

COLORECTAL CANCER ASSOCIATION OF CANADA

COLORECTAL CANCER RESEARCH

Week Ending January 23, 2009

The following colorectal cancer research update extends from January 10 – January 23, 2009 inclusive and is intended for informational purposes only.

DRUGS

1. **Picoplatin May Provide a Neuropathy-Sparing Alternative to Oxaliplatin from Poniard Pharmaceuticals** (Jan. 15/09)

Poniard Pharmaceuticals Inc., a biopharmaceutical company, announced updated efficacy and safety data from its randomized, controlled Phase 2 clinical trial of picoplatin in patients with metastatic colorectal cancer. Results continue to suggest that picoplatin, given once every four weeks in combination with 5FU and leucovorin (FOLPI), is associated with less frequent and less severe neurotoxicity than oxaliplatin given in combination with 5FU and leucovorin in the modified FOLFOX-6 regimen (FOLFOX). Results also continue to indicate that both regimens have similar anti-tumor activity in first-line metastatic crc. These new data continue to suggest that picoplatin is an active platinum agent in colorectal cancer but without the significant neuropathy associated with currently marketed platinum. Picoplatin may provide a neuropathy-sparing alternative to oxaliplatin in patients with advanced colorectal cancer.

www.medicalnewstoday.com/articles/135470.php

2. **Older Patients With Unresectable Metastatic Colorectal Cancer Tolerate Folfiri Plus Avastin: Presented at ASCO-GI** (Jan. 17/09)

French researchers suggest that older patients with colorectal cancer can tolerate newer chemo regimens about as well as younger patients. Investigators specifically concentrated on elderly patients because there is scarce data on outcomes among this group. 125 patients were treated with unresectable metastatic colorectal cancer in 2006. Of these, 25 were older than 70 years. Patients were treated with a regimen of bevacizumab in combination with irinotecan biweekly, plus 5FU and folic acid (FOLFIRI). About 32% of the younger patients achieved an objective response to treatment compared with 28% of the older individuals. In addition, about 18% of younger patients were able to stabilize their disease compared with 20% of older patients. Of younger patients, about 32% experienced disease progression compared with 36% of the older patients. Median time to progression was 18.6 months among younger patients and 13.38 months among older patients, a difference that reached statistical significance. Overall survival for the entire cohort was 29 months, with no significant difference between the older and younger groups. The lead researcher concluded that the study results showed this treatment regimen is clearly feasible in nonselected patients and especially in elderly patients.

2009 GI Symposium, Metges, Jean-Philippe, et al. Presentation Title: Folfiri Bevacizumab in Unresectable Metastatic Colorectal Cancer (UMCC) in the True Life, Feasible in Elderly Patients (EP): Results of the Cohort From OMIT Bretagne-Pays de Loire. Abstract 398

3. **Do CRC Patients with Hyperbilirubinemia and Liver Mets Benefit From Chemo** (Jan. 16/09)

This study attempted to determine if colorectal cancer patients with hyperbilirubinemia (severely elevated bilirubin levels) from liver metastases could benefit from chemotherapy administration. Traditionally, crc patients with severely elevated bilirubin levels were not candidates for chemotherapy and were therefore prescribed best supportive care. Breakthroughs such as in the current study, however, are changing clinical practice and the approach. Specifically, patients with liver mets and marked hyperbilirubinemia may now be prescribed chemotherapy in the hope of improving their hepatic function and improving their clinical outcomes. For in the past, large, prospective clinical trials had not addressed this issue efficiently. Hence, the purpose of the present study was to report outcomes within a group of colorectal cancer patients with severely elevated bilirubin levels from liver mets in an effort to provide more substantive guidance in answering the question of whether these patients could benefit from state of the art chemo. A total of 3,019 patients were initially identified by the Mayo Clinic Tumor Registry and 20 patients met the selection criteria. These patients were newly diagnosed; no prior therapy and all had severely elevated bilirubin levels from liver mets. 6 patients received oxaliplatin based chemo and 4 subsequently sustained a drop in their bilirubin. In one instance, the drop

was extremely significant. These 6 patients lived a median of 71 days in comparison to the patients who received only supportive care who lived a median of 28 days. The lead researcher concluded that the present study provides justification for prescribing chemo to patients with colorectal cancer, liver mets and hyperbilirubinemia; though it remains prudent to continue to rely on clinical judgment in making therapeutic decisions and to discuss risk and benefits with patients and their families at length prior to prescribing chemo.

