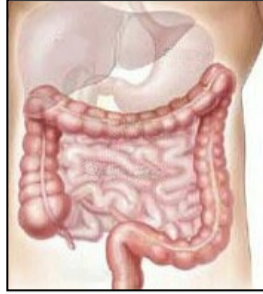


COLORECTAL CANCER RESEARCH UPDATES

Month Ending October 17th, 2014



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

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. CYRAMZA Phase III Second Line Colorectal Cancer Trial Meets Primary Endpoint
2. Adjuvant S-1 May Be an Option for Patients with Stage III Colon Cancer
3. Phase I Trial of Hepatic Arterial Infusion (HAI) of Floxuridine with Modified Oxaliplatin, 5FU and Leucovorin (m-FOLFOX6) in Chinese Patients with Unresectable Liver Mets from Colorectal Cancer

SURGICAL THERAPIES

4. Surgery + HIPEC Improves Survival in Patients with Colorectal Peritoneal Mets Compared with Systemic Chemo Alone

RADIOTHERAPY/INTERVENTIONAL RADIOLOGY

5. SIR-Spheres Y-90 Resin Microspheres Recommended in New European Society of Medical Oncology (ESMO) Clinical Guidelines for Treating mCRC

SCREENING

6. Low Risk Adenoma Removal Associated with Reduced Colorectal Cancer Mortality
7. Once Only Flexible sigmoidoscopy Screening Cuts Colorectal Cancer
8. Good Bowel Cleaning is Key for High Quality Colonoscopy

PSYCHOSOCIAL

9. Cancer Patients Often Struggle with Depression Without Getting Help
10. Cognitive Problems Common in Bowel Cancer

OTHER

11. No Link Found Between Diverticular Disease and Colorectal Cancer
12. Barrett's Esophagus Associated with Increased Risk for Colon Polyps

NUTRITION/HEALTHY LIFESTYLE

13. Colon Cancer Metastasis Blocked by Curcumin
14. Calcium Supplements May Support a Healthy Colon: Harvard Study
15. Obesity Linked to Greater Secondary Cancer Risk for Colorectal Cancer Survivors
16. Colorectal Cancer Risk Decreased with Fiber Laxative Use, Increased with Nonfiber Laxatives
17. Bowel Cancer Risk Reduced by Adopting Multiple Healthy Behaviors

1. CYRAMZA Phase III Second Line Colorectal Cancer Trial Meets Primary Endpoint (Sept.12/14)

The RAISE trial, a Phase III study of ramucirumab (CYRAMZA™) in combination with chemotherapy in patients with metastatic colorectal cancer (mCRC), met its primary endpoint of overall survival. The global, randomized, double-blind study compared ramucirumab plus FOLFIRI to placebo plus FOLFIRI as a second-line treatment in patients with mCRC after treatment with bevacizumab, oxaliplatin and a fluoropyrimidine in the first-line setting. RAISE showed a statistically significant improvement in overall survival in patients treated with ramucirumab plus FOLFIRI compared to placebo plus FOLFIRI. The study also showed a statistically significant improvement in progression-free survival in the ramucirumab-plus-FOLFIRI arm compared to the placebo-plus-FOLFIRI arm. Ramucirumab is a vascular endothelial growth factor (VEGF) Receptor 2 antagonist that specifically binds VEGF Receptor 2 and blocks binding of VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D. VEGF Receptor 2 is an important mediator in the VEGF pathway. It inhibits angiogenesis. Angiogenesis is a process by which new blood vessels form to supply blood to normal healthy tissues as well as tumors, enabling the cancer to grow. The manufacturer Lilly plans to present data from the RAISE trial at a scientific meeting in 2015 and expects to initiate regulatory submissions in the first half of 2015. "Patients with metastatic colorectal cancer - particularly those in the second-line setting - continue to need new treatment options that improve survival," said Richard Gaynor, M.D., senior vice president, product development and medical affairs for Lilly Oncology. "We are pleased that the RAISE study demonstrated a survival benefit and are hopeful that ramucirumab will become a new anti-angiogenic treatment option after first-line bevacizumab-containing therapy for metastatic colorectal cancer patients."

