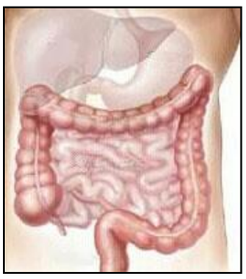
COLORECTAL CANCER RESEARCH

Month Ending October 15th , 2010



The following colorectal cancer research update extends from September 18 – October 15, 2010 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Avastin Not Effective in Treatment of Early Stage Colon Cancer (Sept. 19/10)

Adding Avastin (bevacizumab) to chemotherapy for early stage colon cancer didn't reduce the risk that cancer would return. In fact, preliminary results of the AVANT trial found that chemotherapy alone worked better in preventing recurrences of stage III and high-risk stage II colon cancer, according to a news release from Roche, who were the sponsors of the international clinical trial. This is the second trial in which adding Avastin to chemotherapy after surgery for early stage colon cancer failed to show a disease-free survival benefit. The C-08 trial found that, although Avastin did improve disease-free survival during the first year of treatment, the benefit had disappeared by the third year. The results of the AVANT trial have been eagerly awaited since conclusions of the similar C-08 trial were announced in 2009. After their surgery was over, the Phase III AVANT study randomly assigned 3,451 patients with stage III or high-risk stage II colon cancer to one of three arms:

- FOLFOX (continuous infusion 5-FU, leucovorin, and oxaliplatin) chemotherapy alone for 24 weeks, followed by observation for 24 weeks.
- FOLFOX plus Avastin for 24 weeks, followed by 24 weeks of Avastin alone.
- XELOX (oral Xeloda and oxaliplatin) in combination with Avastin for 24 weeks, followed by 24 weeks of Avastin alone.

The primary aim of AVANT was to find out if adding Avastin to standard chemotherapy improved the percentage of people alive without a cancer recurrence three years after treatment began (*disease-free survival).* Researchers also wanted to measure overall survival at five years and the safety of adding Avastin to chemo. Researchers claimed that it was becoming increasingly clear that the effects of Avastin are different in the metastatic vs. the early disease settings for patients with colon cancer. Avastin is Health Canada approved to treat colorectal cancer that has spread beyond the colon or rectum (*metastatic)*, where it does improve survival time.

Anti-VEGF Therapy

Therapies that inhibit VEGF (vascular endothelial growth factor - a protein believed to be one of the most potent sources of **angiogenesis**, or the development of new blood vessels) may have multiple effects on angiogenesis (tumor growth and delivery of other types of therapy. 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.

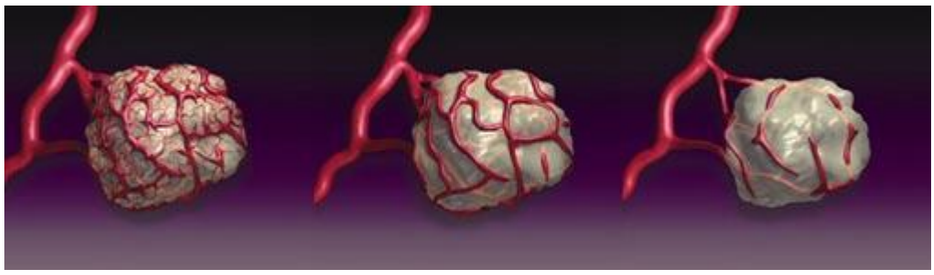


Image Source: http://www.gene.com/gene/products/information/oncology/avastin/vegf-angiogenesis-cancer.html

http://www.roche.com/investors/ir_update/inv-update-2010-09-18b.htm

2. NSAID Vioxx did Not Help Stage II or III Colorectal Cancer Patients (Sept. 30/10)

Results from this study indicate that Vioxx (rofecoxib) did not improve survival for Stage II-III colorectal cancer patients when administered following surgery and adjuvant treatment. This study was closed early due to cardiac safety concerns of Vioxx; reported results represent 7.4 months of the intended three to five years of drug exposure. Vioxx belongs to the class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDS). Vioxx inhibits the COX-2 enzyme, which plays a role in inflammation. The COX-2 enzyme is over expressed in many colorectal cancers, suggesting that inhibitors of this enzyme may play a role in prevention or treatment. Some studies, however, have linked COX-2 inhibitors with an increased risk of cardiovascular problems. Vioxx was withdrawn from the market due to safety concerns over elevated risk of cardiovascular problems associated with long-term use. In the current Phase III randomized study (initiated before Vioxx was withdrawn from the market), researchers evaluated whether Vioxx could improve survival among patients with Stage II or III colorectal cancer. Eligible patients had undergone surgical removal of their cancer as well as adjuvant (post surgical) treatment. The study was originally designed to include 7,000 patients who would receive either Vioxx or a placebo for three to five years. The study was terminated early due to the withdrawal of Vioxx related to

cardiac toxicity concerns. Of the intended 7,000 patients, 2,327 patients were enrolled, and treatment duration was truncated from three to five years to approximately seven months. Patients treated with Vioxx did not experience a statistically significant improvement in survival or recurrence rate compared with placebo. In addition, patients whose tumors expressed COX-2 did not appear to experience a benefit from Vioxx versus placebo. The researchers concluded that Vioxx given for seven months did not improve survival with Stage II or III colorectal cancer when compared with placebo. Nevertheless, the role of COX-2 inhibitors in colorectal cancer is still being investigated, with safety precautions to minimize cardiovascular complications.

Midgley RS, McConkey CC, Johnstone EC, et al. Phase III randomized trial assessing rofecoxib in the adjuvant setting of colorectal cancer: Final results of the VICTOR trial. **Journal of Clinical Oncology** ***[early online publication.] September 13, 2010.***

3. Algae Chemical Being Tested to Treat Colorectal Cancer (Oct. 3/10)

Scientists say that the algae living in the waters of the Florida Keys may provide a drug to fight colon cancer. Largazole, named for the blue-green algae beds of Pickles Reef, off Key Largo, has shown great potential against the deadly disease, according to University of Florida scientists. The oceans have been a largely untapped source of drugs, but now many compounds extracted from marine organisms are being researched. So far, only two marine-based drugs have been approved by the U.S. Food and Drug Administration. Prialt, a non-narcotic painkiller derived from the venom of cone snails, is used to treat severe chronic pain in people failed by standard drugs. Yondelis, made from orange sea squirts that grow on the roots of mangroves in the Florida Keys, is used to treat advanced soft tissue sarcoma abroad. Although developed in the United States, Yondelis has yet to receive FDA approval for sarcoma, but it is approved for women with relapsed ovarian cancer.

