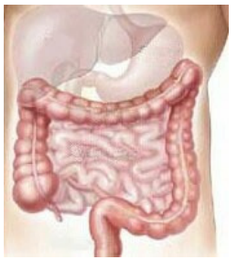
COLORECTAL CANCER RESEARCH

Month Ending December 18, 2009



The following colorectal cancer research update extends from November 14 – December 18, 2009 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. ESAs Increase Blood Clots in Cancer Patients (Nov. 16/09)

Drugs designed to treat anemia in older cancer patients increased their risk of blood clots and didn't reduce the need for blood transfusions. Among over 56,000 cancer patients 65 and older treated in community settings from 1991 through 2002, 27% received an erythropoiesis-stimulating agent (ESA). 15% of those who got ESAs developed a blood clot (*venous thromboembolism*) compared to 10% of patients who didn't have ESA treatment. Although the goal of ESAs was to reduce the need for blood transfusions, the percentage of transfusions remained steady at 22% each year from 1991 through 2002. Overall survival didn't differ between the patients who received ESAs and those who didn't. Chemotherapy can cause anemia when the bone marrow doesn't keep up with the need to replace normally lost red blood cells. Erythropoiesis-stimulating agents such as Procrit and Epogen (epoetin alfa) and Aranesp (darbepoetin alfa) stimulate the bone marrow to produce new red blood cells. Ideally, use of ESAs should reduce the need for blood transfusions during chemo. However, when researchers reviewed data for patients who were diagnosed with colon, lung, or breast cancer or with lymphoma from January 1991, through December 2002 and who received chemotherapy, they found no difference in blood transfusion rates. They did find more blood clots, both in deep leg veins and in the lungs, among those who were treated with ESAs. The rate of venous thromboembolism was 14.3% in the ESA patients and 9.8% in patients who didn't get ESAs. Researchers concluded that use of erythropoiesis-stimulating agents increased rapidly after its approval in 1991, but the blood transfusion rate did not change. Use of erythropoiesis-stimulating agents was associated with an increased risk of venous thromboembolism but not of mortality

Dawn, I et al., Patterns of Use and risks association with erythropoiesis-stimulating agents among medicare patients with cancer. J of National Cancer Institute. Advance Access published online on November 10, 2009. doi: 10.1093/jnci/djp387

http://fightcolorectalcancer.org/research_news/2009/11/esas_increase_blood_clot_risk

2. Treating Colon Cancer with Xeliri (Nov. 16/09)

A newly published study highlights how combining existing cancer treatment medications in new ways can improve survival for those with advanced colorectal cancer. The chemotherapy combined two medications, capecitabine (better known as xeloda) and irinotecan, in a treatment referred to as XELIRI. Researchers studied XELIRI treatment in 53 patients, more than half (55%) of whom were 65 years of age or older. The overall response rate (ORR) to XELIRI in this group was 32% and the disease control rate was estimated to be 66%. The median (similar to "average") survival in the group was 19.2 months, showing that even in people with metastatic (advanced) colorectal cancer, the appropriate treatments can extend life in a meaningful way. Very serious side effects, which are known as grade 4 toxicity, occurred in only 1 patient. Overall, this study supports that XELIRI, which is a combination of two chemotherapy medications - capecitabine and irinotecan - is a promising first-line treatment of advanced colon cancer

Garcia-Alfonso, P, et al., Capecitabine in combination with irinotecan (xeliri) administered as a 2-weekly schedule, as first line chemotherapy for patients with metastatic colorectal cancer: a phase II study of the Spanish GOTI group. British Journal of Cancer. (2009), 101, pp. 1039-1043

3. A Novel Cancer Vaccine (Nov. 1709)

A cancer vaccine is making headway in clinical trials at the University of Pittsburgh School of Medicine. Rather than targeting a cancer-related virus--the way Gardasil targets human papillomavirus to prevent some cervical cancers--the new vaccine triggers the immune system to attack a faulty protein that's often abundant in colorectal cancer tissue and precancerous tissue. The investigators say that if the vaccine is successful, it could potentially obviate the need for repeated colonoscopies in patients at high risk for developing colorectal cancer. These patients have had multiple precancerous polyps, called advanced adenomas, in their large intestine, and they are routinely screened by colonoscopy for signs of recurrence. The vaccine has already proven safe in patients with advanced pancreatic cancer. It is now in clinical trials to gauge the immune response it elicits in patients with a history of advanced adenomas. It works by spurring the body to manufacture antibodies against the abnormal version of a mucous

protein called MUC1. While moderate amounts of the protein are found in the lining of normal intestines, high levels of a defective form of MUC1 are present in about half of advanced adenomas and the majority of colorectal cancers. The vaccine primes the immune system to monitor the gut for emerging cancers by teaching it to recognize abnormal MUC1. If an adenoma develops and begins to produce the faulty version of MUC1, the immune system will raise antibodies to attack and destroy the precancerous tissue. Essentially, you would be using your immune system as a surveillance mechanism to prevent the development of malignancy, which is quite novel and very promising.

http://technologyreview.com/biomedicine/23067/?a=f

4. Avastin Deemed Effective in Older Patients (Nov. 17/09)

Colorectal cancer patients 65 and older without other serious medical problems benefited when Avastin (bevacizumab) was added to chemotherapy. Combining results of four randomized clinical trials of Avastin and chemotherapy in patients with advanced colorectal cancer, researchers found that adding Avastin increased both the time older patients lived and the time before their cancer got worse. Patients who were 70 and older had similar improvements. There were more serious problems caused by blood clots *(thromboembolic events)* in patients who got Avastin, mostly related to arterial events. However, other serious side effects were no more common in older patients than in those who were younger than 65. To get a clearer idea of how adding Avastin to chemotherapy affects patients 65 and older, the research team combined information from three first-line and one second-line trial of Avastin and chemotherapy together including 1,100 patients who were 65 or older. They found that both progression-free survival (time before disease got worse) and overall survival improved when Avastin was added to chemo, and that age made little difference in benefits.