About Angiogenesis

Angiogenesis is the process of making new blood vessels. This process involves the migration, growth, and differentiation of endothelial cells, which line the inside wall of blood vessels. Chemical signals in the body stimulate the repair of damaged blood vessels and formation of new blood vessels during this process. In a person with cancer, angiogenesis creates new blood vessels that give a tumor its own blood supply, allowing it to grow and spread. Some tumors create proteins called VEGF. These proteins attach to the VEGF receptors of blood vessel cells causing new blood vessels to form around the tumors, enabling growth. Blocking the VEGF protein from linking to the blood vessels helps to inhibit tumor growth by slowing angiogenesis and the blood supply that feeds tumors. Of the three known VEGF receptors, VEGF Receptor 2 is linked most closely to VEGF-induced tumor angiogenesis.

<https://investor.lilly.com/releasedetail.cfm?ReleaseID=870557>

2. Adjuvant S-1 May Be an Option for Patients with Stage III Colon Cancer (Sept 1/14)

The oral fluoropyrimidine S-1 is effective as adjuvant chemotherapy for stage III colon cancer, according to findings from the randomized, open-label, phase III noninferiority trial in Japan. Disease-free survival was 75.5% at 3 years in 758 patients with curatively resected stage III colon cancer who were randomized to receive S-1, compared with 72.5% in 760 such patients who received tegafur-uracil plus leucovorin. Postoperative adjuvant chemotherapy for patients with stage III colon cancer is the standard of care internationally, and Western guidelines call for first-line treatment with intravenous 5-fluorouracil (5-FU) and leucovorin (LV) or capecitabine combined with oxaliplatin (the FOLFOX or CapeOX regimens). Fluoropyrimidine monotherapy is also a treatment option.

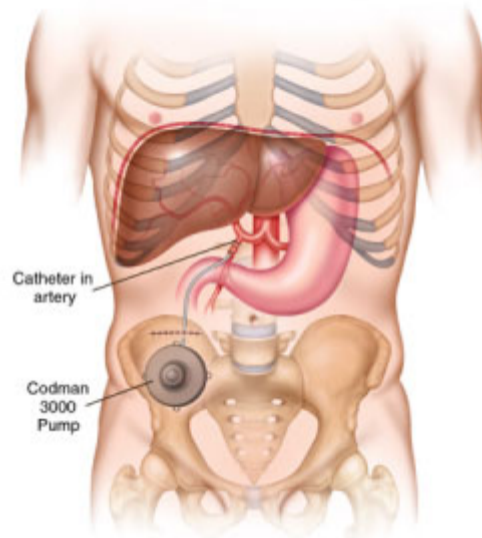
Yoshida, M, et al., S-1 as adjuvant chemotherapy for stage III colon cancer: a randomized phase III study (ACTS-CC trial). Ann Oncol 2014 Sep;25(9):1743-9. doi: 10.1093/annonc/mdu232. Epub 2014 Jun 18.

3. Phase I Trial of Hepatic Arterial Infusion (HAI) of Floxuridine with Modified Oxaliplatin, 5FU and Leucovorin (m-FOLFOX6) in Chinese Patients with Unresectable Liver Mets from Colorectal Cancer (Oct.1/14)

This study sought to determine the maximum tolerated dose (MTD) and preliminary efficacy of concurrent hepatic arterial infusion (HAI) of floxuridine (FUDR) and systemic modified oxaliplatin, 5-fluorouracil and leucovorin (m-FOLFOX6) in Chinese patients with unresectable hepatic metastases from colorectal cancer. Thirty-five patients with unresectable liver metastases with or without extrahepatic disease were treated with concurrent HAI and systemic m-FOLFOX6. HAI FUDR was delivered in a 14-day infusion with escalating dose levels, and each cycle was repeated every 4 weeks. It was determined that the overall response rate was 68.6 % for hepatic metastases and 14.3 % for extrahepatic metastases. The median progression-free survival and overall survival were 8.23 and 25 months, respectively. Investigators concluded that the recommended dose of FUDR was 0.12 mg/kg/day when combined with systemic m-FOLFOX6. This combination achieved a high response rate in hepatic disease and a high control rate in extrahepatic disease. Further study is needed to assess the potential additional value of HAI therapy in converting patients with hepatic metastases to candidates for resection.

About HAI

For some patients whose colon *cancer* has spread to the liver, Hepatic Arterial Infusion (HAI) Therapy is a treatment where the chemotherapy medication is delivered directly to the tumor site via an implanted infusion system. Chemotherapy is dispensed from a specialized infusion system in which a catheter is placed into the hepatic artery to directly deliver the chemotherapy to the liver. A fully implanted system is used so that the pump that connects to the catheter in the hepatic artery is implanted under the skin. This allows for long-term administration of chemotherapy medication directly into the liver. The pump is periodically filled with chemotherapy by your oncologist. **An HAI study is currently underway at the Odette Cancer Centre in Toronto, Ontario headed up by Drs. Paul Karanicolas and Yooj Ko.**



<http://www.surgery.usc.edu/divisions/tumor/pancreas/diseases/web%20pages/laparoscopic%20liver%20surgery/HAI.html>

Li, C et al., Phase I trial of hepatic arterial infusion (HAI) of floxuridine with modified oxaliplatin, 5 fluorouracil and leucovorin (m-folfox6) in Chinese patients with unresectable liver metastases from colorectal cancer. *Cancer Chemother Pharmacol* 2014 Sept 13 Epub ahead of print.

