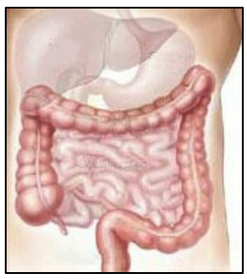
COLORECTAL CANCER RESEARCH

Month Ending April 16, 2010



The following colorectal cancer research update extends from March 20 – April 16, 2010 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Colon Cancer Drugs Prolong Survival But Are Expensive (Mar. 19/10)

According to the results of this study, new chemotherapy agents for metastatic colorectal cancer modestly improve survival time but come with substantial costs. Researchers from Emory University used the Surveillance, Epidemiology, and End Results-Medicare database to evaluate data from 4,665 patients (age 66 and older) diagnosed with metastatic colorectal cancer between 1995 and 2005. All patients received chemotherapy during treatment. The researchers estimated life expectancy and medical costs based on short-term survival rates and costs. They found that life expectancy increased by 6.8 months, and lifetime costs increased by $37,100; this translated into a cost per life-year gained of $66,200. After adjusting for out-of-pocket costs and other factors, the cost per quality-adjusted life-year gained was $99,100. Although this cost does fall below the commonly cited estimates of the "willingness-to-pay for a life-year," it still represents a great cost, and the researchers speculate that these costs will continue to rise.

Howard DH, et al,. The value of new chemotherapeutic agents for metastatic colorectal cancer. **Archives of Internal Medicine*. 2010; 170: 537-542.***

2. Stage III Elderly Not Being Treated Properly (Mar. 22/10)

According to the results of this study, the treatment of Stage III colon cancer does not always follow evidence-based recommendations, especially for older patients. Stage III colon cancer refers to cancer that has spread through the wall of the colon to nearby lymph nodes but is not detected elsewhere in the body. Although patients with Stage III colon cancer may have their cancers completely removed by surgery, they benefit from the addition of chemotherapy and/or radiation (adjuvant therapy) to kill any remaining cells in the body that may go undetected. Randomized trials have clearly demonstrated that adjuvant chemotherapy improves survival in patients with Stage III colon cancer by approximately 30%. Several previous studies have shown that elderly patients benefit from adjuvant chemotherapy to the same degree as younger patients but are less likely to actually receive this therapy. Studies have consistently shown that age is not a predictor of relapse or overall survival in patients receiving adjuvant chemotherapy for Stage II-III colon cancer. Although elderly patients with colon cancer appear to benefit from adjuvant therapy, there is still concern about side effects and quality-of-life issues. Optimally treating patients with other health conditions is an additional challenge in the older population. These are the main reasons given for not administering adjuvant therapy to elderly patients with colon cancer. The current study evaluated data on 675 patients with Stage III colon cancer who had undergone surgery to remove their cancer. The study included patients throughout the United States in a variety of settings including hospitals, university medical centers, and private practice. Of the 675 patients, 202 were 75 years of age or older and 473 were under the age of 75.

- 50% of patients 75 years of age or older received adjuvant chemotherapy compared with 87% of younger patients.
- 14% of older patients received oxaliplatin in the adjuvant regimen compared with 44% of younger patients.
- Older patients received a shorter course of adjuvant chemotherapy than younger patients.
- Patients receiving adjuvant chemotherapy had more adverse events than non-treated patients.
- Late adverse events were lower in older patients than in younger patients, which may have been due to less intensive adjuvant therapy.

According to the investigators, studies have shown that the treatment of Stage III colon cancer with adjuvant chemotherapy improves overall survival and recurrence rates. Treatment plans that follow evidence-based recommendations are crucial to improve outcomes in both the elderly and younger Stage III colon cancer population. Elderly patients with colon cancer eligible for adjuvant therapy should speak with their physician regarding their individual risks and benefits of adjuvant therapy.

Kahn KL,, et al. Adjuvant chemotherapy use and adverse events among older patients with stage III colon cancer. **Journal of the American Medical Association *.2010;303:1037-1045.***

3. Phase II Study of Irinotecan/S-1 Combo Chemo for Patients With Oxaliplatin-Refractory CRC (Mar. 2410)

The goal of this study was to determine the efficacy and tolerance of irinotecan in combination with S-1 (IRIS) for patients whose disease progressed after treatment with an oxaliplatin-based therapy for colorectal cancer. S-1 is an oral drug that was administered twice daily on days 1-14 and 21-35. Irinotecan was administered biweekly. The response rate was 20% (one patient experienced a complete response, 3 with partial response and 7 with stabilized disease; 9 experienced progression of disease). The study, unfortunately, had to be discontinued because two patients died during treatment and investigators recommended the protocol should result in early closure and modification.

Oh, sY et al., Phase II study of irinotecan/S-1 combination chemotherapy for patients with oxaliplatin refractory colorectal cancer. Investigational New Drugs. Published online March 19, 2010. Doi: 10.1007/s10637-010-9409-3

4. S-1 Monotherapy in Elderly & Frail Colorectal Cancer Patients (Mar. 26/10)

S-1 monotherapy was evaluated in this study in previously untreated elderly (>70 years) or frail colorectal cancer patients. 48 patients underwent S-1 oral therapy twice daily for 2 weeks followed by 1 week rest. The overall response rate for patients was 19% . Progression free survival (time before the disease got worse) was 3.9 months and overall survival was 11.3 months. Patients experienced mild to moderate toxicity and investigators concluded that S-1 monotherapy was well tolerated and efficacious in the elderly group. They recommended it as a possible first line therapy in the elderly.

Shin, SJ, et al., Phase II trial of 2-1 monotherapy in elderly or frail patients with metastatic colorectal cancer. Investigational New Drugs. Accessed Online March 20, 2010. Doi: 10.1007/s10637-010-9418-2

5. Two Drug Combo Kills Precancerous Colon Polyps (Mar. 29/10)

According to this study, a two-drug combination destroys precancerous colon polyps with no effect on normal tissue, opening a new potential avenue for chemoprevention of colon cancer. The regimen, tested so far in mouse models and on human colon cancer tissue in the lab, appears to address a problem with chemopreventive drugs -- they must be taken continuously long term to be effective, exposing patients to possible side effects. This combination can be given short term and periodically to provide a long-term effect. The team found that a combination of Vitamin A acetate (RAc) and TRAI (short for tumor necrosis factor-related apoptosis-inducing ligand), kills precancerous polyps and inhibits tumor growth in mice that have deficiencies in a tumor-suppressor gene. That gene, adenomatous polyposis coli (APC) and its downstream signaling molecules, are mutated or deficient in 80% of all human colon cancers. APC-deficient mice were treated with 15 cycles of the RAc/TRAIL combination over six weeks. Others received either RAc or TRAIL and a control group received nothing. One month later, control mice and those treated with one of the drugs averaged between 35 and 42 polyps, while those receiving the combination averaged 10. To test the combination's potential as short-term therapy, APC-deficient mice were treated with two cycles of the combination in one week, causing a 69% polyp reduction two weeks later. A 10-fold increase in dose left treated mice with only 10% of the polyps found in controls. A longer term test of relative survival using five treatments over four months improved survival from 186 days for controls to beyond 213 days for treated mice, with five of seven treated mice living more than eight months. Next, the researchers treated biopsy samples of normal tissue and tumor regions from patients with familial adenomatous polyposis -- an inherited condition that inevitably leads to colon cancer if the colon is not removed. Treatment of normal tissue caused little cell death, while 57% of polyp cells were killed via apoptosis (programmed cell death).

