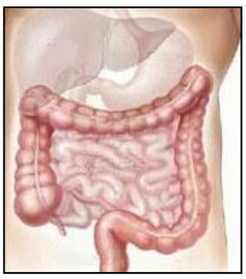
COLORECTAL CANCER RESEARCH UPDATES

Month Ending January 17th, 2014



The following colorectal cancer research update extends from November 18th, 2013 – January 17th, 2014 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Correlation of Bevacizumab-Induced Hypertension and Outcomes of Metastatic Colorectal Cancer Patients Treated with Bevacizumab: a Systematic Review and Meta-analysis (Nov. 28/13)

With the wide application of targeted drug therapies, the relevance of prognostic and predictive markers in patient selection has become increasingly important. Bevacizumab (Avastin) is commonly used in combination with chemotherapy in the treatment of metastatic colorectal cancer (mCRC). However, there are currently no predictive or prognostic biomarkers for bevacizumab. Several clinical studies have evaluated bevacizumab-induced hypertension in patients with mCRC. This study was performed to better understand the relationship between hypertension and outcome of patients with mCRC treated with bevacizumab, and to assess whether bevacizumab-induced hypertension could be used as a prognostic factor in such patients. The primary endpoint was progression-free survival (PFS). This is defined as the length of time during and after treatment in which the patient does not show any progression or death from any cause, in relation to the severity of hypertension in patients treated with bevacizumab. Secondary endpoints were overall survival (OS) and overall response rate (ORR). OS refers to the period of time the patient between randomization and any death, and ORR, the sum of partial and complete response rates according to the Response Evaluation Criteria in Solid Tumors with hypertension occurrence as a predictor. It was found that the occurrence of bevacizumab-induced hypertension in patients was **highly associated** with improvements in PFS, OS, and ORR, as compared to patients without hypertension. This suggests that bevacizumab-induced hypertension may represent a prognostic factor in patients with mCRC.

Cai, J. et al. (2013) Correlation of bevacizumab-induced hypertension and outcomes of metastatic colorectal cancer patients treated with bevacizumab: a systematic review and metaanalysis. World Journal of Surgical Oncology, 11:306. doi:10.1186/1477-7819-11-306.

2. Resistance Mechanism of Colorectal Cancer to Bevacizumab Detailed (Oct.24/13)

The results of this study suggest that when colorectal cancer (CRC) is targeted by the drug bevacizumab (Avastin), tumors may switch dependence from VEGF-A, which is targeted by the drug, to related growth factors VEGF-C, VEGF-D, and placental growth factor. This change to new growth factor dependence may allow CRC to push past bevacizumab's blockage of VEGF-A and continue to drive tumor growth. Think of it like damming a river. Bevacizumab can block the main flow, but then once a tumor's need builds up behind this dam, water starts to flow around the blockage in the form of streams and tributaries. That's like these other growth factors - eventually a tumor becomes able to use these tributaries of VEGF-C, VEGF-D, and placental growth factor to supply itself with the 'water' it needs. The analogy of liquid is an apt one - bevacizumab slows cancer's growth by limiting a tumor's ability to grow the new blood vessels it needs to supply itself with nutrients. Especially in combination with chemotherapy, bevacizumab has proved an effective treatment for colorectal cancer. But then there frequently comes a point at which bevacizumab stops working and the tumor restarts its growth. This study asked why. Specifically, investigators serially tested the levels of other VEGF-related growth factors in 42 patients treated with bevacizumab and chemotherapy. These tests occurred at many points during the course of their treatment. "What we saw is that levels of VEGF-C and placental growth factor went up just before tumors progressed and then stayed high during the periods of tumor growth. Interestingly, VEGF-D was only elevated during progression. But it seems that tumors may be using these growth factors as ways to create blood vessel growth in the absence of VEGF-A, blocked by bevacizumab," says lead investigator Dr. Lieu. The researchers also took a snapshot of levels in 403 colorectal cancer patients, at one time during treatment. Because this group included patients who were and were not being treated with chemotherapy along with bevacizumab, they could show that the rise in VEGF levels was, in fact, due to bevacizumab and not to some interaction with the chemotherapy. "It's too early to say with certainty that VEGF-C, VEGF-D, and placental growth factor are the cause of colorectal cancer resistance to bevacizumab, but the correlation we saw in this study is compelling," Lieu said. Current studies are exploring the use of drugs that block more blood-vessel-growth-promoting factors than VEGF-A. For example, Lieu points to the example of aflibercept (Zaltrap), which was given FDA approval in August 2013 for the treatment of metastatic colorectal cancer, along with the chemotherapy regimen known as FOLFIRI. The drug inhibits placental growth factor along with VEGF-A. “It’s an attractive strategy, and also proof of concept that by targeting not only the primary mechanism of tumor growth but also one or more of these ‘workarounds,’ this drug or other future drugs could stall growth longer than blocking any one of these growth factors, individually,” Lieu says. Lieu points out that in addition to targeting these additional growth factors, the fact that spikes in VEGF-C and placental growth factor presage tumor progression could give doctors and researchers a clue that bevacizumab has lost its efficacy. Though more work is needed, Lieu can imagine using spikes in VEGF-C or prenatal growth factor to recommend evaluating new treatment options.

Lieu, CH. et al. (2013) The Association of Alternate VEGF Ligands with Resistance to Anti-VEGF Therapy in Metastatic Colorectal Cancer. PLoS ONE 8(10): e77117. doi:10.1371/journal.pone.0077117.