SURGICAL THERAPIES

4. Surgery + HIPEC Improves Survival in Patients with Colorectal Peritoneal Mets Compared with Systemic Chemo Alone (Sept.29/14)

Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is increasingly advocated for selected patients with colorectal cancer peritoneal metastases (CPM); however, opinions are divided because of the perceived lack of evidence, high morbidity, mortality, and associated costs for this approach. As there is no clear consensus, the aim of this study was to compare outcomes following CRS+HIPEC vs systemic chemo (SC) alone for CPM using meta-analytical methodology, focusing on survival outcomes. Secondary outcomes assessed included morbidity, mortality, quality of life (QOL), and health economics (HE). An electronic literature search was conducted to identify studies comparing survival following CRS+HIPEC vs SC for CPM. For included studies, 2- and 5-year survival was compared for CRS+HIPEC vs SC alone. Four studies (three case-control, one randomized control trial [RCT]) provided comparative survival data for patients undergoing CRS+HIPEC (n=187) vs SC (n=155) for CPM. Pooled analysis demonstrated superior 2-year and 5-year survival with CRS+HIPEC compared with SC. Mortality ranged from 0 to 8%. No data were available for the assessment of QOL or HE. Although limited by between-study heterogeneity, the data support the assertion that in **carefully selected patients, multimodal treatment of CPM with CRS+HIPEC has a highly positive prognostic impact on medium- and long-term survival compared with SC alone**. There is a paucity of comparative data available on morbidity, QOL, and HE.

Mirnezami, R, et al., Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy improves survival in patients with colorectal peritoneal metastases compared with systemic chemotherapy alone. *British J of Cancer*. 111, 1500-1508

RADIOTHERAPY/INTERVENTIONAL RADIOLOGY

5. SIR-Spheres Y-90 Resin Microspheres Recommended in New European Society of Medical Oncology (ESMO) Clinical Guidelines for Treating mCRC (Sept.29/14)

Newly published European Society for Medical Oncology (ESMO) clinical guidelines for the treatment of metastatic colorectal cancer (mCRC) endorse radioembolization, specifically with Yttrium-90 resin microspheres, as a clinically proven technology to "prolong time to liver tumour progression" in mCRC patients who have failed to respond to available chemotherapy options. SIR-Spheres Y-90 resin microspheres, the lead product of Sirtex Medical Limited, is the only product used for radioembolization or Selective Internal Radiation Therapy (SIRT) that is recommended in the new ESMO guidelines. "We are very pleased that the authors of major international clinical guidelines in the treatment of mCRC have singled out radioembolization, and particularly our unique product, SIR-Spheres Y-90 resin microspheres, as an appropriate treatment for patients with colorectal liver metastases that have failed to respond to chemotherapy," said Nigel Lange, CEO of Sirtex Medical Europe GmbH. "We believe the new ESMO clinical guidelines will have an immediate effect on improving patient access to SIR-Spheres Y-90 resin microspheres across Europe." As clinical evidence for the new ESMO recommendation, the authors cited a multi-centre randomized controlled study conducted by Professor Alain Hendlisz (Brussels, Belgium) and colleagues. The Hendlisz study was a "Phase III trial comparing intravenous fluorouracil infusion with yttrium-90 resin microspheres for liver-limited metastatic colorectal cancer refractory to standard chemotherapy." In April 2013, Sirtex announced that it had completed recruitment of patients for SIRFLOX, a 500-patient randomized clinical study that compares the use of SIR-Spheres Y-90 resin microspheres in combination with standard chemotherapy to standard chemotherapy alone in the treatment of patients recently diagnosed with inoperable mCRC, which is much earlier in the treatment paradigm. Data from SIRFLOX are expected in 2015.

