Food and Drug Administration and the European Medicines Agency in the second half of the year*. The AFFIRM Phase II clinical trial is studying whether ZALTRAP can improve progression-free and overall survival time in combination with FOLFOX chemotherapy as an initial *(first-line)* treatment for metastatic colorectal cancer. It has completed enrolling patients, and results are expected later this year.

http://www.pharmaceutical-int.com/news-releases/sanofi-aventis-and-regeneron-report-positive-phase-iii-results-with-zaltrap-----aflibercept--in-second-line-metastatic-colorectal-cancer.html

6. Drug May Have Utility in Treating Colorectal Cancer (Apr.26/11)

A new study from the University of Michigan Comprehensive Cancer Center suggests a class of drugs that has shown promise for breast and ovarian cancer patients with BRCA gene mutations may also benefit certain colorectal cancer patients, according to a U-M Health news report. The class of drugs, called PARP inhibitors, fights against tumors with a specific mutation in the MRE11 gene. Approximately 15% of colorectal cancers have microsatellite instability, which is an error in the DNA. A large majority of these tumors have the MRE11 gene mutation, suggesting a broader application of PARP inhibitors. Researchers found PARP inhibitors were even more effective when there are two copies of the MRE11 gene mutation. They are planning to launch a phase 1 clinical trial to test the utility of PARP inhibitors in colorectal cancer patients with two mutated copies of MRE11.

Vilar-Sanchez, Eduardo, et al.,* MRE11 *Deficiency Increases Sensitivity to Poly(ADP-ribose) Polymerase Inhibition in Microsatellite Unstable Colorectal Cancers.* Cancer Research*, Vol. 71, No. 7, April 1, 2011

7. Prophylactic Drugs Help Prevent Oxaliplatin-Related Nausea and Vomiting (May 12/11)

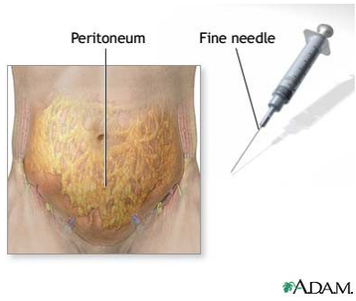
This study sought to prospectively determine the frequency of delayed nausea and vomiting with oxaliplatin-based chemotherapy following day 1 prophylaxis using the drugs 5-HT-$_3$ receptor antagonist and dexamethasone. Patients with colon cancer, ≥ age 18, with a performance status ≤2, receiving oxaliplatin (85–100 mg/m^2) as part of a standard folinic acid, 5-flourouracil, oxaliplatin regimen for the first time were eligible. All patients received a 5-HT$_3$ receptor antagonist and dexamethasone 20 mg on day 1 prior to oxaliplatin. No routine prophylaxis for delayed emesis (vomiting/nausea) was given. Antiemetic outcome was recorded in patient-completed diaries for the 120-h study period following oxaliplatin administration. Primary endpoint was frequency of delayed (24–120 h) emesis (vomiting/retching). Forty-one patients were enrolled and 39 were evaluable. Median age was 70 (34–85) and the female/male ratio was 20:19. Four patients (10%) experienced vomiting or retching during the delayed period. One patient vomited during the first 24 h after oxaliplatin. The overall (120 h) no emesis rate was 87% (34/39). Twenty-one patients (54%) developed delayed nausea. Nine patients had moderate or severe nausea. Eighteen patients (46%) took rescue antiemetics during the delayed period. Delayed and overall complete response (no emesis or use of rescue antiemetics) rates were 54% and 49%, respectively. Researchers concluded that the use of a 5-HT$_3$ antagonist and dexamethasone prior to oxaliplatin results in excellent control of nausea and vomiting during the 24 h after chemotherapy. However, without further antiemetic treatment, complete response in the delayed period decreased to 54%. This study supports the need for routine antiemetic prophylaxis for delayed nausea and vomiting following oxaliplatin-based chemotherapy.

Hesketh, Paul, et al., Prospective evaluation of the incidence of delayed nausea and vomiting in patients with colorectal cancer receiving oxaliplatin-based chemotherapy. Supportive Care in Cancer. Published online. Doi: 10.1007/s00520-011-1180-2

SURGICAL THERAPIES

8. Unresectable Peritoneal Carcinomatosis from Colorectal Cancer (Apr.11/11)

The peritoneum is the membrane that lines the abdominal cavity and covers most of the abdominal organs. See image appearing below.



