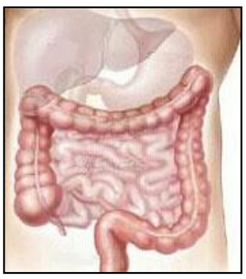
Colorectal Cancer Association of Canada

COLORECTAL CANCER RESEARCH UPDATES

Month Ending September 14th, 2012



The following colorectal cancer research update extends from August 18th, 2012 – September 14th, 2012 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Pre-operative Chemo Safely Treats Colorectal Liver Metastases (Aug.23/12)

According to the results of this study, preoperative chemotherapy may be administered safely without increasing postoperative complications in patients with colorectal cancer (CRC) and multifocal metastatic disease in the liver. There has been concern that the use of chemotherapy before liver resection may decrease the liver's ability to recover and lead to postoperative complications, but this study eases those concerns. Investigators did not see increased rates of liver cancer–related complications in the patients who had chemotherapy. Although preoperative chemotherapy has the potential to increase the number of surgical candidates by downsizing lesions, postoperative safety and survival have not been clearly delineated in patients who undergo this treatment. In the only prospective randomized trial to date that compares preoperative chemotherapy with no chemotherapy, investigators found disease-free survival (DFS) improved modestly in the preoperative chemotherapy group; however, overall survival (OS) did not differ significantly between the two groups. The study's investigators performed a retrospective review of all patients who had liver resections for metastatic CRC between 2003 and 2011to help clarify the usefulness of preoperative chemotherapy. The investigators analyzed data from 157 patients who had a total of 168 liver resections. Median length of follow-up from a first liver resection was 22.3 months. The data showed 114 patients (72%) underwent chemotherapy before liver resection, most frequently with FOLFOX (oxaliplatin, 5-fluorouracil [5-FU], leucovorin; 68%) or FOLFIRI (folinic acid, 5-FU, irinotecan; 12%) protocols. The mean size of lesions in the preoperative chemotherapy group was 3 cm compared with 4 cm in the no-chemotherapy preoperative group. After undergoing a liver resection, patients' OS was 89% at one year, 57% at three years and 27% at five years, and DFS was 61% at one year, 30% at three years and 23% at five years. There was no significant difference in overall complications nor in those related to the liver between patients who received preoperative chemotherapy and those who did not. The study team found that the presence of three or more lesions as well as age older than 70 years were significant predictors of poor survival. Additionally, the presence of several variables—such as older age and multiplicity and synchronicity of liver lesions—pointed to a subset of patients with a particularly high risk for recurrence. The presence of these variables justified the decision to recommend use of chemotherapy. The study team concluded that even with chemotherapy and aggressive resections, only a subset of patients remains free of disease after five years and that preoperative chemotherapy should be considered strongly in patients with risk factors.

Gur, Ilia, et al., Safety and Outcomes Following Resection of Colorectal Cancer Liver Metastases in the Era of FOLFOX. 53rd Annual Meeting of SSAT. 2012.

2. Common Antifungal Drug Shrinks Tumors (Aug.21/12)

An approved generic drug that has been in use for decades is showing promise as a treatment for cancer: in trials on mice it shrank tumors by disrupting their blood supply. Thiabendazole is a generic, FDA-approved, inexpensive antifungal and antihelminthic drug (a drug that expels parasitic worms) that can be taken orally and has been in clinical use for over 40 years. The drug is not currently used to treat cancer. Scientists from the University of Texas at Austin discovered the drug's potential to treat cancer almost by accident while looking for evolutionary links in yeast, frogs, mice and humans. The research team describes the drug's capacity as a "vascular disrupting agent" that destroys newly-established blood vessels. As tumors develop, they grow their own network of blood vessels to fuel their uncontrolled growth. So anything that starves tumors of their blood supply is worth investigating as a potential chemotherapy. In trials on mice, thiabendazole decreased blood vessel growth in fibrosarcoma tumors by more than 50%, and it also slowed the growth of the tumors**.** Fibrosarcomas are cancers of the connective tissue, and they generally have a strong network of blood vessels. More research is required before any conclusions can be made about its activity on cancer cells.

Cha, HJ, et al., Evolutionary repurposed networks reveal well known antifungal drug Thiabendazole to be a novel vascular disrupting agent. PloS Biology. In press 2012.

3. TAS-102 Offers Hope to Patients with Advanced Disease (Aug.27/12)

A new drug treatment could offer hope to patients with advanced colorectal cancer who were intolerant of or did not respond to standard treatments. The drug – called TAS-102 – was tested on 169 patients in Japan with inoperable, metastatic colorectal cancer. The patients had already undergone several rounds of standard chemotherapy, to no effect, or were intolerant of standard drug treatments (which include irinotecan, oxaliplatin, and a group of drugs known as fluoropyrimidines such as 5FU). Researchers found that, compared to placebo, patients treated with TAS-102 experienced improved survival time, reduced risk of death and better overall disease control, leading to hopes that the drug might one day be used as an effective treatment for advanced inoperable colorectal cancer. Patients who received TAS-102 had a median overall survival of 9 months, as compared to 6.6 months for the placebo group. The TAS-102 group were also 44% less likely to die during the trial period than those given placebo. Importantly, TAS-102 appears to be relatively safe, being well tolerated by most patients. While some patients experienced adverse reactions to the drug (mostly blood disorders), in all cases they were able to resume treatment after the blood disorder had been addressed. Results show that TAS-102 has a

promising efficacy and an easily manageable safety profile for a group of patients who have virtually no other treatment options available to them.