About SIR-Spheres Y-90 Resin Microspheres

SIR-Spheres Y-90 resin microspheres are used to deliver SIRT (also known as radioembolization), a proven technology for inoperable liver tumours that delivers substantial, targeted doses of radiation directly to the cancer. In a minimally invasive treatment, millions of SIR-Spheres microspheres are infused via a catheter into the liver where they selectively target liver tumours with a dose of internal radiation up to 40 times higher than conventional radiotherapy, while sparing the adjacent healthy liver tissue. See diagram below.

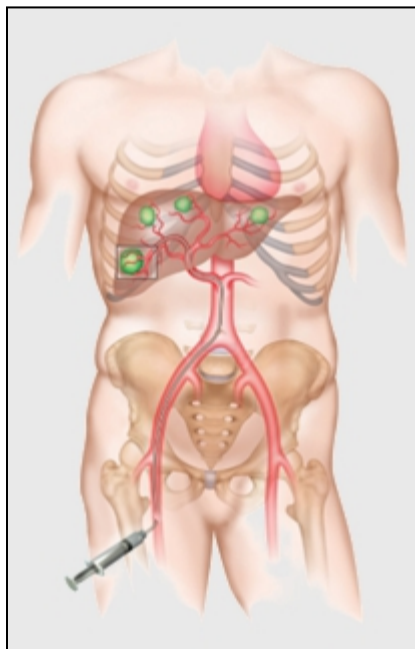


Diagram showing how SIR-Spheres microspheres are administered to the liver

<http://www.sirtex.com/us/patients/about-sir-spheres-microspheres/frequently-asked-questions/>

<http://www.prnewswire.com/news-releases/sir-spheres-y-90-resin-microspheres-recommended-in-new-european-society-of-medical-oncology-esmo-clinical-guidelines-for-treating-metastatic-colorectal-cancer-mcrc-277419811.html>

SCREENING

6. Low Risk Adenoma Removal Associated With Reduced Colorectal Cancer Mortality (Aug.27/14)

Patients who had low-risk adenomas removed demonstrated lower rates of long-term colorectal cancer mortality than those who had high-risk adenomas removed, according to results of a population-based study. The low mortality rate associated with low-risk adenomas may obviate the need for post-colonoscopy surveillance in this population, researchers wrote. Patients with high-risk adenomas — or those with high-grade dysplasia, a villous component or a size ≥ 10 mm — underwent colonoscopy after 10 years, whereas those with three or more adenomas underwent colonoscopy after 5 years in compliance with Norwegian guidelines. Patients with low-risk adenomas did not undergo surveillance.

Median follow-up was 7.7 years (maximum, 19 years). Overall, 1,273 patients were diagnosed with colorectal cancer, and 383 deaths from colorectal cancer occurred. The observed colorectal cancer mortality rate was comparable to that of the general population. Adenoma removal was associated with a reduced risk for colorectal cancer mortality among men (SMR=0.86; 95% CI, 0.74-1) but not women. Researchers determined 141 patients who died had low-risk adenomas removed. Data from the general population indicated that low-risk adenoma removal was associated with a reduced risk for death from colorectal cancer. However, patients who had high-risk adenomas faced a greater colorectal cancer mortality risk. The risk for colorectal cancer mortality also was greater among patients with multiple adenomas (SMR=1.19; 95% CI, 1-1.43), a villous or tubulovillous growth pattern (SMR=1.26; 95% CI, 1.08-1.47), or a high grade of dysplasia. "Our finding that the removal of low-risk adenomas reduces the risk of death from colorectal cancer over a period of 8 years to a level below the risk in the general population is consistent with the hypothesis that surveillance every 5 years after removal of low-risk adenomas may confer little benefit over less intensive surveillance strategies," Løberg and colleagues wrote.

<http://www.healio.com/hematology-oncology/gastrointestinal-cancer/news/online/%7B065f8edd-62c8-4478-a8cc-7c72c8622dd8%7D/low-risk-adenoma-removal-associated-with-reduced-colorectal-cancer-mortality>

7. Once Only Flexible Sigmoidoscopy Screening Cuts Colorectal Cancer (Aug 13/14)

Once-only flexible sigmoidoscopy screening, with or without fecal occult blood testing (FOBT), is associated with reduced colorectal cancer incidence and mortality according to the results of this study. Researchers conducted a randomized trial involving 98,792 individuals, aged 50 to 64 years, to examine the effectiveness of flexible sigmoidoscopy screening. Participants who were randomized to screening underwent once-only flexible sigmoidoscopy (10,283 individuals) or combination of once-only flexible sigmoidoscopy and FOBT (10,289 individuals), while the control group received no intervention (78,220 individuals). After a median of 10.9 years, the researchers found that there were 71 colorectal cancer deaths in the screening group compared with 330 in the control group. There were 253 diagnoses of colorectal cancer in the screening group versus 1,086 in the control group. The incidence of colorectal cancer was reduced among those aged 50 to 54 years and among those aged 55 to 64 years. There was no significant difference between the screening groups. "In Norway, once-only flexible sigmoidoscopy screening or flexible sigmoidoscopy and FOBT reduced colorectal cancer incidence and mortality on a population level compared with no screening," the authors write.

