COLORECTAL CANCER ASSOCIATION OF CANADA

COLORECTAL CANCER RESEARCH
Week Ending October 17, 2008

The following colorectal cancer research update extends from October 4 – October 17, 2008 inclusive and is intended for informational purposes only.

ENCOURAGING

Half of Cancer Patients Survive (Oct. 16/08)

One in three men and one in four women get cancer throughout their lives and half of them overcome the disease, according to cancer statistics for 2003 to 2005 and the five year survival rate of cancer patients released on Wednesday by the Korea Central Cancer Registry under the Ministry for Health, Welfare and Family Affairs. The five year survival rate of cancer patients exceeded 50% for the first time. Between 2001 and 2005 it was 52.2%, a whopping 11% point jump from 41.2% between 1993 and 1995. The 5 year survival rate for five cancers (gastric, liver, **colorectal**, cervical and breast cancer), for which the government is trying to promote early testing, jumped by 10.6% points from 45.7% to 56.3%. Doctors view 5 year survival as a full recovery. Park Eun-cheol, a director of national cancer control programs, said a rising awareness of early diagnosis along with medical improvements gives cancer patients hope that they are 50% likely to survive.

http://english.chosun.com/cgi-bin/printNews?id=200810160008

DRUGS

1. **Arterial Hypertension Clue to Better Outcomes with Avastin** (Oct. 12/08)

Patients who developed hypertension (high blood pressure) with avastin had better response to treatment for colorectal cancer. More had tumors shrink, and it took significantly longer for their cancer to advance. In a small Italian study, researchers measured blood pressure in 39 patients receiving Avastin along with irinotecan and 5FU for the initial treatment of colorectal cancer. 8 patients experienced grade 2 or 3 hypertension, meaning a systolic pressure ranging from 150mm/Hg to over 180mm/Hg. Of those 8 patients, 6 had tumours shrink. On the other hand, only 10 of the 31 patients without an increase in blood pressure had partial responses to treatment. Median time before cancer got worse was 14.5 months for patients with hypertension compared to 3.1 months for those who didn't have high blood pressure. Those without hypertension lived a median of 15.1 months, but median survival time hasn't yet been calculated for patients who responded to avastin with an increase in blood pressure. Dr. Mario Scartozzi and his colleagues concluded: Our data indicate that avastin-induced hypertension may represent an interesting prognostic factor for clinical outcome in advanced colorectal cancer patients receiving first-line bevacizumab.

Scartozzi, M, et al., Arterial Hypertension correlates with clinical outcome in colorectal cancer patients treated with first-line bevacizumab. Annals of Oncology. Advance Access: October 7, 2008

2. **Biothera Completes Enrollment of First Arm of Metastatic Colorectal Cancer Trial** (Oct. 7/08)

Biothera, an immune health company, has completed enrollment in the first arm of its metastatic colorectal cancer trial from July. The dual arm trial is evaluating the combination therapy of Imprime PGG, the company's lead drug candidate, and erbitux, a monoclonal antibody, with or without chemo (irinotecan). The first arm of the clinical trial will assess the safety and efficacy of various dose levels of Imprime PGG in combination with erbitux and irinotecan. The second arm will evaluate Imprime PGG and erbitux alone. This phase Ib/IIa mcrc trial is an open-label, multicenter study in Asia. The first arm of the trial should be completed by the end of 2008. Imprime PGG has already demonstrated a strong safety profile in 4 clinical trials. Imprime PGG is a novel immunotherapy that can enhance the immune response against a number of disease indications. It works in concert with anti-tumour monoclonal antibodies to activate a large population of the body's immune cells (neutrophils) to kill cancer cells. Unlike other drugs that trigger a broad innate immune response, Imprime PGG selectively activates immune cells without inducing pro-inflammatory cytokines, thereby reducing potential side effects from the Imprime PGG. Imprime PGG has the potential to improve patient response rates for existing monoclonal antibody therapies in approved indications, create new indications for these drugs and enhance the efficacy of development –stage monoclonal antibody drugs.

www.marketwatch.com/news/story/biothera

RADIOLOGY

3. Trial Finds Virtual Colonoscopy Comparable to Standard Colonoscopy (Oct. 8/08)

A large, multicenter clinical trial has revealed that computed tomographic (CT) colonography (virtual colonoscopy) is on par with standard colonoscopy for detecting cancer and precancerous polyps. The American College of Radiology Imaging Network (ACRIN) National CT Colonography Trial enrolled more than 2,600 asymptomatic adults aged 50 years or older at 15 sites nationwide. Participants had a CT colonography followed by a colonoscopy, with 99% of both exams performed on the same day. The investigators found that 90% of polyps 10 mm or larger in diameter were detected by CT colonography. Smaller polyps (6 mm or larger in diameter) were detected by CT colonography with 78% accuracy. CT colonography used virtual reality technology that permits a thorough and minimally invasive evaluation of the entire colon and rectum. A small, flexible tube is passed 2 inches into the rectum to allow air to be gently pumped into the colon in order to distend the colon to eliminate any folds that might obscure polyps from the physician's view. A CT scan is then performed to generate a 3D model of the abdomen and pelvis, which the radiologist uses to view the bowel in a way that simulates traveling down the colon.

