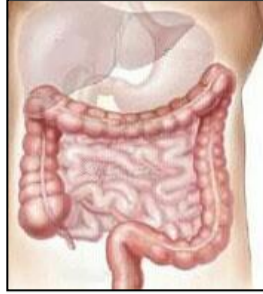


COLORECTAL CANCER RESEARCH UPDATES Month Ending February 17th, 2012



The following colorectal cancer research update extends from January 14th, – February 17th, 2012 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. [Effectiveness of Avastin with First Line Chemo](#)
2. [Diabetes Drug May Help Prevent Cancer](#)
3. [Oxaliplatin Deemed Effective in Stage III Patients](#)
4. [Adding Avastin to Xeliri or Folfiri: Both Are Equally Effective](#)
5. [Avastin Helpful in Second Line Treatment](#)
6. [Xeloda vs. 5FU in Chemoradiotherapy for Rectal Cancer](#)
7. [Regorafenib Shows Promise Against Metastatic Colorectal Cancer](#)
8. [Lactate Dehydrogenase Levels May be a Predictor of Avastin's Efficacy in First Line Therapy](#)
9. [Quebec-based Phase II Clinical Trial Involving Pentamidine for mCRC Patients Undergoing Second Line Therapy](#)

SURGICAL THERAPIES

10. [The Significance of Percentage Drop in CEA Post Curative Colon Surgery](#)
11. [Study on Stent Therapy for Unresectable Colorectal Obstruction](#)

RADIOTHERAPY / INTERVENTIONAL RADIOLOGY

12. [Phase II Study of ThermoDox in Combination with RFA in Colorectal Liver Mets](#)

SCREENING

13. [New Screening Test Offers Greater Accuracy in Early Detection of CRC](#)
14. [Oncotype DX Colon Cancer Test Changes Treatment in One Third of Patients](#)
15. [Repeat Flexible Sigmoidoscopy Increases Detection of CRC](#)

OTHER

16. [Mucinous Adenocarcinomas in Metastatic Colorectal Cancer](#)
17. [Emergency Room Presentation Not the End for CRC Patients](#)
18. [The Connection Between Inflammation, Methylation and Cancer Growth](#)
19. [Possible Link Between Colorectal Cancer and Gum Disease](#)

NUTRITION / HEALTHY LIFESTYLE

20. [Fusion Genes May Guide Treatment with Targeted Therapies](#)
21. [Vitamin D Again Linked to Lower Colorectal Cancer Risk](#)
22. [Celery & Carrots May Help Cut Colon Cancer](#)
23. [Intake of Selected Micronutrients & Risk of Colorectal Cancer](#)
24. [Eating Fish Tied to Lower Risk of Colon Polyps](#)
25. [Alcohol Consumption & Risk of Colon Cancer](#)
26. [Aspirin As Prevention in Colorectal Cancer](#)
27. [Reducing Risk of Colon Cancer With Regular Use of Vitamin & Mineral Supplements](#)

DRUGS / SYSTEMIC THERAPIES

1. Effectiveness of Avastin with First Line Chemo (Jan. 17/12)

Clinical trials have shown that adding bevacizumab (commonly referred to as Avastin) to chemotherapy improves survival for patients with colorectal cancer, although its effectiveness in the Medicare population in the U.S. is uncertain. In this study, researchers identified 2,526 patients with stage IV colorectal cancer diagnosed between 2002 and 2007 who received first-line combination chemotherapy with a fluoropyrimidine (5FU or xeloda) and either irinotecan (33%) or oxaliplatin (67%). Thirty-six percent of patients received bevacizumab with first-line therapy. The primary outcome measured was overall survival. In the first group of patients diagnosed between 2002 and 2007, bevacizumab with combination chemotherapy was associated with improved overall survival although the effect was more modest when restricted to years 2004 to 2007. The observed survival advantage of bevacizumab was more apparent with **irinotecan-based** chemotherapy than with oxaliplatin-based chemotherapy. Combination chemotherapy with bevacizumab, versus combination chemotherapy without bevacizumab, was associated with increased risk of stroke (4.9% v 2.5%, respectively) and GI perforation (2.3% v 1.0%, respectively). Cardiac events and venous thrombosis were not increased with bevacizumab. Investigators concluded that the addition of bevacizumab to cytotoxic combination chemotherapy was associated with small improvement in overall survival as well as increased risk of stroke and perforation, but not cardiac events, among Medicare beneficiaries with stage IV colorectal cancer.

Meyerhardt, Jeffrey, et al., Effectiveness of bevacizumab with first line combination chemotherapy for medicare patients with stage iv colorectal cancer. J Clin Oncology. Published online before print January 17, 2012.

2. Diabetes Drug May Help Prevent Cancer (Jan. 19/12)

The most widely prescribed drug to treat Type 2 diabetes might also help prevent colon cancer in those who are considered at high risk, suggests this new research carried out by a team of Montreal scientists. Metformin has already been shown in previous studies to cut cancer rates by 40% in those taking the medication, compared with diabetics who are not. Researchers at McGill University and the Université de Montréal sought to understand exactly how Metformin might prevent cancer. The prevailing theory before their lab study was that since cancer cells have a voracious appetite for glucose, using a drug to lower glucose levels in the blood for the treatment of Type 2 diabetes might also inadvertently block cancer. The researchers did confirm that the glucose-lowering action of Metformin does play a subtle role in preventing cancer. But they also made a much more important and unexpected discovery: Metformin protects cells from DNA damage that can lead to cancer. "Surprisingly, we found that Metformin protected DNA from mutations," said the study's director, Dr. Michael Pollak, a professor in McGill's departments of medicine and oncology. "It is remarkable that Metformin – an inexpensive, off-patent, safe and widely used drug – has several biological actions that may result in reduced cancer risk." Cells burn nutrients to produce energy. That burning-off process produces what Pollak likens to a kind of cellular exhaust, known as reactive oxygen species. It's this exhaust that can cause DNA damage inside cells, which in turn can spark cancer. Metformin acts as a cellular exhaust "filter," Pollak explained, reducing reactive oxygen species. "The drug seems to selectively prevent (the cellular exhaust) production ... such as those found in cells with oncogenic mutations," said study co-author Gerardo Ferbeyre, of U de M's department of biochemistry. The researchers made the discovery by treating pre-cancerous breast and colon cells with Metformin. The results of their study were published in the journal Cancer Prevention Research.

