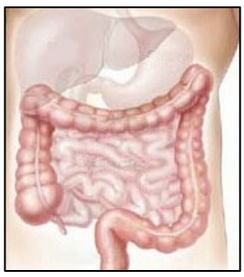
Colorectal Cancer Association of Canada

COLORECTAL CANCER RESEARCH UPDATES

Month Ending January 18th, 2013



The following colorectal cancer research update extends from November 17th, 2012 – January 18th, 2013 inclusive and is intended for informational purposes only.

CONTENT

NUTRITION / HEALTHY LIFESTYLE

DRUGS / SYSTEMIC THERAPIES

1. Bevacizumab Not Helpful for Stage III Colorectal Cancer (Nov.19/12)

Findings from the AVANT trial do not support the use of bevacizumab (avastin) in patients receiving oxaliplatin-based chemotherapy for resected stage III or high-risk stage II colon cancer. The results published indicate that patients treated with the vascular endothelial growth factor inhibitor did not achieve greater disease-free survival (DFS) than controls, and experienced more relapses and deaths due to progression. Consequently, bevacizumab should not be used in the adjuvant treatment of patients with curatively resected stage III colon cancer. The phase III open-label trial randomly assigned stage III patients from 34 countries to receive 12 cycles of the FOLFOX4 regimen (oxaliplatin, leucovorin, and fluorouracil) alone, or alongside bevacizumab 5 mg/kg followed by eight cycles of bevacizumab 7.5 mg/kg for 3 weeks. A third group was treated with the XELOX regimen (oxaliplatin, capecitabine) for eight cycles followed by eight cycles of bevacizumab monotherapy 7.5 mg/kg for 3 weeks. After a median of 48 months, results showed that 25% of FOLFOX4 patients (n=955) had experienced relapse, a new cancer, or died, compared with 29% of bevacizumab - FOLFOX4 patients (n=960) and 27% of bevacizumab-XELOX patients (n=952). Serious adverse events were significantly more common in the bevacizumab-FOXFOX4 and bevacizumab-XELOX patients than FOLFOX4 patients (26 and 25 vs 20%). Treatment-related deaths were reported for one FOLFOX4 patient, two bevacizumab-FOLFOX4, and five bevacizumab-XELOX patients. "Although AVANT was adequately powered to answer the question of whether bevacizumab in combination with adjuvant chemotherapy significantly prolongs DFS in patients with stage III colon cancer, the results are not generalizable outside the adjuvant treatment of colon cancer," notes the lead author. "An active research program is continuing with bevacizumab as adjuvant therapy for other tumour types."

De Gramont, Aimery, et al., Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase III randomized controlled trial. The Lancet Oncology, Vol. 13, Issue 12, Pages 1225 - 1233, December 2012. doi:10.1016/S1470-2045(12)70509-0

2. Screening for KRAS and BRAF Mutations (Nov.28/12)

Metastatic colorectal cancer patients whose tumors harbor mutations in the gene KRAS (and to a lesser extent, in BRAF) are unlikely to respond to costly anti-EGFR therapies such as erbitux and vectibix. Screening of patients who are candidates for these therapies for mutations in one of these genes (KRAS) has been recommended, with the goal of providing treatment to those who are likely to benefit from it while avoiding unnecessary costs and harm to those who are not likely to benefit. However, according to the authors, the real-world impact of mutation screening for both KRAS and BRAF is unclear. To better understand the impact of mutation screening with regard to health outcomes, costs, and value, study authors performed a cost-effectiveness analysis that took into account the treatments, resection of metastases, and survival for the different types of metastases. They conducted patient-level decision analytic simulation modeling comparing four strategies involving KRAS and BRAF mutation testing to select treatments for metastatic colorectal cancer patients:

- no anti-EGFR therapy (best supportive care);
- anti-EGFR therapy without screening;
- screening for KRAS mutations only (before providing anti-EGFR therapy); and
- screening for KRAS and BRAF mutations (before providing anti-EGFR therapy).

The researchers found that compared with no anti-EGFR therapy, screening for both KRAS and BRAF mutations showed a very high (ie, unfavorable) incremental cost-effectiveness ratio, meaning it was very costly in relation to its benefits. Compared with anti-EGFR therapy without screening, screening for KRAS mutations saved approximately $7,500 per patient; adding BRAF mutation screening saved another $1023, with little reduction in expected survival. The authors write, "In general, our results are less supportive of the use of anti-EGFR therapy than previous analyses, and they indicate lower cost savings from KRAS testing than previously reported. Although we cannot confirm that anti-EGFR therapy is a cost-effective use of health care resources, we can affirm that KRAS testing is cost-saving. BRAF testing may offer additional savings."

Behl, Ajay S., et al., Cost-Effectiveness Analysis of Screening for* KRAS *and* BRAF *Mutations in Metastatic Colorectal Cancer* J Natl Cancer Inst *(2012) 104(23): 1785-1795 first published online November 28, 2012 doi:10.1093/jnci/djs433

3. Aspirin May Help Older Colon Cancer Patients Live Longer (Dec.7/12)

Older adults with colon cancer who were prescribed a daily aspirin were less likely to die than those who weren't, according to this new study. While the results need to be confirmed with more rigorous studies, they add to the evidence linking aspirin use to longer survival for cancer patients. Studies have also suggested the inexpensive drug can prevent some types of the disease from occurring in the first place. Medical guidelines currently endorse the use of low-dose aspirin to prevent heart disease, but not to fight

or prevent cancer. The new study included more than 500 colon-cancer patients in the Netherlands aged 70 and older. More than 100 were prescribed daily low-dose "baby" aspirin for heart protection after their cancer diagnosis. Between 1998 and 2007, the death rate for those prescribed aspirin was about half that of the non-aspirin users. The effect was biggest in people with more advanced cancer and in those who received no chemotherapy. Anything that might improve survival in elderly adults with colon cancer would be welcome, since there is no consensus on whether to use chemotherapy in those patients, according to the study. Previous studies have also associated aspirin use with increased survival. Research published in October in the New England Journal of Medicine suggested that aspirin therapy could extend survival for colon cancer patients whose tumors had a specific genetic mutation. Still, more scientifically rigorous randomized controlled trials will be needed to confirm the findings of studies that are based on observation after the fact, and therefore less definitive about what actually causes the effect seen. "We're pretty sure this is a real effect, but we're not sure of the magnitude," said Dr. Gerrit Jan Liefers of Leiden University Medical Center in the Netherlands, an author of the new study. He said he didn't expect randomized trials would show such a large survival advantage. Liefers is working to develop such a trial in the Netherlands. One limitation of the study is that it looked at aspirin prescriptions, not actual use of the drug. (Low-dose aspirin for heart-disease protection isn't available over the counter in the Netherlands.) It's possible that heart benefits from aspirin might have helped the patients live longer, but the study authors said that alone couldn't account for the big difference in death rates. Also, there might be differences between the groups unaccounted for by researchers that led to the improved survival among the aspirin users. Liefers said it's not completely clear how aspirin might combat colon cancer. One likely route: blocking the enzyme cyclooxygenase-2, or COX-2, which is involved in inflammation and is expressed in about 70% of colon tumors. It would be helpful to figure out who would benefit from and who could skip daily aspirin. It's a fairly benign drug, but it has side effects, including bleeding in the gastrointestinal tract and the brain. Patients should discuss with their physicians whether it makes sense to take aspirin at this point. The study results support the concept, but a prospective randomized trial is needed.