3. FOLFOXIRI plus Bevacizumab may Benefit Patients with BRAF-mutant Metastatic Colorectal Cancer (Dec. 03/13)

BRAFV600E mutation plays a negative prognostic role in metastatic colorectal cancer (mCRC), leading to a median progression-free survival (PFS) between 4 and 6 months with first-line conventional

treatments. However, a retrospective analysis of a recent phase 2 trial showed that the addition of bevacizumab (Avastin) to FOLFOXIRI (combination chemotherapy including folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) might confer PFS and overall survival (OS) benefits in these poor-prognosis patients. In this study, investigators wanted to prospectively verify if FOLFOXIRI plus bevacizumab as first-line treatment could be considered a promising approach to improve the outcome of *BRAF* mutant mCRC patients. 214 potentially eligible mCRC patients were screened for *BRAF* mutational status. 15 *BRAF* mutant patients (7%) were included in the validation cohort. Primary end-point was 6 month-progression free rate (6 m-PFR), defined as the proportion of patients free from disease progression 6 months after study entry. The study met its primary end-point as 11 out of 15 patients were progression free at 6 months. The results of this study suggest that the addition of bevacizumab to FOLFOXIRI chemotherapy may be an effective first-line treatment option for patients with *BRAF* mutant mCRC.

Loupakis, F. et al. (2014). FOLFOXIRI plus bevacizumab as first-line treatment in BRAF mutant metastatic colorectal cancer. European Journal of Cancer, Vol. 50, Issue 1: 57-63. doi: 10.1016/j.ejca.2013.08.024.

4. Benefits of Aflibercept plus FOLFIRI Observed across Subgroups of Patients with Pretreated Metastatic Colorectal Cancer (Dec. 05/13)

Past research indicates that Aflibercept (Zaltrap) in combination with FOLFIRI (combination chemotherapy including 5-fluorouracil, leucovorin and irinotecan) is associated with significantly improved survival in patients with metastatic colorectal cancer (mCRC) previously treated with an oxaliplatin-based regimen. This study evaluated outcomes in different subgroups of patients to examine treatment consistency. Patients were randomly selected to receive Aflibercept plus FOLFIRI or placebo every 2 weeks until disease progression or unacceptable toxicity occurred. The investigators then analyzed efficacy and safety with regard to demographics and baseline characteristics. They also stratified results based on prior treatment with bevacizumab (Avastin) and Eastern Cooperative Oncology Group (ECOG) performance status. Among patients previously treated with bevacizumab, median overall survivial (OS) was 12.5 months in the Aflibercept group and 11.7 months in the placebo group. Among patients who had not undergone prior bevacizumab treatment, median OS was 13.9 months in the Aflibercept group and 12.4 months in the placebo group. Researchers observed no heterogeneity across subgroups. The beneficial effect on OS and progression-free survival (PFS) observed with Aflibercept was greater among those with liver only metastases versus with those with no liver metastases/liver metastases with other organ involvement. These results suggest that the benefits of Aflibercept in combination with FOLFIRI in patients with mCRC previously treated with oxaliplatin were maintained across the specified patient subgroups, including in patients with or without prior bevacizumab treatment.

Tabernero, Josep et al. (2014) Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: Prespecified subgroup analyses from the VELOUR trial. European Journal of Cancer, Vol. 50, Issue 2: 320-331. doi: 10.1016/j.ejca.2013.09.013.

5. Potentially Fatal Skin Reactions Linked to Cancer Drug Xeloda: Health Canada (Dec.03/13)

Xeloda (capecitabine), an oral drug used to treat advanced breast and colorectal cancers, has been linked to potentially fatal skin reactions in some patients. The medication's manufacturer, Hoffmann-La Roche Ltd., reported in an advisory from Health Canada that severe skin reactions have been observed in patients taking Xeloda. It is used to treat advanced breast cancer or breast cancer that has spread to other parts of the body, as well as metastatic colorectal cancer and cancer of the colon following surgical removal. Severe skin reactions such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in some cases with a fatal outcome, have been reported during treatment with Xeloda, the company said. Signs and symptoms of severe skin reactions can include flu-like symptoms, fever, skin itching and a painful, red or purplish skin rash that spreads and blisters, causing the skin to shed. Other possible symptoms include mouth sores, eye burning, itching and discharge. The manufacturer emphasized that patients using this drug who develop any of these symptoms should contact their healthcare professional immediately.

http://www.montrealgazette.com/health/Potentially+fatal+skin+reactions+linked+cancer+drug+Xeloda/9241460/story.html

6. Drug Combination Therapy Causes Cancer Cells to "eat themselves" (Dec. 09/13)

The results of this preclinical study show that a new drug combination therapy being developed effectively kill colon, liver, lung, kidney, breast and brain cancer cells while having little effect on noncancerous cells. These results will lay the foundation for investigators to plan a future phase 1 clinical trial to test the safety of the therapy in a small group of patients. They are encouraged by the fact that the drugs used in this therapy are either already approved by the FDA to treat certain cancers or are currently being investigated in other clinical trials. The study showed that the drugs **sorafenib** and **regorafenib** synergize with a class of drugs known as **PI3K/AKT inhibitors** to kill a variety of cancers. Sorafenib and regorafenib work by blocking the production of enzymes called kinases, which are vital to the growth and survival of cancer cells. Sorafenib is currently approved by the FDA to treat kidney and liver cancers, and regorafenib is currently approved for the treatment of colorectal cancer. However, sorafenib and regorafenib do not directly affect PI3K and AKT kinases, which are also very active in promoting cancer cell survival. The addition of a PI3K/AKT inhibitor to the combination of sorafenib and regorafenib dramatically increased cell death and was even effective against cells with certain mutations

that make one or the other drug less effective. Certain cellular processes are frequently dysregulated in cancers and important to cell proliferation and survival, but if you shut down one, then cells can often compensate by relying on another. Here, investigators are blocking several of these survival pathways, and the cancer cells are literally digesting themselves in an effort to stay alive. Results of the study showed that the combination therapy killed the cells by physically interacting with molecules to block the survival pathways and induce a toxic effect known as autophagy. Autophagy is a protective process where cells metabolize themselves when starved of the resources needed to survive. “Many groups are trying the approach of inhibiting two survival signaling pathways, but our approach takes this further by blocking significantly more of these pathways,” says lead investigator Dr. Dent. “Our findings could benefit many different cancer patients based on the broad range of effects seen in multiple cancer types.”

