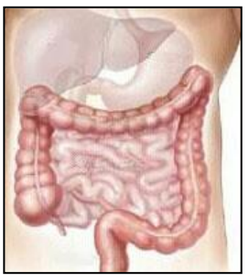
COLORECTAL CANCER RESEARCH UPDATES

Month Ending March 15th, 2013



The following colorectal cancer research update extends from February 16th, 2013 –March 15th, 2013 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Folfoxiri May Be Better Than Folfiri When Avastin is Added (Feb. 21/13)

Adding bevacizumab (also known as Avastin) to the FOLFOXIRI regimen significantly delayed the median time to progression of metastatic colorectal cancer to 12.2 months, compared with 9.7 months when bevacizumab was added to the FOLFIRI regimen, a phase III trial of 508 patients found. Previous data had shown inferior progression-free survival, treatment response, and overall survival rates when

treating metastatic colorectal cancer with FOLFIRI - which combines folinic acid (leucovorin), fluorouracil, and irinotecan - compared with FOLFOXIRI, which adds oxaliplatin to the drugs used in FOLFIRI. The current study confirms the superiority of first-line FOLFOXIRI over FOLFIRI and shows that FOLFOXIRI remains the better regimen when adding bevacizumab (Avastin) for select patients. At 2 years of follow-up, 20% of patients in the FOLFOXIRI/bevacizumab group and 11% in the FOLFIRI/bevacizumab group were free of disease progression. The multicenter study, known as the TRIBE trial, randomized adults in Italy aged 18-75 years who had unresectable metastatic colon cancer with histologically proven adenocarcinoma; at least one measurable lesion; and adequate bone marrow, liver, and renal functions. Patients younger than 71 years had to have an Eastern Cooperative Oncology Group performance status score of 0, and patients aged 71-75 years had a performance status score no higher than 2. Previous adjuvant chemotherapy containing oxaliplatin was allowed if more than 12 months had passed between the end of adjuvant therapy and the first relapse. The overall safety profile of FOLFOXIRI plus bevacizumab was deemed to be "acceptable", according to the study authors. The study did not, however, collect data on patients' quality of life.

Loupakis F, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of metastatic colorectal cancer: Results of the phase III randomized TRIBE trial. 2013 Gastrointestinal Cancers Symposium. Abstract 336. Presented January 26, 2013.

2. Biweekly Xelox as First Line Treatment in Elderly Patients with Metastatic Colorectal Cancer (Mar.13/13)

Results of this non-randomized, multicenter study demonstrated that the combination of capecitabine (also known as xeloda) and oxaliplatin (together known as XELOX) was effective, with mild to moderate toxicity, in **elderly** patients with metastatic colorectal cancer. The combination of oxaliplatin and oral capecitabine (XELOX) has shown to be an active regimen in metastatic colorectal cancer (MCRC). However, the experience with XELOX in elderly patients is limited. This study aimed to evaluate the efficacy and safety of XELOX as first-line treatment in elderly patients with MCRC. Patients aged ≥ 70 years with previously untreated MCRC received oxaliplatin every 2 weeks plus capecitabine twice daily on days 1–7, every 2 weeks. Treatment was continued until progression, intolerable toxicity, or for a maximum of 12 cycles. Thirty-five patients were enrolled. Median age was 78 years (range, 70–83). Patients received a median of 11 cycles of treatment. The objective response rate (ORR) was 49% and the tumor control rate was 86%. Median time to progression and overall survival were 8.6 and 15.5 months, respectively. Toxicities were generally mild to moderate. There was no treatment-related death. The findings show that the biweekly XELOX regimen represents an effective and tolerable first-line treatment option for elderly patients with MCRC.