<http://www.montrealgazette.com/health/Diabetes+drug+prevent+cancer/6016759/story.html>

Pollak, Michael, et al., Metformin reduces endogenous reactive oxygen species and associated DNA damage. Cancer Prev Research. Online First Jan. 18, 2012.

3. Oxaliplatin Deemed Effective in Stage III Patients (Jan. 20/12)

Adding oxaliplatin to a standard chemotherapy regimen boosts survival rates for patients with advanced colon cancer, according to a new study that bolsters previous research on the drug by looking at a broader group of patients. "Physicians and patients should be reassured from our findings that oxaliplatin is associated with marginally but consistently superior survival for patients diagnosed before age 75 years in community settings," claim the study authors. In past studies, oxaliplatin, as an adjuvant to the established treatment of 5-fluorouracil (5-FU), improved survival by up to 23%. But the new study looked at a different group of colon cancer patients, who were older, sicker, more racially diverse and had never participated in a controlled clinical study. Up until 2004, the drug 5-FU -- given in combination with leucovorin, which boosts its effects -- was the chemotherapy of choice for colon cancer, sparking a 26% drop in death rates compared to patients undergoing surgery alone. But in 2004, several U.S. National Cancer Institute studies indicated that by adding oxaliplatin to the 5-FU mix, patients could see survival rates rise by yet another 23%. To determine whether oxaliplatin would show a similar benefit among a "real-world" population of patients, the authors sifted through five cancer registries containing survival information on more than 4,000 people with stage III colon cancer. All were younger than 75, and all had

begun chemotherapy -- either a standard regimen or in combination with oxaliplatin -- within four months of having surgery between 2004 and 2009. Researchers compared their survival rates with those of nearly 8,300 patients who had participated in one of five different clinical trials using oxaliplatin. The addition of oxaliplatin to standard chemotherapy protocols was found to be just as effective in prolonging survival among the community-based set of patients -- including the elderly, minorities and those with additional complicating health issues -- who were not enrolled in studies.

Sanoff, Hanna, et al., Comparative effectiveness of oxaliplatin vs non oxaliplatin-containing adjuvant chemotherapy for stage III colon cancer. J Natl Cancer Inst. First Published online January 20, 2012.

4. Adding Avastin to Xeliri or Folfiri: Both Are Equally Effective (Jan. 25/12)

When Avastin is added to the combination of Xeloda and irinotecan as an initial treatment for advanced colorectal cancer, the treatment is equally effective as Avastin with FOLFIRI. But side effects did differ. After a randomized clinical trial comparing Avastin with XELIRI (Xeloda, irinotecan) to Avastin with FOLFIRI (5-FU, leucovorin, irinotecan), researchers concluded that excessive side effects made using the XELIRI combination unwise. Efficacy-wise there were no significant differences between the two regimens for:

- median progression-free survival(10.0 for FOLFIRI and 8.9 months for XELIRI)
- overall survival (25.7 and 27.5 months)
- response rates (45.5% and 39.8%)

However, diarrhea, fever due to low white cell blood counts, and hand-foot syndrome were significantly more common in patients treated with XELIRI. They also had more treatment delays and dose reductions, and discontinued treatment because of more side effects. Researchers concluded: The progression-free survival of FOLFIRI-Bevacizumab is not superior to that observed with the CAPIRI-Bev regimen. CAPIRI-Bev has a less favorable toxicity profile, requiring dose reductions, in order to be considered as an option in first-line treatment of patients with metastatic colorectal cancer.

Souglakos, J, et al., Randomized phase II trial of capiri (capecitabine, irinotecan plus bevacizumab vs folfiri (folinic acid, 5FU, irinotecan) plus bevacizumab as first line treatment of patients with unresectable/metastatic colorectal cancer (mrcr). British J of Cancer (2012). 106: pp.453-459.

5. Avastin Helpful in Second Line Treatment (Jan. 26/12)

A phase III study (ML 18147) in metastatic colorectal cancer met its primary endpoint of overall survival. People who received Avastin® (bevacizumab) plus standard chemotherapy as initial treatment (so-called “first-line” treatment) for their metastatic colorectal cancer and then continued on Avastin with a different chemotherapy after their cancer progressed (so-called “second-line” treatment) lived significantly longer than people who received only chemotherapy in the second-line setting. No new safety findings were observed and adverse events were consistent with those seen in previous trials of Avastin. Avastin is already a recognized standard of care which can help people with metastatic colorectal cancer live longer when given in combination with chemotherapy in the first or second-line setting. Researchers are encouraged by these data as this is the first randomized study which demonstrates improved survival in people who continue on an Avastin-based regimen after the disease has progressed.

About the **ML 18147 study**: ML 18147 is a randomized, open-label phase III intergroup study (AIO/AMG) evaluating the efficacy and safety profile of Avastin plus standard chemotherapy in patients with metastatic colorectal cancer whose disease had worsened following first-line treatment with Avastin plus standard chemotherapy (irinotecan or oxaliplatin-based). Patients were randomized at progression to one of two treatment arms:

- Arm A: Chemotherapy* plus Avastin
- Arm B: Chemotherapy* alone

*Depending on the first-line chemotherapy backbone (Fluoropyrimidine / Irinotecan-based or Fluoropyrimidine / Oxaliplatin-based) the chemotherapy backbone was switched in the second-line setting. The primary endpoint of the study was overall survival measured from the time patients were randomized to the second-line regimen. The secondary efficacy endpoints of the study included progression-free survival, overall response rate and overall survival from the start of first-line therapy.

http://www.roche.com/investors/ir_update/inv-update-2012-01-26.htm

6. Xeloda v.s. 5FU in Chemoradiotherapy for Rectal Cancer (Jan. 26/12)

This study sought to evaluate the safety and efficacy of preoperative radiotherapy (RT) combined with bolus infusional 5-fluorouracil (5-FU) or oral capecitabine (xeloda) in patients with locally advanced rectal cancer (LARC). Seventy-four patients were retrospectively analyzed. Twenty-seven patients were treated with 5-FU and leucovorin for 5 days/week during week 1 and 5 of RT. Forty-seven patients were treated with capecitabine twice daily for 5 days/week. Both groups received the same RT course for 5 weeks. Patients underwent surgery in 6 weeks after completion of the chemoradiotherapy. Data of the

observational study were collected. Grade 3 or 4 toxicities occurred in 40.7% (5-FU) and 19.1% (capecitabine) of the patients. Six patients in the 5-FU group (22.2%) and six patients in the capecitabine group (14%) achieved complete response. Primary tumor (T) down staging was achieved in 51.9% (5-FU) and 69.8% (capecitabine) of the patients. Researchers concluded that in consideration of the better down staging rate, less severe toxicities, and no need for indwelling intravenous device in the oral capecitabine regimen, the administration of oral capecitabine with RT may be a more favorable option in the neoadjuvant treatment for LARC.

