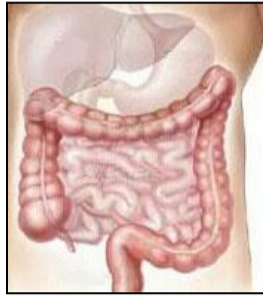


COLORECTAL CANCER RESEARCH Month Ending August 13, 2010



The following colorectal cancer research update extends from July 17 – August 13, 2010 inclusive and is intended for informational purposes only.

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1. New Recommendations for Erbitux Use (Jul. 16/10)

According to this study, the use of the drug cetuximab (erbitux) should be limited to stage IV colorectal cancer patients. Based on earlier studies, cetuximab is now indicated for treatment of patients with advanced colorectal cancer whose tumors do not have a mutation in the KRAS gene. KRAS is one of a series of genes along a pathway that can cause tumor cells to grow, divide and evade signals that shut the cells down causing their death. Based on the results in advanced disease, researchers had hoped to see similar benefits when cetuximab was added to a standard chemotherapy regimen in earlier stages of colon cancer. However, ongoing analysis during the clinical trial found that patients receiving the combination therapy had no significant improvement in survival compared to standard therapy. Cetuximab is a monoclonal antibody that inhibits epidermal growth factor receptor (EGFR) — a cell signaling pathway that contributes to tumor growth. The drug is given by intravenous infusion for treatment of metastatic colorectal cancer and head and neck cancer. Previously, researchers found that patients with a mutated KRAS gene — about 40% of those with metastatic colon cancer — do not respond to the EGFR inhibitors currently in use. However, the genetic test for KRAS mutation was not standard until this trial was well underway. Patients enrolled before KRAS testing were segmented from those in the rest of the study and analyzed separately. Researchers expected that patients with the genetic mutation would not respond to cetuximab, and that is what they found. Even the patients in the study whose tumors did not harbor the KRAS mutation did not benefit significantly from the combination therapy and the standard treatment proved to have the best results. They also found that the combination therapy was more toxic and the side effects of treatment — especially in older patients — negatively impacted their ability to complete the standard treatment. Researchers issued a recommendation that cetuximab should not be used in patients with stage III colon cancer. It remains a valuable tool in treating patients with advanced colorectal cancers whose tumors do not harbor a KRAS mutation and can either be administered as a single agent or with chemotherapy.

<http://www.news-medical.net/news/20100717/Cetuximab-recommended-for-colorectal-cancer-tumors-without-mutation-in-KRAS-gene.aspx?page=2>

2. Phase II Study Involving Irinotecan and S-1 (IRIS) in Advanced Colorectal Cancer (Jul. 21/10)

A combination of irinotecan with continuous infusional 5-fluorouracil (5-FU) is the standard treatment for advanced colorectal cancer. The aim of this study was to determine the efficacy and safety of combining irinotecan and S-1 (IRIS) in patients with advanced colorectal cancer. S-1 was given orally while irinotecan was administered via infusion. A total of 38 patients were enrolled. An intent-to-treat analysis showed a complete response and partial response to occur in 13.2% and 50.0%, respectively. The disease control rate was 84.2%. The median progression-free survival and overall survival were 10.0 months and 29.1 months, respectively. Researchers concluded IRIS is an effective, well tolerated and convenient treatment regimen for patients with advanced colorectal cancer.

Shiosawa, Manabu, et al., A phase II study of combination therapy with irinotecan and S-1 (IRIS) in patients with advanced colorectal cancer. Cancer Chemo and Pharma; DOI: 10.1007/s00280-010-1278-0

3. Evaluating Modafinil for Cancer-Related Fatigue (Jul. 23/10)

Cancer-related fatigue is a debilitating symptom affecting psychosocial functioning and quality of life in 70% to 100% of cancer patients during and after treatment. The authors examined the effect of 200 mg of modafinil daily on the severity of cancer-related fatigue. Modafinil is a stimulant often used in the treatment of various sleep disorders. Patients who reported fatigue were randomly assigned to receive either 200 mg of oral modafinil (Provigil) daily or a placebo. There were 631 patients (315 modafinil, 316 placebo) who provided evaluable data. Patients with severe baseline fatigue (n=458) benefited from modafinil, whereas patients with mild or moderate fatigue did not. Modafinil had no statistically significant effect on depression. Researchers concluded that modafinil may be useful in controlling cancer-related fatigue in patients who present with severe fatigue but is not useful in patients with mild or moderate fatigue.

Jean-Pierre, Pascal., et al., A phase III randomized, placebo-controlled double blind, clinical trial of the effect of modafinil on cancer related fatigue among 631 patients receiving chemotherapy. Cancer. 2010 Jul 15;116(14): pp. 3513-20.