Algae found on the surface of ponds

Image Source: https://www.lakelawnandpond.com/WeedItemGroups.aspx?weed=46

http://envirolib.org/press-releases/algae-chemical-tested-against-colon-cancer/

4. Vectibix Delays Progression of Metastatic Disease in Colorectal Cancer Patients (Oct. 7/10)

Among patients with previously treated, metastatic colorectal cancer, the addition of the targeted therapy *Vectibix*® (panitumumab) to chemotherapy delayed cancer progression. This benefit was only observed in patients whose tumors did not contain a mutation in the KRAS gene. Targeted therapies are anticancer drugs that interfere with specific pathways involved in cancer cell growth or survival. Some targeted therapies block growth signals from reaching cancer cells; others reduce the blood supply to cancer cells; and still others stimulate the immune system to recognize and attack the cancer cell. Depending on the specific "target," targeted therapies may slow cancer cell growth or increase cancer cell death. Vectibix inhibits cancer cell growth and survival by targeting a protein known as the epidermal growth factor receptor (EGFR). Vectibix has been approved for the treatment of EGFR-expressing metastatic colorectal cancer that has progressed on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Vectibix appears to benefit only those patients whose cancers do not contain a mutation in a gene known as *KRAS*. *KRAS* mutations occur in an estimated 40-50% of metastatic colorectal cancers and can be identified by testing a sample of tumor tissue. Two recently published Phase III clinical trials reported on the safety and efficacy of Vectibix in combination with chemotherapy for metastatic colorectal cancer. One of the trials evaluated Vectibix in the first-line (initial) treatment of metastatic colorectal cancer, and the other evaluated Vectibix in the second-line treatment of metastatic colorectal cancer. The study that evaluated Vectibix in newly diagnosed, metastatic colorectal cancer was known as PRIME (Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy). The study enrolled 1,183 patients.

Study participants were assigned to receive treatment with FOLFOX4 chemotherapy alone or FOLFOX4 plus Vectibix.

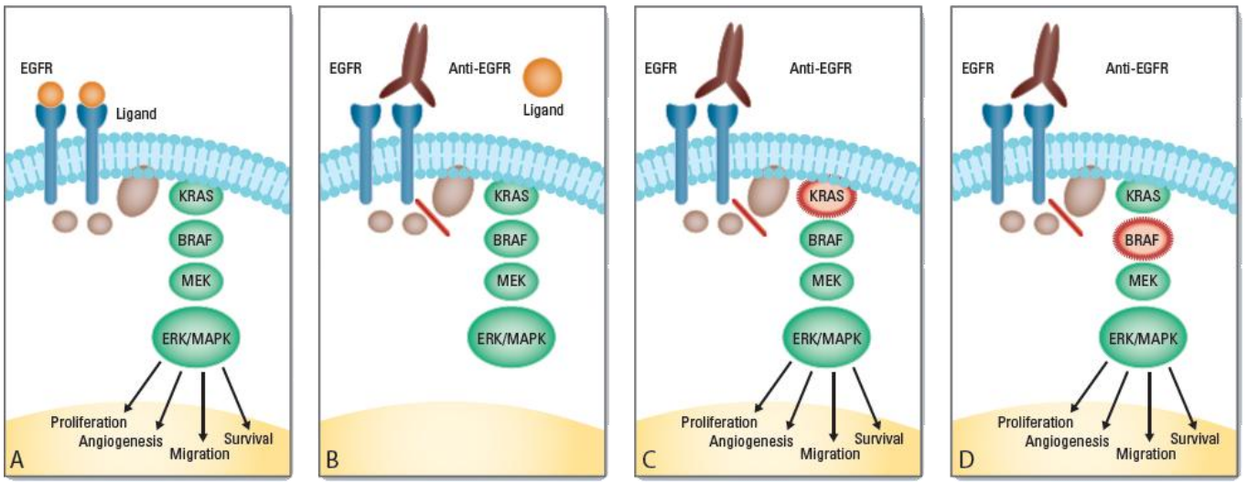
- Among patients without *KRAS* mutations, the addition of Vectibix delayed cancer progression. Progression-free survival was **9.6 months** among patients treated with chemotherapy plus Vectibix compared with 8.0 months among patients treated with chemotherapy alone. Overall survival was **23.9 months** among patients treated with chemotherapy plus Vectibix versus 19.7 months among patients treated with chemotherapy alone, but this result did not meet the criteria for statistical significance, suggesting that it could have occurred by chance alone.
- Among patients with *KRAS* mutations, the addition of Vectibix worsened outcomes. Progression-free survival was **7.3** months among patients treated with chemotherapy plus Vectibix compared with 8.8 months among patients treated with chemotherapy alone.

To evaluate the effectiveness of Vectibix in the second-line treatment of metastatic colorectal cancer, researchers conducted a Phase III study among 1,186 previously treated patients. Study participants were assigned to receive treatment with FOLFIRI chemotherapy alone or FOLFIRI plus Vectibix.

- Among patients without *KRAS* mutations, progression-free survival was **5.9 months** among patients treated with chemotherapy plus Vectibix compared with **3.9 months** among patients treated with chemotherapy alone. Overall survival was **14.5 months** among patients treated with chemotherapy plus Vectibix versus **12.5 months** among patients treated with chemotherapy alone, but this result did not meet the criteria for statistical significance either, suggesting that it could have occurred by chance alone.
- Among patients with *KRAS* mutations, the addition of Vectibix did not improve progression-free or overall survival.

In both studies, side effects of Vectibix included skin rash, low magnesium levels, and diarrhea. These studies indicate that the addition of Vectibix to chemotherapy delays cancer progression among patients with either newly diagnosed or previously treated metastatic colorectal cancer. Because the benefit only applies to patients whose cancer does not contain a *KRAS* mutation, these studies also highlight the importance of *KRAS* testing prior to treatment with this type of targeted therapy.

Anti-EGFR Therapies (Vectibix and Erbitux)



EGFR Signaling Pathway

KRAS and BRAF Mechanisms in Action

- Anti-EGFR therapies (such as vectibix and erbitux) are commonly used in treating patients with metastatic colorectal cancer.
- These therapies heavily rely on blocking the EGFR signaling pathway.
- Recent data strongly suggest the evaluation of downstream markers, such as KRAS and BRAF, are important in selecting which patients will respond to therapy.
- Patients with mutations in the KRAS and BRAF genes are less likely to respond to anti-EGFR therapies.
- Both KRAS and BRAF are prone to mutations in colorectal carcinomas (CRC).
- The combined mutational analysis of both KRAS and BRAF could be used to prospectively select metastatic colorectal cancer patients most likely to benefit from EGFR-targeted treatment. Monoclonal antibodies approved to treat mCRC are

  - ✓ Avastin® (bevacizumab), a monoclonal antibody and anti-angiogenesis drug, blocks the growth of blood vessels to the tumor.
  - ✓ Erbitux® (cetuximab) and Vectibix® (panitumumab) block the effect of hormone-like factors that promote cancer cell growth and binds specifically to the human epidermal growth factor receptor (EGFR).
  - ✓ Both Erbitux (cetuximab) and Vectibix (panitumumab) have proven to be effective in providing clinical benefit in approximately 10% to 20% of patients.