Liefers, Gerrit Jan, et al., Aspirin use after diagnosis improves survival in older adults with colon cancer: a retrospective cohort study. J of the Amer Geriatrics Society. Vol 60, Issue 12, December 2012. Pp: 2232-2236.

4. Hypertension Means Better Survival When Treated with Avastin (Dec.24/12)

Bevacizumab (avastin) indicated to treat metastatic colorectal cancer, is associated with an increased risk of hypertension. But patients who receive the treatment and develop hypertension live long, according to the results of this study. Researchers conducted the study and found that colorectal cancer patients who developed grade II or III hypertension after being treated with avastin had a better overall survival and progression-free survival, compared with those who did not develop hypertension. The study involved 181 patients with metastatic colorectal cancer. Avastin was used jointly with standard first or second line chemotherapy and blood pressure was measured before treatment and monitored during treatment. 44.75% of patients developed grade II or III hypertension and no patient developed higher grade hypertension. Colorectal cancer patients who developed hypertension after avastin treatment had a survival that was shorter than the median survival (43.7 months), but longer than 36.8 months which was for those who did not develop hypertension. Hypertension developers had a better progression free survival than those who did not develop hypertension, 29.9 vs. 17.2 months. The authors concluded: Avastin-related hypertension may represent a biomarker for clinical benefit in metastatic colorectal cancer patients.

Tahover, Esther, et al., Hypertension as a predictive biomarker in bevacizumab treatment for colorectal cancer patients. J of Medical Oncology. December 2012, 30:327.

5. Reduced Risk of Colorectal Cancer with Use of Oral Bisphosphonates (Jan.1/13)

The association between oral bisphosphonate (BP – drugs that treat bone density loss) intake and colorectal cancer (CRC) risk has been investigated in several recent studies with conflicting results. Investigators summarized the evidence from the published studies in a categorical, dose-response meta-analysis (review of past studies). Relevant studies were identified by a search of patient databases through January 15, 2012. Three case-control studies with a total of 16,998 CRC cases and 108,197 controls and one cohort study with 94,405 individuals exposed to BPs and 283,181 unexposed to BPs were included in the meta-analysis. The meta-analysis suggested reduced risk of CRC with exposure to oral BPs. The analysis for 1 to 3 years of use and more than 3 years of use of BPs suggested a significant inverse relationship. This meta-analysis suggests that the use of oral BPs at a dose of 10 or more prescriptions or 1 or more years of duration is associated with reduced risk of CRC. Further randomized controlled trials are needed to prove this association.

Thosani, Nirav, et al., Reduced risk of colorectal cancer withuse of oral bisphosphonates: a systematic review and meta-analysis. J Clin Oncol. 2012 Dec 26. Epub ahead of print.

6. Xelox and Avastin Followed by Single Agent Avastin as Maintenance Therapy in First Line Treatment of Elderly Patients (Jan.1/13)

The addition of bevacizumab (avastin) to oxaliplatin-based chemotherapy significantly improved progression-free survival (PFS) in patients with metastatic colorectal cancer (CRC). An increased risk of arterial thromboembolic events has been observed in some trials in older patients, and the potential benefit of a maintenance therapy with bevacizumab alone has not been clearly demonstrated. This phase II study was designed to evaluate the efficacy and safety of XELOX (capecitabine plus oxaliplatin) plus bevacizumab followed by bevacizumab alone in elderly patients with advanced CRC. Treatment

consisted of bevacizumab 7.5 mg/kg and oxaliplatin 130 mg/m(2) on day 1, plus capecitabine 1,000 mg/m(2) twice daily on days 1-14, every 3 weeks up to a maximum of 8 cycles. Patients then received maintenance therapy consisting of bevacizumab alone (7.5 mg/kg) once every 3 weeks up to disease progression. The primary study end-points were safety and response rate. A total of 44 patients were recruited. The overall response rate was 52% with 86% of patients achieving disease control. Median PFS and overall survival were 11.5 months and 19.3 months, respectively. In all, 10 patients (23%) had grade 3/4 adverse events (AEs), the most common being diarrhea (9%), neutropenia (7%), peripheral neuropathy (7%), and stomatitis (7%). No patients died because of treatment-related AEs. The rate of bevacizumab-related AEs (hypertension, thromboembolic events, and gastrointestinal perforation) was consistent with that reported earlier in the general CRC population. Researchers concluded that the combination of XELOX and bevacizumab is effective and has a manageable tolerability profile when administered to elderly patients with advanced CRC. Maintenance therapy with single-agent bevacizumab may be considered to extend PFS in this setting of patients.

Rosati, G, et al., Xelox and bevacizumab followed by single agent bevacizumab as maintenance therapy as first line treatment in elderly patients with advanced colorectal cnacer: the boxe study. Cancer Chemother Pharmacol, 2013 January; 71(1): pp.257-264

7. CEA Fluctuation During a Single 5FU-based Chemotherapy Cycle for Metastatic Colorectal Cancer (Jan.3/13)

Carcinoembryonic antigen (CEA) is useful in the evaluation of chemotherapy response of metastatic colorectal cancer (CRC). The CEA test measures the amount of this protein that may appear in the blood of some people who have certain kinds of cancers, especially large intestine (colon and rectal) cancer. It may also be present in people with cancer of the pancreas, breast, ovary, or lung. CEA is normally produced during the development of a fetus. The production of CEA stops before birth and it usually is not present in the blood of healthy adults. In this study, researchers studied weekly CEA during one fluorouracil-based chemotherapy cycle, correlated with long-term (8-12 week interval) computed tomography (CT) and CEA responses. CEA, liver function tests and inflammatory parameters were measured prospectively at baseline, day 7, day 14, and after the cycle (day 21/28), in 60 patients with metastatic CRC. CEA non-significantly decreased at day 7 and was increased on day 14. In progressive disease, CEA increased significantly during the evaluation cycle but the level was stable in patients with disease control. CEA fluctuation correlated neither with liver function test nor with inflammatory parameters. Correlation of long-term response was most evident in progressive disease. The study authors concluded that CEA should not be measured during 5-fluorouracil-based oral chemotherapy nor within two weeks from intravenous chemotherapy administration.