Holme, Oyvind, et al., Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality a randomized clinical trial. JAMA 2014; 312(6): 606-615

8. Good Bowel Cleaning is Key for High Quality Colonoscopy (Sept.22/14)

The success of a colonoscopy is closely linked to good bowel preparation, with poor bowel prep often resulting in missed precancerous lesions, according to new consensus guidelines released by the U.S. Multi-Society Task force on Colorectal Cancer. Additionally, poor bowel cleansing can result in increased costs related to early repeat procedures. Up to 20 to 25 percent of all colonoscopies are reported to have an inadequate bowel preparation. "When prescribing bowel preparation for their patients, health-care professionals need to be aware of medical factors that increase the risk of inadequate preparation, as well as nonmedical factors that may predict poor compliance with instructions," according to David A. Johnson, MD, lead author of the guidelines, professor of internal medicine and chief of the division of gastroenterology, Eastern Virginia Medical School, Norfolk. "Gastroenterologists should use this information when determining whether to use a more effective or aggressive bowel preparation regimen, as well as the level of patient education needed about the prep."

Adequate preparation

- Adequate preparation is defined as sufficient to allow detection of polyps greater than 5 mm.
- Such level of cleansing allows for screening and surveillance interval recommendations that comply with guideline intervals appropriate to the findings of the examination. This benchmark should be achieved in 85 percent or more of all examinations on a per-physician basis.

Effect of inadequate preparation on polyp/adenoma detection and recommended follow-up intervals

- Inadequate preparation of the colon is associated with reduced adenoma detection rates.
- Preliminary assessment of prep quality should be made. If the indication is screening or surveillance and the preparation is inadequate to allow polyp detection greater than 5 mm, the procedure should be either terminated and rescheduled, or an attempt should be made at additional bowel cleansing strategies that can be delivered without cancelling the procedure that day.

- If the colonoscopy is complete to the cecum, and the preparation ultimately is deemed inadequate, then the examination should be repeated, generally with a more aggressive preparation regimen, within one year; intervals shorter than one year are indicated when advanced neoplasia is detected and there is inadequate preparation.
- If the preparation is deemed adequate and the colonoscopy is completed, then the guideline recommendations for screening or surveillance should be followed.

<http://www.sciencenewslite.com/articles/2014092221530005.html#footer>

PSYCHOSOCIAL

9. Cancer Patients Often Struggle with Depression Without Getting Help (Aug.30/14)

Cancer patients do not just battle with their physical ailment. Many also suffer from clinical depression. Unfortunately, as many as three-quarters of these patients do not receive effective treatment for their condition, researchers from Oxford and Edinburgh universities in the UK have found. Researchers studied the data of more than 21,000 cancer patients in Scotland. They found that clinical depression tends to be more prevalent among cancer patients compared with the general population. Depression occurs between 6 to 13 percent of cancer patients while the incidence only occurs in 2 percent of the general population. Depression also appears to be more common in patients with lung cancer, affecting about 13 percent of lung cancer patients involved in the study, followed by those diagnosed with gynecological cancer (10.9 percent), breast cancer (9.3 percent), **colorectal cancer** (7 percent) and genitourinary cancer (5.6 percent). Younger patients, those with worse social deprivation scores and women who were diagnosed with lung cancer and colorectal cancer were also found to be more vulnerable to major depression. Despite the prevalence of depression among cancer patients, the researchers found that 73 percent of the patients who were diagnosed with major depression, which causes affected individuals to feel consistently low as well as have difficulty sleeping and eating, were not given any kind of appropriate treatment for their condition. The findings of the study were published as health experts revealed the promising results from trials that test a new nurse-led approach for managing depression in cancer patients. In a study involving 500 patients, the new therapy reduced the depression scores of the participants by over 60 percent. Study researcher Michael Sharpe, from the University of Oxford Department of Psychiatry, described how the program can help cancer patients battling with depression. "We've described a new approach to managing depressed cancer patients that is based on the short-comings of usual care and integrated with cancer care that really has quite spectacular effects in the good prognosis patients and also has efficacy in the poor prognosis patients," Sharpe said. "What this program does is get people back engaged with life and feeling more in control of their lives again."