Gangadharan, B. et al. (2013) Sorafenib/Regorafenib and Phosphatidyl Inositol 3 Kinase/Thymoma Viral Proto-Oncogene Inhibition Interact to Kill Tumor Cells. Molecular Pharmacology, 84:562-571. doi:10.1124/mol.113.088005.

SURGICAL THERAPIES

7. Cytoreductive Surgery plus Hyperthermic Intraperitoneal Chemotherapy Improves Survival of Patients with Peritoneal Carcinomatosis from Colorectal Cancer: A Case-control Study from a Chinese Center. (Dec. 27/13)

The classic scenario for CRC progression is the lymphatic, hematogenous (to the liver, the lungs, etc) and peritoneal metastases. There have been standard treatment strategies for the first two forms of metastases. However, a unified treatment guideline has yet to be formulated for the third form of metastasis, which is typically referred to as peritoneal carcinomatosis (PC), characterized by cancer metastasis to lining of the abdominal cavity. These investigators have established a designated CRS+HIPEC program at their institution. This treatment approach aims to maximally reduce the visible tumor burden by cytoreductive surgery (CRS - surgical removal of the tumor material), and to eradicate residual tumor nodules, micrometastases and free tumor cells by hyperthermic intraperitoneal chemotherapy (HIPEC). The latter procedure involves the bathing of the abdominal organs with conventional chemotherapeutic drugs heated to such a high temperature as to kill cancer cells immediately following surgery. This study compared the efficacy and safety of CRS versus CRS plus HIPEC in Chinese patients with CRC PC. 62 consecutive PC patients were treated with CRS (control group) or CRS+HIPEC (study group). The most important finding was that the median overall survival (OS) could be extended from 8.5 months in the control group to 13.7 months in the study group, with survival prolong rate (SPR) of 61.2%. These results provide new evidence that CRS+HIPEC bring significant survival benefit and acceptable safety for patients with CRC PC.

Huang, C.-Q., et al. (2013). Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from colorectal cancer: A case-control study from a Chinese center. Journal of Surgical Oncology, doi: 10.1002/jso.23545.

SCREENING

8. Researchers Create Online Colorectal Cancer Risk Calculator (Jan. 03/13)

Researchers at Cleveland Clinic have developed a new tool called **CRC-PRO** that allows physicians to quickly and accurately predict an individual's risk of colorectal cancer. CRC-PRO, or Colorectal Cancer Predicted Risk Online, is designed to help both patients and physicians determine when screening for colorectal cancer is appropriate. Current guidelines recommend patients are screened at the age of 50. However, with this new tool, physicians will be better able to identify who is truly at risk and when screenings for patients are necessary. An online risk calculator was created using data from the Multi-Ethnic Cohort Study, which followed >180 000 patients for the development of CRC for up to 11.5 years, to determine which factors were highly associated with the development of CRC. "Creating a risk calculator that includes multiple risk factors offers clinicians a means to more accurately predict risk than the simple age-based cutoffs currently used in clinical practice," said lead investigator Dr. Wells. "Clinicians could decide to screen high-risk patients earlier than age 50, while delaying or foregoing screening in low-risk individuals." The final model for men contains age, ethnicity, pack-years of smoking, alcoholic drinks per day, body mass index, years of education, regular use of aspirin, family history of colon cancer, regular use of multivitamins, ounces of red meat intake per day, history of diabetes, and hours of moderate physical activity per day. The final model for women includes age, ethnicity, years of education, use of estrogen, history of diabetes, pack-years of smoking, family history of colon cancer, regular use of multivitamins, body mass index, regular use of nonsteroidal anti-inflammatory drugs, and alcoholic drinks per day. Wells and his colleagues hope that their new, user-friendly calculator will help improve the efficiency of colorectal cancer screenings. They also believe prediction tools like this can help lower healthcare costs by cutting down on unnecessary testing. An electronic version of the calculator is available at http://rcalc.ccf.org.

Wells BJ, et al. (2014). ColoRectal Cancer Predicted Risk Online (CRC-PRO) Calculator Using Data from the Multi-Ethnic Cohort Study. Journal of the American Board of Family Medicine, 27(1):42-55. http://dx.doi.org/ 10.3122/jabfm.2014.01.130040.

9. New Colon Cancer Screening Test Now Available in Alberta (Dec. 18/13)

People over 50 with an average risk of developing colon cancer can now access a new screening test in Alberta. The fecal immunochemical test has been available since November 2013. Also known as FIT, the test requires a small stool sample that can be collected by patients in their own homes. The test uses antibodies that bind to human blood protein that may be found in the stool. It is able to detect blood specific to bleeding in the colon which can indicate cancer or a pre-cancerous polyp. The FIT test is not intended to replace a colonoscopy, which remains the gold standard for colon cancer screening. Instead, FIT will be used to triage patients considered average risk. The test is really directed towards those that are 50 to 74 years of age who are asymptomatic and lack family history or personal history of colon cancer. Until now, these average risk patients were put to the back of the line for colonoscopy, waiting up to two years for their turn. Average risk patients who show no sign of cancer after their first colonoscopy often wait up to 10 years for a second screening. New Alberta guidelines recommend patients are screened with the FIT test annually. Adults experiencing symptoms like rectal bleeding or who have had a persistent change to their normal bowel habits or who have a family history of colon cancer should still be screened with a colonoscopy.

http://globalnews.ca/news/1039524/new-colon-cancer-screening-test-now-available-in-alberta/