Gunnlaugsson, Adalsteinn, et al., Multicentre phase II trial of capecitabine and oxaliplatin in combination with radiotherapy for unresectable colorectal cancer: The CORGI-L study. European J of Cancer. Doi:10.1016

4. Overall Survival Improves in the Era of Avastin (Bevacizumab) use for Metastatic Colorectal Cancer: Presented at ASCO-GI (Jan. 17/09)

Researchers at the American Society for Clinical Oncology’s 6th Gastrointestinal Cancers Symposium reported that more and more doctors are adding the targeted biologic agent bevacizumab (avastin) to the treatment regimen for metastatic colorectal cancer, patients are surviving significantly longer. During 2003-2004, median overall survival for patients with advanced colorectal cancer was 13.8 months – at a time when 9.6% of patients were receiving bevacizumab, said Dr. Daniel Renouf, from British Columbia Cancer Agency, Vancouver, British Columbia. In 2006, the median overall survival for these patients was 17.3 months, a statistically significant difference. By 2006, 45.2% of patients with metastatic colorectal cancer were receiving bevacizumab. That was the year it was approved as an addition to dual agent chemotherapy for mcr. The bevacizumab study included all patients with mcr who were referred to the British Columbia Cancer Agency, which is affiliated with the University of British Columbia, Vancouver, British Columbia. Dr. Renouf said 969 patients were included in the 2003-2004 analysis, and 448 patients’ outcomes were scrutinized in the 2006 outlook. “We can’t really say that the increase in survival was due to bevacizumab,” he said. “We can just show that the increase in survival occurred at the same time that there was an increase in the use of bevacizumab. The main difference in systemic therapy for metastatic colorectal cancer has been the addition of bevacizumab.”

2009 GI Symposium, Reouf, Daniel, et al., Presentation title: Impact of Bevacizumab on Overall Survival in Patients With Metastatic Colorectal Cancer: A Population-Based Study. Abstract 405

5. Xeloda Plus Oxaliplatin Noninferior to Folfox 4 in Metastatic Colorectal Cancer: Presented at ASCO-GI (Jan. 17/09)

Two year data confirm that a regimen of oxaliplatin and capecitabine (Xelox) achieves similar results compared with oxaliplatin, 5FU, and leucovorin (folfox4) in the treatment of metastatic colorectal cancer. In addition, the addition of bevacizumab to both regimens improves outcomes similarly, researchers said. Dr. James Cassidy from Glasgow University discussed the results at the American Society of Clinical Oncology’s 6th Gastrointestinal Cancers Symposium. The clinical trial began in June 2003 as a direct comparison of the Xelox regimen vs. folfox4. The researchers recruited 317 patients for each arm of the study. However, when data suggested that avastin provided additional benefit in these patients, the trial was amended and 1400 additional patients were enrolled to compare the regimens with and without avastin. Results for overall survival in the different treatment arms were mirror images. The difference between the treatments is in the adverse events analysis as summarized below:

	<u>Xelox</u>		<u>Folfox4</u>
(i)	20% Grade 3	Diarrhea	11% Grade 3
(ii)	7% Grade 3 or 4	Neutropenia	43% Grade 3 or 4
(iii)	1% Grade 3 or 4	Febrile Neutropenia	5% Grade 3 or 4
(iv)	Grade 3	Neuropathy	Grade 3
(v)	Yes	Hand & Foot Syndrome	No
(vi)	26%	Discontinued	24%

Dr. Cassidy concluded that this study confirms that Xelox is noninferior to folfox4, and it gives clinicians a choice in treating patients with metastatic colorectal cancer.