Grande, Carlos, et al., Biweekly xelox (capecitabine and oxaliplatin) as first line treatment in elderly patients with metastatic colorectal cancer. J of Geriatric Oncology. Published online 18 February 2013

SURGICAL THERAPIES

3**. The Beneficial Effect of Palliative Resection in Metastatic Colorectal Cancer** (Mar.14/13)

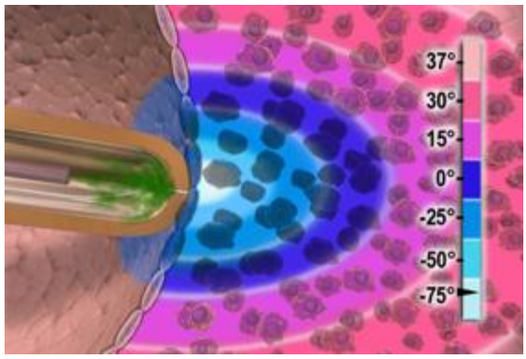
In this study, researchers aimed to determine the role of palliative resection in metastatic colorectal cancer (mCRC) and ascertain which patient populations would benefit most from this treatment. A total of 1015 patients diagnosed with mCRC at Seoul National University Hospital between 2000 and 2009 were retrospectively studied. Of the 1015 patients, 168 patients with only liver and/or lung metastasis received curative resection. The remaining 847 patients were treated with palliative chemotherapy and/or palliative resection combined with best supportive care. Palliative resection was performed in 527 (62.2%) cases (complete resection with negative margin (R0) in 93). Resected patients had a more prolonged median overall survival (OS) than unresected patients (21.3 vs 14.1 months). In an analysis, R0 resection was found to be associated with a **superior** OS compared with R1/2 resection (51.3 vs 19.1 months) and no resection (51.3 vs 14.1 months). Researchers concluded that palliative resection without residual disease and chemotherapy confers a longer-term survival outcome than palliative chemotherapy alone in mCRC patient subset.

Park, JH, et al., The beneficial effect of palliative resection in metastatic colorectal cnacer. British Journal of Cancer advance online publication, 12 March 2013; doi:10.1038/bjc.2013.94

INTERVENTIONAL RADIOLOGY/RADIATION THERAPY

4. Cryoblation to Treat Painful Bone Mets (Mar.4/13)

This study found that the treatment of painful bone metastases with percutaneous cryoablation achieved significant reduction in pain scores and durable relief in patients who were unable to derive adequate relief from standard palliative therapy. **Percutaneous cryoablation is a minimally invasive, image-guided treatment that destroys (ablates) tumors and other targeted tissue with extreme cold while sparing surrounding healthy tissue.**



Cryoablation is a minimally invasive treatment that uses extreme cold ("cryo") to freeze and destroy diseased tissue ("ablation"), including cancer cells. **Source:** **http://upload.wikimedia.org/wikipedia/en/4/47/Cryoablation.jpg**

This study sought to describe the results of a clinical trial using image-guided percutaneous cryoablation for the palliation of painful metastatic tumors involving bone. Over a 44-month period, 61 adult patients with 1 or 2 painful bone metastases with a score of 4 or more on a scale of 0 to 10 (≥4/10) worst pain in a 24-hour period who had failed or refused conventional treatment were treated with percutaneous image-guided cryoablation. Complications were monitored. A total of 69 treated tumors ranged in size from 1 to 11 cm. Prior to cryoablation, the mean score for worst pain in a 24-hour period was 7.1/10 with a range of 4/10 to 10/10. At 1, 4, 8, and 24 weeks after treatment, the mean score for worst pain in a 24-hour period decreased to 5.1/10, 4.0/10, 3.6/10 (, and 1.4/10, respectively. Study authors concluded that percutaneous cryoablation is a safe, effective, and durable method for palliation of pain due to metastatic disease involving bone.

For more information on Cryoblation, please visit: http://www.endocarepercryo.com/

Callstrom, DE, et al., Percutaneous Image-Guided Cryoablation of Painful Metastases Involving Bone: Multicenter Trial. Cancer. 2013 Mar 1; 119(5): pp. 1033-1041.