10. Study Shows Colonoscopy Better than Sigmoidoscopy in Protecting Against Colorectal Cancer (Nov. 22/13)

This study has found that colonoscopies appears to reduce the risk of developing or dying from colorectal cancer (CRC) more powerfully than do sigmoidoscopies. The investigation also identified molecular features that may help explain tumors that are diagnosed despite an individual's having recently undergone colonoscopy. These findings support current recommendations for CRC screening with either of these procedures and provide a rationale for some individuals to consider colonoscopy as a preferred test for their individual situation. Both colonoscopy and sigmoidoscopy allow examination of the internal surface of the colon through a fiberoptic tube with a light and camera at the end, but while colonoscopy visualizes the entire colon, sigmoidoscopy only reaches the lower third on the left side of the body. Current recommendations for colorectal screening in average-risk individuals over age 50 are either a sigmoidoscopy every 5 years – followed by colonoscopy if abnormalities are detected – or a colonoscopy every 10 years. However, the more comprehensive colonoscopy is widely recommended for colorectal screening based on its ability to visualize the whole colon. This study compared the effectiveness of both procedures in reducing the long-term risk of CRCs in different segments of the colon, and examined molecular features of tumors developing soon after a negative examination. To this end, investigators analyzed information from 89 902 participants in the Nurses Health Study and the Health Professionals Follow-up Study. From 1988 to 2008, participants reported whether they had either sigmoidoscopy or colonoscopy in the 2 preceding years and, if they had, whether the examinations were for screening purposes or because of symptoms like bleeding. For participants who developed cancer or who reported having colon polyps removed, the researchers obtained consent to review their medical records and pathology reports. Over the 22 years for which data was analyzed, 1 815 cases of CRC and 474 related deaths were documented. While a negative result – meaning that neither cancer nor polyps were diagnosed – in either examination or having polyps that were removed was associated with a reduced risk of developing left-side colon cancer, only a negative colonoscopy was associated with significant risk reduction in the entire colon. Compared with the 15% of study participants who had no endoscopic colon exam during the study period, having either procedure significantly reduced the overall risk of dying from CRC. **But while sigmoidoscopy only cut the risk of dying from left-side tumors, screening colonoscopy reduced the risk of any CRC-associated death**. Having a single negative colonoscopy significantly reduced the incidence of any colorectal cancer for up to 15 subsequent years, supporting the current recommendations for a 10-year interval between exams. Among participants who had polyps removed, the incidence of subsequent tumors was reduced for up to 5 years, except for those whose polyps had features indicating elevated risk, in whom the risk reduction was not as strong. Among the participants who did develop CRC, molecular data was available on 62 tumors that had been diagnosed within 5 years after colonoscopy. The researchers identified specific cancer-related features more likely to be seen in those tumors than in cancers diagnosed after more time had passed. It is widely believed that tumors with those features develop from a specific type of polyp called a sessile serrated adenoma, which may be particularly difficult to detect endoscopically or to remove completely. Focused efforts to improve detection and removal of these polyps are a high priority. Co-author Chan says that for individual patients, the decision to select colonoscopy over sigmoidoscopy for CRC screening requires discussing with their physicians how the advantages and disadvantages of each test apply to their personal situations. Right now their data support the use of colonoscopy if the primary goal is maximum risk reduction for both left- and right-side CRCs.

Nishihara R. et al (2013). Long-term colorectal-cancer incidence and mortality after lower endoscopy.New England Journal of Medicine, 369(12):1095-105. doi: 10.1056/NEJMoa1301969.

11. Comparison of the Accuracy of CT Colonography and Colonoscopy in the Diagnosis of Colorectal Cancer (Dec. 03/13)

In this study, the existing literature was reviewed to compare the effectiveness of CT colonography with colonoscopy for colorectal cancer (CRC) screening. An electronic search was conducted using the databases Pubmed, EMBASE, Cochrane library and Centre for Reviews and Dissemination, from inception to July 2009. Studies were included if investigations used CT colonography for CRC screening in asymptomatic populations and studies were excluded if investigations were conducted for CRC diagnosis or in elderly, high risk or symptomatic populations. Of the 213 references identified, 9 studies were included. The CT colonography specificity in screening for CRC was high, although it decreased with decreasing diameter of polyp to be detected. The CT colonography sensibility for detection of polyps <6 mm in diameter was low and heterogeneous, although it was higher for polyps > 10 mm. The main factors contributing to the greater sensitivity of CT colonography were the inclusion only of populations with an average CRC risk and colonic insufflation with CO_2. The incidence of adverse effects was very low for rate for both tests. Investigators came to the conclusion that CT colonography has high specificity but heterogeneous sensitivity, although in most cases, it is not as sensitive or specific as conventional colonoscopy. They have advised that CT colonography could therefore be useful as a screening test for populations with an average risk of CRC.

Martín López, JE. et al. (2013). Comparison of the accuracy of CT Colonography and colonoscopy in the diagnosis of colorectal cancer. Colorectal Disease. doi: 10.1111/codi.12506.

12. New Blood Test Could Detect Colorectal Cancer (Dec. 02/13)

VolitionRx Limited has released new data showing that when combining two of its proprietary NuQ® assays into one test, they can achieve 85% detection rates at 85% specificity for colorectal cancer (CRC). The data also shows that this two-assay test can detect more than 50% of precancerous polyps. These new findings come from Volition's ongoing prospective study with CHU Dinant Godinne | UCL Namur Hospital in Belgium. They have now analysed 39 patient samples from the trial which includes both healthy patients and patients with benign colon disorders. Professor Nielsen, at Hvidovre Hospital in Denmark, recently expanded his prospective study evaluating VolitionRx's NuQ panel as a colorectal cancer screening tool. He comments, "The 85% detection rate seen in this latest research is on par with rates achieved by faecal occult blood tests. If we could improve screening compliance by offering the public a simple, less intrusive test that is just as accurate, we could detect even more colorectal cancer cases in the earlier stages and survival rates could drastically improve." This test has the potential to become a global first choice diagnostic tool according to Volition, replacing faecal occult blood tests and preventing unnecessary colonoscopies around the world. The company hopes to apply for CE mark in early 2014 and FDA approval roughly a year later. In addition, a randomised, blinded study has been designed to evaluate the validity of VolitionRx's proprietary NuQ® panel as a first-step screening tool for CRC. Sample collection for this prospective study, which is jointly sponsored by VolitionRx and the University of Copenhagen, is due to commence in April 2014 and be completed by the end of 2015. With the additional blood samples, 8 000 individuals receiving a positive faecal immunological testing (FIT) result and 3 000 individuals receiving a negative FIT result as part of the Danish national screening program will now be tested using Volition's NuQ assay panel. The results will be verified by colonoscopy. Notably, the team is collecting up to 120 data points for each individual included in the trial (e.g. age, gender, other diseases). This will provide a powerful tool in understanding how different diseases and conditions interrelate with CRC. Professor Nielsen comments that this expansion will allow the investigators to make even stronger conclusions about the accuracy of VolitionRx's NuQ blood test.