Progression-free survival time without and with Avastin was:

- For those under 65: 6.7 months vs 9.5 months
- Those 65 and older: 6.9 months vs 9.3 months
- Those 70 and older: 6.4 months vs 9.2 months

Overall survival time without and with Avastin was:

- For under 65: 16.5 months vs 19.9 months
- 65 and older: 15.0 months vs 17.9 months
- 70 and older: 14.1 months vs 17.4 months

As patients got older, arterial thromoembolytic events (ATE) such as heart attack, stroke, TIA's, and angina increased with the addition of Avastin.

- Under 65: no difference in ATEs was found — 2% in both Avastin and non-Avastin groups
- 65 and older: 5.7% ATE for Avastin compared to 2.5 in non-Avastin group
- 70 and older: 6.7% ATE for Avastin, 3.2 with no Avastin

Age made no difference in other serious side effects including bleeding, hypertension, and gastrointestinal perforations. Researchers concluded that this pooled analysis of data from phase II and III metastatic colorectal cancer studies demonstrates that bevacizumab in combination with chemotherapy had a similar impact on PFS and OS in protocol-eligible older versus younger patients. Careful patient selection, however, remains important and should include an objective assessment of the patient's physical and mental status.

Cassidy et al., Effect of bevacizumab in older patients with metastatic colorectal cancer: pooled analysis of four randomized studies. J of Cancer Research and Clinical Oncology., Online First November 10, 2009.

5. Positive Phase II Trial on Picoplatin in Colorectal Cancer (Nov. 18/09)

Poniard Pharmaceuticals, Inc. announced updated clinical data from its randomized, controlled Phase 2 trial of picoplatin in patients with metastatic colorectal cancer. The updated results indicated that picoplatin, given once every four weeks in combination with 5-fluorouracil and leucovorin in the FOLPI regimen, has comparable efficacy to oxaliplatin, given in combination with 5-fluorouracil and leucovorin in the modified FOLFOX-6 regimen, as a first-line therapy for CRC, as assessed by one-year survival rate, progression-free survival (PFS) and disease control.. The randomized, controlled Phase 2 trial is evaluating picoplatin as a neuropathy-sparing alternative to oxaliplatin for the first-line treatment of metastatic CRC in 101 patients who have not received prior chemotherapy. The trial is comparing the safety and efficacy (assessed by objective tumor response, PFS and overall survival) of intravenous picoplatin given once every four weeks in combination with bi-weekly 5-fluorouracil and leucovorin (the FOLPI regimen) with oxaliplatin given in combination with 5-fluorouracil and leucovorin in the mFOLFOX-6 regimen. The new data presented at the AACR-NCI-EORTC Conference continued to demonstrate comparable efficacy between the two arms. The median PFS was 6.8 months for FOLPI-treated patients and 7.0 months for mFOLFOX-6-treated patients. Disease control rates (complete response plus partial

response plus stable disease rates) were also comparable between the two treatment groups with 75% of FOLPI-treated patients and 76% of mFOLFOX-6-treated patients experiencing disease control. To date, the one-year survival rate is 52% for patients treated with FOLPI and 55% for patients treated with mFOLFOX-6.

http://www.medicalnewstoday.com/articles/171280.php

6. Adding Erbitux to Chemo Can Qualify Patients for Surgery (Nov. 25/09)

In patients with inoperable colorectal liver metastases, adding erbitux to neoadjuvant (before surgery) chemotherapy with FOLFOX6 or FOLFIRI shrunk tumors and led to increased resectability or surgery. From December 2004 to March 2008, researchers randomly assigned patients from 17 centers in Germany and Austria to cetuximab (better known as Erbitux) plus FOLFOX6 (group A; n=56) or to cetuximab plus FOLFIRI (group B; n=55). Data from this phase-2 trial were originally presented at the 2009 ASCO Gastrointestinal Symposium in January. 62% of patients showed objective tumor response. Patients with *KRAS* wild-type tumors had higher tumor response than patients with *KRAS* tumor mutations. Additionally, tumor response was observed in 72% of patients whose tumors were wild-type for both *KRAS* and *BRAF* genes vs. 40% of those whose tumors harbored a mutation in either gene. Overall, 34% of patients had R0 (complete) resections; 46% had R0 or R1 (partial) resection and/or radiofrequency ablation. In review, **60%** of tumors were judged as resectable after chemotherapy vs. 32% at baseline . 72% of patients had grade-3 or higher toxicity; the most common toxicities were skin toxicity and neutropenia (diminished blood cell count).

Folprecht, G, et al., Cetuximab in neoadjuvant treatment of non-resectable colorectal liver metastases. Lancet Oncology, 2009. doi:10.1016/S1470-2045(09)70330-4

7. CT Scan Can Predict Overall Survival in Avastin-Treated Colorectal Liver Mets (Dec. 2/09)

In this study, CT-based morphologic (structural) criteria predicted overall survival in patients with colorectal liver metastases treated with bevacizumab (avastin) -containing chemotherapy. Researchers from the University of Texas M.D. Anderson Cancer Center developed new CT criteria based on treatment induced morphologic changes to predict response to bevacizumab, a biologic agent. In their retrospective study, researchers identified 234 colorectal liver metastases from 50 patients who received first-line chemotherapy that included bevacizumab before having hepatic resection between March 2004 and March 2007. They also identified 82 patients with unresectable disease treated with bevacizumab-containing chemotherapy. Contrast enhanced CT was conducted at the start and end of therapy. Three blinded radiologists evaluated the metastases for changes in morphology unrelated to size. Researchers found that optimal morphologic criteria — a cystic-like appearance of the tumors in association with well defined borders — were directly associated with response and survival. In patients who underwent resection, median OS was not reached in responders and was 25 months for nonresponders when morphologic criteria were used. For patients with unresected tumors, median OS was 31 months for those with optimal response and 19 months for those with incomplete or no response by morphologic criteria.

