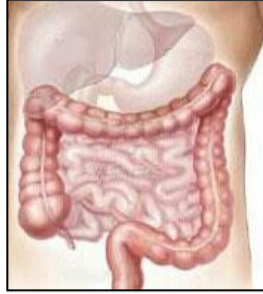


COLORECTAL CANCER RESEARCH UPDATES

Month Ending April 19th, 2013



The following colorectal cancer research update extends from March 16th, 2013 – April 19th, 2013 inclusive and is intended for informational purposes only.

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DRUGS / SYSTEMIC THERAPIES

1. Novel Treatment Regimen Looks Good for Advanced Rectal Cancer (Apr.1/13)

A novel neoadjuvant (pre-surgery) chemotherapy and radiation regimen for advanced rectal cancer could successfully overcome the logistic problems that are associated with the treatment of these patients. Dutch researchers employed short-course radiation followed by systemic therapy in an attempt to achieve local control and treat metastases in a timely manner in a series of 50 patients with stage IV rectal cancers. The regimen involved a preoperative short-course of pelvic radiotherapy (5 fractions of 5 Gy each), followed by capecitabine (xeloda) and oxaliplatin given in combination with bevacizumab. Radical surgical treatment at all tumor sites (which were limited to the rectum, lung, and liver) was carried out 6 to 8 weeks after the end of systemic therapy. Study authors report that radical surgical treatment

was possible in **36 patients** (72%). The 2-year overall survival rate was 80% and the 2-year recurrence rate was 64%. The regimen had a "high tolerability," with 84% completing treatment without delay. There were no treatment-related deaths. The goal of this study appears to have been met. "The combination of short-course radiation followed by fairly aggressive chemotherapy resulted in a high rate of down-staging and pathologic complete response". The authors report that the rate of pathologic complete response of the primary tumor was 26% and that there was no progression of any rectal tumors between the start of radiation therapy and surgery (median, 180 days). "These response frequencies are comparable or better than those with other neoadjuvant chemoradiation schemes, which have pathologic complete response from 10% to 30% in patients with locally advanced rectal cancer," write the authors.

Van Dijk, T.H., et al., Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. Ann Oncol (2013) doi: 10.1093/annonc/mdt124 First published online: March 22, 2013

2. **First Results of Labetuzumab-SN-38 Announced** (Apr.9/13)

Immunomedics, Inc., a biopharmaceutical company primarily focused on the development of monoclonal antibody-based products for the targeted treatment of cancer, autoimmune and other serious diseases, announced that its proprietary antibody-drug conjugate (ADC), **labetuzumab-SN-38**, appears to be safe and reasonably well tolerated within a clinically effective dosage range in patients with advanced colorectal cancer. Results from this Phase I study were presented from the Memorial Sloan Kettering Cancer Center group. Labetuzumab is a slowly-internalizing antibody that recognizes the carcinoembryonic antigen (CEA; CEACAM5 or CD66e), which is expressed in many solid cancers, including more than 80% of colorectal cancer. In prior clinical trials, the antibody was shown to be safe when administered unconjugated or bound to the radioisotope, iodine-131, for radioimmunotherapy. SN-38 is the active metabolite of irinotecan, which is a standard therapy for patients with metastatic colorectal cancer, but has major gastrointestinal and hematologic toxicity. By targeting SN-38 directly to CEA-expressing tumors, delivery of SN-38 may be increased while mitigating systemic toxicity. Preclinical studies have shown that the antibody-drug linkage was susceptible to cleavage in serum, with 50% of SN-38 released in ~1.0 day, leading to a locally enhanced concentration within the tumor site. In animal models of human colorectal cancer, the ADC exhibited high anti-tumor activity. The goal of this single-arm, dose-escalation study was to determine the maximum-tolerated dose of labetuzumab-SN-38 in patients with metastatic colorectal cancer. Patients who had previously been treated with at least one prior irinotecan-containing regimen were enrolled to receive 2 doses of the ADC separated by 14 days. In the absence of unacceptable toxicity or disease progression, treatment continues for at least 24 weeks for a total of 12 cycles. Treatment may continue past 24 weeks if the patient reports a partial response or stable disease, with no unacceptable toxicity. At the time of reporting, 11 patients with a median of 5 prior therapies have been treated at the 2, 4, 8, and 16 mg/kg dose levels. The average number of doses given was 3.9, with 6 of 11 patients receiving 3 or more doses. Five patients received 2 or more doses of 16 mg/kg, of which 1 has currently received 18 doses and has a continuing partial response after 8 doses. One dose-limiting toxicity was observed at 16 mg/kg. Otherwise, the ADC was well tolerated. No human anti-humanized antibodies have been detected to date. Analysis of serum samples showed the intact conjugate clears more quickly than the antibody, consistent with SN-38 being gradually released from the ADC.