Chen, Chin Fan, et al., A observational study of the efficacy and safety of capecitabine versus bolus infusional 5-FU in pre-operative chemoradiotherapy for locally advanced rectal cancer. International J of Colorectal Disease. Online first.

7. Regorafenib Shows Promise Against Metastatic Colorectal Cancer (Jan. 31/12)

The investigational drug **regorafenib** improves survival and delays cancer progression among patients with metastatic colorectal cancer that has worsened in spite of other treatments. These results were presented at the 2012 Gastrointestinal Cancers Symposium. Targeted therapies are anticancer drugs that interfere with specific pathways involved in cancer cell growth or survival. Some targeted therapies

- block growth signals from reaching cancer cells;
- others reduce the blood supply to cancer cells;
- and still others stimulate the immune system to recognize and attack the cancer cell.

Depending on the specific “target,” targeted therapies may slow cancer cell growth or increase cancer cell death. Regorafenib is an investigational targeted therapy that targets multiple biological pathways involved in cancer development. To evaluate regorafenib for the treatment of metastatic colorectal cancer, researchers conducted a Phase III clinical trial among 760 patients whose cancer had progressed (worsened) after standard treatment. Study participants were treated with either regorafenib or a placebo. All study participants also received best supportive care (care to manage symptoms).

- Overall survival was 6.4 months among patients treated with regorafenib and 5.0 months among patients treated with placebo.
- The disease control rate (either stable disease or a reduction in detectable cancer) was 44% among patients treated with regorafenib and 15% among patients treated with placebo.
- The most common severe side effects in the regorafenib group were hand-foot skin reaction (17%) and fatigue (15%).

These results suggest that regorafenib may benefit patients who have previously treated metastatic colorectal cancer. Some patients benefited more than others, and researchers are now exploring the reasons for this.

Grothey A, et al. Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients (pts) with metastatic colorectal cancer (mCRC) who have progressed after standard therapies. Paper presented at: 2012 Gastrointestinal Cancers Symposium; January 19-21, 2012; San Francisco, CA. Abstract LBA385.

8. Lactate Dehydrogenase Levels May Be a Predictor of Avastin’s Efficacy in First Line Therapy (Feb.3/12)

According to the results of this study, lactate dehydrogenase (LDH – please see below for description) may represent a predictive factor in colorectal cancer patients treated with bevacizumab (better known as avastin). Researchers explored the role of pre-treatment LDH levels in the blood of colorectal cancer patients receiving first-line bevacizumab. Metastatic colorectal cancer patients treated with first-line bevacizumab were eligible. A control group including all consecutive patients treated with chemotherapy alone was also considered. Pre-treatment LDH serum levels were collected for all cases. Median progression-free survival (PFS – time before the disease got worse) in the control group for patients with high and low LDH levels was 4.2 and 8 months, respectively. Median overall survival (OS) was 19.6 and 34.9 months for patients with high and low LDH levels, respectively). In the bevacizumab group, partial responses were seen in 14 (58%) high-LDH and 8 (14%) low-LDH patients, respectively; median PFS was 7.3 and 8.5 months, respectively and median OS was 22 and 26.6 months, respectively. Researchers concluded that **high LDH** levels correlated with **worse prognosis**. Bevacizumab seemed capable of improving patient outcomes in this specific group of patients. The improved response rate also suggests a role for LDH as a predictive marker.

Lactate Dehydrogenase:

Lactate dehydrogenase (also called lactic acid dehydrogenase or LDH) is an enzyme found in almost all body tissues. It plays an important role in cellular respiration, the process by which glucose (sugar) from food is converted into usable energy for our cells. Although LDH is abundant in tissue cells, blood levels of the enzyme are normally low. However, when tissues are damaged by injury or disease, they release more LDH into the bloodstream. Conditions that can cause increased LDH in the blood include liver disease, heart attack, anemia, muscle trauma, bone fractures, cancers, and infections such as meningitis, encephalitis, and HIV.

Scartozzi, M, et al., Pre-treatment lactate dehydrogenase levels as predictor of efficacy of first line bevacizumab-based therapy in metastatic colorectal cancer patients. British J of Cancer. Feb. 7, 2012. Published online first.

9. Quebec-based Phase II Clinical Trial Involving Pentamidine for mCRC Patients Undergoing Second Line Therapy (Feb. 17/12)

The purpose of this study is to investigate the safety and efficacy of the use of OCZ103-OS or Pentamidine in combination with standard of care (folfiri or folfox) for metastatic colorectal cancer patients with disease progression following a first line treatment. The objectives of the study are:

- To assess the efficacy of OCZ103-OS in prolonging overall survival duration in metastatic colorectal cancer patients treated concurrently with mFOLFOX6 or FOLFIRI.
- To assess the efficacy of OCZ103-OS in prolonging progression free survival duration in metastatic colorectal cancer patients treated concurrently with mFOLFOX6 or FOLFIRI.