***Chun YS, et al., CT-based morphologic criteria accurately predicted OS in bevacizumab-treated colorectal liver metastases. .* JAMA. *2009;302:2338-2344*.**

8. Adding Erbitux to Chemo in Early Stage Colon Cancer Shows No Benefit (Dec. 4/09)

A Data Monitoring Committee (DMC) determined that in a **phase III** clinical trial for early-stage colon cancer, no group of patients benefited from the addition of the monoclonal antibody cetuximab (Erbitux) to a standard chemotherapy regimen known as FOLFOX. Monoclonal antibodies are a type of protein designed in the laboratory that can locate and bind to substances in the body, including tumor cells. There was some initial evidence that the addition of cetuximab to FOLFOX may have been harmful, particularly in patients age 70 or older. Approximately 1,760 patients with stage III colon cancer (cancer that has spread to the lymph nodes surrounding the colon but not to other parts of the body) after compete surgical removal of the cancerous portions of the colon were randomized between the two treatment arms (groups). All patients had their tumors tested and only those patients with tumors that did not contain mutations in the KRAS gene (called *KRAS* wild-type) were included in the analysis. This study (N0147: A Randomized Phase III Trial of Oxaliplatin Plus 5-Fluorouracil/Leucovorin With or Without Cetuximab After Curative Resection for Patients with Stage III Colon Cancer) was conducted by a network of researchers led by the North Central Cancer Treatment Group (NCCTG). Current recommendations limit cetuximab therapy to patients with metastatic colorectal tumors that do not contain mutations in the KRAS gene.

http://www.cancer.gov/newscenter/pressreleases/CetuximabClosure

9. Hormones Appear to be Helpful with Metastatic Colorectal Cancer (Dec. 4/09)

According to this study, estrogen helps younger women with metastatic colorectal cancer live longer than men. The study of 52,882 patients from the Surveillance, Epidemiology and End Result registry who had metastatic colorectal cancer found that women ages 18-44 had significantly longer survival than men (17 months vs 14 months). However, older women had significantly shorter overall survival at 7 months compared with 9 months. Researchers have known for a while that estrogen prevents colorectal cancer, but this is the first study to suggest it may improve outcomes once you have colorectal cancer. James Abbruzzese, MD, chair of gastrointestinal medical oncology at the University of Texas M.D. Anderson Cancer Center agreed that hormones may play a role in metastatic colorectal cancer survival rates in women, but he says that a look at the data broken down by year is also intriguing. “In terms of the chemotherapy we have available, since 2000 the regimens employ more agents and have become more aggressive. Therefore, it may be expected to inhibit normal hormonal cycles leading to lower hormonal levels in these women, so other factors may be playing a role as well. It may not just be hormones”.

Lenz, Heinz-Josef, et al., Gender Disparities in Metastatic Colorectal Cancer Survival. Clinical Cancer Research. 2009; 15 (20): pp. 6391-6397

10. New Cancer Drug Being Tested for Colorectal Cancer (Dec. 4/09)

University of Florida researchers have found a way to use just a fraction of the normal dosage of a highly toxic, debilitating chemotherapy drug to achieve even better results against colon cancer cells. More research is needed before the therapy can be tested in patients, but the discovery in human colon cancer cell lines and mice with established human tumors suggests that the addition of a small molecule to the cancer drug **Temozolomide** disrupts repair mechanisms in a type of tumor cells that is highly resistant to treatment. Researchers evaluated more than 140,000 small molecules, finally arriving at a tiny molecule that precisely blocks the ability of cancer cells to recognize and repair the DNA damage inflicted by Temozolomide, or TMZ. Their objective was to induce DNA damage (with TMZ), and at the same time block cell repair, which would synergize toxic effects to the cancer cells. Their hope is that with this combination treatment they can reduce the tumors drastically and expand the lifetime of patients much longer than is currently possible. TMZ is commonly used against certain types of brain cancer. It works by damaging the DNA of the cancer. However, the challenge of treating patients is that colon cancer is not a single disease but an array of disorders with distinct molecular mechanisms, with one type being quite proficient at repairing the DNA damage inflicted by the drug.

http://www.medicalnewstoday.com/articles/172947.php

11. Skin Infections & Use of Anti-EGFR Therapies such as Erbitux & Vectibix (Dec. 10/09)

According to this study, patients who experience dermatologic toxic effects from epidermal growth factor receptor inhibitors (EGFRIs such as erbitux and vectibix) have a high prevalence of skin and nail infections. Patients treated with EGFRIs frequently experience toxic effects such as eruptions of the face, dry, itchy skin and nail inflammation. These side effects affect quality of life, but the impact of these effects on the patients' physical health, such as their increased susceptibility to cutaneous (skin) infections, has not been determined. Researchers collected data on 221 patients who were treated in a referral clinic for dermatologic toxic effects of EGFRIs. They examined associations between patient characteristics and the development of these infections. The researchers found that 84 (38%) of the 221 patients showed evidence of skin and nail infections, and 29% developed bacterial infections at sites previously affected by dermatologic toxic effects. Fifty (22.6%) of the 221 patients had cultures positive for Staphylococcus aureus, and 12 (5.4%) of the 221 patients cultured positive for methicillin-resistant S. aureus, which could be resistant to many common antibiotics. The authors write that "…in addition to treating the characteristic dermatologic toxic effects, attention should be paid to preventing or treating complicating infections, with the goal of maintaining quality of life and dermatologic health, both of which are essential for the optimization of EGFRI therapies in cancer patients."