<http://www.benzinga.com/news/13/04/3481760/immunomedics-announces-first-results-of-labetuzumab-sn-38-in-colorectal-cancer-st>

3. **Adding Erbitux to Chemo Enables Patients With Advanced Colorectal Cancer, Liver Mets to Undergo Surgery** (Apr 8/13)

New results from a clinical trial conducted in Shanghai, China, indicate that adding cetuximab (Erbitux) to standard chemotherapy enables some patients, with otherwise inoperable liver metastases due to colorectal cancer, have their metastases surgically removed. Such surgery can be curative, and is generally critical to long-term survival. While this combination regimen is a standard treatment option for many patients with advanced colorectal cancer, this is the first randomized study to explore its impact on inoperable liver metastases. The study also suggests that, compared to chemotherapy alone, combination of cetuximab and chemotherapy improves tumor shrinkage and extends survival, even for patients with inoperable liver metastases who cannot undergo surgery. "Our study suggests that in Chinese patients adding cetuximab to chemotherapy may effectively reduce tumor burden and increase the possibility of surgically removing liver metastases, improving survival and quality of life," said senior study author Jianmin Xu, MD, PhD, a surgeon at the Zhongshan Hospital, Fudan University, in Shanghai, China. "While our study evaluated only Chinese patients, these findings may also be relevant for patients in North America and Europe." The liver is often the first site of metastatic disease and may be the only site of spread in as many as 30-40% of patients with advanced colorectal cancer. Approximately 50% of patients with colorectal cancer develop liver metastases during the course of the disease. This study focused on patients who had liver metastases at the time of initial diagnosis of colorectal cancer, which account for 15-25% of all patients with liver metastases. Surgical removal of metastasis offers the only chance for long-term survival for these patients. Prior studies found that nearly half of patients are alive five years after removal of liver metastases. However, only 10-20% of patients with liver metastases are candidates for surgery. The current practice guidelines recommend giving

“downsizing” chemotherapy or chemotherapy and targeted therapy combination regimens (for example, cetuximab) with the goal of “converting” initially inoperable metastases to operable tumors. This trial is the first study specifically designed to determine if adding cetuximab to chemotherapy would help “convert” initially inoperable tumors to operable ones. In this Phase III clinical trial, patients with stage IV colorectal cancer spread only to the liver were randomly assigned to receive chemotherapy with cetuximab (Group A) or chemotherapy alone (Group B). They received either the FOLFIRI (leucovorin, fluorouracil and irinotecan) or the mFOLFOX6 (leucovorin, fluorouracil, and oxaliplatin) chemotherapy drug combination. Both regimens are standard treatment options for colorectal cancer with comparable efficacy but different side effects. After treatment, 26% of patients (18 out of 70) became eligible for surgery to remove liver metastases in Group A compared to only 7% (5 out of 68) in Group B. Patients in Group A who underwent surgery to remove such metastases lived significantly longer (46.4 months), on average, than those who were not able to have surgery (25.7 months). Compared to chemotherapy alone, combination treatment significantly increased liver tumor shrinkage rates (57 versus 29%) and the predicted 3-year overall survival rates (41 percent versus 18%). Overall, the median survival time for patients in Group A was 30.9 months compared with 21 months for those in Group B. Cetuximab belongs to a class of drugs known as EGFR inhibitors. Such drugs block specific molecular pathways involved in tumor growth. This study included only patients with a so-called wild-type (normal) *KRAS* gene, because cetuximab is known to be ineffective against tumors with alterations in the *KRAS* gene. About 60% of all people with colorectal cancer have a normal, unchanged *KRAS* gene. Routine testing for *KRAS* gene alterations before giving anti-EGFR therapy is recommended.