Zhang, Ling et al., . Chemoprevention of colorectal cancer by targeting APC-deficient cells for apoptosis.* Nature*, 2010; DOI: 10.1038/nature08871

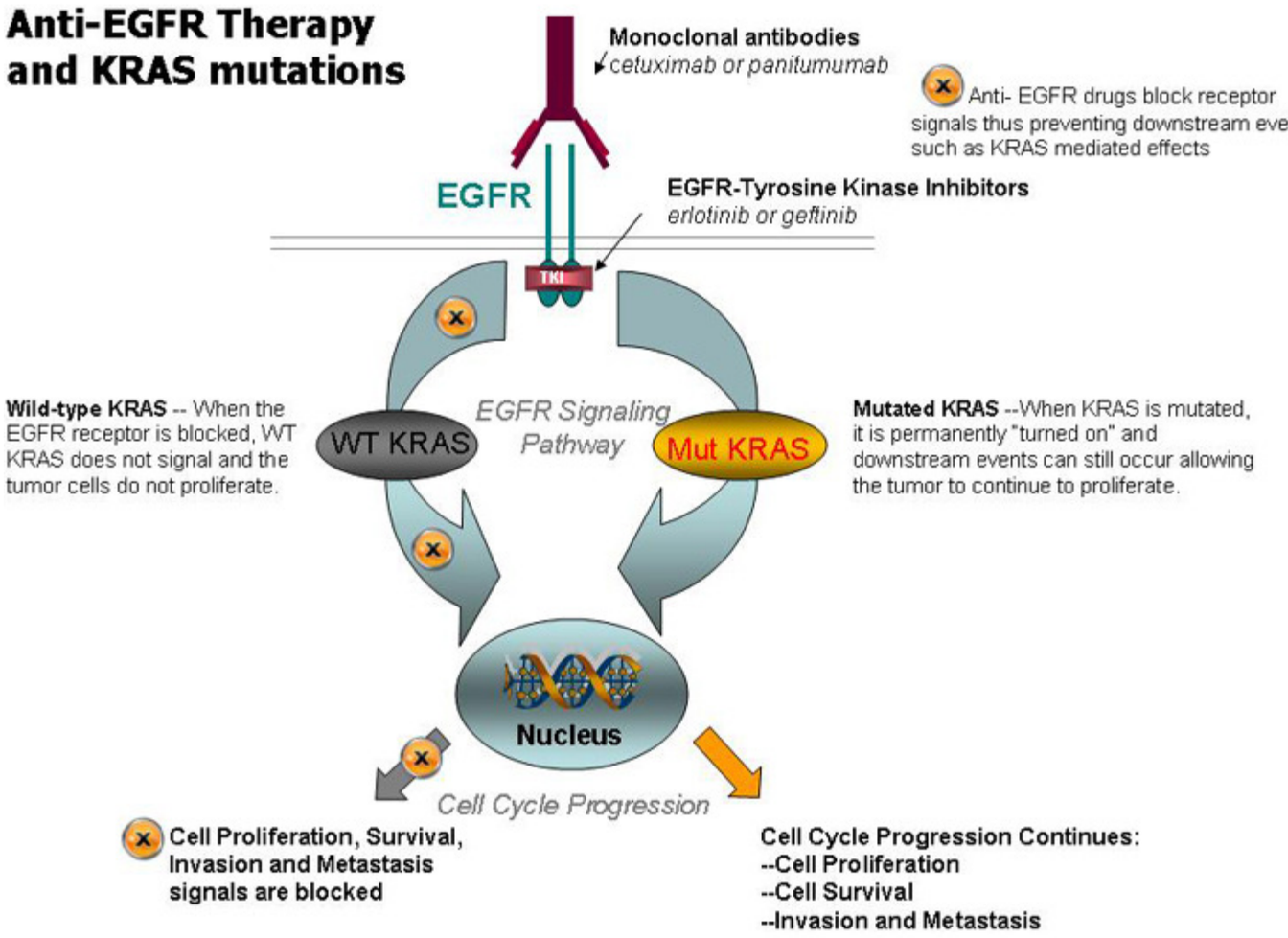
6. Octreotide and Chemoradiation-Induced Diarrhea (Mar 30/10)

In anorectal cancer patients, an acute side effect of chemoradiotherapy is gastrointestinal toxicity, which often impedes treatment delivery. Based on past literature, octreotide acetate is widely recommended for the control of chemotherapy-induced diarrhea. This study sought to evaluate the effectiveness of octreotide in preventing or controlling radiation and chemoradiation-induced diarrhea. A randomized, double-blinded placebo controlled trial was performed to determine if octreotide acetate could prevent the onset of acute diarrhea in patients undergoing chemoradiation therapy for rectal or anal cancer. Investigators found that the incidence rate of acute diarrhea was similar in both the placebo group and the group administered the octreotide. Researchers were forced to conclude that octreotide acetate did not prevent the incidence or reduce the severity of diarrhea and had not notable impact on patient-reported bowel function or quality of life.

Zachariah, Babu, et al., Octreotide Acetate in prevention of chemoradiation-induced diarrhea in anorectal cancer: Randomized RTOG Trial 0315. J of the National Cancer Institute. Doi: 10.1093/jnci/djq063.

7. Incorporating Vectibix (Panitumumab) into Colorectal Cancer Treatment (Mar. 31/10)

Conventional chemotherapy increases progression-free survival (PFS) and overall survival (OS) of metastatic colorectal cancer (mCRC) patients versus best supportive care (BSC). However, the efficacy of chemotherapy is limited. Recently approved monoclonal antibodies (MoAb) have a different mechanism of action, targeting growth factors or their receptors (see diagram below).