For more information, please visit <http://www.colorectal-cancer.ca/en/research-treatments/listing-trials/> or visit the Oncozyme website at:

http://www.oncozymepharm.com/index.php?option=com_content&view=article&id=5&lang=en

http://www.oncozymepharm.com/index.php?option=com_content&view=article&id=5&lang=en

SURGICAL THERAPIES

10. The significance of Percentage Drop in CEA Post Curative Colon Surgery (Jan.26/12)

This study aimed to analyze the hypothesis that increased percentage drop in serum CEA post curative resection for colon cancer is associated with improved survival. Five hundred thirty three patients who underwent colon resection with a curative intent were retrospectively analyzed for their pre- and postoperative CEA levels. The estimated 5-year overall survival for the preoperative serum CEA > 5 ng/mL group with respect to a postoperative CEA level drop rate of **40%, 50% and 60% were 72.9%, 80.9% and 81.8%, respectively.** The estimated 5-year overall survival for the preoperative serum CEA ≤ 5 ng/mL group with respect to each postoperative CEA level drop rate were **86.6%, 97.1% and 97.7%,** respectively. The prognostic factors for poor survival were the depth of invasion and lymph node metastasis. A 60% drop of the CEA level was an independent prognostic factor for survival for patients with a preoperative CEA level > 5 ng/mL. Researchers concluded that determining the preoperative CEA level and the early postoperative percent drop of the serum CEA level may be a helpful factor for the prognosis of colon cancer patients. However, the percent drop from the pre to postoperative CEA level from the normal range was not associated with survival difference.

Lee, Won-Suk, et al., The prognostic significance of percentage drop in serum CEA post curative resection for colon cancer. Surg Onc. Vol. 21, Issue 1: pp. 45-51.

11. Study on Stent Therapy for Unresectable Colorectal Obstruction (Jan. 20/12)

This phase II study of stent therapy for unresectable malignant colorectal obstruction was conducted to determine its clinical efficacy, safety, and procedural feasibility. Study participants consisted of 33 patients having unresectable obstruction of the rectum or sigmoid colon. The treatment protocol was to place an uncovered metal stent through the anus in an obstructive portion under x-ray fluoroscopic guidance. The patients were followed for 4 weeks after therapy, and the degree of improvement in subjective symptoms lasting ≥2 weeks was assessed as effective when the patient was decompressed with stent, or ineffective when not decompressed. The rate of clinical efficacy was defined as the proportion of effective cases. Treatment was effective in 27 patients, ineffective in 4, and unassessable in 1, yielding a clinical efficacy rate of 81.8% (27/33). Death owing to underlying disease stent removal owing to anal pain and occlusion at another location were noted. No recurrences were seen among clinically effective cases. Adverse reactions included grades 2 to 3 diarrhea (n=12), pain (n=5), bleeding (n=1), and dysuria (n=1), but no grade 4 adverse reactions or treatment-related deaths were identified. The researchers concluded that stent therapy for unresectable malignant colorectal obstruction is effective, safe, and feasible.

Inaba, Yoshitaka, et al., Phase II clinical study on stent therapy for unresectable malignant colorectal obstruction (JIVROSG-0206). Amer J of Clin Onc. Vol. 35; Issue 1: pp. 73-76.

RADIOTHERAPY / INTERVENTIONAL RADIOLOGY

12. Phase II Study of ThermoDox in Combination with RFA in Colorectal Liver Mets (Feb.13/12)

The first patient has been enrolled in a randomized Phase II study involving ThermoDox®, a heat-activated liposomal encapsulation of doxorubicin, in combination with radiofrequency ablation (RFA) for

the treatment of colorectal liver metastases (CRLM). The multicenter Phase II study is expected to enroll up to 88 patients with colorectal cancer metastasized to the liver. Patients will be randomized to receive either RFA plus ThermoDox® or RFA alone for the treatment of their liver tumors. Dr. Steven K. Libutti, Professor and Vice Chairman, Department of Surgery and Director of the Montefiore-Einstein Center for Cancer Care at the Montefiore Medical Center and the Albert Einstein College of Medicine in New York City, will serve as the Lead Principal Investigator for the study. In addition to Montefiore, leading research institutions from North America will be included in the Phase II study. The primary study endpoint is based on one year local tumor recurrence, with secondary endpoints of time to progression and overall survival. The liver is a common site of metastases for cancers of the colon and rectum, as it provides a favorable environment for their growth and proliferation. Addressing these metastases allows researchers to improve three- and five-year survival rates among patients with this aggressive disease. While RFA can be effective in treating these tumors, it is often limited to smaller metastases within the liver. Adding ThermoDox® to RFA as adjuvant therapy is a combination which has demonstrated early clinical promise in treating larger tumors and multifocal disease. ThermoDox® is a proprietary heat-activated liposomal encapsulation of doxorubicin, an approved and frequently used oncology drug for the treatment of a wide range of cancers. Localized mild hyperthermia (39.5 - 42 degrees Celsius) created by the RFA releases the entrapped doxorubicin from the liposome. This delivery technology enables high concentrations of doxorubicin to be deposited preferentially in a targeted tumor.

<http://www.marketwire.com/press-release/celsion-announces-first-patient-enrolled-phase-ii-study-thermodoxr-combination-with-nasdaq-clsn-1618740.htm>

SCREENING

13. **New Screening Test Offers Greater Accuracy in Early Detection of CRC** (Jan. 18/12)

Results of 2 studies suggest that a new, investigational colorectal cancer screening test is highly accurate and significantly more sensitive than other noninvasive tests at detecting adenomas and early-stage cancer. Early detection is a key driver of better outcomes for colorectal cancer. The first study shows that a new multi-marker stool DNA test is highly accurate at detecting precancerous polyps and early-stage colorectal cancer. This is the first large-scale, blinded study to measure the new test's effectiveness. The second study shows that the stool DNA test is significantly more accurate than a new plasma test for identifying patients with large precancerous polyps or colorectal cancer, while delivering fewer false-positive results. The findings in these studies underscore the great potential of the stool DNA test as a colorectal cancer screening tool. Along with its high accuracy, this test approach could improve participation rates due to its patient-friendly features. The test is noninvasive; requires no bowel preparation, medication restriction, or diet change; and can be performed on mailed-in samples without the need, expense, or inconvenience of a health care visit. The stool DNA test works by finding signature genetic markers in stool samples mailed in by patients. A positive test would be followed by a colonoscopy to remove the polyps and prevent a subsequent cancer from forming. The first article features results from the first large-scale study to measure the test's accuracy. Across nearly 400 cases, the stool DNA test detected 87% of curable-stage colorectal cancer. Importantly, detection sensitivity was not affected by tumour location or stage. The test detected the majority of large precancerous polyps at high risk for cancer progression. Sensitivity was 64% for polyps >1 cm, 77% for those >2 cm, and 92% for those >4 cm. In the second article, researchers used the results of the first study to compare the sensitivities of the stool DNA test and a plasma test for methylated Septin 9 (SEPT9) in identifying patients with large adenomas or colorectal cancer. Results showed that the stool DNA test detected 82% of precancerous polyps compared with only 14% detected by SEPT9. The stool DNA identified 87% of cancers at any stage, compared with 60% with SEPT9. Stool DNA was even more effective at detecting curable-stage cancer (Stage I, II or III), detecting such cases 91% of the time, compared with just 50% with SEPT9. The SEPT9's rate of false-positives was nearly 4 times that of stool DNA (27% vs 7%). It was important to compare tests head-to-head. Cancerous and pre-cancer cells are shed into the stool and detected by the stool DNA test long before tumours progress to invade the bloodstream for later detection by the plasma SEPT9 screening test.