http://www.keyc.com/story/24117917/new-blood-test-could-detect-colorectal-cancer
http://www.prnewswire.com/news-releases/volitionrx-finds-simple-blood-test-detects-85-of-colorectal-cancers-and-over-50-of-polyps-234051111.html
http://www.volitionrx.com/newsroom/211-newsitem40.html

OTHER

13. Toronto Scientists Claim New Discovery in Treating Colorectal Cancer (Dec. 01/13)

Scientists at Princess Margaret Cancer Centre in Toronto say they have discovered a new approach to treating colorectal cancer (CRC). The investigators replicated human colon cancer in mice to determine if specifically targeting stem cells was clinically relevant. They identified that the gene *BMI-1*, already implicated in maintaining stem cells in other cancers, is the pivotal regulator of colon cancer stem cells and drives the cycle of self-renewal, proliferation and cell survival. Next, the team used an existing small-molecule inhibitor to successfully block *BMI-1*. When they blocked the *BMI-1* pathway, the stem cells were unable to self-renew, which resulted in long-term and irreversible impairment of tumour growth. In other words, the cancer was permanently shut down. Targeting the *BMI-1*-related self-renewal machinery may then provide the basis for a new therapeutic approach in the treatment of CRC.

Kreso, Antonija et al. (2014). Self-renewal as a therapeutic target in human colorectal cancer. Nature Medicine, 20, 29–36. doi:10.1038/nm.3418.

14. Study Suggests Racial Inequality Leads to Higher Cancer Mortality in Blacks (Nov. 22/13)

Black patients with metastatic colorectal cancer (mCRC) have inferior survival compared to white patients. The purpose of this study was to examine disparity in specialist consultation and treatment and

the impact that treatment inequality has on survival. The investigators identified 9 935 non-Hispanic white and 1 281 black patients with stage IV CRC aged 66 years and older from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. The analysis compared patient consultation rates with cancer specialists as well as treatment with surgery, chemotherapy and radiation therapy for white and black patients. The study concluded that black patients were 10% less likely to have primary tumor surgery, 17% less likely to receive chemotherapy, and 30% less likely to receive radiotherapy. Among patients who received chemotherapy, white patients were more likely to receive more than one chemotherapy agent. The researchers also noted that black patients typically received chemotherapy four days later than white patients. Chemotherapy was associated with a 66% decreased risk of death. Of note, their analysis found that 47% of the relative survival difference between black and white patients was attributable to treatment differences and, after accounting for these treatment differences, the race-based survival difference completely disappeared. Thus these results demonstrate racial disparity in specialist consultation as well as subsequent treatment with therapy for mCRC, and suggest that inferior survival for black patients may stem from this treatment disparity. The study did not ascribe a specific cause for the racial disparities but offered six possible explanations: conscious or unconscious provider biases, patient mistrust, health literacy, patient-physician communication breakdown, healthcare access barriers, and/or race-based differences in disease biology. The authors also suspect that this pattern of disparity could be present in other underserved minority groups as well. Further research into the underlying causes of this inequality will improve access to treatment and survival in mCRC.

Simpson DR, et al. (2013). Racial Disparity in Consultation, Treatment, and the Impact on Survival in Metastatic Colorectal Cancer. Journal of the National Cancer Institute, 105 (23): 1814-1820. doi: 10.1093/jnci/djt318.

15. Colon Cancer Linked to Low Diversity of Gut Bacteria (Jan. 06/13)

This study suggests that people who have a less diverse population of bacteria in their gastrointestinal tracts may be more likely to get colon cancer. Researchers have found that colorectal cancer (CRC) patients have a different gut bacteria composition compared to healthy subjects. The human gut contains trillions of bacteria that play roles in digestion, inflammation and immunity. Researchers are just beginning to understand how differences in the gut's bacterial composition might influence health, in general, and diseases such as colon cancer, in particular. In the study, researchers looked at stool samples of 47 people who were newly diagnosed with CRC, and compared them with samples from 94 healthy adults without the disease. They compared the intestinal microbes in the samples by analyzing their DNA. They found that fecal samples from people who had colon cancer had less bacterial diversity compared with samples from healthy individuals, even when they controlled for age, sex, body mass index, race and smoking, factors that can all influence disease risk. A lower amount of bacterial diversity in the gut may indicate a lack of balance in the complex bacterial population residing there. Researchers also looked at the specific types of bacteria present in the stool samples, and found colon cancer patients tended to have higher levels of *Fusobacterium* and *Porphyromonas*, bacteria related to inflammation in the gut, which can fuel cancer growth. And the patients often had lower levels of *Clostridia*, a bacterial class that may prevent the development of colon cancer by helping to break down dietary fiber and carbohydrates. This study found an association, not a cause-and-effect link, between gut bacterial diversity and colon cancer. It has been suggested that some of the same factors that influence a person's colon cancer risk, including diet, physical activity and obesity, can also influence the composition of gut bacteria. Again, this would make it difficult to separate out whether it's a cause of colon cancer, or an effect of it. Researchers say it will take more research to determine if this decreased diversity leads to colon cancer, or is a response to having the disease, though this new work is exciting because it may provide insights into future ways to reduce the risk of CRC.

Ahn, Jiyoung, et al. (2013). Human Gut Microbiome and Risk for Colorectal Cancer. Journal of the National Cancer Institute, 105 (24): 1907-1911. doi: 10.1093/jnci/djt300.