Peritoneal Carcinomatosis is the seeding of the peritoneum with carcinoma cells or cancer cells that may arise from colorectal cancer. For peritoneal carcinomatosis (PC) that cannot be surgically removed, the median overall survival (OS) is 5-6 months but may vary from patient to patient. This study analyzed patients with PC from colorectal cancer (CRC) who were not candidates for surgery that includes debulking and hyperthermic intra-peritoneal chemotherapy (or HIPEC), describing patient- and tumor-related factors possibly affecting survival. From 2005 to 2009, 43 patients presented with unresectable PC from CRC: male/female ratio was 29/14, median age was 57.1 years (range 34.8-76.8). "Unresectability" was defined as:

- six to seven abdominal regions affected by PC,
- involvement of mesentery (a membrane that supports an organ or body part, especially the double-layered membrane of the peritoneum attached to the back wall of the abdominal cavity that supports the small intestine) or small bowel in the PC,
- presence of liver metastases,
- retroperitoneal lymph nodes,
- vascular invasion, and/or
- neural invasion.

The time it took to diagnose PC after the primary tumour was 7.2 months. Primary tumors were right-sided in >50% and had been previously resected in >58%; 74.4% of PC occurred synchronously (at the same time). Ascites was present at primary diagnosis in 37.2% of the patients. In 70% of cases, six to seven abdominal regions were affected and in 58.1% PC involved small bowel/mesentery. Systemic disease (disease present throughout the body) was present in 16.3%. In 18.6% of patients, a palliative diversion or ostomy was constructed. Thirty-one patients (72.1%) received palliative chemotherapy and the median OS was 9.3 months versus 3.1 months without chemotherapy, with less favorable patient and tumor characteristics in the latter group. No other factors clearly influenced OS. The investigators concluded that palliative chemotherapy results in better OS, but this is probably attributable to factors influencing the patient's general condition

Hompes, Daphne, et al., Unresectable peritoneal carcinomatosis from colorectal cancer: a single center experience. J of Surg Oncology. Early Online Edition. DOI: 10.1002/jso.21937

9. Laparoscopic Liver Resection Becoming More Popular (Apr.11/11)

According to the literature, laparoscopic liver resection appears to provide significant intraoperative and postoperative benefits, compared with open hepatic resection, in patients with benign and malignant tumors and it does not compromise 5-year outcomes in hepatocellular carcinoma or **colorectal cancer metastases**. Not yet considered standard of care, "laparoscopic hepatic resection [LHR] has now been performed in more than 4,000 patients worldwide, and the benefits when compared with open hepatic resection [OHR] include

- decreased operating room time,
- less pain,
- less narcotic use,
- shorter length of hospital stay,
- less blood loss when matched for size of tumor and extent of the operation performed,
- faster oral intake, and
- a Band-Aid–sized incision.

Most importantly, there are no oncologic disadvantages," notes the principal investigator of the study. "If we were giving patients a small incision and shortening their recovery but sacrificing margins or recurrences, then it wouldn't be worthwhile". This study performed a review of 31 case-cohort matched studies that directly compared LHR with OHR in nearly 2,500 patients, and an institutional series of 314

patients. Investigators showed that, in addition to the previously reported safety and efficacy findings and patient benefits, the minimally invasive approach was economically advantageous, despite the increased cost associated with disposable instruments, because of the reduced incidence of complications and significantly shorter hospital stays. They do, however, note that LHR may not be appropriate for every patient which necessitates the dialogue between the patient and surgeon.

Nguyen, Kevin Tri, et al., Comparative Benefits of Laparoscopic vs. Open Hepatic Resection. Archives of Surgery. 2011; 146: 348-56

10. Liver Resection in Presence of Extrahepatic Disease (May. 2/11)

Hepatic resection for colorectal liver metastasis (CLM) in the presence of extrahepatic disease (EHD) is a controversial topic. Investigators in this study sought to evaluate the long-term outcome of patients undergoing liver resection for CLM in presence of EHD and identify factors associated with prognosis. From 1996 to 2007, a total of 1629 patients who underwent resection of CLM were identified from an international multi-institutional database. One hundred seventy-one patients (10.4%) underwent resection of EHD. Median number of treated CLM was 2; most patients had solitary EHD, a single anatomic site of EHD. The 5-year survival for patients with EHD was 26% compared with 58% for those without EHD. Recurrence was common (84%). Investigators maintained that concurrent resection of hepatic and EHD in well-selected patients may provide the possibility of long-term survival. The risk of recurrence, however, remains high, and a worse outcome is associated with both number of metastases and location of EHD.