Source: *http://www.exigon.com/dxps/Documents/KRAS%20Mutatioon%20analysis/KRAS-mutation-analyisi-figu.jpg*

Panitumumab is a fully human monoclonal antibody directed against the epidermal growth factor receptor (EGFR). In phase II trials, panitumumab showed preliminary activity in chemorefractory mCRC. This efficacy was confirmed in a randomized phase III trial, which compared single-agent panitumumab plus BSC versus BSC alone. Several ongoing clinical trials are evaluating panitumumab in combination with different chemotherapy regimens in first- and second-line settings. Skin toxicities, hypomagnesemia (decreased magnesium levels), and diarrhea are the most common adverse events associated with anti-EGFR therapy. KRAS status and skin rash have been associated with panitumumab efficacy. This article reviews the data, activity and tolerance of panitumumab in mCRC patients. Potential predictive factors of response are also discussed.

Gravalos, C, et al., Integration of Panitumumab into the treatment of colorectal cancer. Crit Rev. Oncol. Hematol. 2010 April 1; 74(1): 16-26

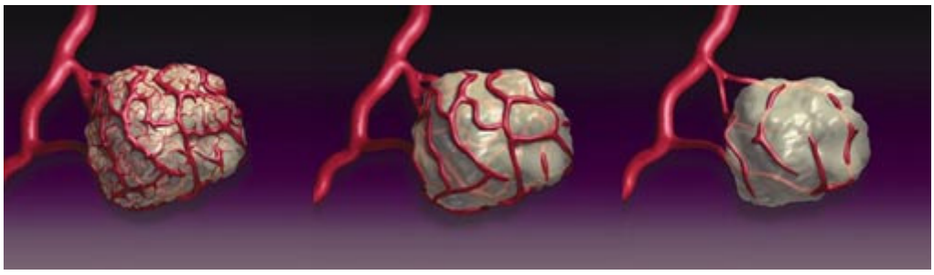
8. Perifosine in Refractory Advanced Colorectal Cancer (Apr. 6/10)

The FDA in the U.S. is approving fast tract designation for **perifosine** in the treatment of refractory advanced colorectal cancer. The FDA's Fast Track program is designed to provide facilitated development and expedited review of new drugs that address unmet medical needs in treating serious or life-threatening conditions. Patients with recurrent or advanced colorectal cancer are often treated with concomitant or sequential administration of 2 or more of 7 approved drugs, including 5-fluorouracil (5-FU), capecitabine (*Xeloda*), irinotecan (*Camptosar*), oxaliplatin (*Eloxatin*), bevacizumab (*Avastin*), cetuximab (*Erbitux*), and panitumumab (*Vectibix*). Patients with wild-type KRAS status who fail 5-FU-, oxaliplatin-, irinotecan-, and bevacizumab-containing therapies typically receive epidermal growth factor receptor monoclonal antibody therapy with cetuximab or panitumumab; no further treatment options are available if this treatment fails. Perifosine is a novel, potentially first-in-class oral anticancer agent According to the company's news release, a randomized, double-blind phase 3 trial of perifosine in combination with capecitabine in patients with refractory metastatic colorectal cancer is expected to begin this quarter of 2010 under a special protocol assessment with the FDA. "We now look forward to the initiation and sponsorship by our partner, Keryx, of this key registration Phase 3 trial in refractory metastatic colorectal cancer in North America which they expect to complete in 2011, with product launch, in the USA, in 2012," noted Juergen Engel, PhD, president and chief executive officer of AEterna Zentaris, in company news release. "These data will be very supportive of our efforts to register perifosine in the rest of the world, and in some countries, we expect they will be sufficient to do so without any additional studies." Perifosine previously was granted Fast Track and orphan drug status by the FDA for the treatment of relapsed/refractory multiple myeloma and is currently in phase 3 trials under special protocol assessment for this indication.

http://www.medscape.com/viewarticle/719787

9. Antiangiogenesis Drugs – Understanding Resistance (Apr. 13/10)

Angiogenesis, the formation of new blood vessels from existing blood vessels, plays an essential role in tumour growth, invasion and metastasis. Vascular endothelial growth factor (VEGF) is one of the key factors responsible for its regulation.



Source: *http://www.gene.com/gene/products/information/images/avastin.jpg*

Therapies that inhibit VEGF (such as avastin) may have multiple effects on angiogenesis, tumor growth and delivery of other types of therapy.[5,6] These effects may include:

- **Reducing the tumor's blood supply by potentially causing** existing small blood vessels **in the tumor to die.**
- **Preventing the development of new blood vessels in the tumor.**
- **Facilitating the delivery of chemotherapy to the tumor cells by potentially making mature tumor vessels, which tend to be leaky, behave more like normal vessels.**

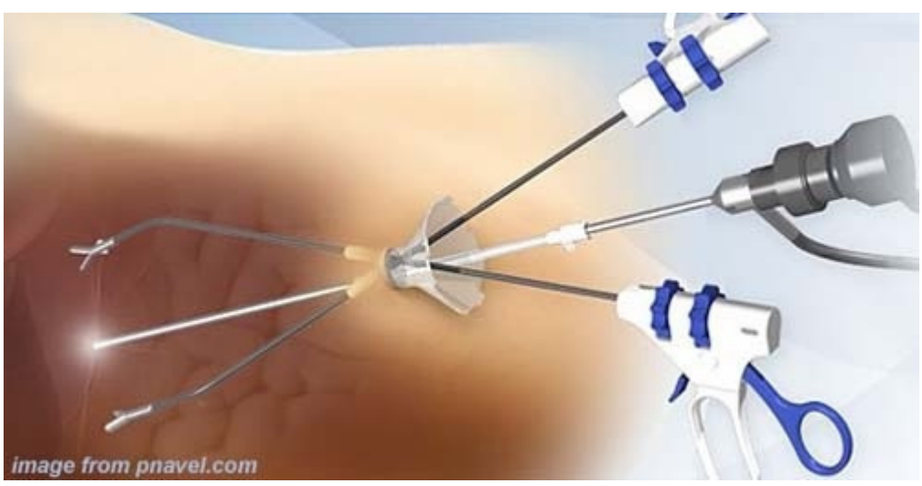
High expression of VEGF has been observed in many cancers, and is associated with worse survival. When antiangiogenic agents such as bevacizumab (avastin) are used alone they typically initially cause reduction in blood flow or vascular permeability in many types of cancer. In some cases tumour regression occurs, mainly in renal cancer. In combination with chemotherapy, such as in colorectal cancer, progression-free survival is often prolonged. Many tumours fail to respond initially – de novo resistance. Others develop resistance over time, with progression after a few months of treatment. The mechanisms of resistance are not well understood. The theoretical benefits of VEGF inhibitors are more likely to be realized by understanding these mechanisms and modifying therapy accordingly. This article reviews current knowledge on resistance mechanisms and the therapeutic implications of VEGF inhibitors.