Ye, L-C, et al., *Randomized controlled trial of cetuximab plus chemotherapy for patients with kras wild type unresectable colorectal liver-limited metastases. J Clin Oncol 2013; DOI: 10.1200/JCO.2012.44.8308*

4. Study Shows Drug Is Effective for Cancer Patients with Neuropathy (Apr.15/13)

Results of a phase III trial show that duloxetine (Cymbalta®) effectively treats painful peripheral neuropathy caused by certain types of chemotherapy. The results, from the first randomized clinical trial to show an effective treatment for chemotherapy-induced peripheral neuropathy (CIPN), were published April 3, 2013, in *JAMA*. CIPN causes chronic pain, tingling, and numbness—mainly in the hands and feet—that can interfere with a patient’s ability to perform everyday activities and to receive needed doses of chemotherapy. CIPN affects 20 to 30% of cancer patients treated with taxane and platinum-based chemotherapy drugs, which can damage nerve cells. CIPN may continue for months or even years after treatment is stopped and may worsen over time. Investigators studied 231 people aged 25 or older who had previously reported high levels of pain from peripheral neuropathy. Patients in the trial had been treated with paclitaxel (Taxol®), **Oxaliplatin (Eloxatin®)**, Docetaxel (Taxotere®), or Cisplatin (Platinol®). The researchers found that 59% of the patients who took daily duloxetine for 5 weeks reported a decrease in pain of any amount, compared with 38% of the patients who took a placebo. The average pain score of patients in the duloxetine group fell about 10%, which the researchers noted is “considered to represent a minimally clinically important change,” while the average scores of those in the placebo group fell about 3%. The difference is similar to that seen in other studies of duloxetine for chronic pain. The most commonly reported side effect was fatigue, which was higher in patients taking duloxetine than in patients taking the placebo. The researchers acknowledged some potential limitations to the study. For example, they did not document the use of other pain medications during the study period and did not study duloxetine treatment beyond 5 weeks. In addition, the dropout rate due to adverse side effects was higher among participants who received duloxetine. “This study is the first to demonstrate statistically significant improvements in established neuropathic pain compared to placebo,” write the study authors. “While duloxetine is approved by the Food and Drug Administration for painful neuropathy caused by diabetes, there are no [approved] treatments for CIPN.”

<http://www.cancer.gov/clinicaltrials/results/summary/2012/neuropathy0612>

5. Locoregional Hyperthermia Now Being Offered at the Marsden Centre of Naturopathic Excellence (Apr.17/13)

Extensive clinical research has shown that hyperthermia can be effectively combined with various modes of treatment to produce a synergistic effect in tumour response and control. For example, using locoregional hyperthermia in conjunction with radiation or with chemotherapy can offer better outcomes than conventional therapy alone. There are various forms of locoregional hyperthermia (LRHT) treatment devices in use. The Marsden Clinic is now the second centre across Canada to offer the Oncotherm 2000 EHY device which is a capacitive, modulated RF generating LRHT. This type of LRHT is unique in its ability to penetrate deep tissues without creating hot spots. LRHT is non toxic and has been proven to be a superior adjunct therapy to conventional cancer therapies. For more information, please visit: <http://www.naturopathiccentre.com/page2/page6/page4/index.html>

www.mcne.ca

SURGICAL THERAPIES

6. **Surgery May Be Avoided in Early Rectal Cancer** (Mar.21/13)

Select patients with locally advanced rectal cancer may be spared surgery and its associated complications, a cancer surgeon suggested at the annual Society of Surgical Oncology Cancer Symposium. Approximately 10%-25% of patients with locally advanced rectal cancer will have clinical complete responses (cCR) to neoadjuvant (pre-surgery) chemotherapy and radiation. The vast majority of these patients will avoid rectal resection, at least within the first 5 years. Although local failure occurs in 10%-25% of patients, most of the failures occur within the first 18 months, and most of these cases can be salvaged with resections. Patients treated with non-operative management appear to have rates of distant recurrence and survival similar to those of patients with pathologic complete responses (pCR) treated with total mesorectal resection. If surgery is required, local excision may be sufficient for some patients with stage T1 lesions and a select few with T2 lesions. If a patient has a favorable T1 lesion and would otherwise face a life-altering procedure such as abdominal perineal resection (APR) and colostomy, the surgeon should at least show the patient the data and discuss local excision as a safe and effective alternative with results comparable to more extensive resections. T2 lesions are more problematic, but a select few patients with this tumor type might be spared the morbidity of standard rectal resection.