Johnson CD, et al., New England Journal of Medicine. 2008; 359 (12): 1207-1217

4. Study Confirms Colonoscopy Associated with Reduced Colorectal Cancer Incidence (Oct. 5/08)

Patients who undergo a complete negative colonoscopy have a reduced incidence of colorectal cancer, confirms a study performed at the University of Toronto and published in Clinical Gastroenterology and Hepatology. However, in the proximal colon (right side), the incidence reduction of colorectal cancer following complete negative colonoscopy differs in magnitude and timing. The reduction of colorectal cancer is observed in about half of the 14 follow-up years and for the most part occurs after just seven years of follow-up. The study raises a question about the effectiveness of colonoscopy in usual clinical practice, as claimed by Linda Rabeneck of the University of Toronto and Institute for Clinical Evaluative Sciences in Toronto and lead investigator of the study. The findings suggest that the effectiveness of colonoscopy is reduced for cancers arising in the proximal colon. Whether this is due to colonoscopy quality or whether it is due to tumor biology is the key issue that needs to be addressed. The relative rate of colorectal cancer overall and the relative rate of distal (left sided) colorectal cancer in the study group remained significantly lower than the control population. The relative rate of proximal (right sided) colorectal cancer was significantly lower than the control population in half of the follow-up years, mainly after seven years of follow-up.

Rabeneck, Linda, et al., Risk of Developing Proximal vs Distal Colorectal Cancer After a Negative Colonoscopy: A population Based Study. Clinical Gastroenterology and Hepatology. October 2008 (vol 6, issue 10) pp.1063-1064

SURGICAL

5. Mayo Clinic Estimates New, Tiny, Super-sensitive Probe Could Cut Colon Polyp Removal In Half (Oct. 8/08)

Based on results of a landmark study, researchers at Mayo Clinic's Florida campus see a future in which virtual biopsies will eliminate the need to remove colon polyps that are not cancerous or will not morph into the disease. Researchers found that the system, known as probe-based confocal laser endomicroscopy (pCLE), was 90% accurate in identifying benign or harmless polyps in patients. With further tweaking, the researchers believe pCLE can reach about 100% accuracy. The goal is to remove only cancerous or precancerous polyps from patients during a colonoscopy and the lead investigator believes they are close to doing that. The pCLE system is a fiber-optic probe 2 mm in diameter that can be passed through a normal endoscope and can see structures as small as 1 micron such as single cells or the nucleus within a cell. This is essentially a miniaturized microscope that can be placed inside the body, so the tissue doesn't need to be removed and placed under a traditional microscope. The pCLE system, which was developed by Mauna Kea Technologies (Paris, France), was tested against the Fujinon color enhancement system (FICE), which uses optical filters to look at a larger area of tissue. "This is like looking at the forest using FICE or the trees with pLCE," Dr. Wallace says. A total of 57 polyps from 38 patients were examined. The FICE technique correctly diagnosed 41 of 57 polyps as benign, whereas pLCE picked up 51 of the benign lesions. The researchers believe

that the best use of these advanced technologies is to use FICE to provide a first look at suspicious areas of a colon during a colonoscopy and then to use pCLE to zero in on polyps in question.