Pulitano, C. et al., Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. Ann Surg Oncol. 2011 May; 18(5): 1380-1388.

11. Sentinel Lymph Node Procedure in Colorectal Cancer (May 3/11)

Sentinel lymph nodes are the first lymph nodes to receive lymphatic drainage from a tumor. For example, sentinel lymph nodes for colon cancer typically are located in the abdomen or the groin area, near to where the tumor is located. During surgery, sentinel lymph nodes may be removed to help the surgeon make an accurate diagnosis and stage the disease. Stage of disease refers to how far beyond the original location a cancerous tumor has spread. Some cancers spread in a predictable fashion from where the cancer started. In these cases, if the cancer spreads, it will spread first to lymph nodes (lymph glands) close to the tumor before it spreads to other parts of the body. The concept of sentinel lymph node surgery is to see if the cancer has spread to the very first lymph node (called the "sentinel lymph node"). If the sentinel lymph node does not contain cancer, then there is a high likelihood that the cancer has not spread to any other area of the body. There are various advantages to the sentinel node procedure. First and foremost, it decreases unnecessary lymph node dissections where this is not necessary, thereby reducing the risk of lymphedema, a common complication of this procedure. Increased attention on the node(s) identified to most likely contain metastasis is also more likely to detect micro-metastasis and result in staging and treatment changes. The main uses are in breast cancer and malignant melanoma surgery, although it has been used in other tumor types (**colon cancer**) with a degree of success. If the sentinel node contains tumor cells, removal of more nodes in the area may be warranted. If the sentinel node is normal, it is unnecessary to perform an extensive dissection of the regional lymph-node basin. No consensus exists on the validity of the sentinel-lymph-node procedure for assessment of nodal status in patients with **colorectal cancer**. Investigators in this study aimed to assess the diagnostic performance of this procedure by performing an examination of studies dealing with this issue. They identified 52 eligible studies, which included 3767 sentinel-lymph-node procedures (2961 [78·6%] colon and 806 [21·4%] rectal carcinomas). Most tumours 2339 (62·1%) were stage T3 or T4. 1887 (50·1%) of patients were male, 1880 (49·9%) female. Investigators found that the sentinel-lymph-node procedure showed a low sensitivity, regardless of T stage, localization, or pathological technique. Investigators maintained that for every patient diagnosed with colon or rectal cancer without clinical evidence of lymph-node involvement or metastatic disease, this procedure in addition to conventional resection should be considered, since the prognostic information provided by this technique could be clinically significant.

Knol, Dirk L. et al., Sentinel lymph node procedure in colon and rectal cancer: a systematic review and meta-analysis. The Lancet oncology, early online publication. May 5, 2011. Doi: 10.1016/S1470-2045(11)70075-4

SCREENING

12. New Test for Colon Cancer Detection (Apr. 11/11)

Many people 50 and older may be relieved to know doctors now have a convenient new test to help check for colon cancer. The new method identifies the cancer's genetic material in a blood sample taken from the patient's arm. The results help the doctor determine if there's a strong likelihood that colon cancer is present. If so, additional testing may be recommended. Testing is important because colon cancer is treatable when caught early, but often has no symptoms and goes undetected. About half the people who should be tested are not, so only approximately 40% of cases are diagnosed in early stages. According to the American Cancer Society, most men and women should be tested beginning at the age

of 50 up until the age of 75. Individuals with special risks, such as a family history or who are smokers, as well as African Americans, should be tested even earlier. Under-testing for colon cancer is a major health problem in the U.S. Colonoscopy is the best method for detecting colon cancer early and the one patients should consider first. It will detect colon cancer 95% of the time and a doctor can remove precancerous growths during the procedure. Colonoscopy is invasive, however, involving a long tube inserted through the rectum and colon. Fecal tests are also good choices for colon cancer screening, but some people find sample collection unpleasant. Other recommended tests include flexible sigmoidoscopy and double-contrast barium enema. While colonoscopy is the best method for detecting colon cancer, many patients resist the procedure. Advanced new blood testing may promote evaluation of patients who refuse to be tested by other methods.