Azam, Faisal, et al., Mechanisms of resistance to antiangiogenesis therapy. European J Cancer. Published online March 18, 2010.

SURGICAL THERAPIES

10. One Incision to Perform Colon Laparoscopic Surgery (Mar. 25/10)

Surgeons at the University of California, San Diego School of Medicine report what is believed to be the nation's **first single-incision laparoscopy** to perform a combined colectomy and kidney-preserving therapy. See image below.



Source: *http://thejewishstar.files.wordpress.com/2009/05/health-bellybutton-viewsingleport.jpg*

During the procedure, tumors were removed from the patient's kidney and colon, and the colon was partially removed and reconstructed. Pioneers in minimally invasive surgery, UC San Diego Medical Center's team of urologic and colorectal surgeons now use this novel micro-incision approach to combine multiple procedures into one operating room visit. "Traditionally, these procedures are performed in separate operations," said Elisabeth C. McLemore, MD, colorectal surgeon at UC San Diego Medical Center and Moores UCSD Cancer Center. "To do what's best for the patient, we have integrated our approach so that the patient can benefit from multiple procedures with one small incision. This means less pain, a quicker recovery and a better cosmetic outcome." During the four-hour procedure, surgeons immobilized the small intestine, colon and kidney. Cryotherapy was performed to freeze and destroy a 2.5 cm kidney mass. The section of diseased colon was then removed and reconstructed. The entire procedure was performed with one incision in the belly button through which tools and cameras were passed and diseased tissue removed. The patient, who suffers from congestive heart failure and high blood pressure, reported a post-surgery pain score of one on a scale of 1 to 10. "With our broad experience in single incision laparoscopic surgeries, we can offer patients with complex medical problems an innovative approach that requires fewer incisions," said Ithaar Derweesh, MD, urologic oncologist at UC San Diego Medical Center and Moores UCSD Cancer Center. "While multi-incision laparoscopy confers significant benefits over open surgery, reducing the number of incisions to one may decrease potential complications and accelerate recovery." Derweesh, a pioneer in single-incision surgery, is currently researching the benefits of minimally invasive techniques for kidney surgery through the UC San Diego Center for the Future of Surgery. He was the first surgeon in California to perform both complete and partial nephrectomies with a single incision and now has a robust practice offering both. McLemore, the most recent member of the Center, is developing minimally invasive techniques for colorectal cancer and inflammatory bowel disease. Established in 1965, the Department of Surgery at UC San Diego Medical Center represents more than 100 leading surgeons with specialties in open, minimally invasive, and scarless surgery techniques. The Department is committed to advancing surgical education by teaching and training the next generation of innovators; researching, testing and developing groundbreaking surgical techniques; providing superior patient care and service; and attracting a world-class faculty. The Moores UCSD Cancer Center is one of the nation's 41 National Cancer Institute-designated Comprehensive Cancer Centers, combining research, clinical care and community outreach to advance the prevention, treatment and cure of cancer.

http://newswise.com/articles/one-tiny-incision-to-perform-lifesaving-surgery?ret=/articles/channels&channel=107&category=feature&page=1&search%5Bstatus%5D=3&search%5Bsort%5D=date+desc&search%5Bchannel_id%5D=107

11. ConvaTec Furnishes No Pouch Colostomy (Apr. 12/10)

A new appliance that eliminates the need for ostomates to wear an external pouch has received pre-marketing approval by the FDA. Expected to be on the US market in the next few months. the Vitala device, seals the stoma, preventing stool from leaving the body for up to 8 hours. Intestinal gas is filtered and vented to prevent odor. An external pouch will still be needed for wear longer than 8 hours. The Vitala Continence Control Device has a built-in expandable container permitting removal without risk of soiling. It is waterproof and can be worn during bathing or swimming. People with colostomies can begin to use the device 6 to 12 weeks after surgery.

http://fightcolorectalcancer.org/research_news/2010/04/no-pouch_colostomy_appliance_approved

RADIATION / INTERVENTIONAL RADIOLOGY

12. CT Colonography or Virtual Colonoscopy Can Find Tumours Outside the Colon (Apr. 2/10)

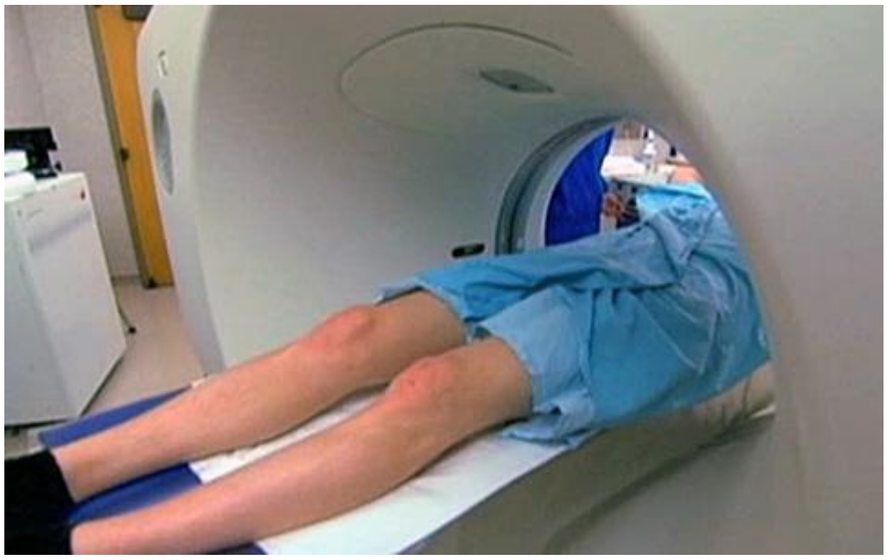
Looking at more than 10,000 screening CT colonography or virtual colonoscopy exams, doctors found cancers in 1 in every 200 patients, but more often those cancers were not colorectal cancer, but unsuspected cancer found outside the colon. The tests found 22 colorectal cancers (1 in every 500 patients examined) and 36 other cancers (1 in every 300 patients). More than half were found at an early stage I. After an average follow-up time of 30 months, only 3 patients had died of cancer. Renal cell cancer was the most frequent extra colonic cancer, discovered in 11 patients who didn't have symptoms. Eight lung cancers were also found along with six cases of non-Hodgkin's lymphoma and eleven cancers in other sites. CT colonography allows radiologists limited views of the body outside of the colon, particularly in the pelvis, abdomen, and part of the lungs. About 6% of the time, the exam leads to additional testing for other diseases, although more than half of that testing will eventually prove benign. If polyps or suspected colorectal cancer is found during CTC screening, referrals are necessary for a traditional optical colonoscopy where polyps can be removed and biopsied. During an exam patients are exposed to approximately 10 millisieverts (mSv) of radiation, about the same amount they receive from normal background radiation in three years. Investigators are finding that virtual colonoscopy screening actually identifies more unsuspected cancers outside of the colon than within it. As with asymptomatic colorectal cancers identified by virtual colonoscopy screening, these cancers are often detected at an early, curable stage. However, they point out that CT colonography does find benign conditions that nevertheless need follow-up. Although extra colonic evaluation at screening CT colonography does carry some disadvantages, such as patient anxiety, inconvenience, or the potential

for benign biopsy, the results suggest that early detection of asymptomatic extra colonic cancer represents an additional benefit of screening CT colonography that is not available with optical colonoscopy. Investigators concluded that the overall detection rate of unsuspected cancer is approximately one per 200 asymptomatic adults undergoing routine screening CT colonography, including about one invasive CRC per 500 cases and one extra colonic cancer per 300 cases. Detection and treatment at an early pre-symptomatic stage may have contributed to the favorable outcome.