<http://www.qihpnews.com/news/top-news/single-article/surgery-may-be-avoided-in-early-rectal-cancer/00e1a33ea980dfc507520c5b36ac4bb7.html>

7. **Can Gum Help The Colon Bounce Back from Surgery?** (Mar.27/13)

Chewing gum after surgery for colon cancer may not help kick the intestines back into gear - but it also probably won't hurt, a new study suggests. The surgery, which involves removing part of the colon, typically keeps patients in the hospital for a week or more while doctors wait for the bowel to start working and for people to be able to eat normally again. Past studies have hinted that gum might help cut that recovery time if the body responds to chewing by preparing the gut to receive food, researchers said. Although the new findings challenge that theory, one colorectal surgeon thinks gum is still worth a go. It's quite reasonable to try sugar-free gum to help stimulate gastrointestinal recovery after major abdominal surgery, as there appears to be no downside, and it's cheap, unlike many other medications. Researchers have combined less-invasive surgery with a set recovery plan to cut hospital stays to two and a half days after so-called colorectal resection, on average. Their plan includes advising patients to chew gum after surgery. For the new study, investigators randomly assigned people having either open or less-invasive colon surgery to chew gum four times a day after surgery or not to chew gum at all. Their study included 157 patients treated at one of two hospitals between 2008 and 2011. What the research team was looking for was how quickly patients regained their bowel function after surgery - measured by when they started producing gas. People who didn't chew gum said it took an average of 51 hours - just over two days - for their intestines to start gearing up again, compared to 43 hours among gum chewers. However, statistically, that difference could have been due to chance, according to the team. It's possible the new study simply didn't include enough patients to tease out a clear difference between the groups. There's data suggesting that it's probably about a 20-hour improvement that comes with gum chewing. "The true result may be that chewing gum still results in a real, but less dramatic improvement, in gastrointestinal function" when combined with other recovery techniques, the researchers wrote in the *Annals of Surgery*. Because there weren't any side effects tied to gum chewing, Lim and his colleagues said the strategy could still have potential among some patients recovering from colon surgery - but more research is needed to determine which ones are likely to benefit.

Lim, Patrick, et al., Sham Feeding With Chewing Gum After Elective Colorectal Resectional Surgery: A Randomized Clinical Trial. Annals of Surgery, online March 6, 2013.

SCREENING

8. **Radiation Can Be Reduced While Maintaining High Quality in CT Colonoscopy** (Apr.4/13)

A new study has found it's possible to maintain high-quality CT colonography diagnostic images while reducing the radiation dose. This is important as the use of CT colonography, or virtual colonoscopy, becomes more widely used for colorectal cancer screenings. found that decreasing the tube voltage would not negatively impact the integrity of the CT colonography. His research is published in the current issue of the journal *Radiology*. "Radiation dose is a concern for many in health care – from the clinicians and patients to the government agencies that regulate the industry," Chang said. "The theoretical risks of radiation exposure as a cancer causing agent must be weighed realistically against the substantial benefits of colon cancer screening. The study was conducted to assess the effect of decreasing the radiography voltage on dose and ultimately on 3D image quality in patients undergoing CT colonography, and how these changes are affected by patient size. After studying the CT colonography results in 63 patients, the results showed a statistically significant decrease in radiation dose while only slightly decreasing 3D image quality in patients of all sizes. Chang says that more study is needed, but that he

and other experts anticipate even more decreases in CT radiation dose in the coming years. "Colorectal cancer screenings are an important part of preventative medicine," Chang said, "and by lowering the radiation dose, we can lower patients' concerns and their exposure, while maintaining the diagnostic quality of the exam and providing early detection and treatment."