16. *Helicobacter pylori* Infection is Associated with Advanced Colorectal Neoplasia (Oct. 28/13)

Though certain epidemiological studies have demonstrated a greater prevalence of colorectal adenomas and/or adenocarcinomas in patients infected with *H. pylori*, the association remains controversial. This study evaluated the prevalence of *H. pylori* infection in patients diagnosed with advanced colorectal neoplasia, defined as cancer or advanced adenoma, undergoing a colonoscopy, compared to patients without neoplasia. All 273 participants in this study underwent a colonoscopy and were tested for *H. pylori* infection. It was found that 75% of partisants diagnosed with neoplastic colorectal lesions and 48% without neoplastic lesions, were found to be seropositive for *H. pylori* infection. In addition, *H. pylori* infection was found in 86% of patients with advanced neoplasia, 51% of patients with nonadvanced neoplasia, and only 48% of patients without neoplasia. Though more studies are needed to confirm these findings, the investigators write that *H. pylori* infection is associated with the development of advanced colorectal neoplasia.

Shmuely, Haim. et al. (2014). Helicobacter pylori infection is associated with advanced colorectal neoplasia. Scandinavian Journal of Gastroenterology, Vol. 49, No. 1: 35-42. doi:10.3109/00365521.2013.848468.

17. Mistletoe May Help Fight Cancer (Dec. 26/13)

Mistletoe may be an effective ally when fighting against certain types of cancer. Several studies on the plant conducted in Europe, and mainly in Germany, have shown its effectiveness against this disease. One of them, carried out between 1993 and 2000, showed how mistletoe extract relieved the adverse symptoms of chemotherapy in 800 patients with colorectal cancer (CRC). This clinical study by the National Center for Complementary and Alternative Medicine and the National Cancer Institute in the US seems to show similar positive results. The objective of this phase I trial was to observe the safety and toxicity of a combination treatment regimen of mistletoe extract (Helixor A) and gemcitabine in patients with advanced solid tumors (advanced pancreatic cancer or non-small cell lung cancer, or recurrent CRC or breast cancer). Gemcitabine is a chemotherapy drug used to treat advanced and metastatic pancreatic cancer, metastatic breast cancer, advanced ovarian cancer, and advanced or metastatic non-small cell lung cancer. Mistletoe extract improved chemotherapy when administered in conjunction. Low toxicity and treatment benefits were observed in almost half the patients. Furthermore, the maximal tolerated dose for the gemcitabine/mistletoe combination in this study was found to be gemcitabine 1380 mg/m^2 given weekly on day 1 and 8 of a 3-week cycle with mistletoe 250 mg s.c daily. Two research groups in the US are further investigating the benefits of mistletoe extract in cancer treatment.

Mansky, Patrick J. et al. (2013). NCCAM/NCI Phase 1 Study of Mistletoe Extract and Gemcitabine in Patients with Advanced Solid Tumors. Evidence-Based Complementary and Alternative Medicine, vol. 2013, Article ID 964592. doi:10.1155/2013/964592.

18. Inhibition of Colon Carcinogenesis by a Standardized Cannabis sativa Extract with High Content of Cannabidiol (Dec. 24/13)

Cannabis extracts and plant-derived cannabinoids have demonstrated anti-cancer effects. In this study, researchers investigated the effect of a standardized Cannabis sativa extract with a high content of cannabidiol (CBD), named CBD BDS (CBD botanical drug substance), on colorectal cancer (CRC) cell proliferation and in experimental models of colon cancer *in vivo*. They found that CBD BDS reduced cell proliferation in colorectal cancer cells but not in healthy colonic cells. CBD BDS also reduced preneoplastic lesions, polyps and tumours induced by the carcinogenic agent azoxymethane (AOM) in mice. Collectively, such results suggest that CBD BDS attenuates colon carcinogenesis and inhibits CRC cell proliferation. The results may have some clinical relevance for the use of *Cannabis*-based medicines in cancer patients.

Romano, Barbara, et al. (2013). Inhibition of colon carcinogenesis by a standardized Cannabis sativa extract with high content of cannabidiol. Phytomedicine. doi: 10.1016/j.phymed.2013.11.006.

NUTRITION & HEALTHY LIFESTYLE

19. Study Suggests Bowel Cancer Benefit in Multivitamins (Nov. 26/13)

Use of multivitamins may reduce the risk of colorectal adenoma, but the duration of use needed is unclear. This study examined the duration of multivitamin use in relation to the occurrence of colorectal adenomas in a cohort of 43 641 young women. The odds of developing adenoma were 14% lower in those who had reported multivitamin use at any time of their lives. Although there was no linear trend in duration of multivitamin use, women who had used multivitamins for over 20 years were 20% less likely to develop an adenoma. Use of multivitamins for over four years was linked to a 25% reduction in the risk of developing a large adenoma (greater than 1cm). Investigators also noted a strong association between multivitamin use and reduced risk of colorectal adenoma among regular drinkers (more than 1.4g of alcohol/day). Collectively, these findings suggest that use of multivitamins is associated with lower risk of colorectal adenoma, even with relatively short duration of use. However, investigators says that studies are needed to better define the duration of use that is required before potential protective effects of multivitamin use can be detected, and whether timing of exposure or duration of exposure is the critical factor in the reduction of risks.

Massa J., et al. (2014). Long-term use of multivitamins and risk of colorectal adenoma in women. British Journal of Cancer, 110, 249–255. doi:10.1038/bjc.2013.664.