Ahliquist, David, et al., Next-Generation Stool DNA Test Accurately Detects Colorectal Cancer and Large Adenomas. Gastroenterology Vol. 142, Issue 2, Pages 248-256

Ahliquist, David et al., The Stool DNA Test Is More Accurate Than the Plasma Septin 9 Test in Detecting Colorectal Neoplasia. Clinical Gastroenterology and Hepatology.

14. **Oncotype DX Colon Cancer Test Changes Treatment in One Third of Patients** (Jan. 31/12)

A survey of oncologists suggests that the Oncotype DX colon cancer test changes treatment recommendations for 29% of patients with Stage II colon cancer. These results were presented at the 2012 Gastrointestinal Cancers Symposium. Gene expression profiling explores the patterns of genes that are active in tumor cells. Studies suggest that gene expression may provide important information about prognosis or likely response to treatment in several types of cancer. For example, among selected women with early-stage breast cancer, the Oncotype DX breast cancer test has been shown to predict the likelihood of cancer recurrence and the likelihood of benefit from chemotherapy. As a result, the test has been added to medical guidelines for early-stage breast cancer in the U.S. A similar test became

available for patients with Stage II colon cancer in 2010. Stage II colon cancer refers to cancer that extends through the wall of the colon but has not invaded lymph nodes or spread to distant parts of the body. Many patients with this stage of disease have good outcomes with surgery alone, and routine adjuvant (post-surgery) chemotherapy is not currently recommended for Stage II colon cancer. Chemotherapy may, however, be considered for Stage II patients with a higher risk of cancer recurrence. Previous research has demonstrated that the Oncotype DX colon cancer test provides information about the risk of recurrence among patients with Stage II colon cancer. Researchers are now evaluating how this information affects treatment decisions. In the current study, researchers surveyed US oncologists who had experience with the Oncotype DX colon cancer test. All participating oncologists had ordered the test for at least three patients with Stage II colon cancer, and were asked to provide treatment information for the most recent patient. The study is ongoing, and the current, preliminary analysis includes information from 92 oncologists.

- Among the patients who had an initial treatment plan (either chemotherapy or observation), 29% had a change in recommended treatment after the Oncotype DX test, including changes from chemotherapy to observation and vice-versa.

These results build upon previous studies of the Oncotype DX colon cancer test by demonstrating that use of the test can influence treatment decisions for Stage II colon cancer.

Cartwright T, et al. Effect of Oncotype® DX Colon Cancer Test Results on Treatment Recommendations in Patients with Stage II Colon Cancer: Preliminary Results. Paper presented at: 2012 Gastrointestinal Cancers Symposium; January 19-21, 2012; San Francisco, CA. Abstract 398.

15. Repeat Flexible Sigmoidoscopy Increases Detection of CRC (Feb.1/12)

Repeated screening by flexible sigmoidoscopy (FSG) increases the detection of colorectal cancer or advanced adenoma in women and men, according to the results of this study. Investigators reported outcomes from participants of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial who were randomly assigned to receive FSG. Patients were screened by 60-cm FSG at study entry and three or five years later. The researchers found that, of 77,447 enrollees, 86.6% had at least one FSG and 50.9% had two FSGs. Diagnostic intervention occurred in 74.9 and 78.7% of patients after a positive first or repeat FSG, respectively. The screening yield increased by 32% based on the second FSG. After the first screening, colorectal cancer or advanced adenoma was detected in 37.8 per 1,000 persons, and after all screenings, in 49.8 per 1,000 persons. The yield of cancer or advanced adenoma was increased by the second FSG by 26% in women and by 34% in men. Of 223 subjects who received a diagnosis of colorectal carcinoma within one year of a positive FSG, stage I and II disease were seen in 64.6 and 17.5%, respectively. The authors conclude: "Repeat FSG increased the detection of colorectal cancer or advanced adenoma in women by one-fourth and in men by one-third".

Weissfeld, Joel, et al., Flexible sigmoidoscopy in the randomized prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial: added yield from a second screening examination. J of the National Cancer Institute. First published online Jan. 31, 2012

OTHER

16. Mucinous Adenocarcinomas in Metastatic Colorectal Cancer (Jan. 23/12)

In this large retrospective analysis of patients with mucinous metastatic colorectal cancer, it was shown that mucinous cancers have distinct clinical, pathologic, and genetic characteristics and the mucinous histology is a strong negative prognostic factor. Mucinous histology of metastatic colorectal cancer (CRC) has been associated with poor prognosis; however this has never been assessed in large well-defined study populations treated with the currently used systemic agents. Researchers investigated the prognostic value of mucinous histology in two large phase III studies in metastatic CRC. The study population included 1010 metastatic CRC patients who were treated with chemotherapy and targeted therapies in two phase III studies. Patients were classified according to the histology of the primary tumour in mucinous adenocarcinomas (MC) and non-mucinous adenocarcinomas (AC). Patients with MC (n=99) were older, had more often a normal serum lactate dehydrogenase (LDH – please see item #8 in this document for an explanation), extrahepatic localization of metastases, larger primary tumour diameter and a higher T classification compared to patients with AC (n=911). A deficient mismatch repair system and BRAF mutations were observed in 17% and 22% of patients with MC, compared to 3% and 7% in patients with AC, respectively. Clinical outcome was investigated in both studies separately, showing a worse overall survival (OS), progression free survival and overall response rate in patients with MC compared to patients with AC. Patients with MC received fewer cycles of treatment compared to AC, but did not suffer from a higher incidence of grade 3/4 toxicity. Researchers therefore concluded that patients with metastatic mucinous CRC have distinct clinico-pathological features and poor response to chemotherapy and targeted agents. The strong negative prognostic value of MC warrants the use of this pathological feature as a stratification factor for clinical trials in metastatic CRC.