Radiology (2013; doi:10.1148/radiol.12120134)

<http://www.oncologynurseadvisor.com/radiation-can-be-reduced-while-maintaining-high-quality-in-ct-colonoscopy/article/287428/>

OTHER

9. Study Finds No Link Between Constipation & Colon Cancer (Mar.21/13)

Long-term constipation doesn't raise risk for colon and rectal cancers according to a new analysis of the existing evidence. Past studies had suggested a possible connection, but researchers said those results may have been skewed by poor study designs. "Someone who's got chronic constipation is unlikely to be associated with colon cancer now or in the future," said study author Dr. Alexander Ford. Established risk factors for the disease include a personal or family history of colorectal cancer, irritable bowel disease, certain syndromes that cause colon polyps, type 2 diabetes, obesity, heavy drinking, smoking and being over age 50. Some experts have hypothesized that chronic constipation, by causing prolonged contact between potentially carcinogenic substances in the stool and the lining of the colon, might also increase the risk of cancer. Studies in recent decades have both supported and refuted that idea, so Ford and his colleagues reanalyzed data across 28 studies that examined the connection between constipation and colorectal cancer. In total, the data included over 250,000 participants from 1966 to 2011. Ford's team found little support for a link between constipation and cancer risk, according to their findings published in the journal *Gastroenterology*. Studies that showed an association typically included questionnaires for participants to recall bouts of constipation. "If they just have constipation in isolation then that does not seem to be a risk factor for colon cancer," said Ford. Symptoms of advanced colon cancer typically include diarrhea or looser stools, unintentional rapid weight loss, abdominal pain, anemia and rectal bleeding. Ford's team also found that studies focused just on colorectal cancer patients did find a significantly higher rate of constipation in patients compared to people without colorectal cancer, but again, those studies had weaknesses.

Ford, Alex, et al., Association Between Constipation and Colorectal Cancer: Systematic Review and Meta-Analysis of Observational Studies. The American Journal of Gastroenterology, online March 12, 2013

10. Men with Lynch Syndrome Face Increased Lifetime Risk of Prostate Cancer (Apr.5/13)

Men with an inherited genetic condition called Lynch syndrome face a higher lifetime risk of developing prostate cancer and appear to develop the disease at an earlier age, according to a new study. Lynch syndrome is an inherited condition linked to a higher risk of several types of cancer. People with Lynch syndrome have up to 80% lifetime risk of colorectal cancer and are also more likely to develop endometrial, gastric, ovarian, urinary tract, pancreatic and brain tumors. Overall, about 1 in 440 people are carriers for the genetic mutation, making it one of the most common inherited cancer conditions. The findings in prostate cancer have implications for screening younger men who may be at higher risk of the disease. Recent guideline recommendations advise against prostate cancer screening in men younger than 75 who do not have any symptoms. For men with an inherited risk factor for prostate cancer, they should still be thinking about prostate cancer screening. The study suggests men with Lynch syndrome might benefit from regular prostate cancer screening. The researchers looked at 198 families who have a strong family history of cancer and were enrolled in registries at the University Of Michigan Comprehensive Cancer Center or at Dana Farber Cancer Institute. These family registries included 4,127 men who were included in this analysis. Among men with a mutation linked to Lynch syndrome, the researchers estimated their lifetime risk of prostate cancer to be 30%, compared to 18% among the general population. Men aged 20-59 who carried this mutation also faced a higher risk of prostate cancer than the general public. Results of the study appear online in the *Journal of Clinical Oncology*. Earlier studies have suggested that Lynch syndrome might play a role in inherited prostate cancer, but studies to date have been controversial. "It's been tricky to figure out if prostate cancer is really associated with Lynch syndrome. It's a very common cancer. When you see it occurring in families, it's difficult to figure out if that's because it's associated with Lynch syndrome or just because it's really common," say study authors. The current study uses a more rigorous statistical analysis and pulls from a larger number of people. This same method has previously linked Lynch syndrome to endometrial cancer and pancreatic cancer.