www.medicalnewstoday.com/news/october8,2008

OTHER

6. Risk of Colon Cancer Associated with Genetic Variants (Oct. 8/08)

Genetic changes in the surrounding region of the ADIPQ gene are associated with a decrease in the risk of developing colorectal cancer. Results such as these may aid in the understanding of genetic risk of various cancers, including colorectal cancer, ultimately changing the way in which cancer is managed. Researchers from the University of Alabama recently conducted a clinical study to evaluate alterations of the adinopectin (ADIPOQ) and adinopectin receptor 1 (ADIPQR1) genes and their potential relationship to colorectal cancer. These genes are involved in the pathway of adinopectin, a hormone secreted by fat (adipose tissue) that plays an important role in the body's regulation of insulin. Adinopectin has demonstrated a relationship with colorectal cancer; specifically, lower levels of adinopectin are associated with an increased risk of developing colorectal cancer and vice versa. Individuals who are obese tend to have lower levels of adinopectin, supporting data indicating that obesity is linked to a higher risk of developing colorectal cancer. Researchers conducted 2 small studies evaluating the ADIPOQ and ADIPOR1 genes and risk of crc. The first study included 41 patients who had been diagnosed with crc and 658 healthy patients; both groups were of Jewish ancestry from New York. The second study included 199 patients who had been diagnosed with crc and 199 healthy individuals. A specific alteration referred to as the single nucleotide polymorphism (SNP) flanking the ADIPOQ gene was associated with a significant decrease in the risk of crc. Results from the 2 studies combined showed that the SNP of the ADIPOQ gene was associated with an approximate 25% reduced risk of developing crc.

Kaklamani V, et al., Variantss of the adiponectin and adiponectin receptor 1 genes and colorectal cancer risk. J of the American Medical Association. 2008; 300: 1523-1531.

7. United States Preventive Task Force Provides Recommendations for Colorectal Cancer Screening (Oct. 10/ 08)

The United States Preventive Services Task Force (USPSTF) – a panel of general care experts who provide recommendations for treatment and prevention of certain diseases – has recently issued recommendations for the screening of colorectal cancer. Recommendations for the screening of colorectal cancer include screening initiation at the age of 50 years for all individuals, or younger for those at a high risk for developing the disease. Because colorectal cancer is a type of cancer that is highly curable in early stages, universal screening of individuals remains of utmost importance in order to improve overall outcomes for the disease. For the first time, the USPSTF has recommended changes to screening for crc as well as additions to the historic recommendations.

a. Individuals aged 50-75 years should undergo screening for crc with a colonoscopy, sigmoidoscopy, or fecal occult blood test (FOBT).
b. Patients between the ages of 75 and 85 should consider crc screening only if they are likely to live for at least another 10 years.
c. Individuals over the age of 85 should not undergo crc screening.
d. Results from a virtual colonoscopy or DNA-based stool testing do not yet provide adequate information to fully understand the clinical role of these tests.

U.S. Preventive Services Task Force. Screening for Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. Annals of Internal Medicine. 2008; 149. October 7, 2008

NUTRITION

8. For Better Digestive Health, Choose Your Fats Carefully (Oct. 4/08)

A recent study suggesting trans fats increase colorectal cancer risk supports the notion that substituting more healthful fats in the diet is the best path to good health. Trans fats are commonly found in items such as margarine, chips, crackers, cookies, donuts, pastries, and other convenience foods. In this study, 622 people who underwent a routine screening colonoscopy were interviewed about dietary and other factors thought to be related to colorectal cancer. Researchers used this information to estimate how much trans fat each person

regularly consumed and compared these numbers to the colonoscopy results. Compared with those who ate the least trans fats, people who ate the most had an 86% higher likelihood of having colorectal adenomas – small growths, or polyps, in the colon and rectum that, if left untreated, can develop into colorectal cancer. Walter Willett, a professor of epidemiology and nutrition at Harvard Medical School and one of the nation's foremost experts on food and health advocates a move away from these unhealthy fats by doing the following:

- Emphasize whole foods: The closer a food is to its natural form, or what it looks like when it comes out of the ground or off the tree or vine, the less likely it is to contain harmful fats.
- Healthier fats, specifically the mono and polyunsaturated types, are often liquid at room temperature. By comparison, the less healthy trans and saturated fats are typically solid at room temperature. To get more good fats in your diet, cook with oils, such as olive oil, and choose foods such as nuts, avocados, and fatty fish over well-done red meats.
- Match your fat intake to your overall health goals: People at risk for obesity, heart disease, diabetes, and cancer should consume no more than 30% total calories from fat. For a 2,000 calorie diet, this means eating no more than 67 grams of total fat per day.
- In general, the same principles that support heart health support the health of your gut as well. Stick to unprocessed items such as vegetables, fruit, nuts and seeds, whole grains, and beans (legumes).

Vinikoor, Lisa, et al., Consumption of trans Fatty Acid and Its Association with Colorectal Adenomas. American J Epidemiology. 2008; 168: 289-297.

9. Metabolic Syndrome Increases Colorectal Cancer Risk (Oct. 6/08)

People with a combination of three common medical conditions together known as metabolic syndrome have a greatly increased risk of colorectal cancer. Metabolic syndrome was defined as having a combination of three common chronic medical conditions: hypertension, diabetes and elevated cholesterol. Reviewing answers from the National health Interview Survey, researchers found that people who reported metabolic syndrome conditions were almost twice as likely to have colorectal cancer. Nearly 58,000 people were interviewed by the NHIS in 2002-2003. Of those 1,200 had metabolic syndrome and 350 had been diagnosed with colorectal cancer. After controlling for age, race, gender, obesity, smoking and alcohol use, people with metabolic syndrome had a 75% increased risk of also having colon or rectal cancer.