Pickhard, Perry J, et al., Colorectal and Extra colonic cancers detected at screening CT colonography in 10,286 asymptomatic adults. Radiology. Vol. 255, Issue 1, pp. 83-88.

13. Radiation Emitted from Virtual Colonoscopy May Be Concerning (Apr. 7/10)

A less invasive procedure known as a virtual colonoscopy is done with a CT scan that passes x-rays through a patient's abdomen. If growths or polyps are found during a virtual colonoscopy, then a conventional colonoscopy must be performed to remove them. There is, however, a concern that CT scan exposes patients unnecessarily to harmful radiation, as much radiation as a patient might receive from 400 chest x-rays. A physician formerly with the FDA in the U.S. (Dr. Julian Nicholas) claims that the arguments for virtual colonoscopy are not sound, however. He claims that there was an absence of sufficient valid scientific evidence that the use of CT devices for colorectal cancer is both safe and effective. Other physicians claim that patients may not be fully aware of the risks involved in a virtual colonoscopy. Physicians make every effort to assure that the technologies that do come on the market are safe and effective, but whether or not they should be used on a given case, a given patient, is a decision that is made by the individual practitioner. With 70 million CT scans being performed in the U.S. every year, the government is under pressure to make an official recommendation on how much radiation is safe during a CT scan.



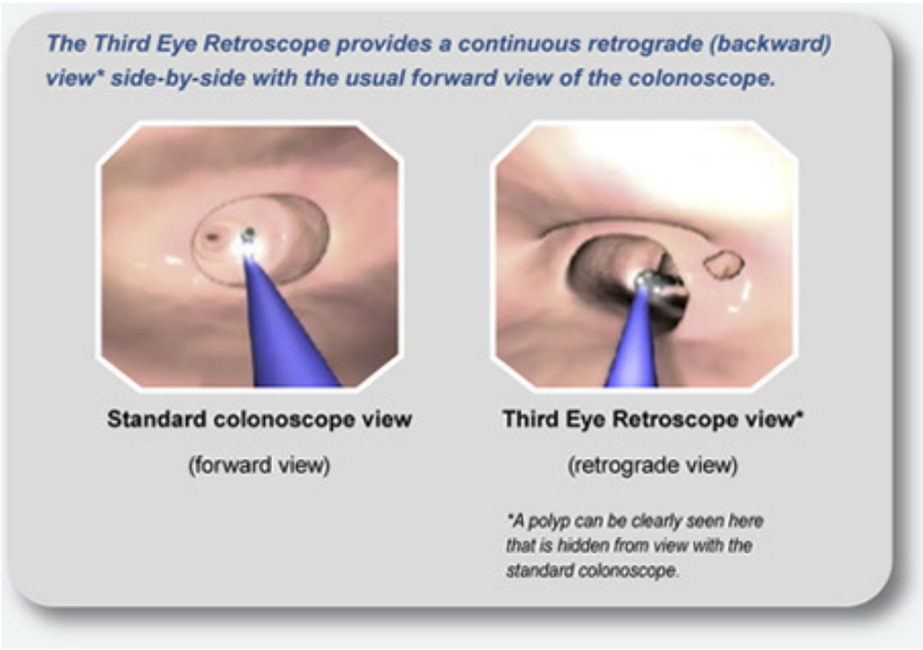
Source:http://www1.voanews.com/english/news/health/Doctors-Debate-Benefits-Risks-of-Virtual-Colonoscopy--90086862.html

http://www1.voanews.com/english/news/health/Doctors-Debate-Benefits-Risks-of-Virtual-Colonoscopy--90086862.html

SCREENING

14. More Polyps Found Using Third Eye Retroscope (Mar. 20/10)

Two new studies show an increase in polyp detection rates using the Third Eye Retroscope (TER), a retrograde viewing device, during colonoscopy (see image below).



Source: ***http://www.thirdeyeretroscope.com/images/sidebyside.jpg***

The first study found that TER added to standard colonoscopy detected 13.2% more polyps than colonoscopy alone, including 11% additional adenomas (precancerous polyps). A second study examined endoscopist experience using TER and its impact on polyp detection rates, concluding that polyp detection rates improved significantly with TER. The Third Eye Retroscope is a disposable catheter imaging device that is inserted through the instrument channel of a standard colonoscope to provide a retrograde view of the colon during the withdrawal phase of a colonoscopy. After the colonoscope has been advanced to the cecum, the TER is inserted through the instrument channel. As it emerges from the distal tip of the colonoscope, the TER automatically bends 180 degrees to form a J shape so that its sensor and integrated light source are directed back toward the tip of the colonoscope. The device is then withdrawn together with the colonoscope, providing a continuous retrograde view to complement the forward view of the colonoscope. Previous studies showed that TER can increase detection rates for adenomas and other polyps. According to the study authors, these results suggest that, compared with routine colonoscopy, a retrograde-viewing device can increase detection rates for clinically significant adenomas without detriment to procedure time or procedure complications.

http://www.medicalnewstoday.com/articles/182916.php

PSYCHO-SOCIAL

15. Anxiety & Cancer (Mar. 30/10)

Anxiety is a normal reaction to cancer. One may experience anxiety while undergoing a cancer screening test, waiting for test results, receiving a diagnosis of cancer, undergoing cancer treatment, or anticipating a recurrence of cancer. Anxiety associated with cancer may increase feelings of pain, interfere with one's ability to sleep, cause nausea and vomiting, and interfere with the patient's (and his or her family's) quality of life. If left untreated, severe anxiety may even shorten a patient's life. Persons with cancer will find that their feelings of anxiety increase or decrease at different times. A patient may become more anxious as cancer spreads or treatment becomes more intense. The level of anxiety experienced by one person with cancer may differ from the anxiety experienced by another person. Most patients are able to reduce their anxiety by learning more about their cancer and the treatment they can expect to receive. For some patients, particularly those who have experienced episodes of intense anxiety before their cancer diagnosis, feelings of anxiety may become overwhelming and interfere with cancer treatment. Most patients who have not had an anxiety condition before their cancer diagnosis will not develop an anxiety disorder associated with cancer. WEBMD furnishes an Anxiety & Panic Disorders Health Center resource online for cancer patients experiencing disease-related anxiety which can be accessed at http://www.webmd.com/anxiety-panic/anxiety-in-cancer-patients . An overview of the disorder is presented as well as description, cause, treatment and post-treatment considerations. Patients battling with disease-related anxiety should speak to their physicians who can provide much needed assistance.