4. 5FU-Hydrogel and Peritoneal Mets (Jul. 30/10)

Colorectal peritoneal carcinomatosis (CRPC) is a common form of metastatic disease occurring in the peritoneum (abdominal lining). Intraperitoneal chemotherapy is a preferable option for colorectal cancer and has been described extensively in previous updates. In this study, researchers reported that a new system, 5-FU-loaded hydrogel system, can improve the therapeutic effects of intraperitoneal chemotherapy. The biodegradable and temperature sensitive hydrogel was developed to load 5-FU. The hydrogel system is an injectable flowing solution at ambient temperature and forms a non-flowing gel depot at physiological temperature. 5-FU-hydrogel was subsequently injected into the abdominal cavity in mice with CT26 cancer cells peritoneal dissemination. The results showed that the hydrogel delivery system significantly inhibited the peritoneal dissemination and growth of CT26 cells. Furthermore,

intraperitoneal administration of the 5-FU-hydrogel was well tolerated and showed less toxicity. The data indicate that the 5-FU-hydrogel system can be considered as a new strategy for peritoneal carcinomatosis, and the hydrogel may provide a potential delivery system to load different chemotherapeutic drugs for peritoneal carcinomatosis of cancers.

Wang, Yongsheng, et al., 5FU hydrogel inhibits colorectal peritoneal carcinomatosis and tumor growth in mice. BMC Cancer. 2010, 10: 402

5. Clinical Trial Will Evaluate the Use of Aspirin in Helping to Fight Colorectal Cancer (Aug. 3/10)

The National Cancer Centre Singapore (NCCS) will lead a regional clinical trial to evaluate the effectiveness of Aspirin in reducing the risk of colorectal cancer recurrence following surgery and chemotherapy. NCCS has set up a network of 19 centres across Asia including Malaysia, Hong Kong, Indonesia, the Philippines, China and India, and more centres are currently lined up to join the study. After completion of standard surgery and chemotherapy, patients with high risk stage II or stage III colorectal cancer will be given either Aspirin or a placebo for a period of three years and be followed up intensively over a period of five years, for recurrence. Researchers warn patients against taking Aspirin outside of the clinical trial setting because the drug thins the blood and can increase one's risk of bleeding. Patients who wish to take Aspirin for colorectal cancer need to be closely monitored and consume it only under strict supervision.

<http://www.channelnewsasia.com/stories/singaporelocalnews/view/1073033/1.html>

6. Hormone Replacement Therapy Linked to Lower Risk of Certain Colon Cancers (Aug. 5/10)

The link between hormone replacement therapy (HRT) and reduced risk of distal (left sided) large bowel cancer in women was reported in this study. According to the results, longer duration of use of hormone replacement therapy is associated with an increased reduction of distal large bowel cancer incidence among women, regardless of race. However, oral contraceptives, when modern-day formulations are included, do not reduce the risk of distal large bowel cancer incidence for both Caucasian and African American women. Researchers concluded that the lower incidence rates of distal large bowel cancer in women who had undergone hormone replacement therapy support the protective role of female hormones.

Long, Millie D., et al., Hormone Replacement Therapy, oral contraceptive use and distal large bowel cancer: a population-based case-control study. Am J Gastroenterol. 2010 August; 105(8): pp. 1843–1850.

7. Avastin With Folfoxiri For First Line Treatment of Metastatic Colorectal Cancer (Aug. 10/10)

The FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinic acid) regimen has been shown to be better than FOLFIRI (fluorouracil, folinic acid, and irinotecan) in a phase 3 trial in patients with metastatic colorectal cancer. Results of various studies have shown that the addition of bevacizumab (avastin) to chemotherapy increases treatment efficacy. Researchers, therefore, assessed the safety and activity of the combination of FOLFOXIRI plus bevacizumab in patients with colorectal cancer. In a phase 2 study, patients (aged 18–75 years) with colorectal cancer, which was judged to be unresectable for metastatic disease, were given the combination of intravenous bevacizumab and intravenous FOLFOXIRI as first-line treatment in seven centres in Italy. Based on the results, investigators concluded that bevacizumab can be safely used with FOLFOXIRI without causing unforeseen adverse events. Treatment achieved promising results in terms of progression free survival (PFS – time before the disease got worse). A phase 3 study for the comparison of FOLFOXIRI plus bevacizumab with FOLFIRI plus bevacizumab is in progress.

Masi, Gianluca, et al., Bevacizumab with folfoxiri as first line treatment for metastatic colorectal cancer: a phase II trial. The Lancet Oncology. Early online publication. August 10, 2010. Doi: 10.1016/S1470-2045(10)70175-3

RADIATION / INTERVENTIONAL RADIOLOGY

8. Patients with Anal Cancer Get Breakthrough Treatment (Jul. 19/10)

The INTEGRIS Cancer Institute of Oklahoma and the ProCure Proton Therapy Center announce a breakthrough treatment approach for anal canal cancer. For the first time in the United States proton therapy is now being used to treat this type of cancer. In the past, patients with gastrointestinal cancers, specifically those in the pelvis, have rarely had proton therapy as an option because the required field size and depths were too large. By using protons and uniform scanning technology, these obstacles can now be overcome. The precision of proton therapy allows for the tumor to be treated with much greater accuracy, with less risk to healthy tissue permitting a more tolerable course of treatment for patients. Traditional forms of radiation therapy can be used to treat this type of cancer, but the dose to the intestines and bladder would be twice as high, a risk patients are unwilling to take. In addition to proton therapy, patients also receive chemotherapy. While treatment options for gastrointestinal cancers such as surgery, chemotherapy and traditional radiation therapy are available elsewhere, what sets this

campus apart from any other cancer treatment facility in the country is the ability to combine those treatment options with proton therapy, in a single location. With a multidisciplinary team of medical oncologists, radiation oncologists, radiologists, GI surgeons and gastroenterologists, patients and their families have access to a medical team that will map out all available treatment options. And because the entire treatment team is at one location, patients can receive all consultations and evaluations in one or two days, rather than waiting weeks between appointments."