SCREENING

5. Screening with Colonoscopy May Reduce Risk for Late Stage Cancer by 70% (Mar.5/13)

Screening with sigmoidoscopy yields similar results in cancer of the left colon, but not the right. Using colonoscopy to screen average-risk adults for colorectal cancer (CRC) reduces the risk for diagnosis of late-stage CRC by about 70% for both the right- and left-sided disease. Previous trials and observational studies have shown that screening with fecal occult blood tests (FOBT) and sigmoidoscopy reduce the risk for CRC incidence and death, but evidence of the effectiveness of screening colonoscopy has been limited. Researchers reviewed health records for 1,012 average-risk adults between the ages of 55 and 85 to examine the association between screening colonoscopy and incident late-state CRC risk. Case patients (n = 474), or those with advanced CRC at the time of diagnosis, were compared to 538 control patients. Those screened with colonoscopy had a ***significant overall reduction in the risk for late-stage colorectal cancer diagnosis.*** The authors simultaneously examined the association between screening sigmoidoscopy and late-state CRC risk. They found that screening sigmoidoscopy was associated with a reduction in risk similar to that of colonoscopy for left-sided late-stage CRC, but showed a modest, statistically ***non-significant*** effect on risk for right-sided colon cancer, which accounts for about 50% of new CRC cases in the United States.

Doubeni, CA, et al., Screening Colonoscopy and Risk for Incident Late-Stage Colorectal Cancer Diagnosis in Average-Risk Adults. A Nested Case–Control Study." 5 March 2013 issue of **Annals of Internal Medicine** ***(volume 158, pages 312-320).***

6. Mailings Linked to Electronic Health Records Double Colorectal Cancer Screening Adherence Rates (Mar.5/13)

Sending automated mailings linked to electronic health records (EHR) led to twice as many persons adhering to colorectal cancer (CRC) screening recommendations compared to usual care. Screening has been proven to reduce morbidity and mortality, but fewer than 60% of Americans aged 50 (the recommended age range for screening) report being current for screening. According to the authors, interventions to increase adherence to recommendations for CRC screening are needed. The researchers sought to determine if interventions using EHR, automated mailings, and stepped increases in support could improve CRC screening adherence over two years. They randomly assigned 4,675 adult Group Health patients aged 50 to 73 years who were not current on CRC screening to one of four interventions:

- usual care;

- EHR-linked mailings that included a letter, a pamphlet, and a fecal occult blood testing kit ("automated");

- automated plus telephone assistance ("assisted"), or

- automated and assisted plus nurse navigation to testing completion or refusal ("navigated").

These same interventions were repeated in year two. Compared with usual care, patients in the automated group, where letters, pamphlets, and fecal occult blood tests were mailed, completed recommended screening twice as often, for less cost. Patients in the assisted and navigated groups had additional but smaller incremental improvements in adherence

Green, Beverly B, et al., An Automated Intervention With Stepped Increases in Support to Increase Uptake of Colorectal Cancer Screening: A Randomized Trial. Annals of Internal Medicine. 5 March 2013, Vol 158, No. 5_Part_1.

7. Computed Tomographic Colonography vs. Colonoscopy for Symptomatic Patients (Mar.4/13)

Colonoscopy is the gold-standard test for investigation of symptoms suggestive of colorectal cancer; computed tomographic colonography (CTC) is an alternative, less invasive test. However, additional investigation after CTC is needed to confirm suspected colonic lesions, and this is an important factor in establishing the feasibility of CTC as an alternative to colonoscopy. Investigators aimed to compare rates of additional colonic investigation after CTC or colonoscopy for detection of colorectal cancer or large (≥10 mm) polyps in symptomatic patients in clinical practice. This trial recruited patients with symptoms suggestive of colorectal cancer from 21 UK hospitals. Eligible patients were aged 55 years or older and regarded by their referring clinician as suitable for colonoscopy. Patients were randomly assigned (2:1) to colonoscopy or CTC by computer-generated random numbers. They analyzed the primary outcome - the rate of additional colonic investigation. 1610 patients were randomly assigned to receive either colonoscopy (n=1072) or CTC (n=538). 30 patients withdrew consent, leaving for analysis 1047 assigned to colonoscopy and 533 assigned to CTC. 160 (30.0%) patients in the CTC group had additional colonic investigation compared with 86 (8.2%) in the colonoscopy group. Almost half the referrals after CTC were for small (<10 mm) polyps or clinical uncertainty. Detection rates of colorectal cancer or large polyps in the trial were 11% for both procedures. CTC missed 1 of 29 colorectal cancers and colonoscopy missed none (of 55). Serious adverse events were rare. Guidelines are needed to reduce the referral rate after CTC. For most patients, however, CTC provides a similarly sensitive, less invasive alternative to colonoscopy.