2009 GI Symposium, Cassidy, James, et al., Presentation title: Xelox-1?NO16966, a Randomized Phase III Trial of First Line Xelox Compared With Folfox4 for Patients With Metastatic Colorectal Cancer (mcr): Updated Survival and Tolerability Results: Abstract 382

6. Frequent Xeloda Dose Reductions Required in “Real World” Colorectal Cancer Treatment: Presented at ASCO-GI (Jan. 18/09)

Australian researchers have found that dose reductions caused by adverse side effects appear to be more frequent among patients taking xeloda (capecitabine) than in those receiving 5FU treatment for colorectal cancer, according to a poster presentation at the American Society for Clinical Oncology's 6th Gastrointestinal Association Foundation. According to the researchers, despite the decrease in doses, about the same percentage of patients taking capecitabine as taking 5FU were able to complete the prescribed treatment. The researchers reviewed data to assess how patients handled treatment for colorectal cancer. Data were collected at 4 hospitals in Victoria from January 2003 through February 2008. Included were 27 patients on 5FU, 146 patients taking 5FU/leucovorin and 72 patients on 5FU, leucovorin and oxaliplatin regimens (folfox). They found that no reductions in dose were required in 37% of patients taking capecitabine and in 74.7% of those on 5FU/leucovorin. About 40.3% of those on folfox needed no dose reductions. One third of patients on capecitabine required 1 dose reduction, and 29.6% required more than 1 reduction. 31.9% of patients on folfox required 1 dose reduction, while 27.8% required more than 1 dose reduction. About 19.9% of patients on 5FU/leucovorin required 1 dose reduction, and 5.5% required more than 1 reduction. The need for dose reduction did not appear to impact the ability of patients to complete the treatment regimen. Researchers presented data showing that 77.8% of those on folfox completed treatment compared with 77.8% of those on folfox completed treatment compared with 74% of those on 5FU and leucovorin and 70.4% of those on capecitabine.

2009 GI Symposium, Field, Kathryn, et al., Presentation Title: Capecitabine in Colorectal Cancer: A 5-Year Review of Use in Routine Clinical Care. Abstract 402

7. Prophylactic Skin Care Markedly Reduces Complications in Colorectal Cancer Patients Receiving Treatment with Panitumumab: Presented at ASCO-GI (Jan. 19/09)

With a pre-emptive, prophylactic skin regimen, patients who receive panitumumab for treatment of metastatic colorectal cancer may be able to avoid some of the skin-associated toxicities, according to data presented at the 2009 American Society of Clinical Oncology Gastrointestinal Cancer Symposium. Dr. Edith Mitchell from Thomas Jefferson University presented data from the study, which was the first prospective study to compare pre-emptive and reactive skin treatment for skin toxicities related to panitumumab. Skin toxicities are the most common adverse effects related to panitumumab, which is a fully humanized monoclonal antibody that targets the epidermal growth factor receptor (EGFR). The toxicities could include erythema (skin redness), dermatitis (Inflammation of skin), pruritus (itching sensation), pustules (collection of pus/acne), rash, and hair and nail changes. Panitumumab and other EGFR inhibitors are now key components to the treatment strategies for metastatic colorectal cancer. But the majority of patients who receive these agents suffer from skin toxicities, and for some patients, the treatment must be interrupted or discontinued. If these toxicities can be prevented, it would be a significant advance in patient care. The researchers studied 95 patients receiving panitumumab in combination with irinotecan-based chemo. The patients were randomized to one of 2 groups:

- Pre-emptive skin toxicity treatment initiated 24 hours prior to the first dose of panitumumab, then given daily through week six, or
- Reactive skin treatment after the skin toxicity developed

The skin treatment included moisturizers, sunscreen, topical steroids and oral doxycycline antibiotic. The incidence of these toxicities was reduced more than 50% in the group that received pre-emptive treatment. Quality of life was also assessed. Researchers concluded that the study supports the notion that, as with other side effects to cancer treatments, it is more advantageous to treat prophylactically, than to wait for the side effect to fully develop. Furthermore, it shows that treatment early on does not affect the benefit received from the anticancer therapy.