<http://www.medicalnewstoday.com/articles/195140.php>

9. **Lack of Insurance Coverage Remains Obstacle To Accessing CT Colonography** (Jul.23 6/10)

A recent questionnaire submitted to a group of patients at one of the U.S.'s largest general hospitals suggests that a significant number of patients, who have previously refused colorectal cancer screening, are willing to undergo computed tomography colonography (CTC) (or virtual colonoscopy), but not willing to pay for the exam themselves when not covered by insurance, according to the results of this study. Noninvasive CTC is increasingly being considered for colorectal cancer screening. It uses CT imaging and computers to produce 2D and 3D images of the colon. Compared to conventional colonoscopies, CTC does not require sedation. The study included 68 patients who had been offered colorectal cancer screening. Patients participated in a questionnaire and were asked about their willingness to undergo CTC and about other relevant factors, such as fees. Patient's reasons for not being screened were also explored. After being informed about CTC screening, most (83%) patients stated they would be willing to undergo a CTC study, however, 70% stated they would not be willing to pay out-of-pocket fees if insurance did not cover the study. And even among the 30% who were willing to pay the fees, the average amount they were willing to pay (mean, \$244; median, \$150) was well below currently charged rates. Researchers concluded that after being informed about CTC as a screening technique for colorectal cancer, the majority of currently nonadherent patients stated that they would be willing to have a CTC screening study, suggesting that CTC availability could improve screening rates. However, the majority of participants were not willing to pay out-of-pocket expenses, and even among those who were willing, most were not willing to pay currently charged fees. The currently charged rate is between \$500 and \$1500.

Hur, Chin, et al., Analysis of Barriers to and Patients' Preferences for CT Colonography for Colorectal Cancer Screening in a Nonadherent Urban Population. American J of Roentgenology. 195: pp. 393-397

10. **Long Term Outcome in Patients with Complete Response to Chemoradiation for Rectal Cancer** (Aug. 10/10)

Locally advanced rectal cancer is usually treated with preoperative chemoradiation (chemotherapy plus radiation therapy). Studies have shown that after chemoradiation and surgery, 15—27% of the patients have no residual viable tumour at pathological examination, or better known as a pathological complete response (pCR). This study established whether patients with pCR have better long-term outcome than do those without pCR. All patients underwent chemoradiation and total mesorectal excision of their primary tumour. Primary outcome was 5-year disease-free survival. Researchers found that patients with pCR had a significantly increased probability of disease-free survival. They concluded that patients with pCR after chemoradiation have better long-term outcome than do those without pCR. pCR might be indicative of a prognostically favorable outcome with less propensity for local or distant recurrence and improved survival.

Maas, Monique, et al., Long term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. The Lancet Oncology. Early online publication, August 9, 2010. Doi: 10.1016/S1470-2045(10)70172-8

SCREENING

11. **Blood Test May Give Early Warning of Colorectal Cancer** (Aug. 5/10)

Careful attention to the results of routine blood tests may provide an early warning of potential colorectal cancer according to this study. Researchers claim signs of anemia may be a warning signal for this common form of cancer. People who have colorectal cancer typically have anemia, characterized by low levels of hemoglobin, the oxygen-carrying, iron-containing factor in red blood cells. Rather than be viewed as a symptom of active disease, however, researchers at Tel Aviv University have found that signs of anemia may serve as a screening tool for colorectal cancer. This would be a significant finding, as current screening methods are allowing polyps to be found earlier when the disease is easier to cure. The addition of another, more effective screening tool could make cancer detection even more efficient and ultimately result in saving more lives. Researchers evaluated blood test data spanning ten years from more than 3,000 individuals with colorectal cancer and compared them with 10,000 controls without the disease. They found that most patients who have colon cancer have a history of consistently declining hemoglobin levels up to four years before they are diagnosed with the disease.

This study represents the first time scientists have quantified the correlation between anemia and colorectal cancer and a decline in hemoglobin levels. Continuous declines in hemoglobin levels in individuals have gone largely unnoticed by clinicians, who typically look for large drops in blood test results. But this is not accurate enough. It is important to look at the continuing trend of each individual. If a person experiences a consistent decline relative to his own average level, it may be cause for concern. In this new study, participants who had colorectal cancer demonstrated a sharp drop in hemoglobin levels. However, because the declines were not outside what is considered to be normal, doctors had not suspected colorectal cancer was on the horizon. The study's authors point out that observing a gradual decline in hemoglobin levels is a screening tool that can be part of a typical physical examination. Compared with current testing for colorectal cancer, which is unpleasant and costly, a routine blood test is convenient, according to researchers. The next step is the creation of an algorithm that will automatically identify declining, "red flag" hemoglobin levels.