Your doctor can order the new blood test, called **ColoVantage**, from **Quest Diagnostics**. There are no dietary restrictions or special preparations and the test can be added to routine blood work. In a clinical validation study, ColoVantage correctly identified colon cancer in 70% of samples of people diagnosed with the cancer. It also correctly detected the absence of colon cancer in about 89% of samples tested. As with any non-colonoscopy test, a positive test result should be followed up by colonoscopy for a more definitive diagnosis as appropriate under the guidance of a doctor.

http://www.healthnewsdigest.com/news/Cancer_Issues_660/New_Test_Makes_Colon_Cancer_Detection_Easier_printer.shtml

13. CT Colonography More Sensitive At Detecting Colorectal Cancer (May.3/11)

According to the results of this study, Computed tomographic (CT) colonography is more sensitive than optical colonoscopy (OC) in detecting colorectal cancer. Investigators assessed the sensitivity of CT colonography for detecting colorectal cancer in 49 studies from 1994 to 2009 that included 11,151 patients. The sensitivity of OC for detecting colorectal cancer was evaluated in a subset of 25 studies that included 9,223 patients, and which included a mechanism to determine true-positive versus false-negative OC diagnoses.

The investigators found that the cumulative prevalence of colorectal cancer was 3.6%. CT colonography was 96.1% sensitive in detecting colorectal cancer. When both cathartic and tagging agents were combined in the bowel preparation, no cancers were missed by CT colonography. OC was 94.7% sensitive for detecting colorectal cancer. The findings suggest that, assuming a reasonable level of specificity, primary CT colonography may be more suitable than OC for the initial investigation of suspected colorectal cancer, according to the authors.

Pickhardt, Perry, et al., Colorectal Cancer: CT colonography and colonoscopy for detection – systematic review and meta-analysis.

Radiology; 259: 393-405.

14. Simple Urine Test for Colorectal Cancer (May. 8/11)

A made-in-Canada urine test appears to be able to spot the signs of early colorectal cancer, and might eventually do away with less appealing screening methods. The urine test is based on "metabolomics," which is the analysis of the chemical fingerprints left by cellular processes in the body, including the

changes of normal cells into cancer cells. It works by identifying cancer cell waste products that are then excreted into the urine by small polyps and tumours.

If the test proves accurate, researchers hope it could one day change the way patients are screened for colorectal cancer and maybe other cancers as well. The test is like a fingerprint. It can tell you what those waste products are and then allows doctors to predict whether you have a polyp or not or whether you have colon cancer. Investigators have released a study which looked at 354 healthy people with normal colonoscopies provide urine samples, as well as 110 people with benign, "hyperplastic" colon polyps, which usually don't develop into cancer and 243 with 'adenomatous" polyps, which are considered pre-cancerous growths that could become cancerous. The urine lab test was over 80% effective at spotting the existing cancer as well as pre-cancerous growths, a success rate that pleased the scientists. So if we can find the growth or the cancer at these early stages, we can prevent or cure the cancer before it's too late. Many provinces already offer patients over the age of 50 a fecal occult blood test, a test that looks for blood in stool and that requires patients to test their own stool at home with a test kit. Fewer than 20% of people offered the test use it. And it only finds cancer about 30% of the time. A simpler and possibly more accurate urine test might encourage more patients to get checked out. When patients come in, if they are more compliant and are more willing to do the test, more lives might be saved because we are making it easier for them. The screening test likely wouldn't replace colonoscopies, which are still considered the definitive test for colon cancer, but it would help doctors decide who should get the more invasive test to find patients before their cancer grows and spreads.

http://edmonton.ctv.ca/servlet/an/local/CTVNews/20110508/colorectal-caner-urine-test-110508/20110508/?hub=EdmontonHome

15. Interval Colorectal Cancers Increased After Flexible Sigmoidoscopy (May. 10/11)

Older patients undergoing flexible sigmoidoscopy were four times as likely to be diagnosed with left-side colorectal cancer within three years as those receiving full colonoscopies, according to this study. So-called interval cancer rates -- those diagnosed from six months to three years after a screening exam -- were 2.6% in patients 67 and older who received screening colonoscopies compared with 11.7% in those examined with flexible sigmoidoscopy.