http://www.webmd.com/anxiety-panic/anxiety-in-cancer-patients

16. Placebos & Cancer (Apr. 12/10)

When people hear the word "placebo", they often think of a "fake pill" or "fake treatment". It's true that a placebo is a non-active treatment and used in some research studies. For example, if a researcher wants to see how well a new medication lowers blood pressure, they will give half of their study participants the active medication and half of their study participants a placebo. No one will know whether they received the real medication or an inactive "sugar pill." This helps researchers separate out the true effects of a medication from the effects that people report simply because they *thought* they received the medication. The power of suggestion can be very strong. In this study, researchers have found that people with cancer-related fatigue may be especially sensitive to the placebo effect. The study found that 56% of people experiencing cancer-related fatigue felt better when given a placebo that they believed would help lessen their fatigue. This can actually be a positive factor. It suggests that people can help themselves manage their own fatigue. Fatigue is one of the toughest problems that people in cancer treatment endure. If the power of suggestion can help more than half of people with fatigue, it is certainly something worth tapping into. If you have fatigue, ask your doctor and nurse for suggestions on how to manage it. Take those suggestions to heart. If you really *believe* that you can help yourself, there's a good chance you can. And should you not feel better, do not as though you have failed. Cancer fatigue is serious. It can greatly affect one's life. Keep the lines of communication open with your health care team so that you can take advantage of all they have to offer. This includes classes on coping, art therapy, support groups, exercise therapy for people with cancer, medications, and anything else that may assist.

De la Cruz, Maxine, et al., Placebo and nocebo effects in randomized double blind clinical trials of agents for the treatment of fatigue in advanced cancer patients. Cancer. 2010 February 1; 116(3): 766

OTHER

17. Comparing Cancer Survival to Heart Failure & Stroke Survival (Mar. 22/10)

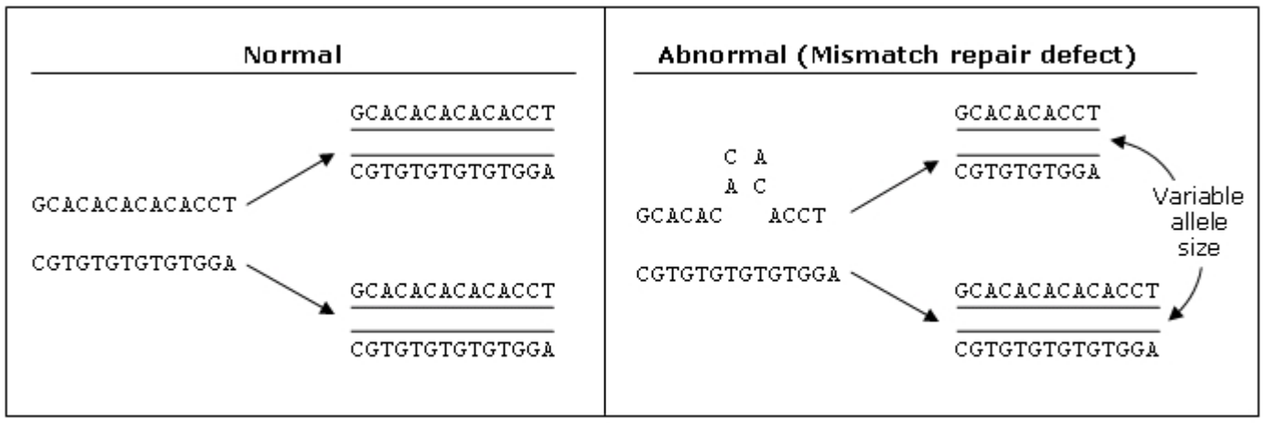
Cancer, heart failure and stroke are among the most common causes of death worldwide. Investigation of the prognostic impact of each disease is important, especially for a better understanding of risks. The aim of this study was to provide an overview of long term survival of cancer, heart failure and stroke patients based on the results of large population- and hospital-based studies. Records for the study were identified. Researchers focused on 5-year survival rates for cancer in general and for the four most common malignancies in developed countries, i.e. lung, breast, prostate and **colorectal cancer**, as well as for heart failure and stroke. Twenty studies were identified and included for analysis. Five-year observed survival was about 43% for all cancer entities, 40-68% for stroke and 26-52% for heart failure. Five-year age and sex adjusted relative survival was 50-57% for all cancer entities, about 50% for stroke and about 62% for heart failure. In regard to the four most common malignancies in developed countries 5-year relative survival was 12-18% for lung cancer, 73-89% for breast cancer, 50-99% for prostate cancer and about **43-63%** for colorectal cancer. Results revealed a survival improvement over the last decades. The results indicate that long term survival and prognosis of cancer is not necessarily worse than that of heart failure and stroke. However, a comparison of the prognostic impact of the different diseases was limited, creating a need for further systematic investigations

Askoxylakis, Vasileios, et al., Long term survival of cancer patients compared to heart failure and stroke: A systematic review. BMC Cancer 2010; 10:105

18. Obesity Not the Cause of Some Colorectal Cancers (Apr. 6/10)

Recent literature has identified that being obese increases risk for most colon and rectal cancers, but the connection isn't true in all types of colorectal cancer. Cancers that are linked to *microsatellite instability (MSI – please see below)* don't appear to be influenced by obesity, strengthening the belief that MSI cancers come about differently than the average colorectal cancer. Overall, in a recent study, body mass index and weight gain during adult life increased risk of colorectal cancer by approximately 30% for men and 20% for women. However, increased risk was limited to microsatellite stable or microsatellite low tumors. A research team compared height and weight at age 20 and recent height and weight for nearly 1,800 people with colorectal cancer to figures for 2,700 of their sex-matched brothers and sisters. They also analyzed tumors for microsatellite instability in 7 out of 10 of the group with cancer. They discovered a 38% increased risk for cancer in patients with microsatellite stable tumors, a 33% increased risk in those who had a low number of microsatellite markers, and no increase in those whose tumors had high number of microsatellite changes (*MSI).* Researchers concluded: The increased risk of colorectal cancer associated with a high BMI might be largely restricted to tumors that display the more common MS-stable phenotype, suggesting further that colorectal cancer etiology differs by tumor MSI status.