<http://www.aftau.org/site/News2?page=NewsArticle&id=12620>

12. DNA Test for Colorectal Cancer Diagnosis (Aug. 9/10)

A new generation of DNA tests for colorectal cancer seems likely to improve the detection both of cancers and of the precancerous polyps that precede them. The tests, if validated, could reduce the burden of disease substantially by detecting tumours at an early stage, including those not picked up by a colonoscopy. Colorectal cancers tend to grow slowly and are easily removed if caught early. But many people over 50 do not comply with the recommendation to have a colonoscopy — a time-consuming procedure in which a tube is threaded up the intestine — and even colonoscopies do not catch everything. Colon tumors provide considerable evidence of their presence by shedding blood and cells that are detectable in the stool. Tests for blood have reduced deaths from colorectal cancer only modestly, because they are not very sensitive to precancerous polyps, the stage at which cancer is best prevented. Researchers turned to measuring mutations in DNA after discovering the series of mutations by which a colon polyp advances to full cancer. But no single mutation predicts a patient's risk, and the mutation tests, though more accurate than the blood tests, have not been a decisive improvement. The new generation of tests being developed depends on a different process in cancer cells. All cells switch off the genes they do not need by attaching small chemicals called **methyl groups** to certain sites along their DNA. In cancer cells, there is generally less methylation than usual, except for certain regions of DNA where the methylation process is taken to excess, perhaps because the cells need to shut down tumour suppressor genes. These and other genes are highly methylated in colon tumors and other kinds of cancer. Exact Sciences, a company based in Madison, Wis., is developing a colon cancer test based on highly methylated DNA. Its researchers reported last month that by testing for methylated DNA at four markers, pieces of DNA drawn from specific genes, they could detect colon tumors and polyps, distinguishing them from normal tissue with 100% sensitivity and with no false positives. The tests of methylated DNA were performed directly on tumors and are expected to be less accurate in the real world, in which they would have to work in stool samples. Almost all of the DNA in stool is from bacteria, and the methylated DNA is a fraction of the 0.01% that is human DNA. But researchers believe the four-marker test, when applied to stool samples, would detect at least half of all precancerous polyps and 85 percent of actual cancers. Results of a trial now under way in 1,600 patients will be reported in October

<http://www.nytimes.com/2010/08/10/health/10cancer.html>

13. Belly Fat and Colorectal Cancer Screening (Aug. 12/10)

According to this study, a large waistline more than doubles the risk that people in their 40s will develop precancerous cells in the colon. The chances of finding abnormal cells during a screening test were just as good in younger men with too much belly fat as in slimmer men over 50. As a result, the researchers recommend lowering the age of colon cancer screening from 50 years to 45 in men with weight problems. The Korean researchers examined more than 1,700 men and women, aged 40 to 59, who had no signs of colon cancer and no family history for the disease. As part of their employer-provided health benefits, each participant in the study underwent screening colonoscopy. One in 40 of those younger than 50 years had late-stage polyps, but no one actually had colon cancer. By contrast, two of those over 50 did, and late-stage polyps were almost twice as common in this age group. To find a late-stage polyp, which may or may not turn into cancer, the researchers calculated they would have to test 23 of the people who were in their 50s. That number was the same in younger people who had large waistlines, and even lower in those with metabolic syndrome, a combination of risk factors including belly fat, high blood pressure and high blood sugar. The paper substantiates what researchers have suspected, that people who are obese have higher risk of colon cancer. During colonoscopy, the doctor inserts a slim, flexible tube into the rectum. A camera at the tip shows the inside of the gut, so that unusual cell clumps can be found and removed. Colonoscopy, used in millions every year, is just one of many methods to detect abnormalities.

Kim, Hwan, et al., Prevalence and risk of colorectal neoplasms in asymptomatic, average risk screenees 40 to 49 years of age. Gastro Endos; doi: 10.1016/j.gie.2010.06.022

14. Colonoscopies Performed by Primary Care Physicians (Aug. 11/10)

According to the results of this study, screening colonoscopies performed by primary-care physicians under strict protocols are as safe and effective as those performed by specialists. Researchers found performance quality indicators and lesion detection rates in screening colonoscopies by primary-care doctors are comparable to documented rates for experienced gastroenterologists. 10,958 colonoscopies by 51 primary-care doctors in the U.S. included in the study were performed under strict protocols to ensure patient safety. The tests were performed at a licensed ambulatory surgery center with specialists (gastroenterologists or GI surgeons) available in case there were technical difficulties in completing the procedure, in removing large polyps or in managing any major complications that can occasionally arise with this procedure. The study looked at colonoscopies performed at the S.C. Medical Endoscopy Center in Columbia. The colonoscopies were performed by a primary-care physician assisted by two technicians and a nurse anesthetist. A specialist was available on site. The study showed the colonoscopies met or exceeded the standards set by gastroenterologists. The researchers emphasized that primary-care physicians must receive training from gastroenterologists or colorectal specialists to be competent and effective. They also must develop close partnerships with specialists and have specialized screening equipment and anesthetists available. Researchers claimed that these are replicable processes by which a patient may receive the same screening results with primary-care doctors if those doctors follow the specialists' guidelines and receive specialist training.