Osterlung, Pia, et al., CEA fluctuation during a single fluorouracil-based chemotherapy cycle for metastatic colorectal cancer. Anticancer Research. January 2013; Vol.33, No. 1: pp. 253-260

8. Vaccine Triggers Immunity to Prevent Colon Cancer (Jan.7/13)

The results of the first human clinical trials of the preventive colon cancer vaccine have been reported. This prophylactic colon cancer vaccine boosts the patient's natural immune surveillance, which potentially could lead to the elimination of premalignant lesions before their progression to cancer. This might spare patients the risk and inconvenience of repeated invasive surveillance tests, such as colonoscopy, that currently are used to spot and remove precancerous polyps. Colon cancer takes years to develop and typically starts with a polyp, which is a benign but abnormal growth in the intestinal lining. Polyps that could become cancerous are called adenomas and typically are removed before cancer develops. The study involved people with a previous history of an advanced adenoma, which places them at higher risk for subsequent colorectal cancer. Around 30 to 40 percent of these patients will develop a new polyp within three years. In this study, researchers demonstrated the ability of the vaccine to boost immunity. Subsequent trials need to evaluate the vaccine for its ability to lower or prevent polyp recurrence and thus progression to colon cancer. The vaccine is directed against an abnormal variant of a self-made cell protein called ***MUC1***, which is altered and produced in excess in advanced adenomas and cancer. MUC1 also is abnormally present in pancreatic, breast, lung and prostate cancer and will be tested in the future in patients with premalignant lesions leading to some of those cancers. To date, no vaccine based on cell proteins made by tumors has been tested in humans to prevent cancer. Preclinical models show the vaccine works by targeting the abnormal cells that grow the cancer. The vaccine was tested in 39 patients ages 40 to 70 without cancer, but with a history of advanced adenomas. It produced a strong protective response in 17 of the patients, or 44%. Researchers said the lack of response in the other 22 patients was likely due to already high levels of cells that suppress the immune system's ability to fight cancer. This suggests that it might be better to vaccinate people against colon cancer at an even earlier stage, or vaccinate only people who do not already have suppressed immune systems. The patients in the clinical trial received an initial dose of the vaccine and then additional shots two and 10 weeks later. Blood samples were drawn to measure immune response at those time points, as well as 12 weeks, 28 weeks and one year later. A booster injection was given at one year to confirm the durability of the immune response. The vaccine was well-tolerated and safe. Side-effects included red skin and discomfort at the injection site and flu-like symptoms after the first injection. Safety of the vaccine and its ability to cause an immune response support plans for a larger randomized trial that will examine its efficacy at polyp prevention.

Finn, Olivera, et al., MUC1 Vaccine for Individuals with Advanced Adenoma of the Colon: A Cancer Immunoprevention Feasibility Study* Cancer Prev Res *January 2013 6:18-26; Published Online First December 17, 2012; doi:10.1158/1940-6207.CAPR-12-0275

9. Erbitux Gets Approved in Canada for First-line Treatment of mCRC (Jan.15/13)

Bristol-Myers Squibb Co. announced that Health Canada has approved Erbitux (cetuximab) as an initial treatment option for Canadians with metastatic colorectal cancer whose tumours have a non-mutated

KRAS gene. Erbitux is a biomarker-directed therapy that was initially approved in Canada in 2008 for the treatment of epidermal growth factor receptor-expressing metastatic colorectal cancer for patients whose disease progressed after chemotherapy. According to the company, the new approval allows Erbitux for use as an initial therapy in combination with the chemotherapy regimen FOLFIRI for patients with non-mutated KRAS, epidermal growth factor receptor-expressing metastatic colorectal cancer. The approval is based on data from the CRYSTAL trial, a European Phase 3 open-label, randomized, multicentre study with progression-free survival as the primary endpoint comparing patients treated with Erbitux plus FOLFIRI versus FOLFIRI alone. Bristol-Myers Squibb Canada will work with health authorities to ensure that patients in Canada with metastatic colorectal cancer who may benefit from Erbitux will have access to it.

http://www.rttnews.com/2036850/bristol-myers-erbitux-for-colorectal-cancer-gets-approval-in-canada.aspx?type=bio

SURGICAL THERAPIES

10. Quality of Life of Older Rectal Cancer Patients Not Impaired by Permanent Stoma (Jan.15/13

The current study was undertaken to investigate the impact of a stoma on Quality of Life with a special focus on age. Rectal cancer patients diagnosed between 1998 and 2007 in 4 hospitals were identified. All patients underwent Total Mesorectal Excision (TME) surgery. Survivors were approached to complete the questionnaires. Quality of Life scores of the four groups, stratified by stoma status (stoma/no stoma) and age at operation (<70 and ≥70), were compared. Median follow-up of 143 patients was 3.4 years. Elderly had significantly worse physical function compared to younger patients. Elderly and patients without a stoma had worse sexual functioning compared to younger patients and patients with a stoma. Older males showed more sexual dysfunction when compared to younger males. In comparison with the normative population, elderly with a stoma had worse physical function but slightly better mental health. Elderly without a stoma had better emotional role function and younger patients had worse sexual functioning and enjoyment. The investigators concluded that older patients with a stoma have comparable Quality of Life to older patients without a stoma or the normative population, indicating the feasibility of a permanent stoma for elderly patients with a low situated rectal carcinoma. The negative impact of treatment on sexual functioning as found in the current study calls for further attention to alleviate this problem in sexually active patients.

Orsini, RG, et al., Quality of Life of older rectal cancer patients is not impaired by a permanent stoma. Eur J Surg Oncol. 2013 Feb; 39 (2): pp.164-170

11. Does Robotic Rectal Cancer Surgery Offer Improved Early Postoperative Outcomes? (Jan.15/13)

Laparoscopic rectal surgery continues to be challenging, especially in low rectal cancers, because the technique has several limitations. Robotic rectal surgery could potentially address these limitations. However, it still remains unclear whether robotic surgery should be accepted as the new standard treatment in rectal cancer surgery. The aim of this study was to provide a comprehensive and critical analysis of the available literature to assess if robotic rectal surgery offers improved early postoperative outcomes in comparison with standard laparoscopic rectal surgery. A systematic review was conducted by researchers following the search of electronic databases for the period 2007 to 2011 by using the key words "rectal surgery," "laparoscopic," "robotic." All studies reporting outcomes on laparoscopic and robotic resection for extraperitoneal and intraperitoneal rectal cancer were included in the review process; all studies on colonic cancer and benign disease were excluded. A comparison was conducted of robotic vs. standard laparoscopic rectal cancer surgery. The primary outcome measured was the assessment of whether robotic rectal cancer surgery provides improved short-term outcomes in comparison with standard laparoscopic rectal surgery. According to the results, robotic rectal surgery was associated with increased cost and operating time, but lower conversion rates, even in obese individuals, distal rectal tumors, and patients who had preoperative chemoradiotherapy regardless of the experience of the surgeon. There is also marginally better outcome in anastomotic leak rates, circumferential resection margin positivity, and preservation of autonomic function, but this did not reach statistical significance. This review has some limitations because it relies on the analysis of data collected from various nonrandomized controlled trials with variable quality and different methodology. The researchers concluded that the current evidence suggests that robotic rectal surgery could potentially offer better short-term outcomes especially when applied in selected patients. Obesity, male sex, preoperative radiotherapy, and tumors in the lower two-thirds of the rectum may represent selection criteria for robotic surgery to justify its increased cost.