Yoshino, T, et al., TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomized placebo-controlled phase Ii trial. Lancet Oncol 2012; DOI: 10.1016/S1470-2045(12)70345-5

4. Clinical Significance of Increase in CEA in Patients with Metastatic Colorectal Cancer Receiving Chemotherapy (Sept.1/12)

An increase in carcinoembryonic antigen (CEA) and/or carbohydrate antigen 19-9 (CA19-9) levels is generally considered as tumor progression in patients with metastatic colorectal cancer (MCRC). However, a transient CEA surge has been observed in patients with MCRC responding to chemotherapy. This study sought to investigate the clinical significance of transient CEA/CA19-9 surges in Chinese MCRC patients. One hundred and twenty-one MCRC patients with histologically proven adenocarcinoma were treated with oxaliplatin and (or) irinotecan-based chemotherapy regimens. Blood CEA and CA 19-9 levels were measured before and after chemotherapy. Of the 121 patients, 14 (11.6%) had transient CEA surges with median baseline CEA level of 45 microg/L and median surge peak level of 80.1 microg/L. The transient CEA surge occurred at a median of 4 weeks (2-6 weeks), and lasted for a medium of 6.5 weeks (4-14 weeks). Of the 14 patients, 11 received oxaliplatin-based chemotherapy; three received irinotecan-based chemotherapy. All the 14 patients showed clinical benefit from chemotherapy, among which seven achieved partial response and seven had stable disease. In the meantime, five patients (3.8%) had transient CA19-9 surges. However, no significant correlation was found between an increase in the CA19-9 level and clinical benefits. The investigators concluded that transient CEA surges can be observed in Chinese MCRC patients receiving oxaliplatin or irinotecan-based chemotherapy, which **does not indicate** tumor progression, but good therapeutic efficacy. A transient elevation of CA19-9 is not correlated to short-term clinical benefits.

Li, Yu-Hong, et al., Clinical significance of a transient increase in carcinoembryonic antigen and carbohydrate antigen 19-9 in patients with metastatic colorectal cancer receiving chemotherapy. Chinese J of Cancer. 28(9).

5. Adjuvant Folfox in Stage II and Elderly Patients (Sept.2/12)

The agent 5-fluorouracil (5-FU) has long formed the backbone of adjuvant chemotherapy regimens for colon cancer. The addition of oxaliplatin to 5-FU and leucovorin in the FOLFOX regimen has potential therapeutic advantages but also risks greater side effects—most notably, cumulative neurotoxicity—so, it should be used judiciously. The survival benefits of combining oxaliplatin with a fluoropyrimidine were established in stage III disease during clinical trials in the 1990s. The benefit in stage II disease, however, has been less clear. Furthermore, due to discordance in ages between clinical trial enrollees and those in the community affected with colon cancer, skewing toward younger patients in the former group, the advantage of oxaliplatin in the elderly has also not been as convincingly demonstrated. The Multicenter International Study of Oxaliplatin/Leucovorin/Fluorouracil in the Adjuvant Therapy of Colon Cancer (MOSAIC) trial was integral to the acceptance of oxaliplatin as an efficacious agent in postoperative treatment, and Tournigand et al now performed a post hoc exploratory analysis of that landmark trial to investigate oxaliplatin's role in treating the subgroups of stage II disease and patients between 70 and 75 years of age. MOSAIC was an open-label randomization of 2246 patients to 12 cycles of either leucovorin followed by bolus and infusional 5-FU (FL), or the same regimen plus oxaliplatin (FOLFOX4). Within this cohort, there were 899 patients with stage II disease, of whom 451 received FOLFOX. High-risk stage II disease—defined as T4 stage, tumor perforation, bowel obstruction, venous invasion, poorly differentiated tumor, and/or <10 examined lymph nodes—was present in 569 patients, of whom 282 received FOLFOX. Disease-free survival (DFS – time to recurrence) was the primary endpoint. And, overall survival (OS) was a secondary endpoint. *Neither high- or low-risk stage II patients experienced DFS or OS benefits from FOLFOX4.* There were 315 patients aged 70 to 75, of whom 155 received FOLFOX. Compared with FL, ***FOLFOX did not improve DFS or OS.*** MOSAIC did not enroll patients older than 75, so it is not possible to draw conclusions about treatment of this age group. Among elderly patients who relapsed, FL recipients were more likely than FOLFOX recipients to undergo surgery for metastases or receive further chemotherapy (which could be oxaliplatin- or irinotecan-based). In conclusion, although MOSAIC was not designed for such exploratory analyses, these new data support 5-FU/LV as the standard of care for adjuvant treatment of elderly and high-risk stage II patients with colon cancer.

Tournigand, T, et al., Adjuvant therapy with fluorouracil and oxaliplatin in Stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the multicenter international study of oxaliplatin, fluorouracil, and leucovorin in the adjuvant treatment of colon cancer trial. J Clin Oncol. 2012 August 20; epub ahead of print.