Xirasagar, Sudha, et al., quality and safety of screening colonoscopies performed by primary care physicians with standby specialist support. Medical Care. August 2010; Vol. 48, Issue 8: pp. 703-709

PSYCHO-SOCIAL

15. End of Life Care (Jul. 30/10)

Planning end of life care can make it easier to cope with a stage 4 colorectal cancer diagnosis. People with stage 4 cancer can live months and even years, but stage 4 cancers may often not be curable. Knowing this, it is important to ensure wishes for end of life care are known. The following options will assist in securing the care needed.

i. Advance Directives

An advance directive is a document that describes what type of medical care you would like if you become unable to make decisions for yourself. The best advance directives are detailed. They describe the kind of treatment you want depending on how sick you are. For example, the document would describe what kind of care you want if you have an illness from which you are unlikely to recover. An advance directive also lets you specify the care you want if you are in a coma or permanently unconscious. Advance directives let you tell your doctor which treatments you do or don't want in various circumstances. An advance directive also lets you indicate that you *do* want a certain treatment, no matter how sick you are. You can ask your doctor or nurse for information about advance directives.

ii. Living Will

A living will is a type of advance directive. Some types of advance directives allow you to select a person who can make health care decisions for you if you are unable to do so yourself; however, a living will does not allow you to select a person to make decisions for you.

iii. Health Care Proxy

A health care proxy is a person you designate to make medical decisions for you in the event that you can't do so yourself. You can fill out a document that provides information to your health care team regarding who you have appointed as your health care proxy. Designating a health care proxy is another type of advance directive. It's important to remember that this person can only make decisions about your health care if you can't do this yourself. If you are able to make decisions, a health care proxy cannot overrule your decisions about what care is best for you.

iv. Medical Power of Attorney

Medical power of attorney is another form of advance directive. This is different from a health care proxy. When you designate someone to have medical power of attorney for you, you give that person the ability to perform legal transactions on your behalf if you are medically incapacitated. For example, if you are in a coma or unconscious, the person you've designated to have medical power of attorney for you can complete bank transactions, sign cheques, apply for disability, write cheques to pay your rent or utilities, and perform other financial transactions for you. If you become able to complete these activities yourself again in the future, the person who is your

medical power of attorney cannot overrule your decisions. You always have the final say on your health care and your legal transactions if you are able to make these decisions for yourself.

<http://coloncancer.about.com/od/additionalresources/a/End-Of-Life-Care.htm>

OTHER

16. Uninsured Rectal Cancer Patients More Likely to Die (Jul. 22/10)

Rectal cancer patients without insurance or covered by U.S. based health plans are almost twice as likely to die within five years as those privately insured. Not only are they diagnosed at a later stage, but fewer receive recommended treatments at every stage. More than half of the difference between patients with private insurance and those without was due to differences in how early they were diagnosed and whether or not they got standard treatment. Researchers looked at information to study insurance and other factors related to survival among 19,154 rectal cancer patients aged 18 to 64 years old. They analyzed the impact of insurance, age, sex, race and ethnicity, neighborhood education and income levels, cancer treatment facility type, stage, pathology features, and treatment on survival at five years. Rectal cancer patients were diagnosed between 1998 and 2002, and their progress was followed until 2007. The following results were reported:

- Uninsured patients were diagnosed at Stage I (17.6%) less often than those with private insurance (31%).
- Uninsured were diagnosed at late Stage IV (22.5%) more often than privately insured (13.8%).
- Uninsured were twice as likely not to have a high school diploma (38.9% versus 19.9%) and be poor (44.8% vs. 24.1%).
- Patients with private insurance were more likely to be treated in comprehensive community cancer centers, while patients with no insurance were more likely to be treated in teaching/research hospitals.

And the following differences in standard treatment were observed:

- Stage I: 95.1% of private patients had surgery with or without chemo/radiation compared to 83.4% of uninsured.
- Stage II: 91.4% of privately insured had recommended surgery with or without chemo/radiation while 79.4% of uninsured did. 7.7% of private patients had chemo/radiation but no surgery compared to 19.2% of uninsured.
- Stage III: 4.7% of private patients had chemo/radiation without surgery while twice as many (9.6%) of uninsured patients received this substandard treatment.
- Stage IV: More than 3 times as many uninsured patients (14.8%) had no treatment at all compared to 4.4% of those with insurance. Again, uninsured patients received less surgery (42.2%) than those with insurance coverage (60%).

Researchers' main finding that most of the excess mortality seen among Medicaid-insured and uninsured patients was explained by 2 modifiable factors (stage and treatment) suggests that improving insurance coverage and reducing cost-related barriers to primary care, CRC screening, and high-quality treatment would have a major impact on CRC survival disparities.