Eilers, RE., et al., Dermatologic infections in cancer patients treated with epidermal growth factor receptor inhibitor therapy. Journal of the National Cancer Institute. Published online on December 9, 2009. Advance Access. Doi:10.1093/jnci/djp439

12. Ontario Has Expanded Access to Avastin for mCRC (Dec. 11/09)

The Colorectal Cancer Association of Canada (CCAC) applauds the Ontario Ministry of Health and Long-Term Care's decision to provide expanded access of Avastin (bevacizumab) to patients with metastatic colorectal cancer. "The CCAC congratulates the Ontario government for expanding access to Avastin to colorectal cancer patients with advanced disease," said Barry D. Stein, president of the Colorectal Cancer Association of Canada (CCAC). "Ontario patients who have been benefiting from the drug will now be assured of receiving Avastin until progression of their disease. That is a big burden lifted off the shoulders of patients who benefit from the drug and who were concerned they would not be able to continue treatment," Stein said. For the past year, the CCAC has been calling for equal and timely access to effective treatments across the country through its "Join the Fight" campaign. Following the decision in New Brunswick to implement both colorectal cancer screening and provide access to Avastin, the campaign will now focus on helping patients in PEI and those in Manitoba that do not have publicly

funded access to Avastin, as well as access across the country to third line treatment with Vectibix and Erbitux in those provinces that do not already provide same.

Ramanathan, RI., et al., Incidence and evolution of oxaliplatin-induced peripheral sensory neuropathy in diabetic patients with colorectal cancer: a pooled analysis of three phase III studies. Annals of Oncology. Advance Access published online on November 3, 2009.

13. Kras Status Made No Difference in Stage III Colorectal Cancer Patients (Dec. 14/09)

According to this study, patients with stage III colon cancer didn't do better or worse if their tumor had mutated KRAS. Studying KRAS in the tumors of about half the patients in a large clinical trial of chemotherapy for stage III colon cancer, researchers found no differences in disease-free, recurrence-free, or overall survival. This remained true no matter which chemotherapy the patients received. Between 1999 and 2001, almost 1,300 patients took part in a clinical trial that compared standard treatment at the time — bolus 5-FU and leucovorin– to adding irinotecan to 5-FU/leucovorin. That trial didn't find a difference between the two chemotherapy arms in preventing recurrences or increasing survival for stage III colon cancer. To see if KRAS status made any difference in outcomes for stage III colon cancer, a research team analyzed tumor tissue from 508 of the 1,264 patients who were enrolled in the CALGB 89803 clinical trial. They found mutated KRAS in 178 tumors, 35% of all participants. Five-year outcomes between KRAS mutant and KRAS wild-type tumor tissue were very similar:

- Disease-free survival was 62% for KRAS mutant versus 63% for KRAS wild-type.
- Recurrence-free survival was 64% for mutant vs 66% for Kras wild-type.
- Overall survival was 75% in mutant and 73% in wild-type tumors.

In addition, the research team found no correlation between KRAS status and clinical features of the cancer, which chemotherapy arm the patients were on, or microsatellite instability (MSI). Researchers concluded, "In this large trial of chemotherapy in stage III colon cancer patients, KRAS mutational status was not associated with any significant influence on disease-free or overall survival".

Ogino, Shugi, et al., Kras mutation in stage Iii colon cancer and clinical outcome following intergroup Trial CALGB 89803. Clinical Cancer Research., Online first November 24, 2009.

SURGICAL THERAPIES

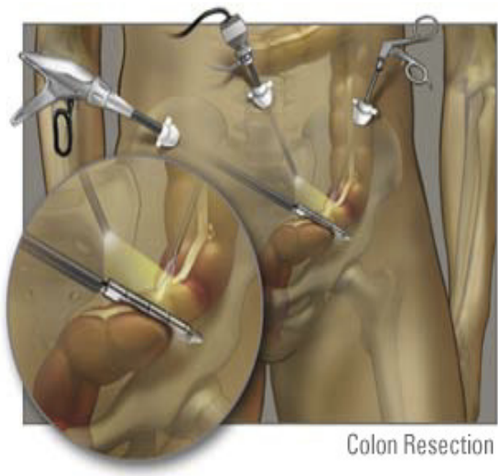
14. Transanal Endoscopic Microsurgery vs. Total Mesorectal Excision of a T1 Rectal Tumour (Nov. 17/09)

This study showed that for T1 rectal adenocarcinomas, TEM (transanal endoscopic microsurgery) is much safer than TME (total mesorectal excision) and survival is comparable. Eighty patients after TEM were compared to 75 patients after TME. TEM patients were eligible when excision margins were negative. TEM was safer than TME as reflected by operating time, blood loss, hospital stay, morbidity, re-operation rate and stoma formation. Mortality after TEM was 0% and after TME 4%. At 5 years after TEM and TME, both overall survival (TEM 75% versus TME 77%) and cancer-specific survival (TEM 90% versus TME 87%) were comparable. Local recurrence rate after TEM was 24% and after TME 0%. Researchers concluded that for T1 rectal adenocarcinomas TEM is much safer than TME and survival is comparable. After TEM, local recurrence rate is substantial, despite negative excision margins.

Graaf, EJR, et al., Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. European J of Surgical Oncology. Vol. 35, Issue 12, pp. 1280-1285. December 2009.

15. Comparing Outcomes for Laparoscopic and Open Surgery for Colorectal Cancer (Nov. 18/09)

Randomized trials in low-risk populations have failed to show any benefit for laparoscopic compared with open colorectal resection in terms of outcomes. Furthermore, it is not known whether laparoscopic colorectal resection (see image below) would yield advantages if randomization were revealed during surgery after a diagnostic laparoscopy. Patients with cancer of the colon or upper rectum were randomly assigned to laparoscopic or open resection in this study. All patients underwent diagnostic laparoscopy to assess whether laparoscopic resection was feasible and the result of randomization was then revealed to the surgeon. Main endpoints were overall, general and surgical morbidity, and mortality. Some 679 patients underwent diagnostic laparoscopy which led to the exclusion of 207; 250 patients were allocated to laparoscopic and 222 to open resection. Conversion to laparotomy (open resection) occurred in 28 patients (11.2%). There were no differences in morbidity (overall 25.2% versus 23.9%) or mortality (1.2% versus 0.9%) between laparoscopic and open groups. Postoperative hospital stay was shorter after laparoscopic resection (10 versus 12 days). Researchers concluded that laparoscopic resection of colorectal cancer is associated with increased operating time but does not decrease morbidity even in a moderate-risk population.