2009 GI Symposium, Mitchell, Edith, et al., Presentation title: Impact of Pre-Emptive Skin Toxicity Treatment on Panitumumab-Related Skin Toxicities and Quality of Life in Patients With Metastatic Colorectal Cancer: Results From STEPP. Abstract 291

8. Erbitux Allows Patients with Nonresectable Colorectal Liver Mets to Undergo Surgery: Presented at ASCO-GI (Jan. 19/09)

Combining chemo (either folfiri or folfox) can effectively shrink tumors and enable surgeons to remove formerly unresectable colorectal cancer that has spread to the liver, offering potentially curative treatment. German researchers randomized patients with unresectable liver mets to treatment with either folfox with erbitux or folfiri with erbitux. Patients in the study either had five or more tumors in their liver; or surgery to remove liver tumors was considered to be technically impossible. After initial treatment with the combined chemo and erbitux regimens, 75% of patients had tumors shrink, 40% were able to have surgery to remove liver mets, and 35% had all visible signs of liver tumor removed. Median time before surgery became possible was five months. 32% of the patients whose tumors had been considered technically unresectable were able to have all signs of cancer in their liver removed. For those patients with 5 or more liver mets, 40% had a resection. The research team concluded, "The combination of erbitux with standard chemo has demonstrated high activity (79% in Kras wild type patients) and an encouraging rate of liver resection. "

2009 GI Symposium, Gruenberger et al., Presentation title: Cetuximab Plus Folfox6 or Cetuximab Plus Folfiri as Neoadjuvant Treatment of Nonresectable Colorectal Liver Metastases: A Randomized Multicenter Study (CELIM Study): Abstract 296

9. Toxicity Associated with Combination Oxaliplatin Plus Fluoropyrimidine With or Without Erbitux (Jan. 22/ 09)

Researchers from Great Britain performed a phase III randomized controlled trial of first line therapy in advanced colorectal cancer, with particular reference to the addition of erbitux to an oxaliplatin-fluoropyrimidine combination. A total of 804 patients were randomized between March 2005 and July 2006 from 78 centers through the United Kingdom. Patients were allocated to oxaliplatin plus 5FU or xeloda (capecitabine) with or without the addition of weekly erbitux. Toxicity data were collected from all patients. 203 patients received 5FU plus oxaliplatin, 333 oxaliplatin + xeloda, 102 received 5FU + oxaliplatin + erbitux and 166 xeloda + oxaliplatin + erbitux. Researchers observed that excess toxicity (diarrhea, nausea, vomiting) was noted in the oxaliplatin + capecitabine + erbitux treated patients which led the trial management group to conclude that a capecitabine dose adjustment was required to maintain safety levels when using this regimen.

Adams, R.A., et al., Toxicity Associated with combination oxaliplatin plus fluoropyrimidine with or without cetuximab in the MRC COIN trial experience. British Journal of Cancer. (2009) 100, 251-258

SURGERY

10. Protruding vs. Flat Polyps (Jan. 24/09)

While most adenomas appear as polyps protruding into the space inside the colon, some lie flat against the colon wall or are even slightly depressed. A study reported in the Journal of the American Medical Association reports that flat or nonpolypoid colorectal neoplasms (NP-CRNs) are more common than previously believed. In addition, the flat or depressed lesions are almost ten times as likely to contain cancer as the polyps that protrude. NP-CRNs are difficult to detect during colonoscopies because they appear very similar to surrounding tissue. Depressed NP-CRNs that sink into the colon lining are especially hard to find and are the most dangerous. For the study report in JAMA, four specially trained endoscopists at a Veterans Affairs hospital out-patients program in California sprayed the colon with a special blue dye that made the flat lesions easier to see. Over a year's time, they performed more than 1800 routine colonoscopies trying to identify how often nonpolypoid colorectal neoplasms occurred. Patients in the study included a screening group, a surveillance group and a group of people with symptoms of colorectal cancer. Nonpolypoid colorectal neoplasms were found in 170 people, about ten percent of the entire group. They were more common in the surveillance group where more than 15% had a NP-CRN. About 6% of the screening and symptoms groups also had NP-CRNs.

Soetikno, Roy M, et al., Prevalance of Nonpolypoid (Flat and Depressed) Colorectal Neoplasms in Asymptomatic and Symptomatic Adults. Journal of the American Medical Association, Volume 299, Number 9, March 5, 2008.