[Microsatellite instability: *Microsatellites are repeated sequences of DNA (genetic material found in cells – see diagram below).*



Adapted from Gruber SB, Kohlmann W (2003) The genetics of hereditary nonpolyposis Colorectal cancer. *J Nat Comp Cancer Net* 1:137-44

Source: ***http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=glossary&rendertype=box&id=further_illus-304***

The normal length of microsatellites in an individual's cells is set at birth, although lengths vary from one person to another. However, during the many divisions cells undergo in a person's lifetime, mistakes can be made duplicating DNA which don't get repaired, so microsatellites change in length in some tissues (as depicted in the diagram above). The presence of abnormally short or long microsatellites indicates that genes that should be repairing DNA are mutated and aren't doing their job. Mutations in DNA repair genes can lead to a particular form of colorectal cancer linked to microsatellite instability. About 1 in 6 or 7 (15%) colorectal cancers are microsatellite instable. Some people are born with mutations in DNA repair genes, as in Lynch syndrome. Others acquire mutations during their lives. Here are the classifications of Microsatellite Instability:

Microsatellite Instability High Tumours: Contain changes in 2 or more regions of the DNA (genetic material) of the tumour
Microsatellite Instability Low Tumours: Contain changes in one region of the DNA of the tumour.
Microsatellite Instability Stable Tumours: Contain no changes in the DNA of the tumour]

Campbell, Peter T, et al., Case control study of overweight, obesity and colorectal cancer risk, overall and by tumor microsatellite instability status. J of National Cancer Institute; Vol. 102, Number 6: pp. 391-400

19. Blacks Less Likely To Access Screening Follow up (Apr. 8/10)

Patients of African descent contract more colorectal cancer than whites and die more often. Whether this is because of different biology or lack of access to high-quality medical care has long been debated. In this study, blacks had very similar rates of polyps found during a screening flexible sigmoidoscopy. But they were less likely to get a recommended follow-up colonoscopy. While about 1 in 4 people had polyps discovered during their sigmoidoscopy, nearly identical percentages for blacks and whites, blacks access colonoscopy follow-up about 12% less often than whites. For those who did get a colonoscopy, adenomas and advanced adenomas were just as likely in whites and blacks, as was the rate of cancers discovered. The PLCO Screening Trial screened 60,572 people for colorectal cancer using flexible sigmoidoscopy. Doctors recommended those who had abnormalities discovered during the screening test have a colonoscopy. However, the trial did not pay for the follow-up exam. Analysis of the PLCO trial found,

- 23.9% of whites had abnormalities found during flexible sigmoidoscopy compared to 25.5% of blacks, which was an insignificant difference.
- 72.4% of whites got a diagnostic colonoscopy compared to 62.6% of blacks
- During colonoscopy, 23.1% of blacks and 22.5% of whites had an advanced adenoma found.
- Nearly identical percentages had cancer discovered (2.1% of blacks and 1.5% of whites).
- Advanced adenomas were more frequently found on the right side of the colon in blacks (8.5%) than in whites (5.5%) suggesting that full colonoscopy that reaches the right side of the colon may be particularly important in screening blacks.

Lead author concluded: "We observed a lower follow-up for screen-detected abnormalities among blacks when compared with whites but little difference in the yield of colorectal neoplasia. Health-care utilization may be playing more of a role in colorectal cancer racial disparity than biology". The study did not look at reasons that African Americans were less likely to get follow-up colonoscopies. However, in an editorial accompanying the study results in the *Journal of the National Cancer Institute,* John Z. Ayanian, discussed some potential barriers to follow-up care. He pointed out that other research has shown:

- Blacks are less likely to have a primary care physician.
- They live more often in low-income communities with limited access to gastroenterologists.
- They may lack insurance that covers colonoscopy.
- They may not be able to afford out-of-pocket costs for colonoscopy not covered by insurance.

The barriers concerned Dr. Ayanian, who wrote, "These gaps in follow-up care were particularly concerning because up to one-quarter of participants who did not undergo colonoscopy were likely to have advanced adenomas that were neither detected nor removed. Valuable opportunities to prevent colorectal cancer were thus lost in these patients". He called for programs like that in New York City which increased colonoscopy screening rates for black adults from 35% to 64% in four years to be expanded to other communities. He further commented: "Colorectal cancer is one important disease in which racial and socioeconomic disparities in outcomes can most readily be eliminated by ensuring that all eligible adults are effectively screened and abnormal findings are fully treated".

Laiyemo, Adeyinka, et al., Race and Colorectal Cancer disparities: health-care utilization vs. different cancer susceptibilities. J of the National Cancer Institute: Advance Access: March 31, 2010.
Ayanian, John Z, et al., Racial disparities in outcomes of colorectal cancer screening: biology or barriers to optimal care? J National Cancer Institute, Advance Access, March 31, 2010.

20. Hormone Replacement Therapy Helps Fight Colon Cancer (Apr. 12/10)

According to this research, hormone replacement therapy (HRT) cuts a woman's risk of developing colon cancer. Millions of women stopped taking HRT when a Women's Health Initiative study showed in 2002 that the hormones raised the risk of stroke, heart disease and breast cancer. But the Women's Health Initiative had also found that HRT protected against colon cancer. According to researchers, some studies have also suggested that oral contraceptives might reduce the risk of the disease, in light of the fact that women are at lower risk of colon cancer than men whose root is from a hormonal role in disease risk. To investigate ties between HRT and colon cancer further, researchers in this study matched 443 women diagnosed between 2001 and 2006 with distal large bowel cancer (meaning tumors at the far end of the colon and the rectum) to 405 healthy control women. The average age of the study participants was approximately 63. They found that women who had ever used HRT were at half the risk of this type of colon cancer compared to women who'd never used hormone replacement, and the longer a woman was on HRT, the lower the risk. For example, women who used hormones for less than four years cut their colon cancer risk by about one-quarter; four to eight years of HRT cut risk by a third; nine to 14 years of use halved risk; and 15 years or more of HRT reduced risk by two-thirds. The effects were the same for African-American women and white women. However, there was no relationship between oral contraceptive use and colon cancer risk, the study team reported. Long-term hormone therapy is no longer recommended for postmenopausal women, researchers note, although it is still sometimes prescribed on a short-term basis to help women with menopausal symptoms such as hot flashes. The major drop off in distal large bowel cancer in recent years could have been related to widespread use of HRT, the researchers say. More research is needed to determine if HRT's protective effects persist after women stop taking hormones, the researchers add, or whether there might be a "rebound" effect with more pre-cancerous polyps developing after a woman halts HRT. "It may become important in the future to tailor timing of women's colorectal screening based on cessation of hormonal therapy," concluded researchers.