In selected patients, laparoscopic surgery is used to remove parts or in some cases the entire colon through small incisions with proven benefits compared with open surgery.

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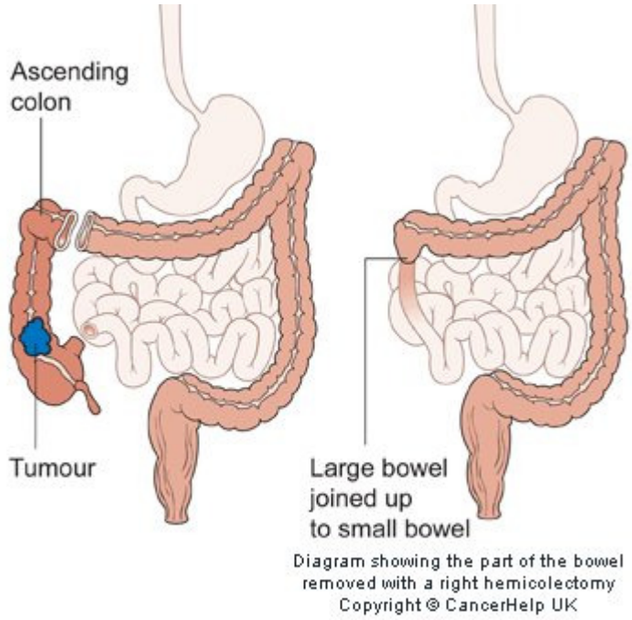


Diagram showing the part of the bowel removed with a right hemicolectomy using open surgery.

Source:
http://images.google.ca/imgres?imgurl=http://www.cancerhelp.org.uk/prod_consump/groups/cr_common/%40cah/%40gen/documents/image/crukmig_1000img-12171.jpg&imgrefurl=http://www.cancerhelp.org.uk/type/bowel-cancer/treatment/surgery/which-surgery-for-bowel-cancer&usg=__ba0QcJS3JV7r3KVFZe4LfOYHGdw=&h=335&w=350&sz=25&hl=en&start=4&sig2=Ot95elv7GuN9on-pBCB6pg&um=1&tbnid=xQOvfl2kGof8XM:&tbnh=115&tbnw=120&prev=/images%3Fq%3Dopen%2Bhemicolectomy%26hl%3Den%26sa%3DN%26um%3D1&ei=dtcnS974B9Wb8Ab2pJ2YDQ

Neudecker, J., et al., Short-term outcomes from a prospective randomized trial comparing laparoscopic and open surgery for colorectal cancer. British J of Surgery. Vol 96, Issue 12, pp. 1458-1467.

RADIATION / INTERVENTIONAL RADIOLOGY

16. Possible Liver Hemorrhaging After Administering Radiofrequency Ablation (Nov. 19/09)

Radiofrequency ablation is increasingly used in the field of oncology, especially in the treatment of liver metastases originating from colorectal cancer. This study reports on the unexplained liver hemorrhage that has been observed after radiofrequency ablation on colorectal cancer liver metastases. Although some studies have found low rates of complications, ranging from 2.4% to 8.9%, the rate of intra-abdominal hemorrhage is low (0.46%-1.6%) but relevant because this technique is increasingly used.

The reported reasons for hemorrhage are usually related to mechanical injuries to the liver blood vessels and occur most often in patients with cirrhosis. Other cases have been attributed to serious coughing or hiccups after the radiofrequency treatment which might cause increased abdominal pressure and tumour rupture. Liver laceration has rarely been described as a cause of hemorrhage. This complication has been associated with inappropriate electrode positioning or mechanical injury of the soft liver during the procedure and possibly displacing the electrode slightly. Although the procedure may go well, the patient could present with this type of complication without known risk factors. This makes it absolutely essential to minimize complications associated with radiofrequency ablation treatments, and to correctly deal with complications which do arise. In all these cases it is important to closely observe patients after this procedure to provide early intervention to minimize the damage and severity of complications.

Una, E, et al., Unexplained liver laceration after metastasis radiofrequency ablation. World J Gastroenterology 2009; Vol.15, Issue 40. pp. 5103-5105

17. Use of PET in Oncology (Nov. 20/09)

This study emphasizes that PET is a crucial technique in molecular imaging, allowing for critical assessment of disease, thanks to its ability to detect very small amounts of radioactive molecules. This is of particular interest in oncology where abnormal metabolism or synthesis in tumor cells but also various tumor characteristics can be studied using this nuclear medicine technique. FDG is currently the most widely used tracer, nowadays essential in the management of various malignancies including colorectal cancer, with large applications in **diagnosis, initial assessment, therapy monitoring, and recurrence detection**. The combination of anatomical information provided by PET/CT further increased its interest. Beyond its widespread use in daily practice, future applications of PET will involve other tracers than FDG and develop research applications in humans as well as in small animals.

Papathanassiou, D., et al., Positron emission tomography in oncology: present and future of pet and pet/ct. Critical Review in Oncology/Hematology. Vol. 72, Issue 3, December 2009. pp. 239-254

SCREENING

18. Predictors of Colorectal Cancer After Negative Colonoscopy (Nov. 16/09)

This study showed how Canadian women were more likely than men to be diagnosed with an early colorectal cancer in the three years following a negative colonoscopy. Researchers in Manitoba studied billing records for nearly 46,000 patients who had a clear colonoscopy and found that women with a negative colonoscopy were about as likely as women in the general population to develop colon cancer during the first three years after their test. Then their risk dropped to approximately 40-50% lower. The men's risk was 40-50% lower throughout the follow up period. Older women and those whose colonoscopy wasn't done by a gastroenterologist were the most likely to have a missed or early colorectal cancer.