A total of 25,541 cases involving cancers of the left colon diagnosed from 1998 to 2005 within three years of a sigmoidoscopy or colonoscopy procedure were included. Exclusion criteria included inflammatory bowel disease, a history of polyps, and family history of colorectal cancer. The interval cancer rate was calculated by dividing the number of interval cancers into the total number diagnosed following the exams, which included the much larger number that were entered into patients' records in the six months immediately after the procedures. Of the 25,541 cases included in the study, all but 841 were detected within the first six months. The researchers also found that interval cancer rates were higher at every location within the left-side colon where tumors were found: descending, sigmoid, rectosigmoid, and rectum. For each of these regions, the interval cancer rate with colonoscopy ranged from 2.2% to 3.3%, whereas with sigmoidoscopy it varied more widely, from 8% (at the rectosigmoid junction) to 18.7% (in the descending colon).

Wang Y, et al "Increased risk of new or missed colorectal cancers after flexible sigmoidoscopy compared with colonoscopy among older patients in the United States: a population-based analysis of the SEER-Medicare linked database, 1998-2005"* DDW *2011; Abstract 906.

OTHER

16. Estrogen Use For a Few Years After Menopause is Safe (Apr.1/11)

For years, gynecologists have prescribed hormone replacement therapy to relieve hot flashes, night sweats and other symptoms of menopause. But there have been concerns raised. A new study indicates women can safely take estrogen for at least a few years after menopause to alleviate symptoms. The new review indicates that, among postmenopausal women with prior hysterectomy, the use of conjugated equine estrogens (Premarin) for a median of 5.9 years was not associated with an increased or decreased risk of CHD [coronary heart disease], deep vein thrombosis, stroke, hip fracture, ***colorectal cancer***, or total mortality. The study, which monitored the women's health for 10.7 years, also noted that "a decreased risk of breast cancer persisted," which is consistent with previous Women's Health Initiative findings. The issue is the length of time women take estrogen following menopause. The Women's Health Initiative estrogen-only trial included women who ranged in age from 50 to 79. The increase in stroke risk occurred because the study included women in their 60s and 70s, as physicians for years condoned the use of estrogen many years after menopause in the belief that it helped protect the heart. Doctors started advising women to shorten the amount of time they used hormone therapy when the government halted the estrogen-only portion of the Women's Health Initiative. This new study substantiates what physicians have observed in the field. "What that showed us is women shouldn't be on it forever and we couldn't honestly say it would protect them against heart disease. Physicians are now coming back to saying, in the younger group, the 50-ish group, that estrogen replacement is OK. It is absolutely safe to take it around those few menopausal years to get through it, to deal with the hot flashes and night sweats and all those things that come with menopause that some women experience. The Johns Hopkins researcher suggests postmenopausal women who want to use estrogen to mitigate symptoms, use it for **fewer than five years**. The professor notes that the study does not address women who use estrogen and progesterone. That combination of hormones is used by women who have not had a hysterectomy. Progesterone is used to counter estrogen's ability to increase a woman's risk of endometrial cancer.

http://onlinehealthnews.org/2011/04/study-estrogen-use-as-hrt-for-a-few-years-after-menopause-is-safe/

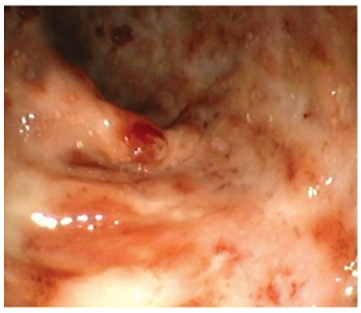
17. Decision Aid for Patients with Advanced Colorectal Cancer Considering Chemo (Apr. 12/11)