Douillard J-Y, J et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. **Journal of Clinical Oncology** ***[early online publication]. October 4, 2010.***

Peeters M, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. **Journal of Clinical Oncology** ***[early online publication]. October 4, 2010.***

5. Variation of Sulindac May Help Prevent Colorectal Cancer (Oct. 6/10)

A drug called sulindac has been used for many years as a way to prevent colon cancer. It's a non-steroidal anti-inflammatory drug (NSAID), which means it's in the same category of drugs as ibuprofen and aspirin. Unfortunately, sulindac and other NSAIDs that reduce colon cancer risk can have negative side effects with long-term use, including kidney damage and bleeding in the gastrointestinal tract. Now, researchers at Stony Brook University School of Medicine have found that a new derivative of sulindac, called phosphor-sulindac, , may be better at preventing colon cancer and with fewer side effects. So far, the researchers have tested the compound only in animals. Future studies to determine if the drug is safe and effective for colon cancer prevention in humans too, are being planned.

Rigas, B, et al., Phospho-sulindac (OXT-328) a novel sulindac derivative, is safe and effective in colon cnacer prevention in mice. Gastro. Vol. 139, Issue 4: pp. 1320-1332

6. Erbitux Does Not Help Early Stage Colorectal Cancer Patients (Oct. 11/10)

Adding the targeted drug cetuximab, or more commonly referred to as erbitux, to a three-drug chemotherapy regimen for first-line treatment of metastatic colorectal cancer does not improve response rate, progression-free survival or overall survival, according to the results of this study. Results from the NORDIC VII study included 566 patients from Sweden, Denmark, Norway, Finland and Iceland who were randomly assigned to either a combination of 5-fluorouracil plus folinate plus oxaliplatin (NORDIC FLOX), FLOX plus cetuximab until disease progression, or FLOX intermittently plus continuous cetuximab. Among the whole study population, there were no statistically significant differences between the treatment groups in terms of response rate, progression-free survival or overall survival, the NORDIC VII researchers found. The lack of significant benefit also applied to sub-groups of patients with mutant and wild-type versions of the KRAS gene. Some recent studies have shown that the beneficial effect of cetuximab was limited to the group of patients without KRAS-mutations. However, unexpectedly, researchers could not find a significant clinical effect in this specific group either. The results do not support the use of cetuximab in first line when given together with an oxaliplatin regimen. The results of trials combining cetuximab with an irinotecan regimen, as well as results from panitumumab-studies in first line, seem to be more positive, according to the researchers. However, they conclude that these drugs are not fully established as part of standard first-line treatment of metastatic colorectal cancer. The results of this study add to a growing body of evidence regarding the role of cetuximab in the treatment of patients with metastatic colorectal cancer in the first-line setting.

http://www.esmo.org/events/milan-2010-congress/news/view.html?tx_ttnews%5Bpointer%5D=3&tx_ttnews%5Btt_news%5D=949&tx_ttnews%5BbackPid%5D=1798&cHash=362b78a0b9

7. Imprime PGG Plus Erbitux Can Double Response in Patients (Oct. 12/10)

A combination of Biothera's Imprime PGG and cetuximab (Erbitux) doubled the overall response rates for second- and third-line metastatic colorectal cancer patients participating in a Phase Ib/IIa clinical trial. The completed trial results were released at the 35th European Society for Medical Oncology (ESMO) Congress. The sequential, dual-arm, open-label, dose-escalation study evaluated the safety and efficacy of Imprime PGG plus cetuximab and irinotecan (Arm #1) or Imprime PGG plus cetuximab alone (Arm #2). The 32-patient trial was conducted in Asia. In both arms of the trial, patients were dosed with Imprime PGG in combination with standard doses of cetuximab and irinotecan. Imprime PGG was safe and well tolerated.

Study Arm 1 Results
This portion of the study compared the combination of Imprime PGG, cetuximab and irinotecan to the standard of care of cetuximab and irinotecan alone for these late-stage patients. The trial results from this Arm demonstrated a **doubling** of the historical overall response rate and a two-month extension in the time to progression of these patients, compared with cetuximab and chemotherapy.

Study Arm 2 Results
This portion of the trial compared the combination of Imprime PGG and cetuximab with cetuximab monotherapy. Chemotherapy was not administrated to avoid the unintentional destruction of immune cells that are integral to Imprime PGG's mechanism of action. The trial results from this Arm demonstrated a **doubling** of the historical overall response rate and the time to progression of these patients, compared with cetuximab monotherapy.

Subpopulation Results
The study also retrospectively looked at subpopulations of the colorectal cancer patients based on those whose tumors expressed wild type versus mutated KRAS genes. In the wild type KRAS patient population, responses were even more pronounced. The results of this dual arm study demonstrate the proof of concept that Imprime PGG is a novel drug that engages and directs innate immune cells to kill cancer. Imprime PGG's ability to engage the innate immune system opens the door to numerous new therapeutic combinations with monoclonal antibodies targeting the vast majority of cancers.

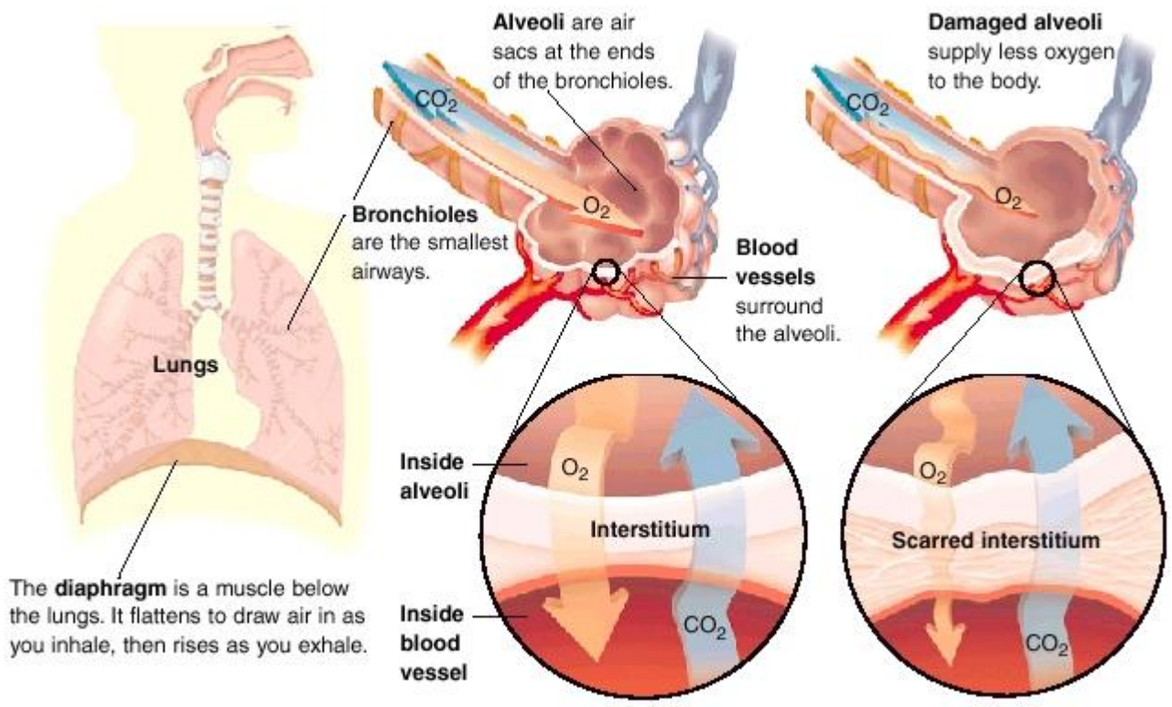
About Imprime PGG
Imprime PGG® is a novel immunotherapy that works synergistically with anti-tumor monoclonal antibodies to activate the largest population of the body's immune cells (neutrophils) to kill cancer cells. Imprime PGG is currently in multiple Phase II clinical trials for lung and colorectal cancer. While some immunomodulatory drugs trigger a broad proinflammatory response, Imprime PGG selectively targets and activates neutrophils without inducing systemic pro-inflammatory cytokines that are attributed to adverse reactions. As a platform therapeutic in oncology, 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.