Singh, Harminder, et al., Predictors of colorectal cancer after negative colonoscopy: a population-based study. The Amer J of Gastroenterology. Advance online publication. Doi:10.1038/ajg.2009.650

19. Identifying Precancerous Polyps with Optical Techniques (Nov. 17/09)

During routine colonoscopy, optical diagnosis may be as reliable and more cost-effective for correctly diagnosing small colorectal polyps than conventional histopathology, according to this study. Researchers compared the diagnosis of 363 colorectal polyps less than 10 mm in 130 patients that were evaluated by white-light colonoscopy, non-magnifying narrow-band imaging, chromoendoscopy, and conventional histopathology. The researchers found that optical diagnosis accurately identified up to 93% of small colorectal polyps (186 of 198 precancerous adenomas and 55 of 62 hyperplastic polyps), which was similar to the overall diagnostic accuracy of standard histopathology. They also found that optical diagnosis allowed 82 patients to be given a follow-up colonoscopy date immediately after the procedure. For polyps less than 10 mm in size, in-vivo optical diagnosis seems to be an acceptable strategy to assess polyp histopathology and future surveillance intervals. According to the researchers, dispensing with formal histopathology for most small polyps found at colonoscopy could improve the efficiency of the procedure and lead to substantial savings in time and cost.

East, James, et al., Optical diagnosis of small colorectal polyps at routine colonoscopy (Detect InSpect ChAracterise Resect and Discard; DISCARD trial): a prospective cohort study. The Lancet Oncology. , Vol. 10, Issue 12, , Pages 1171 - 1178, December 2009

20. Low Risk of Developing Colorectal Cancer After Negative Colonoscopy (Nov. 17/09)

Screening colonoscopy has been deemed to be an effective method to reduce the incidence of and mortality from colorectal cancer (CRC). There is little empirical evidence available about the optimal interval for screening, making this a subject of debate. In this study of participants in the German colonoscopy screening program, the prevalence of colorectal malignancies detected at screening colonoscopy among patients who had undergone a previous colonoscopy without detection of polyps (negative colonoscopy) was studied and determined. Data was compared with that from patients that had not received colonoscopies. No CRCs were detected in participants who had a previous negative

colonoscopy an average of 11.9 years prior, compared with the 8.4 CRC cases expected based on age- and sex-specific prevalences among participants that had not received a colonoscopy. The prevalence of advanced adenoma was also much lower among subjects who had previous colonoscopies. Researchers concluded that the low risk of CRC and advanced adenomas after a negative colonoscopy supports suggestions that screening intervals be extended to 10 or more years.

Brenner, Hermann, et al., Low risk of Colorectal Cancer and Advanced Adenomas More than 10 years after negative colonoscopy. Gastroenterology. 2009, November 9.

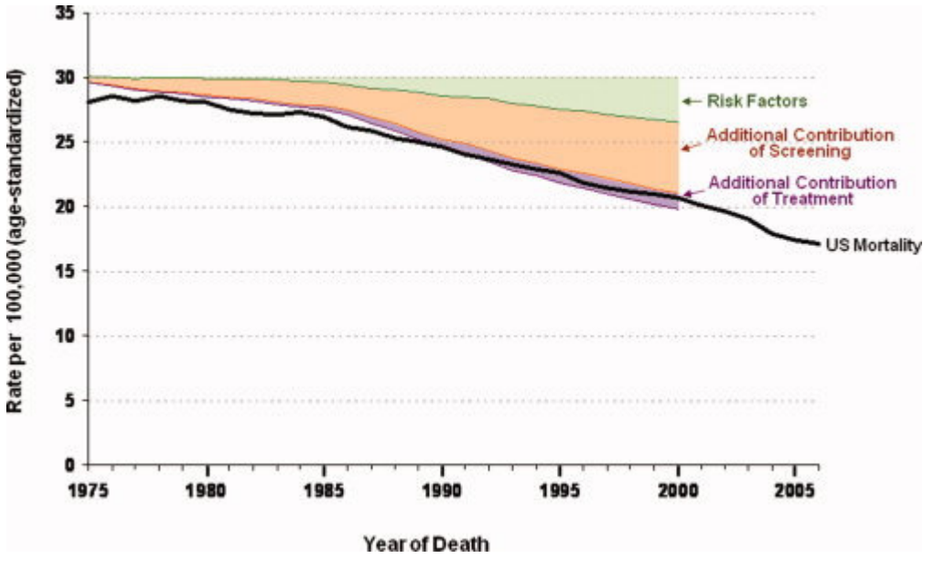
21. New Screening Combo Increases Detection of CRC by 10% (Dec. 3/09)