Decision making in advanced cancer is increasingly complex. Investigators in this study developed a decision aid (DA) for patients with advanced colorectal cancer who are considering first-line chemotherapy and reviewing treatment options, prognostic information, and toxicities. They examined its impact on patient understanding, treatment decisions, decisional conflict, decision making, consultation satisfaction, anxiety, and quality of life by using a randomized trial design. In all, 207 patients with colorectal cancer who were considering first-line chemotherapy for metastatic disease were randomly assigned to receive a standard medical oncology consultation or a consultation in which the DA (take-home booklet with audio recording, reviewed by an oncologist) was used. Participants completed questionnaires post-consultation and post-decision 1 month later. From the 207 patients, 100 patients were randomly assigned to the control arm, and 107 received the DA. Median age of the sample was 62 years, 58% were male, 89% had a performance status of 0 or 1, and 36% had received prior adjuvant chemotherapy. Patients receiving the DA demonstrated a greater increase in understanding of prognosis, options, and benefits, with higher overall understanding. Decisional conflict, treatment decisions, and achievement of involvement preferences were similar between the groups. Anxiety was similar across groups and decreased over time. Most patients were confident in a decision during the first consultation; 74% chose chemotherapy, 7% supportive care alone, and 10% observation. This randomized trial of a decision aid in advanced cancer showed that its use in advanced colorectal cancer improved patient understanding of prognosis, treatment options, risks, and benefits without increasing anxiety. DAs can improve informed consent and can be tested through randomized trials even in the advanced cancer setting.

Krzyzanowska, Monika, et al., Supporting Treatment decision making in advanced cancer: a randomized trial of a decision aid for patients with advanced colorectal cancer considering chemotherapy.

18. How Inflammation Can Lead to Cancer (Apr.19/11)

A new study shows how inflammation can help cause cancer. Chronic inflammation due to infection or to conditions such as chronic inflammatory bowel disease is associated with up to 25% of all cancers. The study found that inflammation stimulates a rise in levels of a molecule called **microRNA-155 (miR-155).** This, in turn, causes a drop in levels of proteins involved in DNA repair, resulting in a higher rate of spontaneous gene mutations, which can lead to cancer. The study shows that miR-155 is upregulated by inflammatory stimuli and that overexpression of miR-155 increases the spontaneous mutation rate, which can contribute to tumorigenesis.



People have suspected for some time that inflammation plays an important role in cancer, and the study presents a molecular mechanism that explains how it happens. The findings also suggest that drugs designed to reduce miR-155 levels might improve the treatment of inflammation-related cancers. MicroRNAs form a large family of non-coding genes involved in many important cell processes. They carry out this function by suppressing the amount of particular proteins in cells, with each type of microRNA often affecting many different proteins. MiR-155 is known to influence blood-cell maturation, immune responses and autoimmune disorders, and high levels of this molecule have been directly linked to the development of leukemias, breast, lung and gastric cancers. For this study, researchers examined the effects of inflammation-promoting substances such as tumor necrosis factor or lipopolysaccharide (found in the outer walls of bacteria) on miR-155 expression and on the frequency of spontaneous mutations in several breast-cancer cell lines. When the researchers exposed breast-cancer cells to the two inflammatory factors, the levels of miR-155 rose abnormally high, and the mutation rate increased two- to three-fold. To understand why, the investigators focused on the WEE1 gene, which stops the process of cell division to allow damaged DNA to be repaired. The investigators learned that miR-155 also targets WEE1 and showed that high levels of miR-155 lead to low levels of WEE1. They reasoned that low levels of WEE1 allowed cell division to continue even when DNA damage is present, leading to a growing number of mutations. It is believed that cancer is caused by an accumulation of mutations in cells of the body. The study suggests that miR-155, which is associated with inflammation, increases the mutation rate and might be a key player in inflammation-induced cancers generally, which could make it an important therapeutic target.

E. Tili, et al., Mutator activity induced by microRNA-155 (miR-155) links inflammation and cancer. **Proceedings of the National Academy of Sciences*, 2011; 108 (12): 4908 DOI: 10.1073/pnas.1101795108***

NUTRITION & HEALTHY LIFESTYLE

19. Vitamin D [25(OH)D] and Colorectal Cancer (Apr. 11/11)

Previous studies have suggested that higher plasma 25-hydroxyvitamin D_3 [25(OH)D] levels are associated with decreased colorectal cancer risk and improved survival, but the prevalence of vitamin D deficiency in advanced colorectal cancer and its influence on outcomes are not that well known. In this study, investigators prospectively measured plasma 25(OH)D levels in 515 patients with stage IV colorectal cancer participating in a randomized trial of chemotherapy. Vitamin D deficiency was defined as 25(OH)D lower than 20 ng/mL, insufficiency as 20 to 29 ng/mL, and sufficiency as ≥ 30 ng/mL. Among 515 eligible patients, 50% of the study population ***was vitamin D deficient***, and 82% were vitamin D insufficient. Plasma 25(OH)D levels were lower in black patients compared to white patients and patients of other race, and females compared to males. Investigators concluded that Vitamin D deficiency is highly prevalent among patients with stage IV colorectal cancer receiving first-line chemotherapy, particularly in black and female patients.