http://www.businesswire.com/news/home/20101012007196/en/Combination-Therapy-Imprime-PGG-Erbitux-Doubles-Response

8. Interstitial Lung Disease and CRC Chemotherapies (Oct. 12/ 10)

Interstitial lung disease is a rare and potentially fatal complication of chemotherapy in patients with colon and rectum cancer. Oxaliplatin plus 5-fluorouracil (5-FU) and leucovorin (FOLFOX) or irinotecan plus 5-FU and leucovorin (FOLFIRI) are current standard first-line treatments of colorectal cancer (CRC). Interstitial lung disease (ILD) is a rare adverse event of chemotherapy that may result in respiratory failure and death. There are a small number of case reports of chemotherapy-induced ILD following FOLFOX or FOLFIRI. This retrospective safety study evaluated clinical features of ILD associated with FOLFOX or FOLFIRI in 11 patients with CRC. The results of this study suggested that oxaliplatin might have a greater effect on the onset of ILD than the other treatments in this study. Previous case studies have reported oxaliplatin-induced ILD. The results also suggest that preexisting pulmonary disorders increase the risk. ILD is a rare, life-threatening complication of chemotherapy for CRC that may occur during or after chemotherapy. Early diagnosis and treatment are critical. Researchers recommend termination of the suspected chemotherapy culprit agent plus follow-up is generally advised. Low-dose corticosteroids may be given for patients with less severe ILD, or steroid pulse therapy with methylprednisolone may be required for patients with more severe ILD.

Interstitial Lung Disease:



Interstitial lung disease—sometimes called restrictive lung disease—refers to a group of lung problems. When you have interstitial lung disease, your lungs become inflamed and scarred. You may find it harder to take deep breaths. Or you may have a dry cough and mild chest discomfort. Interstitial lung disease develops in steps:

- ✓ First, the alveoli are injured and the lungs become inflamed.
- ✓ Then scarring of the lungs develops. The lungs may become stiff.
- ✓ With enough damage from scarring, oxygen can't easily move through interstitium.

Image Source; http://www.healthline.com/sw/khs-interstitial-lung-disease

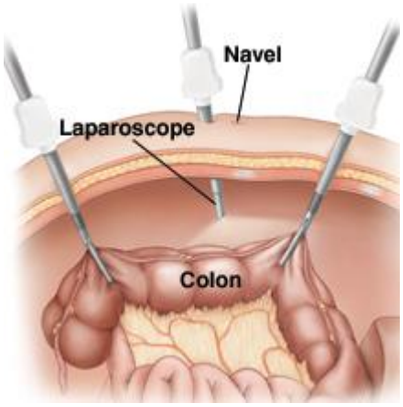
Shimura, T, et al., Clinical features of interstitial lung disease induced by standard chemotherapy (folfox or folfiri) for colorectal cancer. Annals of Oncology. Vol. 21, Issue 10: pp. 2005-2010

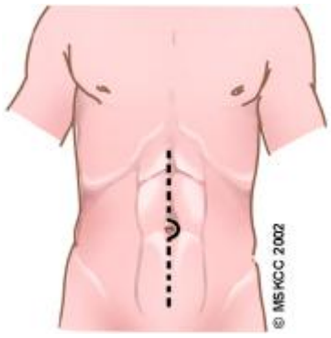
SURGICAL THERAPIES

9. Study Comparing Laparoscopic vs. Open Left Colonic Resection (Sept. 21/10)

The main aim of this study was to compare short-term results and long-term outcomes of patients undergoing laparoscopic versus open left colonic resection. Between February 2000 and December 2004, all adult patients undergoing elective left colonic resection were assessed for eligibility to the study. Some 268 patients undergoing left colonic resection were assigned randomly to the laparoscopic (n = 134) or open (n = 134) approach. The short-term morbidity rate was 20.1% in the open group and 11.9% in the laparoscopic group. Hospital stay was longer in the open group (8.7 versus 7.0 days) for the laparoscopic approach. Quality of life was significantly improved in the laparoscopic group 6 months after surgery, but no difference was found subsequently. The long-term morbidity rate was 11.9% in the open group and 7.5% in the laparoscopic group. The 5-year survival rate of patients with cancer was 66% and 72% for open and laparoscopic groups respectively. Researchers concluded that laparoscopic left colonic resection resulted in an earlier recovery after surgery. As cost-benefit analysis and long-term follow-up showed similar results, the laparoscopic approach should be preferred to open surgery.