Raymond, V.M. et al., Elevated Risk of Prostate Cancer Among Men With Lynch Syndrome. Journal of Clinical Oncology, 2013; DOI: 10.1200/JCO.2012.44.1238

11. Uterine Cancer Survivors Face Colon Cancer Risk (Apr.12/13)

Depending on their age, women diagnosed with uterine cancer may have a higher risk of developing colon cancer later on, according to a new study from Canada. "As the survival has increased among cancer survivors, it's important to know what the other problems they're facing," said Dr. Harminder Singh, the study's lead author from the University of Manitoba in Winnipeg. Cancer of the endometrium - the lining of the uterus - is the most common cancer of the female reproductive tract. Previous research looking at women's risk for colon cancer following endometrial cancer produced mixed results. Also, no study looked at where in the colon those cancers showed up, which can help pick screening techniques. For the new study, the researchers used data on 3,115 women diagnosed with endometrial cancer between 1987 and 2008 in the Canadian province of Manitoba. The researchers then compared those participants to 15,084 women who were never diagnosed with cancer. Using the women's medical records, the researchers then saw how many were diagnosed with colon cancer by 2009. Overall, about 1.9% of women with endometrial cancer went on to get colorectal cancer. That compared to 1.6% of women who never had endometrial cancer. While that's a small increase among women who already had cancer, it could have been due to chance, according to the researchers. They did find, however, that seven women diagnosed with endometrial cancer before age 50 ended up with colon cancer during the study. Although a very small number, it works out to be about a four-fold increase over those who never had cancer. The researchers also found those women and women diagnosed with endometrial cancer between age 50 and 65 years old were more likely to have cancer on the right side of their colons. That finding, says Singh, suggests colonoscopy would be the preferred screening method in those women.

Singh, Harminder, et al., Risk of Colorectal Cancer After Diagnosis of Endometrial Cancer: A Population-Based Study. Published online before print April 8, 2013, doi: 10.1200/JCO.2012.47.6481

12. **New Type of Colon Cancer Discovered** (Apr.14/13)

A unique sub-type of bowel (colon) cancer has been discovered which has a worse outcome than other types of colon cancer and is resistant to certain targeted treatments, according to research published. Researchers from the UK and the Netherlands analyzed tumours from 90 separate patients with stage II colon cancer and found that they could group the samples into three distinct sub-types. They then developed a panel of 146 genes that could distinguish these sub-types, and confirmed their findings by analyzing a further 1100 patients with the disease. Two of these sub-types were already known, but in more than a quarter of the patients a new kind of cancer was detected, which was previously not regarded as a separate sub-type. These patients were more likely to do worse than those with the other types of bowel cancer. Furthermore, their tumours were more aggressive and resistant to the drug Cetuximab (Erbix), which can be used to treat the disease. Cetuximab targets a molecule called epidermal growth factor receptor (EGFR), whose link to cancer was discovered by Cancer Research UK scientists in the 1980s. Further experiments showed that this third group of bowel tumours are likely to develop in a different way from the other types, which may explain their aggressiveness. This highlights the need for further research to understand this particular sub-type of bowel cancer and develop new treatments to target it. Dr. Louis Vermeulen, lead researcher on the study, said: "We identified a new sub-type of bowel cancer by studying how the genes in tumours behaved. This allowed us to develop a quick and easy test to identify this sub-type, which has a poor prognosis and responds poorly to anti-EGFR therapy – a recognized treatment for many bowel cancers." "When we further examined what properties described the three sub-types we found that this third sub-type was already primed to spread from an early stage, something that was previously only thought to occur much later in tumour development. We speculate these differences between the different sub-types may arise from the cell of origin for the tumour rather than any specific mutation."

Felipe De Sousa, Felipe, et al, Poor-prognosis colon cancer is defined by a molecularly distinct subtype and develops from serrated precursor lesions (2013) Nature Medicine, DOI: 10.1038/nm.3174.

NUTRITION & HEALTHY LIFESTYLE

13. **Soybean Meal Peptides Could Stop Colon, Liver and Lung Cancer Growth** (Mar.24/13)

Proteins found in soybeans could inhibit the growth of colon, liver and lung cancers. Soybean meal is a bi-product following oil extraction from soybean seeds. It is rich in protein, which usually makes up around 40% of the nutritional components of the seeds and dependent on the line, and can also contain high oleic acid (a monounsaturated omega-9 fatty acid). The study looked at the role soybeans could have in the prevention of cancer. Using a variety of soybean lines which were high in oleic acid and protein, the researchers looked to monitor bioactivity between the peptides derived from the meals of soybean and various types of human cancer cells. The study showed that peptides derived from soybean meal significantly inhibited cell growth by 73% for colon cancer, 70% for liver cancer and 68% for lung cancer cells using human cell lines. This shows that the selected high oleic acid soybean lines could have a potential nutraceutical affect in helping to reduce the growth of several types of cancer cells.