<http://www.techtimes.com/articles/14486/20140830/cancer-patients-often-battle-depression-without-any-professional-help.htm>

10. Cognitive Problems Common in Bowel Cancer (Sept.16/14)

People diagnosed with colorectal cancer (CRC) suffer far higher rates of cognitive impairment than the general population even before chemotherapy or surgery, say researchers from Australia and Canada. Their study of 360 people with stage I-III disease and 70 healthy controls showed cognitive impairment was three to five times more likely in CRC patients. Deficits were particularly noticeable in verbal learning and memory, processing speed and attention and working memory, and women were significantly more likely to suffer impairment. All patients were tested before receiving adjuvant chemotherapy. Lead researcher Associate Professor Janette Vardy of the University of Sydney and the Concord Cancer Centre says the percentage of patients with cognitive impairment was "far higher" than she'd been expecting.

Vardy, Janette, et al., Cognitive function and fatigue after diagnosis of colorectal cancer. Ann Oncol. 2014. First published online September 11, 2014.

OTHER

11. No Link Found Between Diverticular Disease and Colorectal Cancer (Aug. 25/14)

Colonic diverticular disease does not appear to be linked to an increased risk of subsequent colorectal cancer (CRC), according to research published. Researchers conducted a population-based retrospective study of 41,359 individuals diagnosed with colonic diverticular disease to examine its association with subsequent risk of developing CRC. A cohort of 165,436 individuals matched by age, sex, and baseline year were selected as a comparison group. The researchers observed a significantly higher risk of CRC in the study cohort than in the comparison cohort. When the first 12 months of follow-up after the diagnosis of colonic diverticular disease were excluded from the analysis, no significant difference was found between the study and the comparison groups in the subsequent incidence of CRC.

"Colonic diverticular disease is not associated with an increased risk of subsequent CRC after the first year of diagnosis of colonic diverticular disease," the authors write. "An increased risk was observed in the first year, possibly owing to misclassification and screening effects."

Huang, Wen-Yen, et al., Association between colonic diverticular disease and colorectal cancer: a nationwide population-based study. Clin Gastro and Hep Vol 12, Issue 8, pp 1288-1294, August 2014.

12. **Barrett's Esophagus Associated with Increased Risk for Colon Polyps** (Aug.25/14)

Individuals with Barrett's esophagus demonstrated significantly increased risk for colon polyps, according to results of a case-control study. Results showed those with Barrett's esophagus were 80% more likely to have any type of polyp detected during colonoscopy and 50% more likely to have adenomas detected. "This association might have important implications," **Arthi Kumaravel, MD**, of the Center of Excellence for Barrett's Esophagus at Cleveland Clinic, and colleagues wrote. "Further studies are needed to determine the appropriate screening and surveillance colonoscopy intervals for patients with Barrett's esophagus." A paper published in 1985 suggested an association between Barrett's esophagus and colorectal cancer. Since then, studies have yielded conflicting results. The small sample sizes in some studies and the lack of true control groups in others made the findings difficult to interpret, Kumaravel and colleagues wrote. The current analysis included 519 participants (75% men). Of them, 173 (age range, 50 to 75 years) had biopsy-proven Barrett's esophagus and underwent colonoscopy at Cleveland Clinic between January 2002 and December 2011. The 346 controls, matched for age and sex, underwent colonoscopy and also endoscopy during the same time period and had no evidence of Barrett's esophagus. Individuals with a family or personal prior history of colon cancer or polyps, inflammatory bowel disease or familial polyposis syndromes were excluded, as were those who underwent prior colonic resection. Patients' mean age at first colonoscopy was 61 years. A higher percentage of those with Barrett's esophagus were found to have polyps during index colonoscopy (45% vs. 32%). During follow-up, patients underwent one to five colonoscopies. Results of multivariate analysis — adjusted for age, sex and diabetes diagnosis — showed individuals with Barrett's esophagus were significantly more likely to have colorectal cancer detected during colonoscopy. They also were more likely to have any type of polyp and any adenoma detected. "There have been several potential explanations for the association between Barrett's esophagus and colon polyps or colorectal cancer, but the underlying mechanisms responsible for the higher prevalence of colon polyps in Barrett's esophagus patients are not clearly understood," Kumaravel and colleagues wrote. Patients with Barrett's esophagus may have similar environmental risk factors that are associated with colorectal cancer development, such as obesity, smoking history, alcohol consumption, age and gender. "The genetic pathways leading to colon cancer have been well elucidated; however, the genetic alterations associated with development of Barrett's esophagus and its progression to esophageal adenocarcinoma are not well defined," the researchers wrote. "Certain mutations in the colon adenoma-to-carcinoma pathway, such as mutations to the APC gene and activation of the Src gene, have also been described in Barrett's esophagus ... Other genetic aberrations associated with cancer progression described in both conditions include p53 mutations, as well as allelic loss of chromosomes 17p and 18q. However, these genetic abnormalities have been reported in other cancers, too."