11. Immunomedics Announces Preclinical Therapy Results of SN-38 for CRC (Jan. 21/09)

Immunomedics Inc., a biopharmaceutical company focused on developing monoclonal antibodies to treat cancer, announced that results presented at the 2009 GI Symposium showed that labetuzumab-SN-38, an antibody-drug conjugate, selectively delivers SN-38 to human colon cancer cells in animal models as an effective new therapy. SN-38 is the active metabolite of irinotecan. Due to its toxicity and poor solubility, SN-38 cannot be administered systemically to cancer patients. The Company has previously reported that by conjugating SN-38 to antibodies, the powerful cancer drug can be delivered selectively to tumors, thereby increasing the amount reaching the tumors and minimizing damage to normal tissues and organs. In this study, the therapeutic efficacy of SN-38 conjugated to labetuzumab was evaluated in two animal models of human colon cancer. Labetuzumab is a non-internalizing humanized antibody that binds to the carcinoembryonic antigen (CEA CAM5) expressed by many solid cancers. The company has conducted clinical trials with the naked and radiolabeled antibody in patients with colorectal, breast and pancreas cancers. In a lung metastatic model of colon carcinoma, therapy with labetuzumab-SN-38 conjugate increased median survival time 1.9 to 3.4 fold compared to various controls, with 20% of animals alive at the end of the study. In another colon cancer model, median survival time for the immunoconjugate treatment group increased 4 fold to 86 days compared to untreated animals, and was significantly better than all controls, including irinotecan administered at its maximum tolerated dose. In the meantime, more preclinical evidences are being collected to support the human testing of this new drug immunoconjugate, though the company believes that these results suggest that targeted chemotherapy of colorectal cancer with labetuzumab-SN-38 should enhance the bioavailability and reduce the toxicity of the clinically validated drug irinotecan.

www.medicalnewstoday.com/news.php?newsid+136094

OTHER

12. Nitric Oxide Shown to Cause Colon Cancer – MIT Study Offers Proof of Compound's Role in Disease (Jan. 20/09)

Researchers long ago established a link between inflammation, cancer and the compound nitric oxide, which may be produced when the immune system responds to bacterial infections, including those of the colon. However, the exact nature of the relationship was unknown – until recently. Researchers from MIT have found that nitric oxide produced by inflammatory cells during bacterial infection can cause colon cells to become cancerous. The finding suggests that blocking the compound may help prevent or treat colon cancer. Many years ago it was discovered that gastrointestinal infection by *H. pylori* is often linked to cancer in humans; a related bacteria called *H. hepaticus* has similar effects in mice. Nitric oxide is produced during the inflammatory response to such bacterial infection, but it has been unclear whether it was damaging cells or protecting them. By studying mice, the MIT team found that nitric oxide produced by different types of cells has different effects. Nitric oxide delivered by inflammatory cells, in particular, is important in causing changes in intestinal epithelial cells, setting the stage for cancer development. In mice infected with *H. hepaticus*, the researchers found that blocking an enzyme needed to produce nitric oxide reduced colon cancer rates. More work is needed to study the exact effects of nitric oxide and develop potential clinical therapies for colon cancer. Therapies will need to be targeted to inhibit the damaging effects of nitric oxide while preserving as many of the protective elements of nitric oxide as possible.

Erdman, Susan, et al., Nitric oxide and TNF-alpha trigger colonic inflammation and carcinogenesis in Helicobacter hepaticus-infected, Rag2-deficient mice. Proceedings of the National Academy of Sciences. January 19, 2009 On-line Edition. 10.1073/pnas.0812347106

13. Incidence of Rectal Cancer Increasing in Patients Under Forty (Jan. 20/09)

Researchers from New York have noticed a trend wherein the incidence of rectal cancer in younger patients is increasing, although there is no similar pattern with colon cancer or in older rectal cancer patients. They cannot account for the reason why. First observed in a single cancer centre, the trend toward more rectal cancer in patients under forty was confirmed in review of the SEER database. Physicians at the Weill-Cornell Medical Center in New York thought that their patients with rectal cancer were getting younger. Looking further they found that between 1990 and 1994, 2% of rectal cancer patients at their center were under 40. But, by 2002 through 2006, the number had risen to 7%. Median age when rectal cancer was diagnosed had fallen from 70 to 57. Analyzing the stats from 1973 through 2005, the research team found that incidence of rectal cancer in young US patients increased about 2% a year. At

the same time colon cancer in patients under 40 was falling 0.2% annually. The rectal cancer increase was happening in both men and women and across all races.