SURGICAL THERAPIES

6. Treating Patients with Surgically Unresectable Metastatic Disease and an Intact Asymptomatic Colon Cancer (Aug.21/12)

Despite better screening for colorectal cancer (CRC), about 1 in 5 newly diagnosed patients will have metastatic CRC that already has spread to distant organs. Many will have symptoms of fatigue or weight

loss, but only a minority will have symptoms (significant bleeding or abdominal pain, or a blocked bowel) caused by the colon tumor itself. In those people first diagnosed with stage IV CRC, about 80% have metastases that cannot be removed by surgery. There's been intense debate—but no clear evidence—about whether patients whose colon tumor isn't causing symptoms should have the colon tumor surgically removed routinely before they start chemotherapy. A recent important study provides the first evidence that such patients often do just as well to start systemic chemotherapy immediately ***without*** having their colon tumor surgically removed. The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial is the first—and only—prospective multi-institutional study to study patients to see if they could be safely treated without initial surgery to remove a colon tumor not causing them symptoms. Colon surgery in people who have metastatic CRC can cause many more complications than surgery in people with early CRC. Previous retrospective studies (looking back in time) have shown a 30-day post-surgical death rate as high as 10% in metastatic cancer patients. Other studies have indicated that only 10 to 20% of those patients without primary-tumor symptoms will develop problems from the colon tumor itself. In this prospective, Phase II study, 86 patients (average age 58 years) were started immediately on a FOLFOX plus bevacizumab (Avastin) chemotherapy regimen. After a median follow-up of 20.7 months, results showed that most of the patients could be successfully managed without surgery. Complications from the primary colon tumor did arise in 12—or 14%–of the patients: Ten needed surgery (8 for obstruction, 1 for perforation, 1 for pain), and there were 2 deaths. In this particular study, 86% of the patients did not develop problems from the primary colon tumor that needed surgical removal or that shortened their survival time. In an accompanying editorial, Dr. George Chang of MD Anderson Cancer Center noted that this initial, small study doesn't settle the debate about how to start treatment in these patients. One major difficulty is deciding which patients are truly "asymptomatic" from their primary colon tumor. Another problem is that the study's participants were relatively young; and elderly patients suffer significantly more complications for later, emergency surgery to remove a primary tumor.

McCahill, Laurence E., et al., Primary mFolfox plus bevacizumab without resection of the primary tumor for patients presenting with surgically unresectable metastatic colon cnacer and an intact asymptomatic colon cancer: definitive analysis of NSABP trial C-10. J Clin Oncol. Published online before print August 6, 2012.

7. Preventing Surgical Infections Using Teamwork and Local Wisdom (Aug.27/12)

From 15 to 30% of people who have colorectal surgery will get a surgical-site infection—and those surgical infections (just among colorectal patients) cost an estimated $1 billion *a year*. The surgical infections cause longer hospital stays; are the most common cause of hospital readmission within 30 days; and require more doctor visits, wound-care supplies, and home care. Not to mention the added difficulties for patients and their families. A two-year study at Johns Hopkins Hospital describes how a team of front-line providers used their "local wisdom" plus an evidence-based safety system to cut their infection rate in colorectal surgery patients by 33.3% in one year. Reducing surgical infections improves patient care and saves dollars–a national priority shared by medical staff and patients alike. A national Surgical Care Improvement Project (SCIP) using standardized checklists and measures was launched six years ago, but four recent studies show little connection between compliance and overall patient outcomes. Leaders at Johns Hopkins Hospital decided to add an element seen in other successful quality-improvement programs—intentionally bridging the typical divide between front-line staff and the experts who bring in a standardized improvement system. They formed a team of surgery, anesthesia, nursing, and infection control leaders, plus a team coach (to facilitate meetings and manage improvement projects), and a hospital executive who could help front-line staff overcome institutional barriers. The leadership team also invited other interested front-line nurses, nurse anesthetists, scrub technicians, and anesthesiologists to join what became a 36-member team. They launched a CUSP (Comprehensive Unit-based Safety Program) that used the national SCIP checklist, but also added their own interventions to the checklist:

- Only surgical nurses, rather than a variety of staff, did the pre-op skin preparation on each patient ;
- All patients were given antibiotic-treated wash cloths to use the evening before surgery;
- After studying the literature, the team added oral antibiotics to routine pre-surgical mechanical bowel preparation;
- Because a separate hospital study showed that many patients were hypothermic both before and after surgery, they began warming patients in the pre-anesthesia area;
- When scrub technicians pointed out that instruments used for intestinal suturing were also frequently used for skin closure, the team designed a system to replace all instruments and change the entire teams' surgical gloves after completing the bowel work and again before beginning wound closure; and
- The team found and fixed lapses in giving antibiotics after surgery.

This last action showed why "local wisdom" might improve standardized checklists. Previous compliance was 99% with the national SCIP measure of "appropriate antibiotic selection." But frank talk on the team revealed that staff didn't think all patients were actually getting the correct medications. In fact, before the team was formed, only 33% of penicillin-allergic patients were getting recommended doses of the gentamicin/clindamycin recommended by the infection control staff. (Patients were either under-dosed or not receiving gentamicin because of concerns about side-effects.) After team intervention, 92% of patients received the correct antibiotics. Based on average costs of $6,000 to $10,000 per surgical-site

infection, the study authors estimated that by decreasing their infection rate by 33%, their hospital saved from $168,000 to $280,000 in one year alone— just among its 278 colorectal surgery patients. The authors described study limitations—it was not randomized; it was only at one hospital; and all improvement measures were introduced simultaneously and not analyzed separately for effectiveness. They called for further, multi-institutional studies. But their overall conclusion: “Formation of small groups of front-line providers to address patient harm using local wisdom and existing evidence can improve patient safety. “

http://fightcolorectalcancer.org/research_news/2012/08/preventing_surgical_infections_using_teamwork_and_local_wisdom