Srinivas J.et al., Peptides derived from high oleic acid soybean meals inhibit colon, liver and lung cancer cell growth. Food Research International, 2013; 50 (1): 282 DOI: [10.1016/j.foodres.2012.10.021](https://doi.org/10.1016/j.foodres.2012.10.021)

14. **Fruit & Vegetables May Reduce Colorectal Cancer Risk**

(Mar.24/13)

This study suggests that eating lots of antioxidant rich fruit and vegetables may prevent colorectal cancer. Earlier research shows an association between eating foods with high fiber including fruit and vegetables and reduced risk of colorectal cancer. The current study found total dietary antioxidant capacity was associated with reduced risk of colorectal cancer. Antioxidants are commonly found in fruit and vegetables, rarely in meat and dairy products. The study suggests that eating fruit and vegetables can help prevent colorectal cancer, which should not be surprising. The study was based on data from 1953 patients with incident histologically confirmed colorectal cancer including rectal cancer and colon cancer, and 4154 patients admitted to the same hospital for other disease. Total antioxidant capacity was estimated using food composition tables. The researchers found total antioxidant capacity was inversely correlated with colorectal cancer risk. Those who in the lowest quintile of total antioxidant capacity were about 30% more likely to be diagnosed with colorectal cancer, compared with those in the highest quintile. The seemingly preventative effect was more significant on rectal cancer than colon cancer. The researchers said: This is the first case control study indicating consistent inverse relations between dietary TAC and colorectal cancer risk.

Rossi, Marta et al., Dietary total antioxidant capacity and colorectal cancer: a large case control study in Italy. Internat J of Cancer. Article first published online : 4 APR 2013, DOI: 10.1002/ijc.28133

15. **Black Raspberries Slow Colon Cancer Growth** (Apr. 9/13)

A cancer prevention research team led by Li-Shu Wang, PhD, of the Medical College of Wisconsin, has revealed more information about the effects of black raspberry powder on fatty acid metabolism. By beneficially changing the activity of specific enzymes, the growth of human colorectal cancer is slowed and inflammation associated with abnormal cells is reduced. A key observation was that black raspberries appear to beneficially alter the activity of a patient's fat metabolizing enzymes, as well as enzymes produced by microbes present in the patient's gastrointestinal tract. This combination results in beneficial fatty acid metabolism and appears to have protective health effects for colorectal cancer patients. This study extends previous work by Dr. Wang et al. in human colorectal cancer patients that found key inflammatory proteins, called cytokines, were reduced in patients consuming freeze-dried black raspberry powder. Black raspberries, not to be confused with blackberries, are almost exclusively grown in Oregon, on the west coast of the United States. They have been studied extensively because of their high concentration of certain phytonutrients and antioxidants.

Metabolomic Profiling Reveals a Protective Modulation on Fatty Acid Metabolism in Colorectal Cancer Patients Following Consumption of Freeze-Dried Black Raspberries," was presented April 7, 2013, at the American Association for Cancer Research (AACR) Annual Meeting 2013 in Washington, DC.

16. **Calcium May Reduce Colorectal Adenoma Risk** (Apr.10/13)