20. Researchers Identify Gene Variant that Raises Risk for Colorectal Cancer from Eating Processed Meat (Oct. 24/13)

This study has identified a common genetic variant that affects 1 in 3 people, significantly increasing the risk of colorectal cancer (CRC) from the consumption of red meat and processed meat. In addition, it also reveals another specific genetic variation that appears to modify whether eating more vegetables, fruits and fiber actually lowers your CRC risk. “Diet is a modifiable risk factor for colorectal cancer. Our study is the first to understand whether some individuals are at higher or lower risk based on their genomic profile. This information can help us better understand the biology and maybe in the future lead to targeted prevention strategies,” says lead author Dr. Figueiredo. “But we are not saying that if you don’t have the genetic variant that you should eat all the red meat you’d like,” Figueiredo added. “People with the genetic variant allele have an even higher increased risk of colorectal cancer if they consume high levels of processed meat, but the baseline risk associated with meat is already pretty bad.” The researchers systematically searched the more than 2.7 million genetic sequences for interactions with consumption of red and processed meat. The study looked at 9 287 patients with CRC and a control group of 9 117 individuals without cancer. The risk of CRC associated with processed meat was

significantly higher among people with the genetic variant **rs4143094**. This variant is located on the same chromosome 10 region that includes GATA3, a transcription factor gene previously linked to several forms of cancer. The transcription factor encoded by this gene normally plays a role in the immune system, but carries this genetic variant in about 36% of the population. The researchers speculate that the digestion of processed meat may promote an immunological or inflammatory response that may trigger tumor development. The GATA3 transcription factor normally would help suppress the immunological or inflammatory response. However, if the GATA3 gene region contains a genetic variant, it may encode a dysregulated transcription factor that impacts its ability to suppress the response. But other genetic variants may be beneficial: on chromosome 8, another statistically significant diet-gene interaction was found in variant **rs1269486**. For people with this variant, eating your fruits and veggies may be even better for you when it comes to CRC risk, the research shows. CRC is a multi-factorial disease attributed to lifestyle, environmental and genetic causes, and this discovery sets a first step towards identification of genetic variants linked to carcinogenic risk from diet and nutrition.

Study presented at American Society of Human Genetics 2013 meeting: http://www.ashg.org/2013meeting/abstracts/fulltext/f130123041.htm

21. Many Ways Meat Causes Colon Cancer (Dec. 03/13)

Reasons for meat products leading to colorectal cancer (CRC) are wide-ranging, according to this review. The authors say potential risks include naturally occurring components of meat products such as proteins and heme iron, as well as components generated by the cooking process such as N-nitroso compounds and heterocyclic amines. The authors postulate that compounds linked to high meat consumption, which are not absorbed by the small intestine and thus transferred into the large intestine lumen, may have deleterious effects on the large intestine epithelial cells when present in excess. In addition, increased bacterial fermentation (putrefaction) of undigested protein and production of bacterial metabolites derived from amino acids may also affect colon epithelial homeostasis and renewal. This correlates with the fact that most colonic cancers are detected in the distal colon and rectum where protein fermentation actively occurs. However, there are still large controversies on the relationship between red meat consumption and CRC risk. For more information, this review discusses these meat-related components and the mechanisms by which they may affect the large intestine mucosa and the intestinal gut microbiota.

Kim, Eunjung, et al. (2013). Review of the association between meat consumption and risk of colorectal cancer, Nutrition Research, Volume 33, Issue 12: 983–994. http://dx.doi.org.proxy1.library.mcgill.ca/10.1016/j.nutres.2013.07.018.

22. Weight Loss Reduces Risk for CRC Diagnosis, Mortality

Individuals can lower their risk for colorectal cancer (CRC) by increasing recreational physical activity. Doing so will also significantly reduce the risk for death in patients who have been diagnosed with the disease. The following are a few studies that elucidate the relationship between weight and CRC:

- A large meta-analysis demonstrated that every 5-unit increase in body mass index (BMI) is associated with an 18% rise in risk for CRC. This association is stronger in men than in women, and stronger for cancers that occur in the colon than the rectum (Ning Y et al. Obes Rev 2010;11:19-30)
- An ongoing, prospective study confirmed that BMI is also linked to prognosis. Patients who reported having an obese BMI several years before their cancer diagnosis had a higher risk for death (approximately 30%) from all causes, over the study period. The study also showed that an individual's BMI after diagnosis of cancer had no bearing on their long-term mortality risk, possibly due to the effects of both the disease and its treatment on a person's weight (Campbell PT et al. J Clin Oncol 2012;30:42-52)

Physical activity levels also play a major role in CRC development. Many studies in the US have consistently found that adults with higher levels of physical activity—in intensity, duration or frequency—can reduce their risk for developing colon cancer by 30% to 40% relative to those who are sedentary, regardless of BMI.

- In a recent study, investigators found that people who met the public health recommendation of at least 150 minutes of physical activity per week had a lower risk for all-cause and cardiovascular mortality (Campbell PT et al. 2013;31:876-885)

Clinicians who treat cancer patients have said they are emphasizing the importance of maintaining a healthy body weight and increasing physical activity to help patients manage their risk for recurrence. For example, Dr. Sinicrope at the Mayo Clinic and the lead author of many studies looking at cancer and obesity, said he counsels patients with a BMI of 30 kg/m^2 or higher to consume nutrient-rich foods such as fruits, vegetables and whole grains; to reduce their red meat consumption; and to increase physical activity. Dr. Cusack Jr. at the Harvard Medical School has said he and his colleagues are increasingly working with their patients to help them achieve and maintain a healthy weight before and after surgery. He says that patients rarely have time to make significant changes in the period between diagnosis and surgery, but he does encourage them to participate in a programmatic weight loss and exercise program during neoadjuvant therapy to improve their surgical outcomes and their overall likelihood of surviving the disease. Surgeons also work more closely with patients to help them modify diet and lifestyle in the long term, he commented. Recent data suggest that increased activity levels and weight loss after surgery may improve the likelihood of surviving CRC, providing a strong rationale for the surgeon to initiate the discussion of modifying diet and lifestyle for the long-term benefit of the patient. The take-home message here is that people can mitigate their risk for CRC by losing weight and engaging in physical activity even

while undergoing treatment. However, cancer patients should not lose more than two pounds per week and any weight loss should be achieved through exercise and proper diet.

Sinicrope, F. A., et al. (2013). Body mass index at diagnosis and survival among colon cancer patients enrolled in clinical trials of adjuvant chemotherapy. Cancer, 119: 1528–1536. doi: 10.1002/cncr.27938.