8. Number of Lymph Nodes Tested for Rectal Cancer May Be High (Sept.13/12)

The lymph node (LN) yield needed during rectal cancer surgery following long-course radiotherapy may be considerably less than that recommended for colon cancer, say the authors of a systematic review. "[Our findings] may force clinicians to re-adjust their expectations of what an appropriate LN harvest is especially in radiation treated rectal cancer," say the researchers. The authors reviewed 11 cohort studies of patients with rectal cancer who received long-course radiotherapy in a dose of 45.0-50.4 Gy prior to surgery. In accordance with previous findings, seven of the studies showed that long-course radiotherapy reduced the LN yield. The same proportion of studies also confirmed that patients with node-positive disease had poorer prognosis than those with node-negative disease. While current guidelines for colon cancer recommend a LN yield of 12, the authors identified only one study that showed that a LN yield greater than 11 led to a statistically significant survival benefit over those with a lower LN yield. This study included 210 patients with node-positive or locally advanced rectal cancer. Recurrence was significantly higher at 15.1% in patients with a LN yield less than 11 compared with 7.4% in patients with a yield greater than 11. Five-year cancer-specific survival was significantly greater in the high-yield group at 69.6% compared with 48% in the low-yield group. Another included study of 372 patients with node-negative rectal cancer showed that patients with a LN yield greater than seven had a 61% lower risk for relapse and a 55% lower risk for death from rectal cancer compared with patients with a LN yield lower than seven. Interestingly, a further study indicated that a LN yield as low as three may be sufficient to improve survival compared with lower yields. The study authors conclude that, while they were not able to establish conclusively whether LN yield affects prognosis, several studies demonstrated that a yield of less than 12 was sufficient to improve survival. The authors say that a lack of randomized data limit the ability to provide a specific number for LN yield target and suggest that other markers of prognosis, such as LN ratio, should be used to determine staging and management in rectal cancer. "What is certain is that further and more rigorous studies are required to answer the question of the prognostic significance of LN yield in patients with RC [rectal cancer] receiving long course preoperative RT [radiotherapy]," the authors conclude. They add: "Until this time, RC will rely on staging, appropriate use of RT, competent surgery and adequate pathological analysis of specimens."

Awwad, George E H, et al., Prognostic significance of lymph node yield after long course preoperative radiotherapy in patients with rectal cancer: a systematic review. Colorectal Disease. Online edition. September 7, 2012

SCREENING

9. Post-polyp Detection, Colorectal Cancer Risk Identified by Colonoscopy Factors (Aug.20/12)

According to the results of this study, in the community setting, after colonoscopic polyp detection, colonoscopy-related factors such as incomplete polyp removal and lack of surveillance colonoscopies are more important than polyp characteristics in predicting subsequent colorectal cancer (CRC) risk. To examine the role of colonoscopy-related factors and polyp characteristics on the risk for CRC after detection of colonoscopic polyps, researchers used data from a previously published population-based, case-control study involving 3,148 case participants with CRC and 3,274 control patients. The researchers identified 155 case participants and 260 control participants with physician-validated polyp detection in the preceding 10 years. Among cases, characteristics that were significantly more common included:

- incomplete removal of all polyps;
- no surveillance colonoscopy within five years;
- and detection of three or more polyps

Overall, nearly twice as many CRC cases were due to colonoscopy-related rather than polyp-related characteristics (41.1% versus 21.7%). Researchers concluded that colonoscopy-related factors (in particular, lack of complete removal of all polyps and lack of surveillance colonoscopy within five years) to be more important predictors of CRC occurrence after colonoscopic detection of polyps (other than hyperplastic polyps) than polyp characteristics.

Brenner, Hermann, et al., Role of Colonoscopy and Polyp Characteristics in Colorectal Cancer After Colonoscopic Polyp Detection: A Population-Based Case–Control Study. Annals of Inter Med. 21 August 2012; 157(4): 225-232

10. Four Pills May Do The Same Job as Liquid Laxatives in the Screening Prep (Aug.23/12)

Researchers at the Mayo Clinic in Arizona have unveiled four small pills they say have the same bowel-cleansing effect of the previously prescribed self-cleansing liquid required before the cancer screening. The unpleasant process of drinking several litres of the liquid laxatives has been linked to patients delaying or skipping the cancer's recommending screening all together, according to the doctors. That effect has added to colorectal cancer being the second leading cause of cancer deaths among Americans, the Mayo Clinic reports. 'Some become so anxious about drinking so much liquid that they avoid the entire procedure, putting them at risk of undiagnosed cancer,' the clinic states. But now with the four tiny pills, pictured the size of a round aspirin, there's another option which they say provides the same results of standard liquid laxatives. The catch is: They are only effective for virtual colonoscopies - the first screenings undergone by patients for potentially cancerous polyps. For 88% of colonoscopy patients, however, it's the only one required the Mayo Clinic says. The exception, or the 12%, would be the cases that they find something requiring a standard colonoscopy. 'Our hope is that this will make people less anxious and more likely to get screened and will ultimately result in fewer deaths from colorectal cancer,' said C. Daniel Johnson, M.D., chair of the Department of Radiology at Arizona's Mayo Clinic in a release. Doctors at the Mayo Clinic, which was the first to offer the screenings for routine care, recommend regular screenings for people over the age of 50 but admit that most do not.

http://www.dailymail.co.uk/news/article-2193511/Mayo-Clinic-doctors-unveil-pills-job-liquid-laxatives-colonoscopy-cancer-screening-prep.html