Kumaravel, Arthi, et al., Higher prevalence of colon polyps in patients with Barrett's esophagus: a case-control study. Gastro Rep. 2014. First published online July 31, 2014.

NUTRITION & HEALTHY LIFESTYLE

13. **Colon Cancer Metastasis Blocked by Curcumin** (Aug. 27/14)

According to new research published in the journal PLOS One, curcumin, a bioactive molecule derived from turmeric, can prevent colon cancer metastasis. Researchers from the University of Arizona's Steele Children's Research Center in Tucson, Arizona, curcumin inhibits **cortactin**, a protein necessary for cell movement, in colon cancer. Because cortactin is often over expressed in cancer cells, it provides cancer cells with the ability to move and metastasize to other parts of the body. The researchers discovered the active part of cortactin, Phospho Tyrosine 421 (pTyr421) to be over expressed in malignant colon cancer cells. The malignant cancer cells were then treated with curcumin and found that curcumin inhibited pTyr421. Thus, the colon cancer cells lost their ability to spread and migrate. This study lays the foundation for future studies involving curcumin to be conducted for the prevention of cancer metastasis. Eventually, drugs may be designed with curcumin to block colon cancer cells from spreading.

Radhakrishnan VM, Kojs P, Young G, Ramalingam R, Jagadish B, et al. (2014) "pTyr421 Cortactin Is Overexpressed in Colon Cancer and Is Dephosphorylated by Curcumin: Involvement of Non-Receptor Type 1 Protein Tyrosine Phosphatase (PTPN1)." PLoS ONE 9(1): e85796. DOI: 10.1371/journal.pone.0085796

14. **Calcium Supplements May Support a Healthy Colon: Harvard Study** (Sept.18/14)

Supplements of calcium or non-dairy products fortified with the mineral may reduce the risk of colorectal cancer, according to meta-analysis of prospective observational studies by researchers at Harvard

School of Public Health. For every 300 mg increase in calcium from supplements was associated with a 9% reduction in risk. Every 300 mg increase in total calcium was associated with a similar reduction in risk (8%). The findings have several important clinical and public health implications. First, according to the 2003 to 2006 National Health and Nutrition Examination Survey, a nationally representative cross-sectional survey in the US, median total calcium intake of adults aged over 50 years was approximately 650 mg/day for no calcium-supplement users and 1,000 mg/day for calcium-supplement users. As the benefit of calcium intake on colorectal cancer is expected to continue beyond 1,000 mg/day, not only non-supplement users but also supplement users may further reduce their colorectal cancer risk through additional calcium intake. Second, while dairy products, especially milk, are the major sources of calcium in many countries, they are a substantial source of calories and contain potentially harmful factors such as saturated fat, hormones, and casein proteins. Since our analyses provide evidence for an equivalent benefit of dietary and supplementary calcium, the benefit of calcium on colorectal cancer risk may be obtained through supplements and non-dairy products fortified with calcium.

<http://www.nutraingredients-usa.com/Research/Calcium-supplements-may-support-a-healthy-colon-Harvard-study>

Giovanucci, E.L., et al., Calcium intake and colorectal cancer risk: dose response meta-analysis of prospective observational studies. International J of Cancer. 2014, Vol 135, Number 8, pp.1940-8. Doi: 10.1002/ijc.28840

15. Obesity Linked to Greater Secondary Cancer Risk for Colorectal Cancer Survivors (Oct.1/14)

Colorectal cancer (CRC) patients who are overweight or obese when diagnosed appear to face a slightly higher risk for developing a second weight-related cancer, according to research published. The finding didn't speak to the risk of CRC recurrence, only the potential for developing other cancers associated with obesity. To assess how obesity might affect additional cancer risk post-survival, Todd Gibson, Ph.D., and colleagues at the U.S. National Cancer Institute, focused on 11,598 CRC survivors who were about age 69 on average when first diagnosed. Patient weight had been assessed prior to their initial diagnosis by means of a body mass index calculation. In all, 44 percent of the patients were deemed overweight (BMI, 25 to 29 kg/m²), while one-quarter were obese (BMI, ≥30 kg/m²). The researchers found that when compared with CRC survivors who had been at normal weight at diagnosis, those who had been overweight or obese faced a greater risk for developing a second obesity-related cancer down the road. A higher obesity-driven risk was identified for kidney, pancreatic, esophageal, and endometrial cancers, as well as for postmenopausal breast cancer among female CRC patients. However, the team stressed that the actual risk that an obese or overweight CRC survivor would develop a secondary cancer remained low, even if their relative risk was almost double that of normal-weight survivors.