Dunn, KB, et al., Does robotic rectal cancer surgery offer improved early postoperative outcomes? Dis Colon Rectum 2013 Feb; 56(2): pp. 253-262.

SCREENING

12. Computer-Tailored Intervention Increases Colon Cancer Screening in Low-Income Black Patients (Nov.16/12)

According to this study, a computer-tailored intervention was more effective than a brochure at increasing the completion of fecal occult blood tests and moving low-income black patients toward action. This study sought to address the urgent need to develop effective approaches to increase screening in low-income black patients. The researchers hypothesized that different approaches would yield different results in the proportions of patients who completed fecal occult blood tests or colonoscopy and in the proportions that moved forward in stage of adoption for these tests. The researchers aimed to use interactive computer-tailored interventions, which have been shown to promote positive health behaviors by delivering individualized information and counseling to patients, enabling them to control how often information is presented and to respond to it. This study randomly assigned 693 black primary care patients to either a computer-tailored colorectal cancer screening intervention (n=335) or to a non-tailored

American Cancer Society colorectal cancer screening brochure (n=358). The patients were interviewed by phone at baseline and 6 months later. The interventions were delivered to the patients before they visited their primary care providers. The fecal occult blood test was completed by 12.5% of those who received the computer-tailored intervention and by 7.3% of those who received the brochure intervention. Colonoscopies were completed by 18.5% of the patients in the computer groups and by 14.0% of those in the brochure group, which was not a significant difference between the interventions. While more patients in the computer intervention group moved forward toward adopting the fecal occult blood test (28.4% vs 20.8% in the brochure group), both groups had similar forward movement toward colonoscopy (38.5% in the computer group vs 36.8% in the brochure group). The computer-tailored intervention was more effective for increasing screening rates with FOBT and any screening test than the non-tailored brochure. Despite significant intervention effects, more than three-fourths (78%) of African American patients remained unscreened at 6 months. More comprehensive approaches that simultaneously target patients, families, providers, and healthcare systems may be needed.

http://www.oncologynurseadvisor.com/ons-connections-computer-tailored-intervention-increases-colon-cancer-screening-in-low-income-black-patients/article/268889/

13. Colorectal Cancer Patient Siblings Deserve Screening (Nov.22/12)

Colorectal cancer (CRC) screening should be offered to the siblings of affected patients, recommends a team of researchers from Hong Kong. "We observed a strong and significant increased risk of advanced neoplasms including cancers in close relatives of subjects with CRC," report study authors. "Siblings of individuals with CRC deserve screening." The team performed colonoscopy in 374 siblings of patients who underwent CRC surgery between 2001 and 2011, as well as 374 age- and gender-matched siblings of individuals with a healthy colonoscopy and no family history of CRC. Advanced neoplasms - defined as cancer or adenoma of at least 10 mm in diameter with high-grade dysplasia and/or villous or tubulovillous features - were detected in 7.5% of CRC patient siblings compared with just 2.9% of control siblings. Adenomas greater than 10 mm in diameter were 3.34 times more common in CRC patient siblings than controls (5.9 vs 2.1%), while colorectal adenomas were 2.19 times more common (31.0 vs 18.2%). Moreover, six siblings of CRC patients were found to have CRC, compared with none of the control siblings. Analysis showed that siblings of female CRC patients were significantly more likely to have advanced neoplasms than those of male CRC patients and those of patients aged more than 60 years old. Siblings of CRC patients were also more likely to have advanced neoplasms if the patient had distally located (left sided) rather than proximally located (right sided) CRC. Noting that CRC risk research has focused in Western patients, the researchers say that their study helps establish the risk for CRC among first-degree relatives of Asian CRC patients. This can "provide a background against which screening strategies can be formulated," by helping researchers calculate the life-time risk for CRC among family members and targeting screening to patients when warranted.

Lau, James, et al., Increased risk of advanced neoplasms among asymptomatic siblings of patients with colorectal cancer. Published online November 15, 2012.

14. Polyps With Advanced Neoplasia Are Smaller in the Right Than in the Left Colon (Dec.10/12)

Colonoscopy is consistently associated with reduced left-sided, but not right-sided, colorectal cancer (CRC) incidence and mortality. This might be because polyps with advanced pathology are smaller and more easily missed in the right vs left colon. Researchers in this study explored this postulate by evaluating the relationship among size, location, and histology of polyps from a large nationwide sample. They conducted a cross-sectional study of 233,414 polyps from 142,686 patients (47% women; mean age, 60 years), which were reviewed in 2009. They assessed polyp histology, location, and size of largest fragment submitted. They compared size distribution of right vs left polyps with high-grade dysplasia (HGD) or adenocarcinoma as well as any advanced neoplasia. The average size of right-sided polyps was smaller than that of left-sided polyps with HGD or adenocarcinoma (8.2 vs 12.4 mm, respectively); the same was true for polyps with advanced neoplasia (7.6 vs 11.1 mm, respectively). Most right-sided polyps with HGD, adenocarcinoma, or any advanced neoplasia were ≤9 mm, whereas most left-sided polyps with these findings were >9 mm. Polyps with advanced pathology were 5-fold more likely to be <6 mm in the right vs left colon, 4.06-6.82 for HGD or adenocarcinoma, and 4.34-5.51 for advanced neoplasia. The researchers concluded that polyps with features of HGD, adenocarcinoma, or advanced neoplasia were significantly smaller in the right vs left colon. Strategies to prevent right-sided CRC require more accurate detection of small, advanced polyps.

Gupta, S, et al., Polyps with advanced neoplasia are smaller in the right than in the left colon: implications for colorectal cancer screening. Clin Gastroenterol Hepatol, 2012 Dec; 10(12): pp. 1395-1401

15. Breath Test May Be Able to Detect Colorectal Cancer (Dec.5/12)

A test to determine colorectal cancer often involves looking at blood and stool samples for signs, and then further invasive testing if a positive marker is found. On top of that, only a small fraction of those who test positive will actually have colorectal cancer. A new study published shows that a test that used only exhaled breaths from patients was more than 75% accurate in finding patients who had the disease. "The technique of breath sampling is very easy and non-invasive, although the method is still in the early phase of development," report study authors. "Our study's findings provide further support for the value of breath testing as a screening tool." The U.S. Preventive Services Task Force recommends routine screening for colorectal cancer, such as with a colonoscopy, for adults beginning at age 50 until they are 75 years old. Since cancer tissue metabolizes at a different rate compared to healthy cells, it produces some byproducts called ***volatile organic compounds (VOCs)*** that can be detected in a person's breath. Previous studies have used dogs to detect these odors. Researchers tested the breaths of 37 colorectal cancer patients and 41 healthy others to create a test to find specific VOCs. Then, a probabilistic neural network (PNN) was created to help find the VOCs in question. The test was able to find patients with colorectal cancer in 76% of the cases in a test using 19 patients. While promising, it's often hard to

distinguish between the VOCs and what a person was eating, if they had another illness or if they spent time at a hospital. Additional studies are required.