Laparoscopic vs. Open Colonic Resection





Open vs. Laprasocopic Colonic Resection – Medical Animation Link:

http://hon.nucleusinc.com/generateexhibit.php?ID=14794&ExhibitKeywordsRaw=&TL=&A=1027

Braga, M, et al., Randomized clinical trial of laparoscopic versus open left colonic resection. British J Surg; 2010; 97(8): pp. 1180-6

10. Primary Tumour Resection Not Recommended in Metastatic Colorectal Cancer (Oct. 7/10)

Resection of the primary tumour in patients with metastatic colorectal cancer may hurt more than it helps, according to an analysis of nearly 10,000 cases of metastatic colorectal cancer presented at the 96th Annual Clinical Congress of the American College of Surgeons (ACS). The more complex the form of tumour resection, the worse the outcome for the patient. Abdominal perineal resection, considered the most difficult form of colorectal resection, was 100% more morbid, and had 63% increased severe morbidity, for these patients, than right colectomy, which is considered the standard case or the easiest of the forms of colon resection. Severe adverse events, which were also measured, included organ-space infection, reoperation, or death and of those patients with metastatic disease, 16.4% experienced severe adverse events compared with 9% in the group that had primary colon cancer alone. Researchers claim that these patients would be better served by going straight to front-line chemotherapy before being considered for surgical resection. For the study, 9,893 patients undergoing nonemergent colorectal resection for malignancy between 2005 and 2007 were identified. Of those patients, 742 (7.5% of the patient population) had metastatic colorectal cancer. Those with metastatic disease had a 5.8% rate of 30-day mortality, compared with 1.7% in those without metastatic disease; 32% of the patients with disseminated disease experienced morbidity, compared with 25% of those without disseminated disease. Morbidity was defined by reference to a large number of conditions including superficial wound infections, sepsis, pneumonia, and the need for reoperation. Of those patients with disseminated disease, 8% received chemotherapy, compared with 3% of those without disseminated disease. For radiation therapy, the numbers were 11% and 12% respectively. Laparoscopic resection was associated with better results for those patients with metastatic disease.

http://docguide.com/news/content.nsf/news/852576140048867C852577B5006F791A

11. Elderly Patients with Colon Cancer Benefit From Surgery and Chemotherapy (Oct. 7/10)

This study found that patients with colon cancer aged 80 to 99 years derive a significant survival benefit from chemotherapy and surgery, even though fewer patients in that age group receive aggressive treatment for the disease. People look at patients in this age group and think that they may not be able to tolerate chemotherapy or that since they have a lot less metastatic disease, they don't really need chemo. Researchers reviewed data from 49,505 patients with colon cancer between 1988 and 2006. Of the patients, 8% were aged 18 to 50 years; 21% were aged 51 to 64 years; 45% were aged 65 to 79 years; and 26% were aged older than 80 years. In the youngest age group, 51% of patients were male, compared with 40% in the oldest age group. Of the patients in the oldest group, 73% were white. Five-year survival for patients in the youngest age group was 64%, while 3-year survival (the only measure available) for the oldest patients was 33%. Median survival for the youngest group was 206 months, compared with 33.7 months for the oldest group. Of the youngest age group, 48% received chemotherapy, while only 7% received chemotherapy in the oldest age group. Patients in the oldest age group had a 2-year survival with chemotherapy, compared with 1.45 years without chemotherapy. Rates of surgery were higher noting that 93% of patients in the youngest age group received surgery for colon cancer, compared with 87% of those in the oldest age group. The oldest patients had a 33.7-month survival rate if they underwent resection, compared with 4 months if they did not. Of older patients who had surgery, 33% had a 5-year survival, compared with 5% in those who did not have survival.

http://docguide.com/news/content.nsf/news/852576140048867C852577B5006A5648

SCREENING

12. Little Adherence to FOBT Screening (Sept. 18/10)

Fecal occult blood test (FOBT) is an effective colorectal cancer screening method, but it needs to be repeated every one or two years to reduce the risk of dying from colon or rectal cancer. But almost half of a group of insured patients initially screened with fecal occult blood testing didn't follow-up with another FOBT within two years, as recommended. A large insurance health plan found 11,000 people who had been screened with FOBT during a 2 year period. They then looked to see if they'd had another FOBT or other colorectal cancer screening exam within the following two years. Nearly a half (46.8%) didn't. Having gone to the doctor for a preventive health checkup rather than for treatment of an illness made a difference. Those people who had a preventive health visit during the 2 years following their first FOBT were 11 times more likely to have had a follow-up test. Researchers concluded that longitudinal adherence with FOBT screening was low in this insured population, potentially compromising its effectiveness in population CRC mortality reduction. Interventions to promote adherence may be necessary to achieve high effectiveness in population-based FOBT screening programs.

FOBT Kit

Image Source: http://www.health.gov.on.ca/en/ms/coloncancercheck/public/fobt/fobt_hometestkit.aspx

Fenton, Joshua, et al., Longitudinal adherence with fecal occult blood test screening in community practice. Annals of Family Med. 8: pp. 397-401

13. Screening for Colorectal Cancer Through A Small Amount of Blood (Oct. 4/10)

At the recent International Conference on Molecular Diagnostics in Cancer Therapeutic Development, researchers announced a new colon cancer screening test. What makes this test so exciting is that it may be able to detect early colon cancer with a blood test. The experimental colon cancer screening test starts with a small piece of genetic material called **micro RNA**. Micro RNA helps to regulate genes, which are the instruction manual for running cells in the human body. Micro RNA is a bit like a switch, helping to determine which genes are turned on or off at any given time. It turns out that micro RNA can be detected in the blood. The micro RNA that comes from cancer cells is somewhat different than the micro RNA that comes from healthy cells. By detecting the abnormal micro RNA from colon cancer cells, researchers hope to detect the presence of colon cancer before symptoms even arise. If the blood test shows cancer is present, a person can undergo colonoscopy or another type of test that allows for direct

views of the colon. Small tumors can be removed before they become larger and spread to other areas of the body. Colon cancer is easier to treat and cure if detected before it spreads beyond the colon. This screening test is still in the experimental phase, but researchers hope to validate the method as reliable and accurate with further testing in larger groups of people.

http://www.aacr.org/home/scientists/meetings--workshops/molecular-diagnostics-in-cancer-therapeutic-development/abstracts.aspx

14. Unsedated Colonoscopy Using Novel Water Method Better Tolerated (Oct. 610)

The results of two randomized controlled trials of unsedated colonoscopy comparing water infusion versus air insufflation to distend the colon both showed that patient tolerance with the water method during unsedated colonoscopy was greater than with air insufflation and enhanced patient willingness to undergo a repeat unsedated exam; however, the cecal intubation and adenoma detection rates varied somewhat between the two studies. Unsedated colonoscopy is common worldwide, but in the United States, conscious sedation is dominant and deep sedation is gaining support. Without sedation, the exam can cause discomfort due to the air pumped into the colon which causes the colon to stretch in order to more easily insert the colonoscope. Scheduled unsedated colonoscopy has been requested by seven percent of U.S. patients. In unsedated patients, discomfort during colonoscopy limits cecal intubation (colonoscope insertion reaching the cecum, which is the pouch that marks the beginning of the large intestine also known as the colon), which is essential for a complete exam. Methods for reducing discomfort have included several water-related techniques. Researchers at Veterans Affairs Healthcare System facilities in California developed a novel water method for scheduled unsedated colonoscopy using water infusion in lieu of air insufflation to more comfortably open the colon and insert the colonoscope. In their observational study of veterans, they showed that the novel water method enhanced cecal intubation and patient willingness to undergo a repeat scheduled unsedated colonoscopy. In this prospective, randomized controlled trial, the researchers' objective was to confirm these beneficial effects. From November 2007 to April 2009, eighty-two veterans underwent scheduled unsedated colonoscopy by either the air method (40 patients) or water method (42 patients). The main measurements were discomfort and procedure-related outcomes. The colonoscopies were performed by a single colonoscopist without registered nurse support. The study confirmed that the water method significantly enhanced cecal intubation and patient willingness to undergo a repeat scheduled unsedated colonoscopy. The cecal intubation rate in the water group **was 98%,** significantly higher than that in the air group which was **78%**. The percentage of patients reporting a willingness to repeat a scheduled unsedated colonoscopy was also significantly higher at **93%** for the water group compared to **78%** with the air group. The proportion of patients with at least one adenoma (precancerous polyp) showed a trend in favor of the water group at **36%, versus 23%** in the air group. This trend was present for all indications in the proximal colon and for polyp size of 10 mm or larger. The cleansing effect of the water might have contributed to the higher adenoma detection yield. The adenoma detection rates were comparable to those in sedated colonoscopy.