Campbell, Peter T. et al. (2013). Associations of Recreational Physical Activity and Leisure Time Spent Sitting With Colorectal Cancer Survival. JCO, vol. 31, no. 7 876-885. doi: 10.1200/JCO.2012.45.9735.

23. Body Mass Index and Microsatellite Instability in Colorectal Cancer: A Population-based Study (Oct. 14/13)

Previous studies reported a positive association of body mass index (BMI) with microsatellite-stable (MSS) but not with microsatellite-instable (MSI-high) colorectal cancer (CRC). Microsatellite instability describes a change that occurs in the DNA of certain cells (such as tumor cells) in which the number of repeats of microsatellites (short, repeated sequences of DNA) is different than the number of repeats that was in the DNA when it was inherited. The cause of microsatellite instability may be a defect in the ability to repair mistakes made when DNA is copied in the cell. Investigators conducted a population-based case-control study (DACHS) in Southern Germany, including 1 215 patients with incident CRC and 1 891 matched controls. Information on risk factors of CRC was obtained in standardized interviews and microsatellite instability was analyzed. They found that BMI was positively associated with both risk of MSI-high CRC and risk of MSS CRC. The association with MSI-high CRC was limited to women and most pronounced among ever users of postmenopausal hormone replacement therapy. This population-based study confirms previous findings of increased risk of MSS CRC with obesity between both sexes, and suggests that overweight and obesity may also be associated with increased risk of MSI-high CRC among women.

Hoffmeister, M. et al. (2013). Body Mass Index and Microsatellite Instability in Colorectal Cancer: A Population-based Study. Cancer Epidemiology Biomarkers Prevention, 22(12):2303-11. doi: 10.1158/1055-9965.EPI-13-0239.

24. Lifestyle Changes can cut your Risk of Colon Cancer (Dec. 04/13)

About 50% of colorectal cancers (CRCs) can be prevented through daily diet, physical activity and weight management, making it one of the most preventable cancers. 5 specific steps toward that goal come from an evidence-based report on reducing risk of CRC released by the American Institute for Cancer Research (AICR) and World Cancer Research Fund (WCRF) as part of their Continuous Update Project (CUP). Here is a summary of recommended strategies:

1. Fill up on foods with fiber: each 10 grams of dietary fiber is linked with a 10% lower risk of CRC. Whole grains stand out as particularly linked to lower risk. Fiber adds bulk and reduces the time your digestive tract is exposed to carcinogens. Also, high-fiber diets encourage growth of health-promoting types of bacteria.
   - Focus on whole plant foods - vegetables, fruits, whole grains, beans, and nuts - in order to reach levels of fiber linked with lowest risk as they provide fiber along with protective nutrients and phytochemicals
   - Add beans or tofu to soups, stews and stir-fries
   - Start eating whole grain bread and pasta, then expand to a variety of unprocessed, cooked grains, such as bulgur, whole wheat couscous, quinoa, and whole-grain polenta
   - Add some nuts or seeds (including ground flaxseed) to your morning cereal or smoothie
2. Cut calories if you're carrying extra weight, especially if it's around your waist. Excess body fat secretes inflammation-inducing proteins and creates cancer-promoting changes in hormones like insulin and growth factors. Each 1-unit increase in body mass index (BMI), which corresponds to 5-7 pounds for most adults, is linked with a 2% increase in CRC risk. Fat deep in the abdomen poses the most risk. Each 1-inch increase in waist links to a 5% increase in CRC risk. The key: don't simply add healthy foods; swap them for less healthy foods to boost nutrition and keep calories the same or lower.
   - Sip water, seltzer, tea or coffee instead of soda or sugary tea and coffee specialty drinks
   - If you're not hungry, relax with a walk, meditation, music or a book instead of food
3. If you drink alcohol, limit it to no more than 1 (for women) or 2 (for men) drinks a day. Alcohol is metabolized to compounds that damage cells and can lead to cancer. Based on similar alcohol content, one standard drink is considered 12 ounces beer, 5 ounces wine, 1.5 ounces 80-proof liquor or 1 ounce 100-proof liquor. For each one standard drink consumed daily, CRC risk increases 14%, according to analysis of multiple studies. Cancer risk is linked with alcohol content, not choice of beverage.
   - Watch your glass size. With today's larger glasses, what you may consider one drink may be more
   - Choose seltzer flavored with fruit essence, or add slices of fruit to club soda for a more enticing option than plain water
4. Limit red meat (beef, lamb and pork) and avoid processed meat. Each 3½ ounce portion of red meat eaten daily increases CRC risk 17%. Processed meat is even more strongly linked with risk; each portion half that size eaten daily increases risk 18%. Recommendations include limiting red meat, even if lean, to no more than 18 ounces a week, and to save processed meat for occasional consumption.

- By swapping a couple of fish or seafood meals per week for red meat, you reduce colon cancer risk while promoting overall health. Add a few more meatless meals to your week, making sure to include beans, lentils or some other source of protein.

5. Get moving: even if you don't lose weight, a little extra activity every day can stop or slow weight gain. What's more, regular physical activity fights cancer development directly by reducing elevated insulin levels and reducing inflammation regardless of weight. Each 30 minutes of daily recreational physical activity is linked with an 11% decrease in CRC risk.
   - You needn't get the recommended 30 minutes or more of daily physical activity all at once. See how many 10-minute blocks of movement you can include throughout your day.
   - Get up just a little earlier and start the day with a 10-minute walk.
   - Get off public transit one stop early, walk 10 minutes at lunch or between projects, head outside or turn on your favorite tunes and dance before or after dinner.

Collins, Karen. (2013). 5 Steps to Cut Colon Cancer Risk. Environmental Nutrition 36, no. 11: 1-6.

Perera, P.S. et al. (2012). Recent Evidence for Colorectal Cancer Prevention Through Healthy Food, Nutrition, and Physical Activity: Implications for Recommendations. Current Nutrition Reports, Volume 1, Issue 1: 44-54. doi: 10.1007/s13668-011-0006-7.