According to this study, the combination of sigmoidoscopy and fecal immunochemical test (FIT) detects advanced proximal (right-sided) tumors better than either test alone. African Americans, the elderly and women have a higher incidence of proximal colon tumors. The study results suggest that colorectal cancer (CRC) screening with sigmoidoscopy and FIT is superior to and more effective than screening with either alone, making this combination a viable and useful screening option. According to the researchers, this strategy should be considered, especially in communities that are not capable of colonoscopy screening. In the study, doctors analyzed data from 21,794 asymptomatic persons who had undergone colonoscopy and FIT. When colonoscopy was performed for a positive FIT result alone, for a positive sigmoidoscopy finding and for either a positive FIT result or sigmoidoscopy finding, the sensitivities in detection of advanced proximal malignancies were 22.3%, 16.3% and 31.7%, respectively. The sensitivities for detection of proximal invasive cancer were 58.3%, 8.3% and 62.5%, respectively. The incremental yield of advanced malignancies detection by using both tests is approximately 10%. FIT adds the most in terms of finding proximal cancers in a screening program that uses both tests. In addition, FIT has been replacing the standard guaiac-based test and is expected to become more prevalent. Therefore, this study is relevant to CRC screening strategy in the near future. While the optimal screening interval is still unknown, repeated testing is necessary, even for this combined strategy. The use of sigmoidoscopy as a screening test for CRC does not allow gastroenterologists to view the right side of the colon to screen for polyps, only the rectum and the lower end of the colon. If a polyp or abnormality is found, patients may require a regular colonoscopy for further evaluation. Right-sided adenomas cannot be viewed using a sigmoidoscopy. Colonoscopy, which provides the most comprehensive view of the colon, is the definitive test for CRC screening. Colonoscopies allow gastroenterologists to view the entire colon and rectum for polyps or cancer and during the same exam remove pre-cancerous polyps. It is the test most gastroenterologists recommend as the single best screening exam for CRC. It is the only method that combines both screening and prevention (by removal of pre-cancerous polyps.

Kato, Jun, et al., Combination of Sigmoidoscopy and a Fecal Immunochemical Test to Detect Proximal Colon Neoplasia. Clinical Gastroenterology and Hepatology. Vol. 7, Issue 12, pp. 1341-1346.

22. Improved Screening Cuts Colorectal Cancer Rates (Dec. 16/09)

According to this report, new diagnoses and death rates in the U.S. continue to decline for colorectal cancer, and the positive trend is expected to continue into the future. Increasing the number of people who are screened could make the rates fall even faster.



According to the study's lead author, increased screening probably has had the greatest impact on decreasing rates, as stipulated in the Annual Report to the Nation on the Status of Cancer in the US, but improved treatments have also contributed. If trends continue at the same rate, the number of colorectal cancer deaths per 100,000 people in the United States would fall from the current 19.9 per 100,000 to 11.9 by 2020, about a 40% reduction. However, with increased efforts to reduce risk factors, increase screening, and reach more patients with optimal chemotherapy it could cut the rate almost in half — from 19.9 to 10.5. In the period between 2002 and 2006, the average annual change in new cases of colorectal cancer in men has fallen by 4.2% while incidence for women has decreased each year by an

average of 2.4%. Death rates declined 3.9% for men and 3.4% for women. If current trends continue, death rates from colorectal cancer will decline by about 40% by 2020, although it will take continued efforts to reduce risk factors, reach people who need screening, and ensure that patients get recommended chemotherapy.

Edwards et al.,* Annual Report to the Nation on the Status of Cancer, 1975-2006,Featuring Colorectal Cancer Trends and Impact of Interventions (Risk Factors, Screening, and Treatment) to Reduce Future Rates, Cancer*, Early View, December 7, 2009.

OTHER

23. Colon Cancer Prevention Vaccine (Nov. 13/09)

Since vaccines are fast becoming the "new frontier" in terms of cancer research, this new study is focusing on a vaccine to prevent colon cancer before it can even form. Most of the cancer vaccines under development are for people who already have cancer (see Item #3 on page 2). For them, the treatment aims to help them fight the disease or prevent its recurrence. Researchers at the University of Pittsburgh Cancer Institute are testing a vaccine that may help reduce the risk of developing cancer in patients with advanced adenomas, a type of polyp that carries a high risk of becoming cancerous. Researchers are tackling the notion of how the body's immune system can be used as a means of fighting a foreign invader, in this case, the invader being cancer. For people who have been diagnosed with precancerous polyps, the vaccine may consist of injections to target changes in a specific protein on polyps (mucin protein) called "muck 1" or mucin 1. Although all polyps contain this protein, it is somewhat altered in polyps that are abnormal and in those that turn into cancer. Researchers maintain that the vast majority of cancers have changes in these mucins. The vaccine is designed to ramp up the immune system to recognize this abnormal muck 1, and stage an attack, hopefully preventing it from evolving into cancer. Ideally, researchers are attempting to harness the body's immune system thereby using the body's own defenses to fight the disease. The study is still recruiting participants to evaluate the vaccine. The Pittsburgh researchers are hoping to enroll 50 to 60 people in the study and more information may be obtained regarding criteria by calling 412-648-9116.

http://www.wxow.com/Global/story.asp?S=11535607

24. Discovery of Important Proteins (Nov. 29/09)

Swedish researchers have found a drug that inhibits a dangerous cell pathway while leaving a protective one intact pointing the way to preventing colon polyps from becoming cancerous. Researchers at the Karolinska Institute in Sweden have discovered that a group of signaling proteins can both promote the growth of cells in the colon into polyps (*adenomas)* and, paradoxically, also inhibit the development of polyps into cancer. **EphB** controls two pathways in the cell — one leading to cell division and another that curbs the cell's progress toward cancer. They have also found that imatinib (Gleevec) can inhibit the first dangerous pathway while leaving the protective one in place. So far the drug has kept cells from dividing in test tubes and in mice, but no human trials have been done.