Robbins, Anthony, et al., Insurance status and survival disparities among nonelderly rectal cancer patients in the National Cancer Data Base. Cancer; early online edition. Doi: 10.1002/cncr.25317

17. Lynch Syndrome and Breast Cancer (Jul.30/10)

Although breast cancer has not traditionally been considered one of the cancers associated with Lynch syndrome, evidence is building that there might be a link. Breast cancer may actually be within the spectrum of Lynch cancers. An Australian team reviewing the pathology of breast cancers in women who carried a mutation for Lynch syndrome (hereditary non-polyposis colon cancer) found that half of the breast tumors were mismatch repair deficient — a hallmark of Lynch cancers. The team found 107 cases of breast cancer and 90 families in the Colorectal Cancer Family Registry where

- both breast and colon cancer co-occurred
- families had at least one colorectal cancer occurring before age 50
- breast tissue was available in the tissue bank for mismatch repair (MMR) testing

Among those breast cancers, 35 women with a Lynch mutation had been diagnosed with breast cancer. Of these, 18 (51%) showed deficient mismatch repair and testing found proteins missing that were the same as the family mutation. Researchers concluded: Mismatch repair deficiency was identified in 51% of breast cancers arising in known mutation carriers. Breast cancer therefore may represent a valid tissue option for the detection of MMR deficiency in which spectrum tumors are lacking.

18. Slowing Cancer with Alphavirus-based Vaccine (Aug. 3/10)

An experimental vaccine based on a virus that causes encephalitis (inflammation of the brain usually caused by a virus) in the wild appears to block tumor growth in some cases of advanced cancer, including colorectal cancer, according to researchers at Duke University Medical Center. Scientists say the vaccine is able to stimulate an immune response, even in the face of profound immune system suppression, a condition most patients with advanced cancer experience. Scientists removed the genes that enable the Venezuelan equine encephalitis virus -- an alphavirus -- to replicate itself, and replaced them with genes that make the biomarker CEA, present in many malignant colon, breast and lung cells. Alphaviruses have been used before in designing treatments for infectious diseases, but this is the first time one has been used in patients with cancer. The Phase I/II study included 28 patients with advanced cases of lung, colon, breast, appendix or pancreatic cancers who had already been treated with multiple courses of chemotherapy, but whose cancers kept coming back. Cancer vaccines, unlike traditional vaccines, are designed to boost the body's own immune system to recognize and destroy tumors, not prevent disease. Scientists often use genetically altered viruses as vaccines, stripping the virus of any harmful parts and inserting genes related to their anticancer strategy. But in many cases, the immune system still sees the incoming virus as a foreign invader and springs into action, generating antibodies and T cells that destroy it before it has a chance to do any good. Based on earlier research, investigators at Duke believed that by using the alphavirus for Venezuelan equine encephalitis as a carrier they might be able to thwart that response. The beauty of alphaviruses is that they are naturally attracted to dendritic cells, cells that stimulate the production of large numbers of T cells and antibodies. Essentially, researchers are hoping that once infected, the dendritic cells would activate T cells and antibodies to go after anything that had the tumor antigen CEA on it -- in this case, the quickly growing cancer cells. At the end of the study, two patients with no evidence of disease remained in remission; two patients were able to maintain stable disease, and one patient with pancreatic cancer saw a lesion in his liver disappear. The other patients in the trial did not respond to the therapy. These were patients with very advanced disease that nothing else had been able to stop. Researchers believe that in this small number of patients, the vaccine was able to stimulate the body's defense system to destroy significant numbers of cancer cells despite the presence of an army of neutralizing antibodies and regulatory T cells. Those who seemed to benefit the most were those who had the smallest amount of tumor. Because of this, the team is planning future trials that will test the vaccine in people with cancers that have been removed, but who are high risk of recurrence. Other trials will couple the vaccine with additional immune system stimulants such as interleukin-12 that may make the vaccine more powerful.

Morse, Michael, et al., An alphavirus vector overcomes the presence of neutralizing antibodies and elevated numbers of Tregs to induce immune responses in humans with advanced cancer. *Journal of Clinical Investigation*. doi:10.1172/JCI42672.

19. Dealing with Alternative Cancer Therapies (Aug. 2/10)

This study tackles the topic of doctor-patient communication about complementary and alternative medicine. This includes things like dietary supplements, massage, acupuncture, meditation, and more. The paper highlights why talking to your doctor about alternative medicine treatments is critical to your cancer care. Some of the reasons why this is so vital include:

- Many complementary and alternative treatments don't have clear evidence of effectiveness. It can be hard for the average person to sort through which alternative therapies may help and which aren't worth taking the time to try.
- These treatments may cause harm when mixed with certain types of conventional cancer treatments. They need to be considered on a case-by-case basis to ensure they are safe in any given situation.
- Even if a treatment looks promising for one type of cancer, it might not be right for you. Sometimes, it can take a person with medical training to sort out these differences.
- Many types of complementary and alternative medicine cost money. It is helpful to know if a treatment is likely to be helpful for you before investing your money into it. This is especially true for people who have hefty co-pays or health insurance that doesn't cover all treatment costs. Cancer treatment can put a family under a great deal of financial stress.