http://www.cbsnews.com/8301-204_162-57557380/breath-test-may-be-able-to-detect-colorectal-cancer/

16. Rate of Early/Missed Colorectal Cancers After Colonoscopy in Older Patients with Or Without IBD (Jan.11/13)

Patients with inflammatory bowel disease (IBD) have an increased risk for colorectal cancer (CRC). Previous studies on early/missed CRCs after colonoscopy excluded IBD patients. The aim of this study was to compare the rate of early/missed CRCs after colonoscopy among IBD and non-IBD patients, and identify factors associated with early/missed CRCs. All patients who were 67 years or older at colonoscopy during 1998-2005 and those who were subsequently diagnosed with CRC within 36 months were identified from a database. CRCs diagnosed within 6 months of colonoscopy were categorized as detected CRCs; CRCs diagnosed 6-36 months after colonoscopy were categorized as early/missed CRCs. The rate of early/missed CRCs was calculated as number of early/missed CRCs divided by number of detected and early/missed CRCs. Of 55,008 CRC patients (304 Crohn's disease; 544 ulcerative colitis (UC)), the rate of early/missed CRCs was 5.8% for non-IBD patients, 15.1% for Crohn's, and 15.8% for UC. Compared with older non-IBD patients, early/missed CRCs among older IBD patients were less likely right-sided. The risk of early/missed CRCs was three times as high for IBD patients. Researchers concluded that older IBD patients had a higher rate of early/missed CRCs after colonoscopy. Their finding supports intensive surveillance colonoscopy for older IBD patients as recommended by guidelines.

Wang, YR, et al., Rate of early/missed colorectal cancers after colonoscopy in older patients with or without inflammatory bowel disease in the united states. Am J Gastroenterol advance online publication, 8 January 2013; doi:10.1038/ajg.2012.429.

17. Oldest Patients May Not Need Cancer Screening (Jan.10/13)

Patients with a life expectancy of less than 10 years derive little benefit from screening for breast or **colorectal cancer**, a meta-analysis of randomized trials suggested. For every 1,000 women screened for breast cancer, almost 11 years would pass before one breast cancer death would be prevented. More than 10 years would pass before a single death from colorectal cancer would be prevented for every 1,000 persons screened. Increasing the number screened to 5,000 reduced the intervals to 3 and 5 years for prevention of one death by breast or colorectal cancer. The study results suggest that screening for breast and colorectal cancer is most appropriate for patients with a life expectancy greater than 10 years. Clinical guidelines target screening for breast and colorectal cancer to healthy older individuals with a substantial life expectancy, a position backed by the rationale that screening does not provide immediate benefits. The benefits of cancer screening come from early detection of asymptomatic cancers that would cause symptoms or death years later, according to the authors. As such, screening is associated with a "time lag to benefit." When life expectancy is shorter than the time lag, patients are exposed to immediate risks of screening, which has little chance of providing a benefit. However, the life expectancy required to benefit from screening for breast or colorectal cancer remains unclear. To examine the issue of time lag to benefit, researchers performed a survival meta-analysis of major clinical trials of screening mammography and fecal occult blood testing (FOBT). They excluded studies that targeted younger populations. For screening mammography and FOBT, investigators calculated the number of years required to prevent a single cancer-related death with screening thresholds of 500 to 10,000 patients. A review of multiple databases identified five mammography trials and four trials of FOBT suitable for meta-analysis. The mammography trials involved 13,811 to 61,004 patients, and follow-up ranged from 10 to 20 years. Investigators limited their analysis to women ages 55 to 74. The primary outcome of all the trials was breast cancer mortality. The colorectal cancer screening trials included 30,964 to 150,251 patients, ages 45 to 80, and follow-up ranged from 8 to 19 years. Patients younger than 50 were excluded from analysis. The authors determined that 2.8 colorectal cancer deaths would be prevented after 5 years for every 10,000 patients screened by FOBT. With a screening threshold of 5,000 patients, the time-lag interval was 4.8 years to prevent a single death from colorectal cancer. The interval increased to 10.3 years per cancer prevented for a threshold of 1,000 patients. The mammography analyses showed that 5.1 breast cancer deaths were prevented over 5 years for every 10,000 women screened, one death in 3 years for a screening threshold of 5,000 women, and one death prevented every 10.7 years for every 1,000 women screened. The frequency of serious harm has been estimated at three in 10,000 for breast cancer screening and one in 1,000 for colorectal cancer screening, the authors wrote. As a result, an absolute risk reduction of one in 1,000 would be reasonable as the threshold wherein potential benefit probably outweighs potential risk. "Therefore, patients with a life expectancy greater than 10 years should be encouraged to undergo screening for colorectal cancer and breast cancer," they said. "Conversely, patients whose life expectancy is less than 3 to 5 years...should be discouraged from screening, since the potential risks probably outweigh the small probability of benefit." "Between these extremes is an intermediate zone of small or unclear benefit, in which patient preferences and values should have the dominant role in deciding whether screening is appropriate," they added. The analysis had some limitations. All of the studies included multiple rounds of screening so the authors may have underestimated the true time lag to benefit for one screening test. Also, the study focused on cause specific mortality that could have been subject to ascertainment bias.

Lee, SJ, et al., Time lag to benefit after screening for breast and colorectal cancer: Meta-analysis of survival data from the United States, Sweden, United Kingdom and Denmark. BMJ 2013. ; DOI: 10.1136/bmj.e8441