Long, Millie, et al., Hormone replacement therapy, oral contraceptive use, and distal large bowel cancer: a population based case control study. Amer J of Gastroenterology; Advance Online Publication March 30, 2010. Doi: 10.1038/ajg.2010.123

NUTRITION & HEALTHY LIFESTYLE

21. Magnesium & Colon Cancer (Mar. 17/10)

Several studies have demonstrated that diet and nutrition can affect colon cancer risk. Now researchers are honing in on which nutrients may be an important part of the colon cancer-food connection. In this study, Japanese researchers collected diet and health information from 87,117 people with an average age of 57. They followed this group for about eight years to see who developed colon cancer and whether this was related to a person's dietary habits. Men with the highest average intake of magnesium had 52% lower risk of developing colon cancer compared with men getting the least magnesium. The men with reduced colon cancer risk were getting at least 327 milligrams (mg) of magnesium per day. This study focused on magnesium from food sources, not dietary supplements. But that's not the only reason to focus on magnesium-rich foods, rather than pills. Magnesium supplements can have an unpleasant side effect: loose stools and diarrhea. In fact, many laxatives contain magnesium. It is relatively easy to get at least 327 mg of magnesium each day. I requires that you focus on the foods that give you the most magnesium available. The best sources of magnesium include:

- Whole grains, especially buckwheat flour and bulgur wheat
- Oats and oat bran
- Barley
- Dark chocolate - go for at least 60% cocoa content

- Dark green leafy vegetables, especially spinach
- Nuts and seeds, especially pumpkin seeds
- Beans, including soy beans
- Fish, especially halibut

A 5-ounce serving of halibut, a half cup of cooked spinach and a handful (1 ounce) of pumpkin seeds provides 483 mg of magnesium. It's not difficult to obtain the magnesium you need for best colon health, as long as one can enjoy a variety of healthy, minimally processed foods.

Ma, E., et al., High dietary intake of magnesium may decrease risk of colorectal cancer in Janpanese men. J of Nutrition; vol. 140: pp. 779-785

22. Apples May Safeguard Against Colorectal Cancer (Mar. 27/10)

According to this new Polish research, eating **apples** regularly may reduce the risk of developing colorectal cancer. The tests compared 592 patients suffering from the disease with 765 patients without at the same hospital. Research concluded that those with cancer had eaten 9.5 servings a week, compared to those without the disease, who had 11 servings a week. A reduced risk was observed with those who ate one apple a day, while eating more than one apple a day reduced the risk by about half. Eating other fruit or vegetables did not have the same effects on the risk of colorectal cancer.

According to researchers, the protective properties of apples may be as a result of their high content of flavonoids. These act as antioxidants found concentrated in the skin of apples, preventing molecules or free radicals from inflicting damage on tissue and which can inhibit cancer onset and cell proliferation. Antioxidants were five times more prevalent in the apple skin than the actual flesh - hence wash, but do not peel before the apple is eaten.. However, the World Cancer Research Fund says its research has shown that the risk of all cancers can be reduced by between 30 to 40% by making simple lifestyle changes, such as eating more fruit and vegetables, taking regular exercise and watching one's weight

http://english.sina.com/life/p/2010/0327/311259.html

23. Obesity & Colon Cancer (Mar. 29/10)

This study confirms that obesity not only causes colon cancer but it also appears to worsen the chances of surviving after a diagnosis. Patients who are obese and diagnosed should raise this issue with their medical care team. The discussion may start by acknowledging that one is overweight and that this may not necessarily be a good thing in terms of overall survival. Working with the physician to ensure a healthier weight is a step in the right direction. Something else to bear in mind is that obesity can affect levels of hormones in the body such as insulin, insulin-like growth hormone, leptin, and others. These hormones, in turn, can affect how cancer cells behave in the body. It is through the hormone connection that many health experts believe obesity may worsen colon cancer survival. This is important because other things affect hormone levels as well such as exercise. Moving your body more will keep hormone levels in a healthier range. So instead of fretting about whether the needle on the scale is moving, try to focus on other positive changes you can make. Just like body weight, exercise can affect colon cancer survival. People who exercise have better survival rates, according to researcher. A nice walk on most days of the week will do wonders for your physical *and* mental health. Ask your doctor if it's OK for you to add in a little more activity during or after treatment. Aim for 20 to 30 minutes of walking or other movement for each exercise "session."

Sinicrope, Frank A., et al., Obesity is an independent prognostic variable in colon cnacer survivors. Clin Cancer Res; Vol. 16, Issue 6: pp. 1884-93

24. Antioxidants & Distal (Left sided) Colorectal Cancer (Apr. 2/10)

The objective of this study was to investigate the relationship between antioxidant nutrient (vitamins C and E, carotene, selenium) and DNA methylation-related (see below) nutrients (folate, vitamins B6 and

B12) and distal colorectal cancer risk in whites and African Americans and to examine intakes from food only versus total (food plus dietary supplements) intakes. The findings provide evidence that antioxidant and DNA methylation-related nutrients may lower the risk of distal (left sided) colorectal cancer in whites, and selenium may lower risk in African Americans. Optimal micronutrient intakes from food alone may be more beneficial than supplementation.

[DNA methylation is a type of chemical modification of DNA that is stable over rounds of cell division but does not involve changes in the underlying DNA sequence of the organism.]

Williams, CD, et al., Antioxidant and DNA methylation-related nutrients and risk of distal colorectal cancer. Cancer Causes and Control; Online Access: doi: 10.1007/s10552-010-9544-3

25. Vitamin D Study Running Out of Roswell Park (Apr. 7/10)

A researcher at Roswell Park Cancer Institute (RPCI) in Buffalo has been awarded a $108,000 grant from the National Cancer Institute to study a possible link between vitamin D3 metabolism and colorectal cancer. Josephia Muindi, MD, PhD, a scientist and assistant professor in the department of medicine at RPCI, believes some genes involved in vitamin D3 biotransformation may play a role in how well the body absorbs the nutrient either naturally or through supplementation. Her research may help to explain in part the variations that lead to vitamin D3 deficiency and serve as a paradigm to predict the efficacy of vitamin D3-based interventions, in addition to predicting those at higher risk for developing cancer and various chronic conditions.

Source: ***http://www.vancouversun.com/health/Falling+vitamin/2616986/story.html***

http://www.roswellpark.org/media/news/national-cancer-institute-funds-vitamin-d3-colorectal-cancer-study-roswell-park-cancer-in