[About Mucinous Adenocarcinoma:](#)

Colorectal cancer comes in many forms, including:

- adenocarcinoma,
- leiomyosarcoma,
- lymphoma,
- melanoma, and
- neuroendocrine tumors.

Adenocarcinoma is the most common type of colorectal cancer and has two subtypes, signet ring cell and mucinous adenocarcinoma. "Adeno-" is a prefix that means "gland". In general, glands secrete things and are classified as endocrine or exocrine. Endocrine glands secrete things into the bloodstream, like hormones. Exocrine glands secrete things that go outside of the body, like mucus and sweat. A carcinoma is a malignant tumour that starts in epithelial tissue. When the two words are put together, you get "adenocarcinoma," which means a malignant tumor in epithelial tissue, specifically in a gland.



A mucinous colorectal tumour. Source: <http://mucinous.org/>

The term "mucinous" means that something has a lot of mucus. Adenocarcinomas that are comprised of at least 60% mucus are referred to as mucinous adenocarcinomas. Scientists think that the presence of mucus allows cancer cells to spread faster. As a result, mucinous adenocarcinomas are considered more aggressive than regular adenocarcinomas. Mucinous adenocarcinomas account for approximately 10-15% of all adenocarcinomas. Source: http://coloncancer.about.com/od/typesofcancer/a/Mucinous_Tumor.htm

Mekenkamp, LJM, et al., Mucinous adenocarcinomas: poor prognosis in metastatic colorectal cancer. Eur J Cancer, Jan. 6, 2012. Epub Ahead of Print.

17. Emergency Room Presentation Not The End for CRC Patients (Jan. 24/12)

According to the results of this study, curative therapy is still a possibility, even if a colon cancer patient is seen for the first time in the emergency department with acute symptoms such as abdominal pain, bleeding, and obstruction. Emergency presentation as the first indication of colorectal cancer is generally thought to be associated with advanced disease and poor outcome. Yet, in a retrospective analysis of 376 colon cancer patients identified in a three-year period, 33 presented to the emergency department with acute symptoms and only 15.5% of those were given only palliative treatment. In comparison, of the 339 patients who initially presented in other departments, 20.5% received palliation. Better than 80% of these patients proved eligible for curative intent surgery, radiation therapy, and chemotherapy. The goal of this study was to describe the characteristics of patients presenting to the emergency department at their index diagnosis, and to determine whether emergency presentation precludes treatment with curative intent. The authors pulled data from their institution's registry to identify colorectal cancer patients diagnosed from 2008 to 2010. Emergency medical records were reviewed to identify which patients presented to the emergency department with acute symptoms of colorectal cancer as the initial sign of their illness. Of the 376 patients, 57% were male and 43% were female, with mean age of 60.6. The authors found that acute emergency department presentation with colorectal cancer symptoms did **not** preclude treatment with curative intent. Compared with presentation in other departments, patients who presented emergently were more likely to be female (64% versus male 41%) and older (65 versus 60). There was no statistically significant relationship between age, gender, tumor location or type, and treatment approach. Individuals who first present with symptoms in the emergency department should not be considered as having untreated, incurable disease, the authors state. The assumption is that patients who present with symptoms must be further along in their disease course, and therefore are more likely to just get palliative therapy and die. For some reasons which are unclear right now, presenting emergently doesn't have much relation to the extent of their disease. The take-home message from this study is that the vast majority of people who present with symptoms of colon cancer are still curable. However, researchers noted that the study did not describe the type of colorectal cancer patients who presented to the emergency room: Financially sound individuals with health insurance are more likely to seek care compared with individuals who do not have health insurance or do not regularly see doctors until they experience acute symptoms.

Barnett A, et al Curative versus palliative therapy for patients with colorectal cancer presenting to the emergency department. J Clin Oncol 2012; 30(4); Abstract 433.

18. The Connection between Inflammation, Methylation and Cancer Growth (Jan. 29/12)

Two seemingly separate influences have been found to promote colorectal cancer when they occur together. New research published revealed that while chronic inflammation occurs with DNA methylation (see description below), it promotes the development of cancer by blocking the genes that would normally fight it. The findings could help the treatment of colorectal cancer with the possibility of

combination therapies. Study researchers explain that scientists knew that chronic inflammation increases cancer risk and progression, while it was also known that in colorectal cancer, tumour-suppressing genes are shutdown. However, nobody had made a molecular connection between these inflammatory mediators and changes in gene expression or silencing of genes through affects on DNA methylation. On experiments with mice, while the use of either anti-inflammatory drug or a demethylating agent shrunk the number and size of tumour, combined use had the most significant impact.

Methylation:

Methylation is a process in which certain chemicals called 'methyl groups' are added to various constituents of proteins, DNA and other molecules. These are needed to keep them in good 'working' condition. Methylation of certain parts of your DNA can switch off unnecessary genes and prevent abnormal DNA division. This means that these abnormalities are not passed on to future generations of cells...a most important component in successful aging. *As we age the methylation processes in our bodies start getting 'tired' and become less efficient with a resulting build up of homocysteine, DNA damage and the development of other flow on effects such as depression.*

Xia, Dianren, et al., . Prostaglandin E2 promotes intestinal tumor growth via DNA methylation. Nature Medicine, 2012; DOI: [10.1038/nm.2608](https://doi.org/10.1038/nm.2608)

19. Possible Link Between Colorectal Cancer and Gum Disease (Feb.14/12)

The bacteria associated with the most common cause of tooth loss in adults could be a pre-cursor for the development of colorectal cancer, according to a team of scientists. The link comes as scientists at the Dana-Farber Cancer Institute and the Broad Institute in America found an abnormally large number of *Fusobacterium* – a bacterium associated with the development of periodontal disease – in nine colorectal tumour samples, pointing to the possibility the two could be associated. Although lead author believes further research is needed to discover the extent of the link, the research suggests the bacterium could be a factor in the development of cancer. At this point, researchers don't know what the connection between *Fusobacterium* and colon cancer might be. It may be that the bacterium is essential for cancer growth, or that cancer simply provides a hospitable environment for the bacterium. Further research is needed to see what the link is.