2009 GI Symposium. Meyer et al., Abstract 315.

NUTRITION

14. Caffeine and Colorectal Cancer (Jan. 20/09)

A study reported by the United Kingdom Tea Council attempted to answer the question as to whether or not caffeine increases your risk of developing colorectal cancer. The study observed men and women beginning in the early 1980s and continuing on until 1998. The study observed dietary habits, and other factors, among them caffeine consumption through drinking coffee or tea. Throughout the course of the study, just over 1400 cases of colorectal cancer were observed. The study noted no increase in the incidence of colorectal cancer in those people who drank tea or coffee over those who did not consume these caffeinated beverages. Hence, researchers concluded that drinking tea and coffee with caffeine was perfectly safe and do not increase your colorectal cancer risk. However, one additional finding in the study is particularly interesting. While the study did not find that drinking caffeinated beverages increased your crc risk, it did find that drinking decaffeinated coffee seemed to actually lower your risk of rectal cancer over those people who never drank decaffeinated coffee. The finding was surprising as little research had been performed on any health benefits associated with decaffeinated beverages. Furthermore, it was unclear and more studies and conclusions are required before the ramifications of drinking coffee and tea are fully understood, whether caffeinated or not. As for the reasons these beverages might contain health benefits: Both coffee and tea are good sources of anti-oxidants. Anti-oxidants are important because they neutralize the free radicals created by the body during the digestion process. Left unchecked, these free radicals cause disease and aging. But with the proper dose of daily anti-oxidants, free radical-induced damage can be prevented. Good sources of dietary anti-oxidants are fruits and vegetables.

[www.cancerezine.com/?Does Caffeine Increase Your Risk Of Colorectal Cancer ?id+395974](http://www.cancerezine.com/?Does+Caffeine+Increase+Your+Risk+Of+Colorectal+Cancer+?id+395974)

15. A Study of Colonic Adenomas and Abdominal Obesity (Jan. 15/09)

This study sought to investigate the association between colorectal adenoma and waist circumference. 165 adenoma **cases** and 365 polyp free **controls** with a normal colon were compared in this study where all subjects underwent screening colonoscopy. Factors such as smoking habits, waist circumference, dietary intakes and abdominal obesity were examined. Age, waist circumference and BMI were significantly higher in cases than controls. And smokers and men were more prevalent among cases than controls. Among the abdominal obese subjects, 45.6% had 1 or more adenoma, and 9% of these had advanced adenoma, whereas among subjects with a normal waist circumference, only 25.7% had 1 or more adenomas. The prevalence of adenoma was higher among abdominal obese group. Researchers concluded that abdominal obesity is associated with an increased risk of colorectal adenoma.

Kim, YoungJoo, et al., *An Association between colonic adenoma and abdominal obesity: A cross sectional study. BMC Gastroenterology. 2009, 9: 4 Online Edition.*

16. Colon Cancer and Vitamin D (Jan. 14/09)

A new study in the journal Nutrition and Cancer finds that people who increase their intake of vitamin D might reduce their risk of colorectal cancer by as much as 30%. Vitamin D may be an important factor in colon cancer prevention and is a potentially modifiable risk factor according to the lead researcher who performed a large scale study in 6 areas of Italy. Researchers collected health and diet information via face to face interviews with 1953 patients who had colon or rectal cancer and compared them to 4154 non cancer patients from the same hospital. The more vitamin D patients received through diet, the lower their risk of colon cancer, the researchers discovered. People with the highest dietary vitamin D intake (more than 4.29 micrograms a day) had a 30% lower risk of colon cancer than people with the lowest intake. The benefit was more pronounced among women than men. Vitamin D did not appear however, to have any significant effect on lowering rectal cancer risk. The reason is unknown. The specific location of the colon cancer seemed to affect how well vitamin D reduced risk. Although about two thirds of colorectal cancers are in the transverse and descending colon, this study found that vitamin D had more of a protective effect on cancers located in the ascending colon. The evidence seems to suggest that vitamin D may lower colon cancer risk, and researchers

recommend incorporating the vitamin into the diet for its many other known health benefits as well, including bone strength. Experts say that getting 1,000 IU a day of vitamin D may help reduce colon cancer risk, although no “optimal” dose has been established. Study authors say that boosting the collective vitamin D intake might ultimately help prevent 250,000 colorectal cancer cases worldwide each year.