Garrow, Donald, et al., Metabolic Syndrome is a Risk Factor For Colorectal Cancer in the United States, American College of Gastroenterology 2008 Annual Scientific Meeting, October 6, 2008.

10. Women Who Smoke Less Have Equal Risk For CRC as Heavy Male Smokers (Oct. 11/08)

Both women and men who are heavy smokers have twice the risk of colorectal cancer or an advanced colon polyp as people who never smoked. However, women who smoke less have the same risk as men who are heavier smokers. In a recent study of more than 2,700 men and women, heavy smokers were divided into two groups:

- Heavy exposure A: People who were still smoking or had quit within the last ten years and had exposure of less than 30 pack years.
- Heavy exposure B: Those still smoking or quitting less than ten years before and with exposure of 30 pack years or more.

Pack years are calculated by the number of packs smoked each day times the number of years an individual has smoked. Thirty pack years are equivalent to smoking a pack of cigarettes a day for thirty years or two packs a day for fifteen years.

- Men who were heavy smokers but smoked less than 30 pack years had about a 25% increased risk of serious precancerous polyps or cancer compared to never smokers, but women who smoked the same amount had twice the risk.
- Men who smoked thirty or more pack years had almost three and a half times the risk, while women continued to have a double risk.
- Overall, both male and female heavy smokers – those who were still smoking or had quit less than ten years ago – had twice the risk of serious colon neoplasia as those who never smoked.

The lead investigator concluded that although males and females have a similar 2 fold risk for significant colorectal neoplasia from smoking, women require less exposure in pack years to have an increase in risk.

Anderson J.C. et al., Smoking and Colorectal Neoplasia: Women Require Less Tobacco Exposure For Similar Increased Risk as Compared To Men. American College of Gastroenterology Annual Scientific Meeting, October 6, 2008

11. Study Suggesting That Vitamin C Could Reduce Effectiveness of Chemotherapy for Cancer Patients Is Questioned (Oct. 7/08)

Orthomolecular Health critiques the research generated by Sloan Kettering Cancer center wherein as little as 100 mg of Vitamin C may interfere with the efficacy of chemotherapy. Here are some of the points made:

- The research involved mice with implanted cancerous tumours; it was not a trial on cancer patients. A mouse study is a long way from a human clinical trial. This obvious difference was conceded by the study authors. However, there is a more subtle and probably much more important factor they did not consider: ***all mice make their own vitamin C***. Indeed, mice make quite a lot of it. Adjusted for body weight, mice synthesize the human body weight equivalent of approximately 10,000 mg of vitamin C each day. Incredibly, sick mice make even more. Mice given transplanted tumours become sick mice.
- Previous research has demonstrated that mice with cancer respond well to high dose vitamin C therapy. One study found: "With an increase in the amount of ascorbic acid there is a highly significant decrease in the first-order rate constant for appearance of the first spontaneous mammary tumor…Striking differences were observed between the 0.077% ascorbic acid and the control groups, which synthesize the vitamin." Another study concluded that: "A pronounced effect of vitamin C in decreasing the incidence and delaying the onset of malignant lesions was observed with high statistical significance. " Interestingly enough, when this research was first publicized, the media discounted these findings saying that mouse studies were not particularly applicable to people.
- A mouse's ability to make vitamin C, and a great deal of it, is an overlooked confounding factor that may well render the entire experiment invalid. If the Sloan-Kettering team had tried their experiment on Guinea pigs, their results might have been very different. Guinea pigs are more like human beings in that they cannot make their own vitamin C. As controls for comparison, the researchers also treated "no added vitamin C" mouse cancers with chemotherapy. Chemo worked just fine on those mice, by the researchers own admission. And each of those mice was internally synthesizing a body weight equivalent of 10,000 mg/day of vitamin C, even though given none via supplementation. So why did 10,000 mg of vitamin C not interfere with chemo treatment, and 2,000 mg or even 100mg supposedly does?

A sweeping recommendation warning cancer patients to not take supplemental vitamin C, not even 100mg, is irresponsible. It is impossible to justify caution about taking 100 mg of vitamin C daily when your animal subjects made the equivalent of one hundred times that amount, and chemotherapy in them was still reported as effective. You cannot have it both ways. If a synthesized 10,000 mg of C does not interfere, there can be no real "interference" or "blunting" from a supplemental 2,000 mg. And most certainly not from 100mg.

www.cancercompass.com