OTHER

18. Key Process Discovered That Allows Colon Cancer to Metastasize (Nov.19/12)

A team of researchers has determined that the ability of colon cancer to metastasize lies in the healthy cells, called **stroma**, that surround the tumour. Although the stroma has long been hypothesized to be complicit in this process, this study marks the first time that healthy cells in the tumour's microenvironment have been observed to play a fundamental role in allowing metastasis to occur in a specific tumour type. The discovery could translate into direct benefits for patients given that in a little more than five years, tests could be available to predict relapse allowing doctors to target treatment according to prognosis. By studying 345 cases of colon cancer, using information in public databases and samples of patients provided by three hospitals in Barcelona, the team was able to identify the factors key to colon cancer metastasis. They showed that when tumour stem cells reach the liver, a common target of colon cancer metastasis, they release a molecule called ***TGF-beta*** into the microenvironment. The surrounding cells, including macrophages, leukocytes, fibroblasts and endothelial cells, respond by releasing a different set of molecules. The researchers found that the cells in the tumour microenvironment produce interleukin-11 (IL11) and cause a series of genetic changes in the tumour stem cells that allow it to survive in the foreign organ. This study proposes a change in paradigm. Until now, if we wanted to know whether a colon cancer patient was likely to develop metastasis, we would look at their tumour cells. This study has shown us that, instead of looking at the seed, we need to be looking at the earth. We can predict if a plant will grow if the ground, or substrate, in which the seed is planted is fertilized. TGF-beta is the fertilizer that changes the earth in which the tumour seed grows. The scientists also observed that tumour cells in the original organ already possess the ability to change their microenvironment. We can tell whether there will be metastasis through indirect means. If we see that the stroma is already modified in the primary tumour site in the colon, it means that the tumour cells will also be able to change the microenvironment when they disseminate to the liver. **I**n about five years, we will likely have a test on the market that identifies those patients at risk of metastasis, allowing doctors to fine tune their treatment regimes. The scientists have observed that about 15% of patients never develop metastasis and this is related to whether or not the stroma has been modified by TGF- beta. This means that armed with a diagnostic test that analyzes the genetic signature of the stroma (whether or not molecules including TGF-beta and interleukin-11 are present), doctors may be able to identify patients at risk of developing metastasis. If the data from this study are confirmed, between 10-15% of patients may no longer require chemotherapy, leading to direct benefits for their health and to a better use of resources. On the other hand, if the test predicts a high risk for metastasis, patients would be able to receive more aggressive treatment and undergo more thorough monitoring. The team of researchers also show that metastasis can be prevented from occurring by eliminating the TGF-beta signal in the stroma. They treated mice with aggressive colon tumours with a TGF-beta inhibitor that is already in clinical trials for other illnesses. Their tumours did not metastasize. "This experiment proves that TGF-beta and the tumour stroma must 'speak to each other' in order for metastasis to occur. Our results in mice also show that patients with activated TGF-beta, and who are in the initial phases of the disease, may benefit from taking a TGF-beta inhibitor," explains the study author. As far as the researchers can tell, dependence on TGF-beta is limited to the initial phases of metastasis. Once metastasis takes hold in the foreign organ, the administration of the inhibitor is no longer effective. "Even so, we must point out that the development of a drug to treat colon cancer metastasis is a complicated process." "Today, the vast majority of inhibitors must first be tested in patients with irreversible prognosis. Clinical trials are designed to slow down tumour growth, while the molecules that we administered to mice don't act on tumour growth but at an earlier step. We have presented our evidence in this article, and we open the door to a future development of a TGF-beta based inhibitor."

Batlle, Eduard, et al., Dependency of colorectal cancer on a TGF-beta driven program in stromal cells for metastasis initiation. Cancer Cell (2012). November 13, 2012. 22 (5): 571 DOI: 10.1016/j.ccr.2012.08.013

19. Barrett's May Double Bowel Cancer Risk (Nov.29/12)

Barrett's oesophagus may substantially raise the risk of colonic tumours including colorectal cancer, according to this study. Pooled data from eleven studies and over 2,500 cases of Barrett's oesophagus (BO) showed there was a 96% increased risk of any colonic tumours in BO patients compared with the general population. BO was linked to a 69% greater chance of developing benign adenomatous tumours. But the association was even stronger for colorectal cancer with a 90% increased risk, the researchers found. Further studies are needed to confirm the relationship.

Andrici, J, et al., Meta-analysis: Barrett's esophagus and the risk of colonic tumours. Alimentary Pharmacology & Therapeutics. Early online edition. Doi: 10.1111/apt.12146

20. Multimodality Salvage of Recurrent Disease After Local Excision for Rectal Cancer (Dec.1/12)

Local excision, alone or in combination with chemoradiation, is increasingly considered for rectal cancer. Higher risks of disease recurrence have been demonstrated after local excision though. The aim of this study was to examine the outcomes of current multimodality salvage for recurrent rectal cancer after local excision. This study was conducted between 1993 and 2011. Forty-six patients with recurrent rectal cancer after initial local excision were included. Multimodality salvage treatment was performed as appropriate. The primary outcomes measured were

- the pattern of disease recurrence,
- salvage treatments, and
- resultant overall and re-recurrence-free survival.

After the initial local excision, recurrent disease was diagnosed after a median interval of 1.9 years:

- local/regionally in 67%,
- distantly in 18%, and
- both in 15%.

Four patients (9%) had recurrence that was unsalvageable, 2 (4%) declined treatment, and 40 (87%) underwent surgical salvage. Preoperative chemoradiation was given in 30 (75%) patients. The R0 (complete) resection rate was 80%, requiring multivisceral resection (33%), total pelvic exenteration (5%), and metastasectomy (25%). The rate of sphincter preservation was 33%, and perioperative morbidity was 50%. The first site of failure after salvage was distant in 38% and was local only in 10%. The 5-year overall and 3-year re-recurrence-free survival were 63% and 43%. Pathologic stage at initial local excision, receipt of neoadjuvant chemoradiation before local excision, recurrence pattern after local excision, pathologic stage at salvage, and R0 resection at salvage influenced re-recurrence-free survival. Failure after local excision for rectal cancer may not be salvageable. When feasible, multimodality treatment, including multivisceral resection, pelvic irradiation, and chemotherapy, was associated with potentially lasting treatment-related morbidities and only modest success in long-term disease control. These findings should be compared with the expected stage-specific outcomes of standard rectal surgery for early-stage rectal cancer, when local excision is being considered.

You, YN, et al., Multimodality salvage of recurrent disease after local excision for rectal cancer. Dis Colon Rectum, 2012 December. 55 (12): pp. 1213-9

21. Patients With Family History of Colorectal Cancer May be at Risk for Aggressive Form of the Disease (Dec.112)

According to the results of this study, when people with a family history of colorectal cancer develop the disease, their tumors often carry a molecular sign that the cancer could be life-threatening and may require aggressive treatment. The finding draws on data from studies that have tracked the health of tens of thousands of people over several decades. It suggests that colorectal cancer patients could one day have their tumor tissue tested for the molecular sign, and, if necessary, receive more powerful therapies and a familial cancer-risk assessment for their relatives. It further suggests that such patients' relatives could be eligible for more frequent colonoscopies to catch the disease at the earliest possible stage. Unlike other abnormalities that raise the risk of colon cancer in some families, the newly discovered sign is not linked to a gene mutation that can be inherited from one's parents or grandparents. It appears in DNA segments that are thought to have entered the human genome millennia ago, possibly through infection by retroviruses. These sections, known as ***long interspersed nucleotide element 1 (LINE-1)***, are sprinkled throughout the human genome and make up about 17% of our DNA. Normally, LINE-1 doesn't cause much trouble, because it's blanketed by methyl groups (packets of one carbon atom bound to three hydrogen atoms). In the current study, researchers found that for many colorectal cancer patients with a family history of the disease, the LINE-1 in their tumor cells was nearly bare of methyl groups (a condition known as hypomethylation). "Previous studies have suggested that some colorectal cancers exhibit an instability of the epigenome, the cell's system for controlling when genes are active," says the paper's first author. "One of the signs of this deficiency, it was proposed, is hypomethylation of LINE-1. We wanted to find whether a family history of colorectal cancer creates a higher risk of such hypomethylation." In contrast to a small, previous study, which suggested that LINE-1 hypomethylated colorectal cancers cluster in certain families, the new study took a large-scale "prospective" approach to gain more definitive insights. Investigators used data from the Nurses' Health Study and the Health Professionals Follow-up Study -- which follow the health of tens of thousands of people for decades -- to see if participants who had a family history of colorectal cancer tended to develop colorectal cancer with low-level methylation of LINE-1. "We found that, compared to individuals without a family history of colorectal cancer, people who had first-degree relatives affected with the disease indeed had a higher risk of developing colorectal cancer with hypomethylated LINE-1," study author says. "Because this variety of colorectal cancer can quickly become dangerous, testing colorectal cancer patients for tumor LINE-1 hypomethylation may offer a valuable way of identifying those in greatest need of aggressive treatment. Such testing could also help identify patients whose relatives may be at increased risk for the aggressive form of the disease. Further study is needed to determine how this type of testing can be used in a clinical setting."