Colonoscopy Procedure

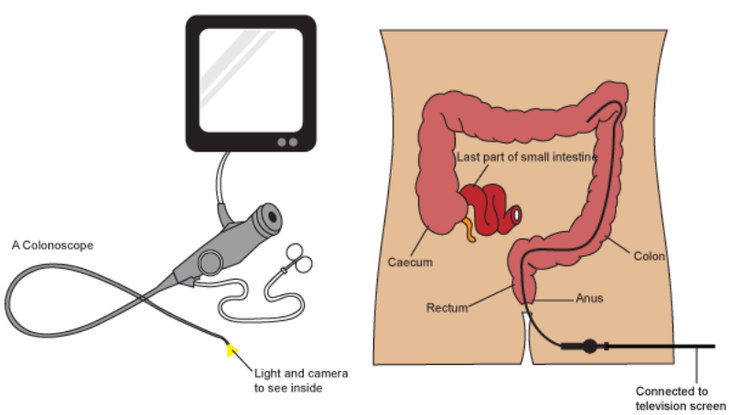


Image Source: http://www.bestcoloncleaning.com/2009/03/index.html

Leung, Felix W. et al., A proof-of-principle, prospective, randomized, controlled trial demonstrating improved outcomes in scheduled unsedated colonoscopy by the water method. **Gastrointestinal Endoscopy*, 2010; DOI: 10.1016/j.gie.2010.05.020***

Radeelli, Franco, et al., Warm water infusion versus air insufflation for unsedated colonoscopy: a randomized, controlled trial. **Gastrointestinal Endoscopy*, 2010; DOI: 10.1016/j.gie.2010.06.025***

15. 7% or More of Colorectal Cancers May Be Missed by Colonoscopy (Oct. 6/10)

Colonoscopy screening may miss as many as one in every 13 colon cancers, according to this new study. In the study, Canadian researchers identified almost 5,000 Manitoba residents ages 50 to 80 who were diagnosed with colon cancer between 1992 and 2008. The team found that about eight percent, or one in every 13 cancers, had been missed during colonoscopies conducted six months to

three years prior to diagnosis. Women were a third more likely to have had their cancer missed. During a colonoscopy, a flexible camera is passed through the colon in search of abnormal growths known as polyps and other warning signs of early tumors. It is one of a few screening tests for colon cancer, the second-leading cancer killer in Canada. Women were a third more likely to have had their cancer missed, report the researchers and general practice physicians missed cancers 60% more often than gastroenterologists. There are three likely reasons for these "misses," noted by the researchers. Tumors may simply have gone unidentified on the exam, or were seen but not completely removed. While rare, they also noted that it is possible that an undetected cancer was actually not present at the exam, but rather grew very quickly afterwards. No improvement in colonoscopy can do anything to avoid the latter. But the first two reasons are potentially avoidable.

Singh, Harminder, et al., Rate and Predictors of Early/Missed Colorectal Cancers After Colonoscopy in Manitoba: A Population-Based Study. **Am J Gastroenterol Advance online publication 28 September 2010; doi: 10.1038/ajg.2010.390**

16. Screening For Advanced Colon Cancer Patients Not Beneficial (Oct. 14/10)

According to this study, a considerable amount of patients with advanced cancer continue to undergo cancer screening tests that do not have a meaningful likelihood of providing benefit. For the study, cancer screening procedures (mammography, Papanicolaou test, prostate-specific antigen [PSA], and **lower gastrointestinal [GI] endoscopy**) were assessed in 87,736 fee-for-service Medicare enrollees aged 65 years or older diagnosed with advanced lung, **colorectal**, pancreatic, gastro-esophageal, or breast cancer between 1998 and 2005. Researchers followed up with the participants “until death or Dec. 31, 2007, whichever came first,” according to the study’s abstract. A group of 87 307 Medicare enrollees without cancer were individually matched by age, sex, race, and SEER registry to patients with cancer and observed over the same period to evaluate screening rates in context. For each cancer screening test, utilization rates were defined as the percentage of patients who were screened following the diagnosis of an incurable cancer. For all patients following advanced diagnosis compared with controls, lower GI endoscopy was received by 1.7% vs. 4.7%. Researchers concluded that a sizeable proportion of patients with advanced cancer continue to undergo cancer screening tests that do not have a meaningful likelihood of providing benefit.

Sima, Camelia, et al., Cancer Screening Among Patients With Advanced Cancer. J American Med Assoc. 2010; 304(14): pp. 1584-1591.

OTHER

17. African-Canadian Patients Face Greater Risk of Mortality (Sept. 23/10)

According to study results, black patients diagnosed with colorectal cancer face a greater risk of mortality than white patients affected by the same disease. Using data from death certificates across the United States from 1960 to 2005, researchers compared the observed survival rates between black and white patients. Researchers also compared survival rates among patients diagnosed with different stages of colorectal cancer, correcting for differences caused by the time of patients’ diagnoses. Overall, colorectal cancer mortality rates have a strong racial disparity. There is progress against Caucasian mortality rates and stagnation for African-Americans. Things have gotten better for whites over time and comparatively worse for African-Americans. For overall colorectal cancer mortality rates, researchers found that, while mortality rates for white females declined 54% over the time period of 1960 to 2005, rates for black females decreased by only 14%. For white men, mortality rates dropped 39%, while mortality rates for black men instead rose 28%. The study also analyzed mortality rates within the specific stage of colorectal cancer at the time of diagnosis and found that mortality rates were higher for blacks in each group than for whites during each of the last four decades. The researchers were the first group to illustrate that the risk of death for black colorectal cancer patients is growing over time, across genders and all stages of the disease, according to the study.

Soneji, Samir, et al., Racial disparities in stage-specific colorectal cancer mortality: 1960-2005. American J Public Health. Published Ahead of Print. August 2010.