Atkin, W., et al., Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomized trial. Lancet. 2013 Feb 14; epub ahead of print.

8. New Colon Cancer Screening Test for Quebecers (Mar.9/13)

A new home-based procedure in screening for colorectal cancer is being introduced in Quebec, provincial health minister Réjean Hébert announced. The Fecal Immunochemical Test, or FIT test, will be rolled out in two phases. This year, screening will be done at eight test sites, and doctors will be able to order the test for their patients. But once fully implemented across Quebec next year, the program will be available to everyone aged 50 to 74. People will be able to do the home test every two years. It consists of putting a stool sample into a vial and sending it off to a test centre. The FIT test allows for screening of microscopic amounts of blood in stool; if blood is detected, a colonoscopy is in order. "We hope people will open the envelope when they get the test, and do the test," said Nathalie Rodrigue of Coalition Priorité Cancer Quebec. Hebert says that type of screening will streamline cancer treatment and reserve more invasive testing for those who really need it.

http://www.cbc.ca/news/canada/montreal/story/2013/03/09/montreal-quebec-colonoscopy-test-fit-rejean-hebert-cancer-screening.html

9. Screening Asymptomatic Siblings of CRC Patients (Mar.13/13)

Asymptomatic siblings of Chinese colorectal cancer patients are at threefold higher risk for advanced colorectal cancer and at twofold higher risk for any colorectal adenoma (polyps), compared with siblings of healthy Chinese adults. Given these findings from a large prospective cross-sectional study, colorectal screening, with the removal of any premalignant lesions that are found, is warranted in this high-risk group. Current guidelines recommend earlier and more frequent screening of close relatives of patients who have colorectal cancer, but what to expect on these screenings is unclear because data from well-conducted prospective studies are lacking. Investigators compared the prevalence of advanced neoplasms in such siblings against the prevalence in siblings of patients who underwent colorectal screening but had normal results. During a period of 10 years, 374 siblings (mean age, 53 years) of CRC patients aged 40-70 years participated in the study, as did 374 age- and sex-matched control subjects. The quality of bowel preparation was similar between the two groups. All three study endoscopists were experienced, and they had comparable rates of adenoma detection. The primary outcome was the prevalence of advanced neoplasms, defined as cancers or adenomas at least 10 mm in diameter that had high-grade dysplasia or villous/tubule-villous histologic traits. This prevalence was approximately

three times higher in the siblings of CRC patients (7.5%) as in the siblings of healthy controls (2.9%). Cancers were detected in six siblings of CRC patients, but in none of the control subjects. These included two stage I cancers, two stage II cancers, and two stage III cancers. Similarly, the prevalence of large adenomas was approximately three times as high in siblings of CRC patients (5.9%) as in controls (2.1%). Siblings of CRC patients also had a higher prevalence of smaller adenomas (31%) than did control subjects (18.2%). When the data were analyzed by lesion location, the siblings of CRC patients had a higher prevalence of every type: distal (left sided) adenomas (13.1% vs. 8.3%), proximal (right sided) adenomas (12.0% vs. 6.2%), and synchronous adenomas (5.9% vs. 2.7%). The prevalence of hyperplastic polyps was comparable between the two groups (27.3% and 21.4%). When the data were analyzed by subject age, siblings of CRC patients had a higher prevalence of all colorectal adenomas whether they were younger than 50 years (21.0% vs. 9.8%), 50-60 years old (34.4% vs. 23.9%), or older than 60 years (41.0% vs. 20.5%). Among the siblings of CRC patients, the risk of detecting an advanced adenoma was higher if the affected sibling's cancer was located in the distal colon than if it was located in the proximal colon. This risk also was higher if the affected sibling was a woman than a man; however, this finding must be interpreted with caution because the number of subjects in these subgroups was small.

Ng, Siew C., et al., Increased Risk of Advanced Neoplasms Among Asymptomatic Siblings of Patients with Colorectal Cancer. Gastroenterology (doi:10.1053/j.gastro.2012.11.011).