OTHER

11. Genes carried by Bacteria Linked to Colon Cancer (Aug.16/12)

Scientists at the University of Liverpool have identified a type of E. coli bacteria that may encourage the development of colon cancer. The Liverpool team had previously shown that people with colon cancer and with the inflammatory bowel diseases, Crohn's disease and ulcerative colitis, have high numbers of a sticky type of E. coli in their colons. The team has now found that E. coli bacteria, which carry **pks genes** that encode a toxin that damages DNA in the cells of the gut lining, are more commonly found in the colons of patients that have inflammatory bowel disease and colon cancer than those that do not have these conditions. Approximately two thirds of patients with colon cancer carry these E. coli compared with one in five with a healthy colon. Research, in collaboration with the University of North Carolina, showed that mice with colitis are more likely to carry these E. coli and they often develop colon cancer when carrying E. coli containing pks genes. They did not, however, develop cancer with identical E. coli that did not contain pks. They also found that the presence of E. coli carrying the pks genes did not appear to increase inflammation of the gut. "The fact that the pks-positive E. coli seemed to promote colon cancer in mice without causing increased inflammation led us to investigate its possible role in human colon cancer. The marked increase in the presence of these bacteria in the colon, not only in patients with inflammatory bowel disease, but also in patients with colon cancer who do not have inflammatory bowel disease, suggests that damage caused to DNA, as a result of the toxin that the pks genes produce, may promote the development of colon cancer", cites one of the researchers. "The research suggests that E. Coli has a much wider involvement in the development of colon cancer than previously thought. It is important to build on these findings to understand why this type of bacteria, containing the pks genes, is present in some people and not others." The Liverpool team involved in this study were also the researchers that discovered that dietary agents, particularly plantain and broccoli, could prevent the uptake and transport of E. coli through cells in the gut. They also found that fat emulsifiers in processed food encouraged the movement of bacteria through the cells.

Janelle C. Arthur, et al., Intestinal Inflammation Targets Cancer-Inducing Activity of the Microbiota. Science, 16 August 2012 DOI: 10.1126/science.1224820

12. Personalized Colon Cancer Therapy Based on Genetics of Specific Cancer (Aug.24/12)

University of Minnesota Medical School and Masonic Cancer Center researchers have partnered with geneticists from Genentech, Inc., to discover how some proteins may cause the development of some forms of colon cancers. The proteins -- part of **R-spondin family** -- normally help activate cell proliferation during embryonic development. Now, University of Minnesota researchers have discovered that when two types of R-spondins -- **RSPO2 and RSPO 3** -- are reactivated in adults through certain gene mutations, they can signal cells to restart the cell proliferation process, which can lead to tumor growth in the colon. The discovery, which involved multiple researchers from the University's Masonic Cancer Center, could lead the way to more personalized colon cancer therapy designed around the genetics of a patient's specific cancer. "These results suggest there is a potential for personalized therapies based on knowing a tumor's specific genetics," cited one of the researchers. "And because these R-spondins are related to embryonic growth, and seem to not have major roles in the adult, targeting them would likely be low in side effects." To arrive at the results, researchers analyzed more than 70 pairs of human colon tumors and a mouse model. Through a series of investigations, researchers identified 36 rearrangements that result in gene fusions, including two recurrent ones involving R-spondin family members RSPO2 and RSPO3. While the results could generate more personalized approaches to the treatment of colon cancer, researchers stress more research is needed before these results can be applied to actual patient care. “What we're finding is that tumors may look the same, but they're

fundamentally different". "Diagnosis may be less about the tissue where the tumor is found, like the breast or colon, but the drivers of the tumor's growth." Researchers are beginning work on a study that will help determine if a blocking agent could be useful in treating tumors driven by R-spondin production. If this project is successful, it could help create new therapeutic approaches useful in certain patients after a tumor genetic test is done.

Seshagiri, Somasekar et al., Recurrent R-spondin fusions in colon cancer. Nature, 2012; DOI: 10.1038/nature11282

13. Mutation Determines How Tobacco Smoking Affects Colorectal Cancer Risk (Aug.25/12)

Tobacco smoking is known to raise the risk of colorectal cancer. But a study in the American Journal of Gastroenterology suggests that among women, those who carry a certain mutation are **not** susceptible to the risk for the lung cancer induced by tobacco smoke. The study found many tobacco smoking variables were associated with increased risk of KRAS mutation-negative colorectal cancer, but not the mutation positive tumors. The study was based on 1,233 patients with colorectal cancer registered in the IOWA Cancer Registry, who were part of a population-based cohort study of cancer incidence among 41,836 randomly selected Iowa women aged 55 to 69 years of age at baseline in 1986. For the study, participants self-reported their habits of tobacco smoking at baseline, and the researchers had archived tissue specimens from colorectal cancer cases recorded through 2002, analyzed for tumor KRAS mutation status. The researchers found the risk of developing KRAS mutation negative colorectal cancer was associated with age at initiation of tobacco smoking, average number of cigarettes per day, and cumulative pack-years among other things. But these variables were not correlated with KRAS mutation positive colorectal cancer. Women who smoked equal to or greater than 40 cigarettes per day on average were 2.38 times as likely as those who never used tobacco to develop the KRSA mutation negative colorectal cancer. Kras gene performs an important function in tissue signaling and the mutation of this gene has been associated with a number of cancers. The significance of this mutation has been recognized in the treatment of colorectal cancer. Colorectal cancer with KRAS mutation does not respond well to panitumumab (Vectibix®) and cetuximab (Erbitux®) therapy in the treatment of stage IV colorectal cancer. Nothing can be done to change one person's KRAS mutation status. But quitting tobacco use is one thing smokers can do to reduce risk of colorectal cancer. Another important thing everyone can do to reduce the risk is to follow a healthy diet which is featured with high intake of fiber-rich foods like whole grains and green leafy vegetables and low intake of fat and meat.

http://www.foodconsumer.org/newsite/Non-food/Lifestyle/kras_mutation_tobacco_colorectal_cancer_082520120822.html

14. Targeting Inflammation to Stop Cancer (Aug.28/12)

Chronic inflammation is frequently at the route of multiple cancers, particularly in colorectal cancers where ulcerative colitis increases the risk of developing colon cancer 20-fold. Patients with ulcerative colitis are often treated with drugs called NSAIDs to reduce inflammation, which can reduce their cancer risk by 50%. Molecules that drive inflammation may be attractive therapeutic targets to prevent and treat inflammation-driven cancers. Chemokine receptors are one of the primary classes of molecules that regulate inflammation and many cancers express molecules that activate these receptors. Researchers at the University of Glasgow in Glasgow, Scotland recently demonstrated that the chemokine receptor **CXCR2** is a critical mediator of inflammation-driven tumor growth. In this study, Thomas Jamieson and colleagues show that mice lacking CXCR2 or mice that are treated with CXCR2 inhibitors are less susceptible to inflammation-driven colon and skin cancer. These studies indicate that CXCR2 inhibitors may have potential as a therapy to treat or prevent inflammation-driven cancers.