Ogino, S, et al., Prospective Study of Family History and Colorectal Cancer Risk by Tumor LINE-1 Methylation Level.* JNCI Journal of the National Cancer Institute*, 2012; DOI: 10.1093/jnci/djs482

22. Cancer-Related Fatigue: Real, Treatable and Under Treated (Jan.8/13)

Life-altering fatigue will affect 80% of people getting chemotherapy or radiation therapy, plus most people who have metastatic cancer, and even many survivors long after treatment is done. Yet fatigue in cancer patients has been under-reported, under-diagnosed, and under-treated, according to an expert panel convened by the National Comprehensive Cancer Nework (NCCN) a decade ago to recommend cancer-related fatigue treatment guidelines. However, a recent Dutch study found that advanced cancer patients can get significant relief from serious fatigue, when their fatigue and other symptoms are regularly monitored and treated according to guidelines. Some less good news: A small U.S. study published in *Support Care Cancer* found that even at an excellent cancer center, most metastatic cancer patients did not get any of the recommended treatments for even severe fatigue. In one of the first randomized controlled studies of cancer-related fatigue, Dutch researchers randomly assigned 152 advanced cancer patients with significant fatigue (mean age 58, with 57% female and 65% on palliative chemotherapy) to receive either usual treatment, or usual treatment plus nurse appointments at 1, 2, and 3 months for evaluation of nine symptoms—including pain, nausea or vomiting, lack of appetite, and fatigue. In the nurse-monitored group, patients having symptoms of average or higher intensity received treatment according to evidence-based, palliative care guidelines. Standard-care patients had their usual clinic visits with symptom treatment according to clinicians' preferences rather than specific guidelines. After several months, patients getting the nurse visits and protocol-guided symptom treatment showed modest but statistically significantly improvement in fatigue and related symptoms (e.g. anxiety and daily activity levels). Improvement was seen with control of symptoms such as pain, vomiting, diarrhea, lack of appetite, rather than fatigue itself. Systematic monitoring of symptoms seemed to be the key in this and other studies, the researchers reported. In another study published in *Supportive Care in Cancer*, Mayo Clinic researchers found that only 15% of colorectal cancer patients with moderate to severe fatigue

recalled receiving advice or treatment which would have followed evidence-based guidelines for cancer-related fatigue. Researchers surveyed 160 patients having stage IV breast, lung, prostate or colorectal cancer who reported moderate to severe fatigue. NCCN "cancer-related fatigue" guidelines list four treatment categories if fatigue continues despite control of associated conditions (e.g. pain, nausea, vomiting, diarrhea, anemia). The telephone interviewer asked patients if they recalled receiving any counseling, instructions, or treatment from their oncology care team for:

- general fatigue-reducing strategies, e.g. saving energy for vital tasks;
- increased activity techniques, e.g. starting an exercise program, seeing a physical therapist;
- psychosocial strategies such as relaxation and sleep techniques, or cognitive therapy;
- medication (either stimulants or sleep-inducers).

Even the 40% of study participants reporting severe fatigue rarely received fatigue-related counseling, instructions, and prescriptions were rarely provided. Among all stage IV cancer participants, about 37% received prescriptions (almost all for sleep-inducing drugs), but activity-enhancement and psychosocial approaches having the strongest scientific evidence for effectiveness were the least likely to be prescribed. Significantly more patients with breast cancer (47.5%) recalled mention or receipt of psychosocial interventions, compared to 25% of patients with prostate cancer; 17.5% having lung cancer; and just 15% of colorectal cancer patients. Although this study only covered patients in one site, the authors wrote, it was done at a "resource-rich" cancer specialty center rather than a community setting where 85% of patients receive cancer treatment. That, they wrote, indicates that cancer-related fatigue, like cancer pain, is seriously under-treated throughout the U.S.

Fatigue-Busting Programs Work Even in Advanced Cancer," **Medscape*, Jan 04, 2013;***

*"**Systematic Monitoring and Treatment of Physical Symptoms to Alleviate Fatigue in Patients With Advanced Cancer: A Randomized Controlled Trial,"*** **Journal of Clinical Oncology *published online Jan. 2, 2013 ;***

*"**Appropriateness of the treatment of fatigue in patients with stage IV cancer,"*** **Support Care Cancer *(2013) 21:229-233 ;***

NCCN Guidelines for Cancer-Related Fatigue

http://fightcolorectalcancer.org/research_news/2013/01/cancer-related_fatigue_real_treatable_and_under-treated

NUTRITION & HEALTHY LIFESTYLE

23. Supplements Are No Substitute for Dietary Fibre (Nov.15/12)

At the University of Adelaide in Australia, scientists are interested in how the extract of mistletoe could either assist chemotherapy or act as an alternative to chemotherapy as a treatment for colon cancer. Mistletoe extract is already authorized for use by sufferers of colon cancer in Europe, but not in some countries such as Australia and the United States due to a lack of scientific testing. Researchers compared the effectiveness of three different types of mistletoe extract and chemotherapy on colon cancer cells. They also compared the impact of mistletoe extract and chemotherapy on healthy intestinal cells. In their laboratory studies, they found that one of the mistletoe extracts -- from a species known as *Fraxini* (which grows on ash trees) -- was highly effective against colon cancer cells in cell culture and was gentler on healthy intestinal cells compared with chemotherapy. Significantly, *Fraxini* extract was found to be more potent against cancer cells than the chemotherapy drug. "This is an important result because we know that chemotherapy is effective at killing healthy cells as well as cancer cells. This can result in severe side effects for the patient, such as oral mucositis (ulcers in the mouth) and hair loss," says one of the researchers. "Our laboratory studies have shown *Fraxini* mistletoe extract by itself to be highly effective at reducing the viability of colon cancer cells. At certain concentrations, *Fraxini* also increased the potency of chemotherapy against the cancer cells". "Of the three extracts tested, and compared with chemotherapy, *Fraxini* was the only one that showed a reduced impact on healthy intestinal cells. This might mean that *Fraxini* is a potential candidate for increased toxicity against cancer, while also reducing potential side effects. However, more laboratory testing is needed to further validate this work". "Mistletoe extract has been considered a viable alternative therapy overseas for many years, but it's important for us to understand the science behind it" . "Although mistletoe grown on the ash tree was the most effective of the three extracts tested, there is a possibility that mistletoe grown on other, as yet untested, trees or plants could be even more effective.