10. Many Colonoscopies For Seniors May Be Inappropriate (Mar.13/13)

A considerable percentage of colonoscopies that are performed on seniors could be potentially inappropriate, researchers say. **They** set out to determine how frequently potentially inappropriate colonoscopies are performed on elderly Medicare beneficiaries in Texas. They also aimed to examine variations among doctors and across geographic regions. The researchers gathered and examined data from Medicare claims in Texas, as well as a sample from the rest of the USA. The authors suggest that **23.4% of all colonoscopies performed in Texas and across the USA on seniors aged 70+ years, all of them Medicare beneficiaries in 2008-2009, were potentially inappropriate**, according to screening recommendations or the results of a previous screening. Below is a list of patient age and the percentage of potentially inappropriate colonoscopies:

- 70 to 75 - 9.9%
- 76 to 85 - 38.8%
- 86 years or older - 24.9%

There was a wide variation in the percentages of potentially inappropriate colonoscopies across the 796 colonoscopists the researchers looked at. After taking into account variables such as patient ethnicity, sex, race, education level and a number of co-morbid conditions, the authors found that:

- 73 colonoscopists had percentages ranging from 28.7% to 45.5% (above the mean of 23.9%)
- 119 colonoscopists had percentages ranging from 6.7% to 18.6% (below the mean of 23.9%)
- The colonoscopists who were surgeons, graduates of US medical schools, and medical school graduates before 1990 tended to have percentages considerably above the mean

There is increasing evidence of colonoscopy screening overuse. A significant number of Medicare patients with negative findings may be undergoing a second screening too early. Colonoscopies for this age groups costs Medicare approximately $500 million annually; patients are subsequently put at an increased risk of bleeding and other side effects, the investigators found. Researchers concluded: *"Inappropriate use of colonoscopy involves unnecessary risk for older patients and consumes resources that could be used more effectively. The likelihood of undergoing potentially inappropriate colonoscopy depends in part on where patients live and what physician they see."*

Sheffield, Kristin M.,et al., Potentially inappropriate screening colonoscopy in medicare patients: variation by physician and geographic region. JAMA Intern Med. 2013; 1-9.

OTHER

11. Familial Cancer Risk Present in Both Young and Older Diagnosis (Feb.19/13)

Although early onset cancers tend to have a more pronounced hereditary component than cancers that develop at a later age, there is still an increased risk of some familial cancers even when a parent is diagnosed at an older age. The chance of an individual developing cancer depends on both genetic and non-genetic factors. A genetic factor is an inherited, unchangeable trait, while a non-genetic factor is a variable in a person's environment, which can often be changed. A genetic predisposition means that a person may be at higher risk for a certain cancer if a family member has that type of cancer. Of course, a family history of cancer is not a modifiable risk factor—however, researchers continue to explore the risks and develop a better understanding of familial risk in order to improve screening and prevention for the disease. Researchers used the nationwide Swedish Family-Cancer Database in order to examine the familial risk of concordant cancer (meaning parent and offspring have the same type of cancer) for offspring as a function of the age at which a parent was diagnosed. The study population included more

than 12.2 million people born after 1931. Since they were examining familial risk in advanced age, researchers limited their results to cancers with at least 50 cases in the offspring of parents whose cancer was diagnosed at age 80 or older. They found that the highest familial risk occurred in people who were diagnosed at an early age and whose parents were diagnosed with the same type of cancer at an early age; however, an increased risk still exist for several cancers when diagnosed at advanced ages. In fact, for some types of cancer, the excess risk that results from family history included cancers diagnosed in parents even at ages 90 and older—including skin cancer (90 percent excess risk), **colorectal cancer** (60 percent), breast cancer (30 percent), and prostate (30 percent). The researchers concluded that the highest familial risks of cancer are observed in offspring whose parents received a diagnosis of a concordant cancer at an earlier age, but increased risks exist even in several cancers of advanced ages. They suggest that increased clinical surveillance is important even in families where parents are diagnosed at a late age.