Gibson, Todd, et al., Body mass index and risk of second obesity-associated cancers after colorectal cancer: a pooled analysis of prospective cohort studies. J of Clin Onc. Published online before print September 29, 2014. Doi: 10.1200/JCO.2014.56.8444.

16. Colorectal Cancer Risk Decreased With Fiber Laxative Use, Increased With Nonfiber Laxatives (Oct.7/14)

Use of fiber laxatives was associated with a decreased risk for colorectal cancer, while nonfiber laxative use was linked with an increased risk, according to this study. Investigators prospectively evaluated 75,214 participants of the Vitamins and Lifestyle study in the state of Washington to determine associations between colorectal cancer (CRC) risk and laxative use. Participants completed questionnaires (2000 to 2002) regarding bowel movement frequency and average 10-year nonfiber laxative use, fiber laxative use and constipation. They also were followed up for CRC incidence through 2008, at which time there were 558 cases. Participants who reported low (one to four times annually) or high (five or more times annually) use of nonfiber laxatives had 43% to 49% increased risk for CRC compared with those who used them less than once annually. CRC risk was lowest in participants who reported high-fiber laxative use for at least 4 days per week for at least 4 years compared with those who never used them. Researchers said there was no decreased risk associated with low-fiber laxative use and no associations between CRC risk and bowel movement frequency or constipation. Researchers observed that nonfiber laxative use was associated with an increased risk for CRC, whereas fiber laxative use was inversely associated with risk. They concluded that further research of specific laxative types is needed before conclusions can be drawn about recommending any specific type of laxative to patients with constipation.

Citronberg, Jessica, et al., A Prospective Study of the Effect of Bowel Movement Frequency, Constipation, and Laxative Use on Colorectal Cancer Risk. The American Journal of Gastroenterology 109, 1640-1649 (October 2014) | doi:10.1038/ajg.2014.233

17. Bowel Cancer Risk Reduced By Adopting Multiple Healthy Behaviors (Oct.9/14)

Adoption of a combination of five key healthy behaviors is associated with a reduction in the risk of developing bowel cancer also known as colorectal cancer. Researchers from the German Institute of Human Nutrition Potsdam-Rehbruecke quantified the impact of combined multiple healthy lifestyle behaviors on the risk of developing bowel cancer, and found that this impact is stronger in men than in women. The research analyzed the data of 347,237 men and women from 10 countries from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study using a healthy lifestyle index. Over the 12-year study period, 3,759 cases of bowel cancer were recorded. The healthy lifestyle index was composed by the following lifestyle factors:

- a healthy weight;
- low abdominal fat;
- participating in regular physical activity;
- not smoking and limiting alcohol; and
- a diet high in fruits, vegetables, fish, yoghurt, nuts and seeds, and foods rich in fiber, and low amounts of red and processed meat.

For each of the five behaviors, study subjects were assigned one point for having the healthy factor and zero for not having the healthy factor. These points were then summed to generate a cumulative score for each participant. Data confirmed that with an increasing number of healthy lifestyle behaviors the risk that a person will have of developing bowel cancer decreases. The researchers found that the more healthy lifestyle factors the cohort adopted, the lower their risk of bowel cancer. Compared to people who had followed up to one healthy lifestyle behavior, those who practiced a combination of two, three, four and all the five healthy behaviors had a 13%, 21%, 34% and 37% lower risk of developing bowel cancer, respectively. The authors noted a difference between men and women. Study authors commented: "Estimates based on our study populations suggest that up to 22% of the cases in men and 11% of the cases in women would have been prevented if all five of the healthy lifestyle behaviors had been followed. Our results particularly demonstrate the potential for prevention in men who are at a higher risk of bowel cancer than women."

Krasimira Aleksandrova, et al., Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. *BMC Medicine*, 2014; 12 (1): 168 DOI: [10.1186/s12916-014-0168-4](https://doi.org/10.1186/s12916-014-0168-4)