Lipworth, L, et al. Dietary vitamin D intake and cancers of the colon and rectum: A case-control study in Italy. Nutrition and Cancer. 2009; 60: 70-75

17. **Apple Pectin Helps Prevent Colorectal Cancer** (Jan. 11/09)

The pectin from apple peels and extracts of apple juice appear to increase the production of a chemical associated with protection from colon cancer, according to a new study conducted by German researchers and published in the journal *Nutrition*. The researchers fermented fecal slurry from healthy volunteers with either apple pectin, apple juice extract, or a combination of the two. They found that the concentrations of a short chain fatty acid (SCFA) known as butyrate were higher in the samples that had been fermented with apple pectin. Concentrations of other SCFAs were also elevated. Butyrate not only serves as a major nutrient for the lining of the colon, but is also thought to play an important role in the protective effect of natural fiber against colorectal cancer according to the researchers. Butyrate appeared to inhibit the production of HDACs, which have been linked to the development of precancerous cells and tumors. When the researchers tested the fermented fecal slurries on both healthy and cancerous colon cells, they found that the production of HDAC was significantly inhibited. The slurries fermented with apple juice did not have butyrate levels as high as those fermented with pectin, but they inhibited HDAC production just as effectively. A combination of pectin and apple juice, however, was no more effective than pectin alone. This led the researchers to hypothesize that while apple juice contains still-unknown HDAC inhibitors other than butyrate, butyrate is the most significant inhibitor for the human body.

Waldecker, Markus, et al., Histone-deacetylase inhibition and butyrate formation: Fecal slurry incubations with apple pectin and apple juice extracts. Nutrition. Volume 24; Issue 4 (2008): pp. 366-374.

18. **Folate and Colorectal Cancer Prevention** (Jan. 17/09)

This British study sought to review the currently existing body of evidence concerning the efficacy and safety of folate (folic acid) as a potential colorectal cancer chemopreventive agent. The study suggests that depending upon when folic acid is administered in relation to the development of colorectal neoplasms, a “dual modulator” role for folate in colorectal carcinogenesis is being proposed. In other words, an individual who chooses to increase their folate intake with folic acid supplements may experience either **beneficial or detrimental** effects in terms of crc risk depending upon the following: the existence of early neoplastic lesions in their colorectal epithelium, ie. adenomas. And this relationship may be further influenced by their genotype, as well as their prior level of dietary folate intake. Researchers note that according to the evidence reviewed, moderate dietary increases initiated before the establishment of neoplastic foci appear to have a protective influence. Whereas, excessive intake or increased intake once early lesions are established increases tumorigenesis (the development of tumors). However, the lead researcher does note that the net effect on crc incidence of increased folate intake across the population remains unknown, and depends on whether the preventive influences against neoplastic transformation in the normal colorectal epithelium are outweighed by later enhancement of the growth of early neoplastic lesions that may develop despite early protection. Hence, the efficacy and safety of folate in crc prevention remains undetermined and will depend on the relative size of these 2 potential effects, the levels of increased exposure and the nature of the population exposed in terms of age and other crc risk factors. Only randomized primary preventive trials can provide definitive data to address these issues and would ideally recruit young patients who are unlikely to have pre-existing early colorectal lesions. In the meantime, recommendations should be based on a synthesis of available data from **observational data, genetic studies, mechanistic and animal studies** and **randomized secondary preventive studies**, most of which have yielded positive results in respect of the nutrient. The study is published in the *British Journal of Cancer* where a listing of the research in support or in refutation of the nutrient’s chemopreventive properties is published for perusal.

Hubner, R A, et al. Folate and Colorectal Cancer Prevention. British Journal of Cancer. (2009): 100, 233-239. Published online December 16, 2008.