About.com has created a section containing information on why you should discuss this topic with your medical team and *how* to bring it up with your doctor. It can be accessed at <http://coloncancer.about.com/od/coloncancertreatment/a/Talk-To-Your-Doctor-About-Alternative-Cancer-Therapies.htm>

<http://coloncancer.about.com/b/2010/08/02/with-alternative-cancer-therapies-do-ask-do-tell.htm>

20. Outcomes for Colorectal Cancer Patients whose Metastatic Disease is Identified Synchronously vs. Metachronously (Aug. 10/10)

Synchronous metastases (metastatic disease identified at the same time as the primary tumour) of colorectal cancer (CRC) are considered to be of worse prognostic value compared with metachronous (metastatic disease identified after the primary tumour) metastases, but only few and conflicting data have been reported on this issue. Researchers retrospectively investigated patient demographics, primary tumour characteristics and overall survival (OS) in 550 advanced CRC patients with metachronous vs synchronous metastases. For this purpose only patients with a prior resection of the primary tumour were considered. Despite some unfavourable features in patients with synchronous metastases with a resected primary tumour compared to patients with metachronous metastases, no difference in the median OS was observed. Possible explanations include a (partial) chemoresistance in patients with metachronous disease because of previous adjuvant treatment, whereas differences between the two groups in screening procedures resulting in a lead time bias to diagnosis or in prognostic molecular markers remain speculative. Investigators concluded that survival was not significantly different between patients with colorectal cancer who had synchronous or metachronous metastases in this study of 550 patients.

Mekenkamp, LJM, et al., Clinicopathological features and outcome in advanced colorectal cancer patients with synchronous vs. metachronous metastases. British J of Cancer, 2010. Vol. 103, pp. 103159-164

NUTRITION & HEALTHY LIFESTYLE

21. Leptin May Promote Colorectal Cancer (Jul. 21/10)

While researchers have known that obesity increases the risk for the development of colorectal cancer, the underlying molecular mechanisms have remained unclear. Now, for the first time, a collaborative study of researchers have found that an increase in leptin, a hormone that is normally increased in obese or overweight individuals, may promote colorectal cancer by activating colorectal cancer stem cells. Cancer stem cells constitute a small sub-fraction of tumor cells that are characterized by long lifespan and capacity for self-renewal, and are responsible for tumor development, resistance to treatments and cancer recurrence. In colon cancer, leptin is able to increase the growth, survival, and resistance to certain chemotherapy treatments in this key cell population. Leptin, a fat tissue-derived hormone regulating appetite and energy balance in the brain, also controls many physiological and pathological processes in peripheral organs, including carcinogenesis – the development of cancer. Colon cancer has increased in developed countries, possibly due to sedentary lifestyles and high caloric diets. Prior research has linked obesity to colorectal cancer risk by .4-1.0 fold in men and up to 2.0 fold in premenopausal women. Since targeting cancer stem cells may be a relevant strategy to improve clinical outcomes, interfering with leptin signaling by targeting leptin receptors might become a novel attractive option for colorectal cancer treatment, particularly in obese patients. It is important to consider that cancer stem cells have been identified in several human malignancies. Understanding how cancer stem cells interact with a tumor environment, including hormones like leptin, is likely to have significant implications for treatment management of different cancer types in human patients. Researchers hope to not only test the effects of leptin compounds on colon cancer stem cells but also to study the results of leptin stimulation on cancer stem cells isolated in other cancer tissues.

Bartucci, Monica, et al., Obesity hormone leptin induces growth and interferes with Cytotoxic effects of 5FU in colorectal tumor stem cells. Endocrine-Related Cancer (2010); online edition. DOI: 10.1677/ERC-10-0083

22. Sitting for Extended Periods of Time is Unhealthy (Aug. 4/10)

Researchers followed more than 123,000 men and women for 14 years to study the effect of sitting during leisure time on risk of death **from cancer**, heart disease, and other causes. Leisure time is any time you aren't working, such as during the evenings or on weekends if you work a typical 9-5 job. The findings are startling. Over the course of the study, the researchers found:

- **Women** who sat for 6 or more hours per day during leisure time had 40% higher rate of death than women sitting less than 3 hours daily.
- **Men** who sat for 6 or more hours per day during leisure time had 20% higher rate of death than men sitting less than 3 hours daily.
- Sitting for 6 or more hours per day increased the death rate by 94% in the **least active women** compared to more active women.
- Sitting for 6 or more hours per day increased the death rate by 48% in the **least active men** compared to more active men.
- Deaths due to both cancer and heart disease were increased in those sitting for 6+ hours of their leisure time every day.

Note also that it wasn't just that sitting leads to not enough exercise. The researchers point out that sitting itself is detrimental. Even among people who regularly exercise, say, by taking a walk or hitting the gym, sitting damages health. But it's much worse if you don't exercise. The study authors conclude that people who sit a lot should be encouraged to stand up and walk around throughout the day to get more physical activity. It's important to limit long periods of sitting. And don't forget about getting up at work. If you have a desk job that ties you to the computer most of the day, make it a point to avoid sitting constantly.