18. Reviewing the Genetics of Hereditary Colorectal Cancer (Sept. 25/10)

Colorectal cancer is a common disease, and approximately 25% of patients have a familial component. Single gene germline mutations giving rise to a true hereditary susceptibility account for around **5% to 6%** of all cases. Lynch syndrome is the most common hereditary form of colorectal cancer. Much of the hereditary component in the remaining familial cases of colorectal cnacer is likely polygenic (one of a group of genes), and many of the genetic changes involved are as yet unidentified. This article addresses the most clinically important colorectal cancer genetic syndromes. Reviewing its content is recommended.

Power, Derek, et al., Clinical Genetics of Hereditary Colorectal Cancer. J Hema.Onc Clinics. Vol. 24, Issue 5: pp. 837-859

19. Music Eases Cancer Pain (Sept. 28/10)

According to the results of this study, listening to just thirty minutes of music significantly reduced pain and distress for cancer patients. The patients were receiving medication, but still had pain. Music reduced pain scores by more than 50% for almost half of them compared to fewer than 1 in 10 similar patients who just rested in bed. Nurses randomly assigned Taiwanese patients to listen to their choice of music for 30 minutes or to rest without music. They measured pain at the beginning and end of the time using a visual scale. 42% who listened to music had their pain scores fall by 50% or more, compared to 8% of those who merely rested. A statistical test showed a large effect of the music for both changes in the sensation of pain and changes in the distress patients felt. The patient had their choice of folk songs, Buddhist hymns, or American harp and piano music. Although 7 out of 10 chose the Taiwanese music, the American music was also enjoyed and effective. Researchers concluded that offering a choice of familiar, culturally appropriate music was a key element of the intervention. Soft music was safe, effective, and liked by participants. It provided greater relief of cancer pain than analgesics alone. Thus, nurses should offer calming, familiar music to supplement analgesic medication for persons with cancer pain.

Huang, S. et al., Music reduced cancer pain via relaxation and distraction. The J of Pain. Vol. 8, Issue 4, Supplement 1, page S58.

20. Short Duration of Sleep Increases Risk of Colorectal Adenoma (Oct. 7/10)

Short duration and poor quality of sleep have been associated with increased risks of obesity, cardiovascular disease, diabetes mellitus, and total mortality. However, few studies have investigated their associations with risk of colorectal adenomas. Three hundred thirty-eight (27.3%) of the 1240 participants were diagnosed with incident colorectal adenomas. The authors found a statistically significant association of colorectal adenoma with the Study Questionnaire component 3, which corresponds to **sleep duration**. Cases were more likely to average less than 6 hours of sleep per night (28.9% vs 22.1% in controls). Individuals averaging less than 6 hours per night had an almost 50% increase in risk of colorectal adenomas as compared with individuals sleeping at least 7 hours per night. Cases were also more likely to report being diagnosed with sleep apnea (9.8% vs 6.5%) and more likely to have worked alternate shifts (54.0% vs 46.1%). Researchers concluded that shorter duration of sleep significantly increases risk of colorectal adenomas. The authors' results suggest sleep duration as a novel risk factor for colorectal neoplasia.

Thompson, Cheryl, et al., Short duration of sleep increases risk of colorectal adenoma. Cancer. Article first published online: 8 OCT 2010 DOI: 10.1002/cncr.25507

21. Low Socioeconomic Status Linked with More Severe Colorectal Cancer (Oct. 7/10)

According to this study, people living in economically deprived neighborhoods were more likely to be diagnosed with late-stage, non-localized colorectal cancer, even after researchers controlled for known colorectal cancer risk factors. Researchers evaluated data from the NIH-AARP Diet and Health Study, a prospective cohort of participants from six U.S. states and two metropolitan areas. Data were obtained from 1995 to 2003, and none of the participants had a history of colorectal cancer. Findings revealed 6,934 cases of colorectal cancer among 560,288 eligible participants; 59% of these cases were non-localized, defined as regional, distant or unstaged tumors. After adjusting for age and sex, the researchers reported a colorectal cancer incidence of 17.5 per 10,000 person-years. **Those participants who resided in the least socioeconomically deprived neighborhoods had an incidence rate of 16.2% compared with 19.8% for those living in the most disadvantaged neighborhoods**.

Doubeni, Chyke et al., Low Socioeconomic Status Linked With More Severe Colorectal Cancer. Amer Assoc for Cancer Research. Published Ahead of Print Oct. 1, 2010.

NUTRITION & HEALTHY LIFESTYLE

22. Study Shows Multivitamins Do Not Improve Outcomes (Sept. 20/10)

According to the results of this study, in patients with Stage III colon cancer, use of multivitamins during and after chemotherapy did not improve survival or reduce the risk of recurrence. Stage III colon cancer refers to cancer that has spread to lymph nodes surrounding the colon but not to other parts of the body. Treatment of Stage III colon cancer often involves surgery followed by adjuvant chemotherapy. Dietary supplements such as multivitamins are widely used by the U.S. and Canadian population. Roughly 30% of people use multivitamins in the hope of preventing or treating common chronic diseases such as cancer. The effects of multivitamins on health, however, remain uncertain. To explore whether multivitamin use during or after adjuvant chemotherapy improves outcomes among patients with Stage III colon cancer, researchers evaluated information from 1,038 participants in a chemotherapy clinical trial. Roughly half of the patients reported using a multivitamin during chemotherapy. Use of multivitamins during and/or after adjuvant chemotherapy did not significantly affect risk of cancer recurrence or overall survival, nor did multivitamin use reduce the gastrointestinal side effects of chemotherapy. These results suggest that multivitamin using during and after adjuvant chemotherapy does not significantly improve outcomes in patients with Stage III colon cancer. Patients are advised to talk with their doctor about any dietary supplements that they are using or considering.

Ng K, et al. Multivitamin use is not association with cancer recurrence or survival in patients with Stage III colon cancer: findings from CALGB 89803.* Journal of Clinical Oncology. *Early online publication August 30, 2010

23. Cancer Risk and Waist Expansion (Sept. 21/10)

Health researchers have suggested for some time that a large waist is associated with higher risks of heart disease and early death. Now they report convincing evidence that being overweight increases colon cancer risk. The study shows that abdominal fat around the waist is particularly harmful for bowel cancer, even in people who are close to normal weight or only moderately overweight. This latest study adds to the already strong evidence that carrying excess body fat increases your risk of cancer. In fact, scientists now say that, after not smoking, maintaining a healthy weight is the most important thing you can do for cancer prevention. As well as confirming the link between body fat and bowel cancer, this study has strengthened the evidence that where we carry the fat is also important. This means that people who do have a large waist should consider losing weight even if they are in the normal BMI range. This study indicates that people should pay attention to the abdominal fatness even if they are in the normal range of weight, and it confirms that being overweight increases risk of this type of cancer. This study gives us a better picture on how body fat affects risk of bowel cancer. More research is needed to understand how abdominal fatness can be prevented in both normal and overweight individuals.