Wu, J. et al., The Proinflammatory Myeloid Cell Receptor TREM-1 Controls Kupffer Cell Activation and Development of Hepatocellular Carcinoma*. Cancer Research, *2012; 72 (16): 3977 DOI: 10.1158/0008-5472.CAN-12-0938

15. A Closer Picture at the Cell's DNA Unveiled (Sept.7/12)

In a blizzard of more than 30 scientific papers recently published in multiple basic scientific journals, an international research collaboration has flung open the door of the "wiring closet" of human cells– exposing at least ***four million gene switches*** that can both flick our genes on and off, and, like an electric outlet dimmer, work together in minute adjustments to turn genes up or down. Scientists had originally assumed that only 3% of DNA was active in directing cell functions through the genes, with the other 97% of the human genome nicknamed "junk DNA" or DNA "dark matter." Understanding the other 97% of DNA will help scientists understand how both genetics and environmental exposures can cause diseases—from lupus to heart disease to cancer—to appear, even in one identical twin but not the other. ENCODE (the Encyclopedia of DNA Elements) is a nine-year effort involving hundreds of researchers across the U.S., United Kingdom, Spain, Singapore and Japan performing more than 1,600 sets of standardized experiments, with the help of the equivalent of 300 years of lightning-fast computer analyses on more than 15 trillion bytes of raw data, and biochemical technology that didn't exist five years ago. This is a paradigm shift in terms of how we look at the genetic basis for disease. With diseases, "it's not necessarily the gene but probably a network of genes that are working together," and

these “switches” or “regulatory” DNA orchestrate entire networks. It will likely change considerably how people use the genome to identify targets for pharmaceuticals. The researchers also found that many seemingly different diseases such as Crohn’s and lupus may actually share some regulatory genes. That means that a specific treatment might work in several different subtypes of diseases. The Human Genome Project, which determined the entire sequence of human DNA was like getting a picture of Earth from space. It doesn’t tell you where the roads are, it doesn’t tell you what traffic is like at what time of the day, it doesn’t tell you where the good restaurants are, or the hospitals or the cities or the rivers. The discoveries also can reveal which genetic changes are important in cancer, and why. Now you can follow the roads and see the traffic circulation. That’s exactly the same way we will use these data in cancer research. ENCODE results will help provide a road map with traffic patterns for alternate ways to go after cancer genes.

http://fightcolorectalcancer.org/research_news/2012/09/the_worldview_of_dna_busted_wide_open-2#more-16890

***National Human Genome Research Institute press release*; *NIH News Sept. 5 2012* ; *AAAS* Science Now *; Sept. 5 2012* New York Times**

16. Metastatic Switch Could Lead to Cancer Therapies (Sept.13/12)

A multidisciplinary research team has shed new light on how cancer cells metastasize by identifying a key chemical signaling factor that triggers the process. What's more, they have engineered a low-cost, surgery-free genetic "switch" that turns metastatic behavior of colorectal cancer cells on and off, allowing for easy, repeatable study of this process. The researchers found that particular signaling mechanisms called chemokines induce metastasis of colorectal cancer cells. Chemokines are "motility factors" because they help cells move throughout the body. They are known, for example, to be important in the body's immunoresponse, which requires immune cells to travel quickly to areas of inflammation or infection. The researchers established a link between a particular chemokine receptor, called **CCR9**, and its ligand chemokine **CCL25**, to the metastatic behavior of colorectal cancer cells. Normal expression of these chemokines keeps the cancer cells in the gut, but once the cells lose CCR9 expression, they can spread. In other words, cancer cells hijack the signaling mechanism. This discovery in itself could form the basis for targeted anti-metastatic therapies. A barrier to cancer research, however, is the lack of good animal models to test therapies and human clinical trials often fail as a result. Hence, investigators used their engineering background to take things a step further: They made a mouse with a CCL25 and CCR-9 metastatic "switch" that could be turned on and off after cancer cells were injected into the mouse. At first, the cells expressed the CCR9 receptor, and the tumor only formed in the gut. Turning off the switch made the cells lose the signaling mechanism, and metastasis occurred. This switch could eliminate the traditional way scientists study metastasis: expensive, low-throughput surgical implantation of metastasized cancer cells. With the switch, metastasis can be studied and repeated by a simple injection of colorectal cancer cells.