Castellarin, Mauro, et al., Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res. 2012. 22: 299-306.

20. Fusion Genes May Guide Treatment with Targeted Therapies (Feb.16/12)

Novel gene abnormalities discovered in lung and colorectal tumors could potentially identify patients with a good chance of responding to highly specific "targeted" drugs already in use for treating other cancers. The genetic alterations -- pieces of two genes fused together -- showed up in a massive search of the DNA in stored tumor samples of non-small cell lung cancer and colorectal cancer. These specific genetic abnormalities had not been previously linked to the two cancer types. Other cancers with similar genetic alterations often respond to "targeted" drugs that block overactive proteins called tyrosine kinase inhibitors. This suggests that the same drugs may also be effective against lung and colorectal tumors driven by the newly found gene fusions. Because these drugs are already approved to treat cancer, it should be possible to move rapidly to clinical trials in colorectal and lung cancer, the authors claim. If the trials are successful, physicians could potentially test patients' tumors for the presence of the gene fusions and prescribe a medication matched to those alterations. Scientists also sequenced DNA samples from 40 patients with colorectal cancer. Along with numerous known mutations, the researchers identified a novel gene alteration, **C2orf44-ALK**, that causes a 90-fold over-expression of the ALK protein leading to cancerous proliferation. Over expressed ALK is also found in a small percentage of lung cancer cases and can be inhibited by the targeted drug **crizotinib**. This raises the possibility of using crizotinib to target the C2orf44-ALK fusion gene in colorectal cancer, the researchers maintain.

Jänne, Pasi A., et al., Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. Nature Medicine, 2012; DOI: [10.1038/nm.2673](https://doi.org/10.1038/nm.2673)

NUTRITION & HEALTHY LIFESTYLE

21. Vitamin D Again Linked to Lower Colorectal Cancer Risk (Jan. 17/12)

According to the results of this study, high blood levels of vitamin D may lower the risk of colorectal cancer by almost 40%, and the effects were influenced by certain genes. Dietary intakes of calcium were also linked to a reduction in colorectal cancer risk, with increased blood levels of the mineral also linked to reductions in the region of 30%. The influence of genes appeared limited to the sunshine vitamin however, with vitamin D levels found to interact with specific sections of the vitamin D receptor gene, with increased vitamin D levels linked to even greater risk reductions with some forms of the gene. These findings underline the importance of vitamin D in colorectal carcinogenesis, at least in its early stage. The investigators confirmed that maintaining optimal vitamin D status is important for reducing risk of colorectal cancer independent of the calcium effect.

22. **Celery & Carrots May Help Cut Colon Cancer** (Jan. 29/12)

Korean researchers say carrots and celery may help lower the risk of colon cancer. In their study, doctors discovered the antioxidant luteolin is capable of blocking the cell signals needed for colon cancer growth. Previous research has shown luteolin might be a cancer-preventing agent, but this new study is the first to show that the antioxidant inhibits cell signals needed for growth. Although there are risk factors that can't be changed such as age and family history, there are lifestyle factors you can control like physical inactivity and diet. Other foods high in luteolin include parsley, hot peppers and lemons.

<http://latino.foxnews.com/latino/health/2012/01/25/celery-and-carrots-may-help-cut-colon-cancer-risk-researchers-say/>

23. **Intake of Selected Micronutrients & Risk of Colorectal Cancer** (Jan. 30/12)

The impact of micronutrient intake and colorectal cancer (CRC) risk is poorly understood. The objective of this study was to evaluate the associations of selected micronutrients with risk of incident CRC in study participants from Newfoundland, Labrador (NL) and Ontario (ON), Canada. Researchers conducted a population-based study among 1760 case participants and 2481 age- and sex-matched control participants. Information on diet and other lifestyle factors were measured using a food frequency questionnaire and a personal history questionnaire. Highest compared to lowest quartile intakes of certain micronutrients were associated with lower risk of CRC, including:

- calcium (from food and supplements,
- vitamin C
- vitamin D
- riboflavin and
- folate

Higher risk of CRC was observed for **iron intake**. The authors concluded that this study presents evidence that dietary intake of calcium, vitamin D, vitamin C, riboflavin and folate are associated with a lower risk of incident CRC and that dietary intake of iron may be associated with a higher risk of the disease.

*Sun, Zhouyu, et al., Reported intake of selected micronutrients and risk of colorectal cancer: results from a large population-based case-control study in Newfoundland, Labrador and Ontario, Ontario. *Anticancer Research*. Vol. 32, No.2: pp.687-696.*

24. **Eating Fish Tied to Lower Risk of Colon Polyps** (Jan.31/12)