Ng, Kimmie, et al., Vitamin D status in patients with stage IV colorectal cancer: findings from intergroup trial n9741. J of Clin Oncol. Published Ahead of Print. Doi: 10.1200/JCO.2010.31.7255

20. Alcohol and Cancer (Apr. 11/11)

According to the results of this study, alcohol has been linked to the onset of cancers that include breast, colorectal, liver and esophageal. Investigators are stressing that moderate intake of alcohol is important to safeguard against the onset of these cancers.

For males: 2 drinks per day is considered moderate intake and for females: one drink per day. One drink is the equivalent to 12 ounces of beer, 5 ounces of wine or 1.5 ounces of liquor. Investigators stress that alcohol is also full of empty calories, potentially sugar-loaded, blended with diet drinks full of aspartame, mixed with caffeine, hard on the liver, and not great for the skin. Promoting a healthy lifestyle is important to reduce the risk factors, and they include:

- Eating healthy
- Avoiding sugar
- Smoking cessation
- Maintaining a normal body weight
- Exercising regularly
- Getting regular check ups
- Taking vitamin d

Schutze, M,. et al., Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study. BMJ 2011; 342:d1584

21. Study Shows No Link Between Folates & Colorectal Cancer (Apr. 19/11)

Increased intake of folic acid from fortified foods and dietary supplements is not linked to increased risk of colorectal cancer, according to this new study. The study found that neither high intakes of natural folate nor folic acid were associated with an increased risk of colorectal cancer. The researchers noted that while other unknown factors may influence risk of colorectal cancer, "many known colorectal cancer risk factors were accounted for in the study."

Leafy greens, dried beans and peas, fortified cereals and grain products, and some fruits and vegetables are rich sources of folate

Researchers investigated the association between folate intake and colorectal cancer among 43,512 men and 56,011 women in the Cancer Prevention Study II (CPS-II) Nutrition Cohort; 1,023 were diagnosed with colorectal cancer between 1999 and 2007, a period entirely after folate fortification began. Intakes of high levels of natural folate or folic acid were **not** significantly associated with risk of colorectal cancer. Total folate intake was significantly associated with lower risk. The researchers, therefore, concluded that intake of high levels of total folate reduces risk of colorectal cancer; there is no evidence that dietary fortification or supplementation with this vitamin increases colorectal cancer risk.

Stevens, Victoria, et al., High levels of folate, from supplements and fortification, are not associated with increased risk of colorectal cancer. Gastroenterology. Published online April 15, 2011.

22. Office Desk Job Doubles Colon Cancer Risk (Apr. 19/11)

Employees who spend 10 years or more behind a desk at work have an increased risk of colon cancer, according to the results of this study from Australia. Investigators claim the research suggests sedentary behavior may increase the risk of some chronic diseases. The study involved a total of 918 cases and 1,021 controls who participated in a population-based case-control study of colorectal cancer in Western Australia from 2005 to 2007.

Data was collected on lifestyle, physical activity and job history. The estimated effects of sedentary work on the risk of cancers of the proximal (right sided) colon, distal (left sided) colon and rectum were analyzed. Compared with employees who did not spend any time in sedentary work at a desk, study participants who spent 10 or more years working at a desk had almost twice the risk of distal -- descending -- colon cancer and a 44% increased risk of rectal -- the final portion of the large intestine -- cancer. Sedentary work was not associated with the risk of proximal colon cancer -- the ascending colon and transverse colon, or the right side of the abdomen. However, the findings were independent of recreational physical activity -- no matter how much exercise the study participants did performed.

Boyle, Terry, et al., Long term sedentary work and the risk of subsite-specific colorectal cancer. Amer J of Epidemiology; Vol. 173 (10): pp. 1183-1191

23. Smokers Diagnosed With Colon Cancer Have Greater Likelihood of Dying (Apr. 20/11)

According to the results of this study, people who smoked before their diagnosis of colon cancer had a higher risk of dying — both from colon cancer and from other causes. The risk was considerably higher in patients whose tumor was microsatellite high, but didn't extend to those with rectal cancer or younger patients under age 50.