Researchers have identified a potential explanation for inconsistent results from prior research about the association between calcium intake and risk for colorectal adenomas, which are precursors to colorectal cancers. The findings may help identify patients who would benefit from higher calcium intake or calcium supplementation. Previous studies suggested that a high intake of calcium was associated with a reduced risk for colorectal adenomas and cancer, but data from the Women's Health Initiative did not support the benefit for colorectal cancer after seven years of follow-up, according to Xiangzhu Zhu, M.D., M.P.H. Zhu and colleagues conducted a two-phase study to investigate whether the associations between risk for colorectal adenoma and intake of calcium and magnesium, as well as the calcium/magnesium ratio, were modified by common changes in 14 genes involved in controlling the amounts of calcium and magnesium in the body. They evaluated 1,818 cases and 3,992 controls from the Tennessee Colorectal Polyp Study, a colonoscopy-based case-control study conducted in Nashville. Patients with the highest calcium intake showed no reduction in their risk for colorectal adenoma if they had no changes in either of two of the 14 genes analyzed, the KCNJ1 and SLC12A1 genes, both of which were identified and replicated in the two-phase study and are essential in calcium re-absorption in the kidney. Fifty-two percent of the study population carried genetic changes in at least one of the two genes, and 13% of the population carried genetic changes in both genes. The highest calcium intake — patients in the top 33% — was significantly related to a 39% reduction in adenoma risk for patients who carried a genetic change in one gene and a 69% reduction in adenoma risk among those who carried genetic changes in both genes. In addition, the corresponding reduction in risk for advanced or multiple adenomas was 89% among those with genetic changes in both genes. According to Zhu, based on these data, a person with genetic changes in any of the two genes will see an increased risk for adenoma if they consume less than about 1,000 mg of calcium a day, especially if they carry genetic changes in both genes. The risk will increase by more than 50% for an adenoma and by 120% for advanced or multiple adenomas. "These patients should increase their calcium intake to reduce the risks," Zhu said. "Our results may provide one possible explanation for the inconsistency in previous studies on calcium intake and colorectal abnormalities because calcium may primarily prevent colorectal cancer in the early stage and reduce risk only among those with genetic changes in calcium re-absorption, which involves KCNJ1 and SLC12A1," Zhu said. "If confirmed in future studies, our findings will be critical for the development of new personalized prevention strategies for colorectal cancer."

<http://www.aacr.org/home/public--media/aacr-in-the-news.aspx?d=3099>

17. **Smoking Linked to Poorer Prognosis in Colon Cancer** (Apr.13/13)

Patients with stage III colon cancer who have a history of smoking are more likely to have worse outcomes, according to a large, randomized phase III trial. Researchers analyzed the data from the North Central Cancer Treatment Group phase III adjuvant trial N0147 and found that smoking was significantly associated with shorter disease-free survival (DFS) and time to recurrence in these colon cancer patients, despite accounting for various patient and tumor characteristics. The adverse relationship was most pronounced for those patients whose colon cancer was ***BRAF* wild-type** or ***KRAS*-mutated**. Prior studies had suggested that smoking is associated with an increased risk of any colorectal cancer and *BRAF*-mutated colorectal cancer specifically. Therefore, the association of *BRAF* wild-type colorectal cancer tumors with worse survival was surprising to the study authors. “This may suggest that smoking has an impact on the different stages of tumor development and progression for these two different types of cancer.” Compared with never-smokers, those who had any history of smoking had a significantly shorter DFS (time before disease came back) — the 3-year DFS was 74% for never-smokers compared with 70% for ever-smokers. Smoking status was associated with a shorter DFS in those colorectal cancer patients with wild-type *BRAF*, but not mutated *BRAF*. Smoking was more strongly associated with a poorer DFS in those patients whose colorectal cancer harbors a mutated *KRAS* gene compared with those who have a wild-type *KRAS* gene. However, only the interaction by *BRAF* mutation (not by *KRAS* mutation) was statistically significant. The results were comparable when the time to recurrence, rather than the DFS, was analyzed. “*BRAF* and *KRAS* mutations are increasingly tested for in certain clinical settings to help guide treatment decisions and inform prognosis,” said study author Phipps. “We also know that these particular mutations can drive different pathways of tumor development, so we often see that risk factors for colorectal cancer differ according to *BRAF* and *KRAS* mutation status. Our results indicate that these tumor markers are also important in terms of prognostic factors.” It is clear that *BRAF* wild-type colorectal tumors are biologically different from *BRAF*-mutated tumors, and that *KRAS* status also results in biologically different tumors. However, how the mutation status of the *BRAF* and/or *KRAS* genes and smoking history impacts tumor biology and prognosis is not yet understood. Additionally, the components in cigarette smoke that can impact different growth and progression pathways in colorectal tumors are not clear either.

Phipps, Amanda, et al., Associations Between Cigarette Smoking Status and Colon Cancer Prognosis Among Participants in North Central Cancer Treatment Group Phase III Trial N0147. J of Clin Oncology. Published online before print April 1, 2013, doi: 10.1200/JCO.2012.46.2457