Kharazmi E, et al. Familial risk of early and late onset cancer: nationwide prospective cohort study. **British Medical Journal.** ***2012;345:e8076.***

12. Resistant Starch Battles Colorectal Cancer (Feb. 21/13)

As the name suggests, you can't digest resistant starch so it ends up in the bowel in pretty much the same form it entered the mouth. Once in the bowel this resistant starch does some important things, including decreasing bowel pH and transit time, and increasing the production of short-chain fatty acids. These effects promote the growth of good bugs while keeping bad bugs at bay. The current study shows that resistant starch also helps the body resist colorectal cancer through mechanisms including killing pre-cancerous cells and reducing inflammation that can otherwise promote cancer. Resistant starch is found in peas, beans and other legumes, green bananas, and also in cooked and cooled starchy products like sushi rice and pasta salad. You have to consume it at room temperate or below -- as soon as you heat it, the resistant starch is gone. But consumed correctly, it appears to kill pre-cancerous cells in the bowel. There are studies showing that rats fed resistant starch show decreased numbers and sizes of lesions due to colorectal cancer, and an increased number of cells that express the protein IL-10, which acts to regulate the body's inflammatory response. Resistant starch may also have implications for the prevention of breast cancer say study authors. For example, if you let rats get obese, get them to lose the weight, and then feed half of the rats a diet high in resistant starch -- these rats don't gain back the weight as fast as rats fed a regular, digestible starch diet. This effect on obesity may help to reduce breast cancer risk as well as having implications for the treatment of colorectal cancer. There are a lot of things that feed into the same model of resistant starch as a cancer-protective agent. Much of this information currently comes from rodent models and small clinical trials but the evidence is encouraging.

Higgins, Janine A., et al., Resistant starch. **Current Opinion in Gastroenterology,** ***2013; 29 (2): 190 DOI: 10.1097/MOG.0b013e32835b9aa3***

13. Referring Colorectal Cancer Patients to Genetic Counseling for Lynch Syndrome (Mar.13/13)

The most effective method for identifying patients with colorectal cancer who may have Lynch Syndrome was to send results of the microsatellite instability and immunohistochemistry tests directly to the colorectal surgeon and a genetic counselor, and for the counselor responsible to contact positive patients to recommend genetic counseling, according to the results of this study. The use of this approach resulted in a 100% referral rate for genetic counseling, with 71% of patients attending counseling and 66% undergoing genetic testing. Lynch syndrome is the most common adult-onset colorectal cancer syndrome, occurring in one in 35 colon cancer patients diagnosed. It confers an 85% lifetime risk of colorectal cancer (vs 5% in the general population), 40% endometrial cancer risk (vs 4% in the general population), and 10% ovarian cancer risk (vs 0.5% in the general population). In 2009, the *Evaluation of Genomic Applications in Practice and Prevention* recommended that all colorectal cancers be screened for Lynch Syndrome using microsatellite instability (MSI) and immunohistochemistry (IHC). However, methods for implementing this screening approach have not been studied. Cleveland Clinic has screened colorectal cancer specimens for Lynch Syndrome since 2004, using three methods in the last 8 years. This study examined the rate of referral to a genetic counselor, the rate of attendance to a genetic counselor, and the rate of genetic testing using three approaches:

Approach 1: Between January 2004 and July 2007, MSI and IHC results went only to the colorectal surgeon and not to a genetic counselor.

Approach 2: Between August 2007 and June 2008, both the surgeon and a genetic counselor received the results with the counselor e-mailing the surgeon with the patients identified as being appropriate for referral to genetic counseling.

Approach 3: After July 2008, the surgeon and the counselor received the results and the counselor contacted appropriate patients to facilitate referral to a genetic counselor.

At the end of the study period, 16% of patients screened for Lynch Syndrome had abnormal MSI/IHC results. Using approach 1, 55% of patients with abnormal results were referred for genetic counseling, with 32% of patients undergoing counseling and 26% of patients undergoing genetic testing.

"Implementing even the most rigorous research into routine clinical care is difficult, as approach 1 shows," study author said, noting that the results of approach 1 were "a shock." "Although the pathologists noted the results of the Lynch tumor screen in their pathology reports, only a small subset of screen positive patients were referred to geneticists by their surgeons of record," she said. In contrast, using approach 2, 82% of patients with abnormal MSI/IHC results were referred to counseling with 64% undergoing counseling. Forty-five percent of patients in this group underwent genetic testing. These are compared with a 100% referral rate, a 71% attendance rate and a 66% genetic testing rate seen with approach 3. "[Approach 3] takes away the onus of calling screen positive patients out of busy surgeons' hands and places the responsibility in a cancer genetic counselor's hands to scan the screen positive list and to reach out to those patients to arrange for their genetics care," study author said. These findings should help other facilities in the implementation of more widespread screening for Lynch Syndrome by allowing them to "leapfrog" to approach 3 used by the Cleveland Clinic.