Drinking alcohol before diagnosis didn't affect death rates. Compared to people who had never smoked:

- Smokers were 30% more likely to die of colon cancer.
- Smokers were 50% more likely to die of any cause.
- Smokers with tumors that were microsatellite-high were almost four times (3.83%) likely to die from colon cancer.

Researchers at the Seattle Family Colon Cancer Registry identified patients with colon or rectal cancer between 1998 and 2007 in 13 counties in western Washington State. They telephoned them to discuss their smoking and alcohol use before diagnosis, and then followed up with links to the National Death Index. Investigators concluded: "In addition to an association with disease risk, smoking is associated with increased mortality after colorectal cancer diagnosis. This association is especially pronounced for colorectal cancer with high microsatellite instability".

Phipps, Amanda, et al., Prediagnostic smoking history, alcohol consumption, and colorectal survival. Cancer: Early View. Doi: 10.1002/cncr.26114.

24. Eating Anything At Anytime & Risk of Colorectal Cancer (Apr. 26/11)

Although numerous studies have assessed the effect of foods and nutrients on colorectal cancer, few studies have investigated human eating behavior in relation to risk of colorectal cancer. In this study, researchers assessed whether the reported behavior of eating anything at anytime influenced colorectal cancer risk and related plasma biomarkers. They prospectively followed 55,540 women in the Nurses' Health Study who were aged 48 to 73 years, had no history of cancer, ulcerative colitis, or diabetes, and responded to the item "I eat anything I want, anytime I want" in the 1994 questionnaire. Blood samples were collected in 1989-1990 and analyzed for 1,994 women. During 12 years of follow-up, 552 colorectal

cancer cases were documented. After adjusting for age, smoking, body mass index, physical activity, red and processed meat, and other known risk factors for colorectal cancer, women who reported eating anything at anytime ***experienced an increased risk of colorectal cancer*** compared with those who did not report this behavior. In addition, reporting eating anything at anytime was associated with higher fasting plasma levels of insulin. Researchers concluded that reports of eating anything at anytime are associated with an increased risk of colorectal cancer in this large prospective cohort study, independent of other potential risk factors for colorectal cancer.

Bao, Ying, et al., Reported behaviour of eating anything at anytime and risk of colorectal cancer in women. International J of Cancer. Published online. Doi: 10.1002/ijc.26150

25. Thin People Face Colon Cancer Risk As Well (May 2/11)

Not only those with overweight problems face higher risk of colon cancer, but the thin people are also in the same boat, a latest study has found. The surprising finding emerged from the Singapore Chinese Health Study, a long-term research involving more than 50,000 participants and funded by the United States National Cancer Institute. Among those with a good body-mass index (BMI) of 21.5 to 24.4, only 89 out of 100,000 had colon cancer, the study found. Among those with BMIs of 18.5 to 21.4 and 24.5 to 27.4, the number of cases went up to 103. And among those with BMIs of 18.5 or less, or the skinny folk, the incidence shot up to 119 or 33% higher than the ideal group, the study found. The BMI is calculated by dividing the weight by the square of height, all in metric form. A person who is 1.65 meters tall and weighs 50 kilograms would fall in the skinny category, which makes up about 7.5% of the study group of 63,000 aged between 45 and 74. Among those with a BMI of 27.5 or above, the incidence of colon cancer was 130 out of 100,000, about 46% higher than the ideal group. The results surprised the research team, whose members included researchers from the University of Minnesota in the United States. The principal investigator of the study, said, "We are trying to understand how this is biologically plausible." The researchers suggest in their paper that the higher risk of colon cancer among underweight people could be due to something called "oxidative DNA stress," or mild inflammations that hit the underweight, damaging their immune system and allowing cancer cells to proliferate. This is unlike what causes cancer in the overweight, who are believed to have more insulin in their system, which might be responsible for decreasing the body's ability to prevent tumors from forming. The researchers also covered rectal cancer, but find there was hardly a difference between the different groups. Researchers maintain the results of the study could apply across all races, as the studies in Japan and South Korea also found a link between obesity and a higher risk of colon cancer.

http://english.sina.com/life/2011/0502/371456.html