http://www.sciencedaily.com/releases/2012/11/121130094725.htm

24. Dietary Fibre, Whole Grains and Risk of Colorectal Cancer (Dec.3/12)

Following a diet high in fibre, particularly from whole grains and cereals like brown rice and oats, is linked to a lower risk of colorectal cancer, according to researchers in Britain and The Netherlands who pooled all available published evidence, covering nearly 2 million people. For every additional 10g of fibre in the diet, there was a 10% reduction in risk of colorectal cancer. Research has already established a clear link between reduced risk of cardiovascular disease and eating fibre and whole grains. But links between reduced colorectal cancer risk and fibre and whole grains remain somewhat unclear, and studies have shown inconsistent results, despite the suggestion having been around for the best part of 40 years. For this study, the researchers analyzed the results of 25 prospective studies involving nearly 2 million participants. To reduce any bias, they took into account the design and quality of the studies. The type of analysis they performed is known as a "**meta- analysis**", which is a way of pooling results from several studies and treating them as if they came from one large study. They found that although the overall reductions in colorectal cancer risk were not large, there was a clear, gradual and positive "dose-

response" relationship with amount of fibre consumed. They ranked the participants according to how much daily fibre they ate and found that compared to those with the lowest intake, each 10g a day increase in total dietary fibre was linked to a 10% reduction in risk of colorectal cancer. There was a similarly sized link with cereal fibre. They also looked at whole grains on their own and found that adding three servings (90g a day) of this food in the diet was linked to around 20% reduced risk of colorectal cancer. Whole grain foods include oatmeal, porridge, brown rice and whole grain breads and cereals. Whole grains and cereals are not the only source of fibre in the diet: vegetables and fruit also contain fibre, but the researchers found no link between fibre intake from these foods and risk of colorectal cancer. But they said that a previous analysis had shown a link between eating large amounts of fruit and vegetables and reduced colorectal cancer risk, suggesting something other than fibre might be responsible for such an effect in these foods. Since eating more dietary fibre and whole grains is also likely to reduce people's risk of cardiovascular disease, developing type 2 diabetes, becoming overweight and obese, and possibly also, early death, there are numerous health benefits to doing so, said the researchers. One way to do this is to replace foods made with refined grains with those made with whole grains. The researchers conclude that: "... our meta-analysis suggests that a high intake of dietary fibre, particularly from cereal and whole grains, is associated with a reduced risk of colorectal cancer." They suggest further studies be done to examine links between different types of dietary fibre and specific sites of cancer in the rectum and colon, for people with varying lifestyles and diets. They also recommend researchers report more details when they publish studies in this area so that they can be included in future pooled analyses.

Aune D, et al., Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. BMJ. Doi: 10.1136/bmj.d6617

25. Snacks Tied to Colon Cancer (Dec.17/12)

Unhealthy snack food may increase the risk of developing colorectal cancer in people with specific gene mutations, says a new study. The study included 486 people with Lynch syndrome, an inherited condition caused by mutations in genes that help repair DNA within cells. People with the condition have a high risk of developing colorectal cancer, endometrial cancer and other cancers at an early age. Previous research has shown that consuming alcohol and red and processed meats can increase the risk of cancer in people with Lynch syndrome. Smoking and obesity are other possible risk factors. The participants in this study provided information about their eating habits and were followed for an average of 20 months. During that time, colorectal polyps (precancerous growths) were detected in 58 of the patients, according to the study. "We saw that Lynch syndrome patients who had an eating pattern with higher intakes of snack foods — like fast-food snacks, chips or fried snacks — were twice as likely to develop these polyps as Lynch syndrome patients having a pattern with lower intakes of snack foods". The results suggest that eating habits may influence the development of colorectal polyps in people with Lynch syndrome. "Unfortunately, this does not mean that eating a diet low in snack foods will prevent any polyps from developing, but it might mean that those Lynch syndrome patients who eat a lot of snack foods might have more polyps than if they ate less snack foods". While the study found an association between eating certain snack foods and the development of polyps in people with Lynch syndrome, it did not establish a cause-and-effect relationship.

Botma, Akke, et al., Dietary patterns and colorectal adenomas in Lynch syndrome. Cancer. December 17, 2012. Volume 118, Issue 24. doi: 10.1002/cncr.27726

26. Grape Seed Extract and Colorectal Cancer (Jan.18/13)

A University of Colorado Cancer Center study shows that the more advanced are colorectal cancer cells, the more Grape Seed Extract (GSE) inhibits their growth and survival. On the other end of the disease spectrum, GSE leaves healthy cells alone entirely. "We've known for quite a while that the bioactive compounds in grape seed extract selectively target many types of cancer cells. This study shows that many of the same mutations that allow colorectal cancer cells to metastasize and survive traditional therapies make them especially sensitive to treatment with GSE," says one of the study's investigators. She notes this is an especially important finding in light of increasing colorectal cancer rates (due in part to increasingly high-fat diets and sedentary lifestyles) and a low screening rate; that means 60% of patients diagnosed have already reached the advanced stage of the disease. "Finding a way to selectively target advanced colorectal cancer cells could have major clinical importance". The group performed their experiments on colorectal cancer cell lines representing various stages of the disease. Whereas it generally takes much more chemotherapy to kill a stage IV cancer cell than a stage II cancer cell, investigators saw that the reverse was true with grape seed extract. "It required less than half the concentration of GSE to suppress cell growth and kill 50% of stage IV cells than it did to achieve similar results in the stage II cells". The group also discovered a likely mechanism of GSE's preferential targeting of advanced colorectal cancer cells: when cancer cells were treated with antioxidants, the GSE induced cell death was reversed and so investigators consider it likely that GSE targets colorectal cancer through inducing oxidative stress that leads to the programmed cell death known as apoptosis. "A colorectal cancer cell can have upwards of 11,000 genetic mutations – differences from the DNA in healthy cells. Traditional chemotherapies may only target a specific mutation and as cancer progresses more mutations occur. These changes can result in cancer that is resistant to chemotherapy. In contrast, the many bioactive compounds of GSE are able to target multiple mutations. The more mutations a cancer presents, the more effective GSE is in targeting them". The Agarwal Lab continues its preclinical work studying the effectiveness and action of dietary compounds against cancer and encourages further exploration of their findings in clinical settings.

http://www.eurekalert.org/pub_releases/2013-01/uocd-acc011613.php