According to the results of this study, women who eat about three servings of fish per week have a somewhat lower chance of having polyps found during a routine colonoscopy than women who eat just one serving every two weeks. A polyp, also called an adenoma, is a mushroom-shaped tag of tissue that grows in the colon and can develop into colorectal cancer. The idea researchers have been pursuing is that the omega-3 fats in fish might have an anti-inflammatory effect, similar to aspirin that could prevent the development of polyps. Earlier experiments in animals have shown that omega-3 fats can reduce the risk of this cancer, but that studies of humans have had mixed results. In the latest study, the researchers surveyed more than 5,300 people about their eating habits. All of the participants had come in to the researchers' practices for a colonoscopy. The team then compared more than 1,400 women without polyps to 456 who had adenomas detected during the procedure. Among women with adenomas, 23% were in the bottom fifth among fish eaters, while 15% were in the top fifth. That means people who eat lots of seafood are somehow protected against polyps, because otherwise the percentages should have been the same. After accounting for differences like age, smoking and aspirin use, women who ate the most fish -- three servings a week -- were 33% less likely to have a polyp detected than those who ate the least -- less than a serving a week. Of course, it's never possible to rule out that other factors could explain the findings. For instance, it's possible that fish lovers have other healthy behaviors that decrease their risk of polyps. What's more, the study didn't follow the women to see whether either group was more likely to go on to develop cancer. But the lead author of the study said polyps are a reliable predictor for cancer risk. "Adenomas are generally believed to be the precursor" to cancer. The men in the study who ate a lot of fish did not see the same reductions in polyp risk as women, however. Researchers do not have a good explanation for that, but perhaps men are less sensitive to the omega-3s in fish and need to eat more to get any benefit. It could also be that men might eat more omega-6 fats, counteracting the effects of the omega-3s. Omega-6 fatty acids are related to the production of a hormone called prostaglandin E2, which is associated with inflammation. Researchers explained that eating omega-3 fatty acids tamps down the body's levels of omega-6 fatty acids. In turn, the body then has reduced levels of prostaglandin E2. They demonstrated this by showing that the women in the study who ate more fish -- and presumably, more omega-3s -- had lower levels of prostaglandin E2. "We know people who have higher levels of this (hormone) are more likely to develop colorectal cancer. So in essence, by eating more omega-3 fatty acids, it's almost like taking an anti-inflammatory medication," claim the researchers.

25. Alcohol Consumption & Risk of Colon Cancer (Feb.1/12)

A study based on more than 87,000 women and 47,000 men in the Nurses' Health Study and the Health Professionals Follow-up Study, looks at whether there is a link between colon cancer and alcohol, and if so at what level of consumption, and the importance of a family history of the disease. A total of 1,801 cases of colon cancer were diagnosed during follow-up from 1980 onwards. The authors results found that subjects with a family history, whose average alcohol intake was 30 or more grams per day (about 2 ½ typical drinks by US standards or 4 UK units) had an increase in their risk of colon cancer. Those at greatest risk also ate the most red meat, smoked the most, and had the lowest intake of folate (suggesting they ate fewer green vegetables and cereals). Hence, these people have the unhealthiest lifestyles in general of the populations studied. There was not a significant association between alcohol consumption and colon cancer among subjects without a positive family history in this study. Forum reviewers were concerned that the pattern of drinking (regularly or binge drinking) was not assessed, and that there was not a consistent increase in risk of cancer with greater alcohol intake found. Further, adequate folate intake was found to lower risk, with the highest risk for subjects with a positive family history of colon cancer, low levels of folate, and in the highest category of alcohol consumption, indicating the importance of other lifestyle facts such as a healthy diet. The present study provides some support for an association between higher levels of alcohol intake and the risk of colon cancer among subjects with a positive family history of such cancer.

Giovannucci EL, et al., Alcohol consumption and the risk of colon cancer by family history of colorectal cancer. Am J Clin Nutr 2012;95:413.

26. Aspirin As Prevention in Colorectal Cancer (Feb.3/12)

Considerable evidence supports the effectiveness of aspirin for chemoprevention of colorectal cancer (CRC) in addition to its well-established benefits in the prevention of vascular disease. Studies have consistently observed an inverse association between aspirin use and risk of CRC. Results from a recent study follow-up of nearly 14,000 patients from 4 randomized, cardiovascular disease prevention trials showed that daily aspirin treatment for about 5 years was associated with a 34% reduction in 20-year CRC mortality. A separate study of nearly 3,000 patients with a history of colorectal adenoma or cancer in 4 randomized adenoma prevention trials demonstrated that aspirin reduced the occurrence of advanced adenomas by 28% and any adenoma by 17%. Aspirin has also been shown to be beneficial in a clinical trial of patients with Lynch syndrome, a hereditary CRC syndrome; in those treated with aspirin for at least 2 years, there was a ≥ 50% reduction in the risk of CRC commencing 5 years after randomization and after aspirin had been discontinued. A few observational studies have shown an increase in survival among patients with CRC who use aspirin. Taken together, these findings strengthen the case for consideration of long-term aspirin use in CRC prevention. Despite these compelling data, there is a lack of consensus about the balance of risks and benefits associated with long-term aspirin use, particularly in low-risk populations. The optimal dose to use for cancer prevention and the precise mechanism underlying aspirin's anticancer effect require further investigation.

Chan, Andrew, et al., Aspirin in the chemoprevention of colorectal neoplasia: an overview. Cancer Prev Research. Published online first. Feb. 2012; 5, 164.

27. Reducing Risk of Colon Cancer with Regular Use of Vitamin & Mineral Supplements (Feb.6/12)

A study found that rats given regular multivitamin and mineral supplements showed a significantly lower risk of developing colon cancer when they were exposed to carcinogens (cancer causing agents). It has been unclear whether multivitamin supplementation to cancer patients is helpful, has no effect, or is even detrimental during therapy. This study is important because it gives some direction to cancer patients in desperate need of guidance on the value of multivitamins and minerals administered during cancer. The authors studied rats that were fed a high-fat diet (20% fat) over a 32 week period. The rats were divided into 6 groups, which were exposed to different combinations of supplements and carcinogens; the colon carcinogenesis induced in the study rats has characteristics that mimic human colon cancer. Rats fed a high-fat plus low-fibre diet and exposed to carcinogens developed pre-cancerous lesions; whereas, rats undergoing similar treatment, but **provided with daily multivitamin and mineral supplements**, showed a significant (84%) **reduction in the formation of pre-cancerous lesions and did not develop tumours**. The authors conclude that "multivitamin and mineral supplements synergistically contribute to the cancer chemopreventative potential, and hence, regular supplements of multivitamins and minerals could reduce the risk of colon cancer."

Baskar, Albert et al., Multivitamin and mineral supplementation in 1,2-dimethylhydrazine induced experimental colon carcinogenesis and evaluation of free radical status, antioxidant potential, and incidence of ACF. Canadian Journal of Physiology and Pharmacology, 2012; 90 (1): 45 DOI: [10.1139/y11-100](https://doi.org/10.1139/y11-100)