http://www.futurity.org/health-medicine/as-waist-grows-so-does-cancer-risk/

24. New Research on the Benefits of Traditional Chinese Medicine When Treating Chemo Side Effects (Oct. 1/10)

The results of a recent study indicated that Traditional Chinese Medicine (TCM) was effective in the treatment of the gastrointestinal side effects caused by chemotherapy during the treatment of patients with colon and rectal cancer. The study is understood to be the first study which conclusively proved the benefits to patients of TCM through clinical trials. The study examined the efficacy of four ancient Chinese herbs in the treatment of colon and rectal cancer patients, when used as a means of reducing the side effects of the chemotherapy treatment they were receiving. The results of the study clearly indicated that the four ancient Chinese herbs were able to ***restore the intestinal cells which were damaged by the chemotherapy treatment, and were also found to actually enhance the anti tumor activity of Irinotecan, the chemotherapy drug being used to treat the patients with colon and rectal cancer***. The cocktail comprises Chinese peonies, Chinese liquorice, the fruit of the buckthorn tree and flowers of the Chinese skullcap plant. In China, they call it 'Huang Qin Tang' and have used it to treat gastrointestinal problems for about 1,800 years. The team at Yale was able to pursue this avenue of research when no one else would support it. They have now been able to prove that these traditional medicines actually do deliver real benefits that may improve the lives of cancer patients. The results of the study were published in a recent issue of Science Translational Medicine.

Lam, W. et al. The Four-Herb Chinese Medicine PHY906 Reduces Chemotherapy-Induced Gastrointestinal Toxicity. Sci. Trans. Med. Volume 2, Issue 45 p. 45ra59 (2010)

25. Green And Black Tea Deemed Helpful (Oct. 3/10)

Green tea has been touted as a "cancer-fighting" beverage for years. This recent study suggests green tea may lower cancer risk through its ability to protect against DNA damage. Damage to DNA can lead to cancerous changes in the cells of our body and daily green tea drinking may reduce DNA damage by as much as 20%! But some people don't like the taste of green tea. The latest research on the connection between black tea and cancer is also very promising. Researchers in India, a country of black tea drinkers, found that compounds in black tea may have potent anti-cancer properties too. Black tea appears to turn on proteins that halt out-of-control cell growth and encourage damaged cells to die, rather than develop into cancer. The researchers looked at liver cancer specifically, but the ways in which black tea inhibit liver cancer cells are likely applicable to other cancers too. They noted that the proteins affected by black tea are common to many cancers, including **some colon cancers**. By influencing a whole network of molecules that control cell death mechanisms, black tea may lead to cancer risk reduction. Researchers concluded that both green and black tea are healthy beverage options. And both, when consumed regularly, may offer some protection against colon and other cancers.

Murugan, Senthil, et al., Intrinsic apoptosis and NF-kB signaling are potential molecular targets for chemoprevention by black tea polyphenols in HepG2 cells in vitro and in a rat hepatocarcinogenesis model in vivo. Food and Chemical Toxicology. Published online ahead of print, doi: 10.1016/j.fct.2010.09.02 .

26. Exercising with Cancer (Oct. 7/10)

More and more studies are showing that exercise is an important part of healthy survivorship after cancer. But should you get started right away, during treatment? Or should you wait until after treatment is finished? You need to know whether it's safe to exercise with cancer before you get started. Not only is it safe to exercise with cancer, health experts say it is necessary. The National Cancer Institute (NCI) just published the findings from a panel of 13 experts in cancer, fitness, exercise, and obesity. The panel was created by the American College of Sports Medicine (ACSM). Experts claim that patients should stay active. They say this is true for all cancer survivors, including people still in cancer treatment. Exercise with cancer is safe and it can help people cope with cancer and treatment-related side effects.

Furthermore, exercise may improve survival after diagnosis as well. Exercise with cancer is safe, but are there any benefits to being physically active during and after cancer treatment? According to the experts, the benefits of exercise for cancer survivors are numerous. Exercise can lessen fatigue, one of the most common complaints of patients undergoing cancer treatment. Exercise can help people sleep better and lessen the likelihood of insomnia during treatment. And exercise improves physical functioning in cancer survivors during and after treatment. All of this adds up to significantly better quality of life for cancer survivors. This means a whole lot more well-functioning, and very likely happier, people. For many cancer patients, doctors advise walking as a good way to get some exercise. Beyond walking, what and how much you should do depends on a number of things:

- What your level of physical activity was before you were diagnosed with cancer
- Other health conditions you have
- The type of cancer you have
- The type of cancer treatment you are undergoing
- Symptoms and side effects you are experiencing
- Whether you have had surgery recently
- Whether you have experienced bone loss due to your cancer or its treatment
- Whether you have a history of, or are being treated for, blood clots
- Your age and gender
- Other factors mentioned by your doctor or nurse

For example, if you were very active before your cancer diagnosis, there is a good chance you can keep up much of your usual exercise routine when you feel up to it. If you were not physically active before your cancer diagnosis, you should talk to your doctor before you begin an exercise program. You need to get the OK from your medical team that your exercise plan is appropriate for your current level of fitness. Also remember that other conditions you have, such as heart disease or diabetes, may affect the types and amount of exercise that are right for you. In general, walking is safe for most people. If you have not been physically active, short walks are a good place to start. But ask your doctor for more information and guidance before you begin. There are some situations in which it is not safe to exercise. Examples of times when it is not safe to exercise with cancer include:

- Recent surgery. If you have had surgery, ask your doctor when you can begin exercising. Also ask your doctor what types of exercise are safe, given your history of surgery.
- Issues with blood clotting. If you are taking medications to manage coagulation (blood clotting), such as warfarin (Coumadin) or heparin, you may need to avoid certain types of exercise. Exercise that results in high impacts to your body, such as jogging, running, or basketball, may not be safe.
- Bone loss. If your cancer or its treatment causes bone loss, or if you have tumors in your bones, exercise may not be safe for you.
- Dizziness or extreme fatigue. If you suffer from dizziness or have very severe fatigue, exercise may not be safe for you. Ask your doctor for guidance.

These are some examples of when it is not safe to exercise with cancer. There may be others. If in doubt, always check with your doctor before beginning any new activity during cancer treatment. The bottom line is that for most people with cancer, regular physical activity can help you feel better and live better, both during and after treatment.

American Cancer Society. Nutrition and Physical Activity After Cancer Treatment. August 15, 2010. http://coloncancer.about.com/gi/o.htm?zi=1/XJ&zTi=1&sdn=coloncancer&cdn=health&tm=711&gps=191_420_1020_480&f=22&tt=12&bt=1&bts=0&zu=http%3A//www.cancer.org/Treatment/SupportProgramsServices/Programs/ParticipateinaCancerEducationClass/ICanCopeOnline/nutritionandphysicalactivityaftertreatment