Eng, Charis, et al., Implementation of universal microsatellite instability and immunohistochemistry screening for diagnosing lynch syndrome in a large academic medical center. JCO published online on February 11, 2013; DOI:10.1200/JCO.2012.45.1674.

NUTRITION & HEALTHY LIFESTYLE

14. Alcohol Causes Colorectal Cancer (Feb.19/13)

Alcohol consumption can increase risk of colorectal cancer, according to a review recently released in Current Nutrition Reports. Alcoholic beverages are recognized human carcinogens (cancer causing agents) by both the US National Toxicology Program and the International Agency for Research on Cancer. The review's author says that the evidence that alcohol intake is associated with colorectal cancer risk is convincing although it remains largely unknown how alcohol can cause colorectal cancer. Genetic polymorphisms (changes or differences in genetic material) are suggested to influence the effect of alcohol on colorectal cancer development. The author suggests that although it remains unknown how alcohol affects the risk of colorectal cancer risk, the avoidance of excess intake of this carcinogen can substantially reduce risk and burden of colorectal cancer induced by alcohol consumption. Other recent studies have shown that there is no safe threshold for alcohol consumption, meaning that drinking any amount of alcohol can increase risk of cancer. It is just that a higher intake leads to a higher risk.

http://www.foodconsumer.org/newsite/Nutrition/Food/alcohol_causes_colorectal_cancer_0219130730.html

15. Weight and Exercise Play Key Role in Colon Cancer Risk (Feb. 27/13)

Obesity increases a person's risk for a certain type of colorectal cancer, while exercise lowers the risk, according to this new study. Researchers analyzed data from women in the U.S. Nurses' Health Study and men in the Health Professionals Study to determine if there was a link between weight, exercise, and the risk for CTNNB1-positive or CTNNB1-negative colorectal cancer. CTNNB1 is a molecule implicated in cancer and obesity. A higher body-mass index, or BMI (a measurement of body fat based on height and weight), was associated with an increased risk of CTNNB1-negative colorectal cancer, while physical activity was associated with a lower risk. BMI and physical activity had no effect on the risk for CTNNB1-positive colorectal cancer, according to the study results. The results provide additional evidence for a causal role of obesity and a physically inactive lifestyle in a specific molecular subtype of colorectal cancer. If physicians are able to identify individuals who are prone to develop CTNNB1-negative cancer, then it would be possible to strongly recommend physical activity. The findings also suggest that CTNNB1 could be a potential target for drugs to prevent and treat colorectal cancer in certain patients.

Ogino, Shugi, et al., Prospective Analysis of Body Mass Index, Physical Activity, and Colorectal Cancer Risk Associated with β-Catenin (CTNNB1) Status. Cancer Research. March 1, 2013 73:1600-1610; Published OnlineFirst March 3, 2013; doi:10.1158/0008-5472.CAN-12-2276

16. Lifestyle Affects Colon Cancer Recurrence & Progression Risk (Feb. 26/13)

New evidence confirms that recurrence or progression of colon cancer is affected by daily dietary choices. A Western pattern diet, characterized by high intakes of meat**, fat, refined grains and sugar**, has been implicated as a risk factor for colon cancer, but little is known about its role in recurrence and survival of colon cancer. Researchers analyzed food intake among colon cancer patients and the results were published. Data was obtained by abstracting survival results and analyzing food frequency questionnaires (FFQs) completed by patients enrolled in the NCI-sponsored Cancer and Leukemia Group B (CALGB) 89803 trial. All participants in this multicenter study had stage III colon cancer with positive regional lymph nodes. Subjects had undergone a resection of the primary tumor within 56 days of completing the initial FFQ and were enrolled in chemotherapy treatment. The final sample size of 1,011 participants completed two surveys (the first upon enrollment and the second six months after completion of adjuvant therapy) that self-reported lifestyle habits and diet, in which they noted how often they consumed portions of specific foods. Researchers computed a glycemic load by multiplying the frequency and nature of carbohydrate consumption by glycemic index. The study end points were disease-free survival, occurrence of a new primary colon tumor or death from any cause. To avoid potential bias due to declining health, results from patients with a cancer recurrence or death within 90 days of completing the FFQ were excluded. Researchers sought to determine if certain dietary features, including high