Stand up every time your phone rings. Even if you sit right back down, just getting up gets your blood flowing. Walk to ask your coworker a question instead of emailing. Take a 3 minute, mid-morning break to do a lap or two around the cubicle farm. Of course, it's even better if you can add in some structured exercise too. But even if you can't, just moving more will help you stay healthier. It's enough to get me to stand up and stretch for a couple of minutes. Even taking the stairs instead of the elevator or taking a 10 minute walk a couple of times per day is enough to help your heart and ward off cancer. ANY movement you get is better than none.

Patel, Alpa, et al., Leisure Time Spent Sitting in relation to total mortality in a prospective cohort of US adults. Amer J of Epidemiology. Online edition: doi: 10.1093/aje/kwq155

23. **Colorectal Cancer and Meat** (Aug. 10/10)

Several studies have found a connection between eating red and processed meat and colorectal cancer. But the reason for that connection hasn't been clear. To answer the question, researchers collected detailed information about the type of meat eaten by a large group of over 300,000 men and women and how the meat was cooked. Linking that information to data on meat iron content, chemicals used in processing meat, and chemicals produced when meat is cooked at high temperatures, they were able to find that heme iron, nitrates and nitrites, and *heterocyclic amines (HCAs)* from high-temperature cooking increase risk for colon and rectal cancer. Among 300,948 patients enrolled in a large, prospective trial, 2,719 developed colorectal cancer. When researchers ranked diets from those who ate the least red and processed meat to those who ate the most, they found:

- Heme iron was associated with a 13% increase in risk.
- Nitrates from processed meats increased risk by 16%.
- HCAs produced during high temperature cooking raised risk by 19%.

Generally, risks were higher for rectal cancer than for colon cancer, with the exception HCA proteins, which only increased colon cancer risk.

- Heme iron is available in the diet from meat, poultry and fish. Nonheme iron comes from plants, including lentils and beans. It is also added to enriched cereals, flour, and grain.
- Nitrates and nitrites are used to process meat into bacon, hot dogs, and sausage.
- HCAs are produced during high temperature cooking like grilling.

Researchers concluded that they found a positive association for red and processed meat intake and colorectal cancer; heme iron, nitrate/nitrite, and heterocyclic amines from meat which may explain the associations.

Cross, Amanda, et al., A large prospective study of meat consumption and colorectal cancer risk: an investigation of potential mechanisms underlying this association. Cancer Res. Vol. 70, No. 6: pp. 2406-14

24. **Coffee Consumption and Colorectal Cancer** (Aug. 12/10)

In this study, a meta-analysis of case-control studies on coffee consumption and colorectal cancer risk was conducted. Twenty-four eligible studies published before May 2010 were identified, including a total of 14,846 cases of colorectal, colon or rectal cancer. The results of this meta-analysis of case-control studies suggest a moderate favorable effect of coffee consumption on colorectal cancer risk. It may reflect a real protection but also partly or largely be due to reverse causation, i.e. decreased coffee consumption among cases following the onset of bowel symptoms.

Galeone, Carlotta, et al., Coffee consumption and risk of colorectal cancer: a meta analysis of case control studies. Cancer Causes and Control. DOI: 10.1007/s10552-010-9623-5

25. **Vitamin D and Colorectal Cancer** (Aug. 13/10)

Increased blood levels of vitamin D may reduce the risk of colorectal cancer by 40% according to the results of this study. Scientists report that the potential benefits of the sunshine vitamin were even greater when people were also taking non-steroidal anti-inflammatory drugs (NSAIDs). The results, echo those of a large European study published earlier this year in the *British Medical Journal*, which was said to be the largest of its kind to date. Scientists correlated blood levels of vitamin D3 - 25-hydroxyvitamin D3 (25(OH)D3) – against colorectal cancer risk in 616 people with colorectal cancer and 770 polyp-free controls. Researchers reported that: “Higher circulating 25(OH)D3 concentrations were statistically significantly associated with decreased colorectal adenoma risk”. In people using NSAIDs, the potential risk reduction of higher vitamin D levels was increased to 66%, added the researchers. “These findings support the hypothesis that greater vitamin D exposure may reduce the risk of colorectal adenoma and suggest that it may do so more strongly in combination with anti-inflammatory agents,” concluded the scientists. Vitamin D refers to two biologically inactive precursors - D3, also known as cholecalciferol, and D2, also known as ergocalciferol. The former, produced in the skin on exposure to UVB radiation (290 to 320 nm), is said to be more bioactive. Both D3 and D2 precursors are hydroxylated in the liver and kidneys to form 25-hydroxyvitamin D (25(OH)D), the non-active 'storage'

form, and 1,25-dihydroxyvitamin D (1,25(OH)₂D), the biologically active form that is tightly controlled by the body. While our bodies do manufacture vitamin D on exposure to sunshine, the levels in some northern countries are so weak during the winter months that our body makes no vitamin D at all, meaning that dietary supplements and fortified foods are seen by many as the best way to boost intakes of vitamin D.

Fedirko, V. et al., Blood 25-Hydroxyvitamin D3 Concentrations and Incident Sporadic Colorectal Adenoma Risk: A Pooled Case-Control Study. American Journal of Epidemiology. Published online ahead of print, doi:10.1093/aje/kwq157