Chen, Huanhuan Joyce, et al., Chemokine 25–induced signaling suppresses colon cancer invasion and metastasis. J Clin Invest. Vol. 122, Issue 9: p. 3184

NUTRITION & HEALTHY LIFESTYLE

17. Coffee Could Protect Against Colorectal Cancer (Aug.28/12)

Drinking several cups of coffee a day could help protect against bowel cancer, according to new research. It can cut the risk of developing a tumour by between15% and 25%, the study of almost half a million people found. Some previous studies have hinted that coffee could have a protective effect, but their findings have been inconclusive. However, researchers at the US National Cancer Research Institute in Rockville, Maryland, have found evidence of a possible protective effect. They looked at 490,000 people who agreed to have their health monitored for a decade, after answering questions about their lifestyle and diet in the mid 1990s. Among those who said they drank four or more cups a day, the risk of being diagnosed with bowel or rectal cancer over the decade was 15% lower than non-drinkers of coffee. Among those who drank at least six cups a day, their risk was 24% lower than non-drinkers. The researchers noted that drinking decaffeinated coffee appeared to have some beneficial effect, although it was not as strong, while drinking tea had no observable effect. They concluded: “Additional investigations of coffee intake and its components in the prevention of colorectal cancer … are warranted.” It is particularly encouraging to see that coffee consumption may lower the risk of bowel cancer given that over 40,000 men and women are diagnosed with it in the UK every year, making it the third most common cancer. However, pregnant women should follow NHS advice to moderate their intake of caffeine to 200mg per day from all sources, as any more than that can increase the risk of miscarriage. Every year in Britain 40,000 people are diagnosed with bowel cancer, and it claims 16,000 lives annually. In middle age the disease disproportionately affects men, perhaps due to lifestyle factors such as eating more red and processed meat. If caught early the chances of long term survival are markedly better than if it is only diagnosed late, when it has spread. In January ministers launched a nationwide bowel cancer campaign, costing £8.5 million, after advisers said the best way of increasing survival rates was to get people to recognize potential symptoms early, such as bleeding bowels. A spokesman for Beating Bowel Cancer, a charity, said the study was "inconclusive". He advised: "Anyone

wanting to reduce their chance of bowel cancer should primarily make sure they have a healthy diet, take exercise, and stop smoking. Those considering increasing their coffee consumption should consult their doctor first. Many studies have looked at whether people who drink more coffee have a higher or lower risk of different kinds of cancer than those who drink a little or none at all. Taken together they paint a confusing picture, suggesting that it's unlikely that coffee has a strong effect on cancer risk overall. This new research looked at the effects of coffee on bowel cancer, and although the results suggest a reduced risk among people who drank the most coffee, it's only one study, and requires more to be able to say for sure whether this effect is 'real', or due to chance.

Sinha, Rashmi, et al., Caffeinated and decaffeinated coffee and tea intakes and risk of colorectal cancer in a large prospective study. Am J Clin Nutr 2012. 96: 374-381.

18. Balanced Diet Required in Prevention of Cancer (Sept.3/12)

Balancing your diet with protective foods rich in fibre and vitamin C can help prevent the formation of cancer causing compounds in the gut. Researchers at the University of Aberdeen Rowett Institute of Nutrition and Health have carried out the first study to investigate the impact of a combination of different foods on the formation of compounds that can lead to colorectal cancer. A total of 48 obese men took part in trials at the Rowett's human nutrition unit and followed nine different diets varying in red meat and foodstuffs rich in vitamin C, fibre and nitrates. Red meat has already been linked with cancer but a diet that relied only on nitrate-rich foods such as lettuce leaves, spinach, radishes, beetroot and turnips could also be problematic. Investigators claim that red meat intake is high in the Western world - on average more than 90 grams per day of red meat is eaten by UK men and exceeds the level recommended by the World Cancer Research Fund of 70 grams per day. But high red meat consumption is associated with an increased risk of developing colorectal cancer. Therefore, the popularity of high protein and high meat diets that aid successful weight loss may cause problems for intestinal health. Formation of carcinogenic N-nitroso compounds in the gut is a suggested mechanism to explain the link between red meat consumption and colorectal cancer. Although red meat is considered the most important dietary component linked to the formation of carcinogenic compounds, other dietary components may also play a role. Researchers conducted three controlled dietary intervention trials, where obese men were fed different weight loss diets with varying amounts of red meat, protein, carbohydrate, fibre, vitamin C and nitrate. They then measured N-nitroso compounds in stool samples, and correlated these with the intakes of each of the dietary constituents. The results confirmed that a high red meat intake significantly contributes to the formation of carcinogenic N-nitroso compounds. But they also found that a high nitrate intake found in leafy salads and some root vegetables is also associated with an increase in these carcinogenic compounds. The study also showed that that the intake of dietary vitamin C and dietary fibre decrease the formation of N-nitroso compounds in the human gut. This is the first study to assess the influence of several dietary contributors to endogenous formation of N-nitroso compounds simultaneously. It highlights the importance of balancing potentially problematic foods such as red meat and high-nitrate foods such as some leafy and root vegetables with protective foods that are rich in vitamin C and dietary fibre.

http://medicalxpress.com/news/2012-09-diet-required-cancer.html

19. Diet and Exercise Strongly Related to Higher Rates of CRC in Patients with Lower Education/Income (Sept.8/12)

Fewer people in the U.S. are getting colorectal cancer (CRC), but that progress is seen much more often in well-off and highly educated Americans. In fact, the gap is widening in the rate of colorectal deaths in people with less education and/or who live in deeply disadvantaged communities. Researchers now have shown that differences in weight, diet and physical activity play a huge role in the higher rates and deaths from CRC among people of lower socioeconomic status. A careful statistical analysis of a 10-year observational study of a half-million people indicated that helping people of lower education or income to change their diet, body weight, smoking and physical activity could be nearly as important as improved screening for reducing CRC deaths. In the past 10 years, rates of colorectal cancer have dropped 2 to 3% each year. Half of that decrease, researchers say, can be explained by changed behaviors—such as eating less red meat and increasing exercise. The other half is probably due to improved screening which detects CRC before it starts or advances. That decrease, however, in CRC, is seen disproportionately more often among more educated and affluent Americans. Researchers analyzed data to quantify how much "modifiable" health behaviors like exercise and diet might be responsible for higher rates of CRC among less educated and lower-income people. They used data from the NIH-AARP Diet and Health Study, which followed 506,000 middle-aged and elderly men and women over 10 years (1995-2006), to study the 7,676 study participants who developed colorectal cancer. After adjusting for age, sex, race, CRC family history, and state of residence, the authors analyzed how physical activity, smoking, diet, and body weight contributed statistically to different risks and locations of colorectal cancer in people according to their education level and socioeconomic status. The study revealed that:

(1) CRC incidence rates were 42% higher among the least educated , and 31% higher among those living in the most disadvantaged neighborhoods, compared to better educated adults in higher-income neighborhoods;

(2) The diagnosis gap between socioeconomic groups was much greater for distal (left) colon and rectal cancers (which are easier to detect than right-colon cancers by screening);

(3) Overall, the combination of health behaviors and body mass index (BMI) explained about 44% of association between education and CRC risk; and 36% of the association between socioeconomic status of the subjects' neighborhood and CRC risk.

Although this is the largest prospective study yet done, the authors cautioned that it is an "observational" study that doesn't establish cause. In an accompanying editorial, Dr. John Ayanian of Harvard Medical School discussed possible biological explanations, such as:

(a) Higher ingestion of charred red meat and lower vitamin D intake, plus higher bile acids in the proximal colon, affects the colon's bacteria and "microbiome";

(b) Lower physical activity and obesity are linked with higher insulin levels that might stimulate the Wnt signaling pathway to stimulate cancer formation.

Dr. Ayanian called for public health authorities to consider using screening colonoscopies which detect proximal and flat lesions better than other screening methods; "chemoprevention through the use of aspirin" or NSAIDs; and targeted efforts to improve diet and exercise among people living in disadvantaged communities.

Journal of the National Cancer Institute (doi: 10.1093/jnci/djs346); and Medscape Oncology News Sept. 5 (http://www.medscape.com/viewarticle/770355).

http://fightcolorectalcancer.org/research_news/2012/09/diet_and_exercise_strongly_related_to_higher_rates_of_crc_in_people_with_lower_education_andor_income#more-16940

20. Fish Oil May Be Helpful During Therapy (Sept.13/12)

Colorectal cancer patients like patients with many other types of malignancies experience a great deal of inflammation and oxidative stress induced by chemotherapy and radiotherapy or the disease itself. A new study suggests that taking a moderate amount of fish oil each day during chemotherapy can improve their nutritional status indicators. It is merely a suggestion because the trial study was small. Researchers conducted the study and found colorectal cancer patients taking 2 grams of fish oil per day during chemotherapy maintained baseline weight and improved the C-reactive protein/albumin ratio, which are desirable. The clinical trial involved 23 patients with colorectal cancer in two groups who were assigned to take either a placebo or 2 grams of fish oil containing 600 mg of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for 9 weeks during which all patients were using chemotherapy. Nutritional and inflammatory biomarker status was assessed both at baseline and 9 weeks of chemotherapy in both the fish oil supplemented group and the control group. Both groups had similar nutritional profiles at baseline. At 9 weeks of chemotherapy, the fish oil supplemented group maintained body mass index and did not experience weight loss whereas those in the control groups changed body mass index and body weight. Additionally, colorectal cancer patients supplemented with fish oil experienced a *clinically relevant decrease in the C-reactive protein/albumin relation*. The researchers concluded "low doses of the fish oil supplement can positively modulate the nutritional status and the C-reactive protein/albumin ratio." What may help prevent colorectal cancer, according to previous studies include dietary fiber, green tea, vitamin d, walnuts, flaxseed, yogurt, cocoa, fruit and vegetables, tofu, and garlic among other things. Fish oil is known to provide antioxidative effect and it is believed to be beneficial for cancer patients.

De Aguiar Pastore Silvaa, Juliana, et al., Fish Oil Supplement Alters Markers of Inflammatory and Nutritional Status in Colorectal Cancer Patients. Nutr & Cancer. Vol. 64, Issue 3: pp. 267-273

21. Obesity, Inflammation and Colorectal Cancer (Sept.14/12)

A new review summarizes the ways in which inflammation and altered metabolism are associated with colorectal cancer in obese individuals. Researchers reviewed the interactions between adipocytes (fat storing cells) and immune cells that may alter the metabolism towards promotion of colorectal cancer. The researchers found that obese and lean adipose tissue had distinct immunogenic profiles, body fat distribution, and metabolic profiles. Free fatty acids, adipokines (cell-to-cell signaling proteins secreted by fat tissue), and pro-inflammatory cytokines were released by obese adipose tissue and played a role in regulating malignant transformations and cancer progression. Two different types of macrophages (type of white blood cell that ingests foreign materials) were identified in adipose tissue: M1 macrophages, which were found in obese adipose tissue, produced pro-inflammatory cytokines, while M2 macrophages, which were the main type found in lean adipose tissue, produced anti-inflammatory cytokines such as interleukin-10. "Despite establishing unequivocal epidemiological evidence of links between obesity and colorectal cancer, at least some of the mechanisms linking the two remain elusive," the authors write. "To identify these mechanisms, it is necessary to understand how obesity interacts with colorectal cancer at the molecular and cellular levels."

Yehuda-Shnaidman, E., et al., Mechanisms linking obesity, inflammation and altered metabolism to colon carcinogenesis. Obesity Reviews. Article first published online Sept.3, 2012. Doi:10.1111/j.1467-789X.2012.01024.x