glycemic load, fructose intake and carbohydrate intake affect colon cancer recurrence and survival. The negative association between diet and a disease-free state was heightened among those who were overweight or obese (body mass index ≥25 kg/m^2). Similar results were seen in patients with increased glycemic load and increased total carbohydrate intake. This study offers further evidence that dietary choices may affect colon cancer recurrence or progression.

Meyerhardt, Jeffrey, et al., Dietary Glycemic Load and Cancer Recurrence and Survival in Patients with Stage III Colon Cancer: Findings From CALGB 89803* Journal of the National Cancer Institute *2012;104:1702-1711

17. Job Stress Not Linked With Cancer Risk (Mar.13/13)

Job stress was not directly associated with the risks of lung, breast, colorectal, or prostate cancer in a large retrospective study. According to the study authors, work-related psychosocial stress is unlikely to be an important risk factor for these cancers. Thus, though reducing work stress would undoubtedly improve the psychological and physical well-being of the working individuals as well as the working population, it is unlikely to have an important impact on cancer burden at a population level. The study does not completely exonerate the role of stress in predisposing to cancer, claims one of the study authors. "For example, in a meta-analysis of different types of stress and risk of breast cancer, stress from adverse life events was consistently associated with an increased risk (Breast Cancer Res. 2011;13:208). ... In a French study, people with brain cancer were more likely to report adverse life events than controls without cancer, but there was no clear evidence for a difference in terms of stress at work between these groups (J. Neurooncol. 2011;103:307-16)." The review included 116,056 subjects who had participated in 10 different trials conducted in Denmark, Finland, and Sweden. The mean follow-up in these studies was 12 years, but follow-up ranged from 5-23 years. This long span is a particular strength of the review, the authors noted, "because most cancers have a latent period of years or even decades. If a true association between job strain and incident cancer existed because the physiological stress response has a role in cancer promotion or progression (for example, via the regulation of the inflammatory pathways), the follow-up periods in our analyses should have been long enough to detect such an association." At baseline, the subjects were a mean of 38 years old. Most (62%) were of normal weight. A quarter of the subjects smoked tobacco at baseline, while 10% were classified as heavy drinkers, defined as consuming at least 15 drinks per week for women and 22 drinks per week for men. Psychological stress at work was defined as a combination of high work demand and low control at the workplace. The results were examined as stress or no stress, and in quartiles of

- high-stress job (high demand/low control);
- active job (high demand/high control);
- passive job (low demand/low control); and
- low-strain job (low demand/high control).

The investigators also controlled for age, gender, socioeconomic position, body mass index, smoking, and alcohol intake. The overall rate of cancer was 5% (5,765). The largest proportion of these cancers was breast cancer (0.9% of the study cohort; 1,010), followed by prostate cancer (0.7%; 865), **colorectal cancer (0.5%; 522)**, and lung cancer (0.3%; 374). In the analysis of job stress/no job stress, there was no significant association with overall cancer risk. Nor were there significant associations between job stress and colorectal cancer, breast cancer, lung cancer, or prostate cancer. "There was also no clear evidence for an association between the categories of job strain and the risk of cancer," the authors wrote. The study "suggests that many of the previously reported associations ... between work-related stress and risk of cancer could have been influenced by chance, low power in some studies, different covariate adjustment, or residual confounding from possible unmeasured common causes of work stress and cancer. Such common causes could include shift work (for which there is some evidence of an association with risk of breast cancer) or other sources of stress, perhaps combined with one another."

Heikkila, Katriina, et al., Work stress and risk of cancer: meta analysis of 5700 incident cancer events in 116,000 european men and women. BMJ 2013;346:f165 (Published 07 February 2013)