Eriksson, Malin, et al., Dissociation of EphB2 signalling pathways mediating progenitor cell proliferation and tumour suppression. Cell. Vol. 139, Issue 4, pp. 679-692

25. Mutations in the PIK3CA Gene Linked to Rectal Cancer Recurrence (Nov. 30/09)

According to this study, PIK3CA genetic mutations in tumors from patients with rectal cancer can predict local recurrences. The authors explain that previous studies have shown PIK3CA mutations to be associated with poor prognosis among patients with resectable stage I to III colon cancer and poor survival in colorectal cancer patients, but the prognostic value of PIK3CA mutations in rectal cancer patients has not been reported. Researchers, in the Netherlands, investigated the frequency of PIK3CA, and two other genetic mutations called KRAS and BRAF, in tumors from 240 patients with rectal cancer and assessed whether such mutations could be used as prognostic markers. PIK3CA mutations were found in 19 (7.9%) rectal tumors, KRAS mutations in 81 (33.8%), and BRAF mutations in 5 (2.1%) tumors, the authors report. Overall, 95 cases (39.6%) had mutations in at least one gene, and 10 (4.2%) had mutations in two genes (PIK3CA and KRAS). There were no tumors with mutations in both KRAS and BRAF. The presence of PIK3CA mutations was associated with a 3-fold increase in the local recurrence rate and a tendency to shorter intervals from surgery to recurrence, but PIK3CA mutations were not associated with distant metastases, overall recurrences, or overall survival. In the analysis, PIK3CA mutation remained an independent predictor of local recurrences, along with TNM stage. KRAS and BRAF mutations were not associated with local recurrences, distant metastases, or overall survival. Researchers report: "The findings suggest that prospective evaluation of PIK3CA mutation status could reduce overtreatment by preoperative radiotherapy for the low-risk patients who might otherwise only experience the side effects. These results are a timely contribution to the goal of using molecular profiles to personalize cancer care. The hope is to characterize molecular details of individual tumors for both prognostic and predictive means, allowing providers to further optimize treatment regimens." "With continued studies such as this," the editorial concludes, "we can treat rectal cancer more effectively,

more safely, and with fewer untoward side effects."

Myers, Andrea P, et al., Getting Knit-PI3Ky: PIK3CA Mutation Status to Direct Multimodality Therapy? Clin Cancer Res 2009;15:6748-6750,6956-6962.

26. Genetic Mutations in PTEN, BRAF, and EGFR Linked to Lack of Response to Anti-EGFR Therapies (Nov. 30/09)

The occurrence of a mutation in the *KRAS* gene found in colorectal tumours is predictive of nonresponse and shorter survival in patients treated with anti–epidermal growth factor receptor (anti-EGFR) inhibitors, such as erbitux (cetuximab) and vectibix (panitumumab), for metastatic colorectal cancer (mCRC) thereby limiting the use of anti-egfr therapies to patients with wild-type *KRAS* tumors. Yet, only half of these patients will benefit from treatment, suggesting the need to identify additional biomarkers predictive of anti-egfr therapy efficacy. Researchers in this study retrospectively collected tumors from 173 patients with mCRC. All but one patient received a cetuximab-based regimen as second-line or greater therapy. *KRAS* and *BRAF* status were determined. EGFR status was determined as well. and the expression of PTEN was also assessed. In patients with *KRAS* wild-type tumors (n = 116), *BRAF* mutations (n = 5) were weakly associated with lack of response but were strongly associated with shorter progression-free survival and shorter overall survival (OS). An EGFR amplification was found in 17.7% of the patients and was associated with response. PTEN expression was found in 19.9% of the patients and was associated with shorter OS. After performing an analysis, *BRAF* mutation and PTEN expression status were associated with OS. Researchers concluded that *BRAF* status, *EGFR* amplification, and expression of PTEN were associated with outcome measures in *KRAS* wild-type patients treated with a cetuximab-based regimen. Subsequent studies will be required to confirm the clinical utility of these markers.

Laurent-Puig, P, et al., Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type Kras metastatic colon cancer. J of Clinical Oncology. Early Release, published online ahead of print Nov. 2, 2009. doi: 10.1200/JCO.2008.21.6796

27. Updated NCCN Guidelines for Colon and Rectal Cancers (Dec. 3/09)

The NCCN Clinical Practice Guidelines in Oncology for Colon Cancer and for Rectal Cancer have been updated and published. Both NCCN Guidelines are now available in v.1.2010. Several updates were made based on BRAF gene status. Updates include a new section for BRAF testing added to the Principles of Pathologic Review. For patients with metastatic disease, determination of tumor BRAF gene status was added to the workup recommendations as an option if Kras is not mutated. A new footnote was added stating that “Patients with a known V600E BRAF mutation should not be treated with anti-egfr monoclonal antibodies such as erbitux or vectibix. For the complete updated versions of the NCCN Clinical Practice Guidelines in Oncology and the NCCN Drugs and Biologics Compendium, please visit http://www.nccn.org/interactive/podcasts/mp3/annual_conference_2009/CRC_GLs.asp .

http://www.nccn.org/interactive/podcasts/mp3/annual_conference_2009/CRC_GLs.asp

NUTRITION & HEALTHY LIFESTYLE

28. Obesity Linked to Several Cancers Including Colorectal (Nov. 16/09)

The American Institute for Cancer Research recently released new numbers on how obesity is linked to the number of cancer cases in the US each year. Not surprisingly, the numbers are discouraging. When it comes to colon cancer, it is estimated that at least 13,200 cases each year are due to obesity. In other words, studies suggest that nearly 10%, or one-tenth, of all colon cancer cases never would occur each year if obesity were not a problem in the US. Other health experts believe this estimate may very well be on the low side. Another study on this topic suggests that about 30% of all colon cancer cases in the US are due to people having a body mass index (BMI) greater than 22.5 kilograms per meter squared (kg/m2). There are many things that can be done to personally tackle overweight and obesity. Reviewing the section on healthy lifestyles appearing on the Colorectal Cancer Association of Canada’s website is a good start. It can be accessed at www.colorectal-cancer.ca

http://www.aicr.org/site/PageServer

29. The Benefits of Qigong During Cancer (Nov. 16/09)

For people living with cancer, a decrease in quality of life is one of the most difficult aspects of the disease to manage. Many struggle with fatigue and stress, anxiety, and depression. For people seeking non-medical ways of coping with cancer side effects, Qigong may offer relief. Qigong ("chee-kung") is a Chinese meditative practice which uses slow graceful movements and controlled breathing techniques to promote feeling calm, peaceful, and more content. The latest research in respect of Qigong shows that when cancer patients regularly practice Qigong, it improves their overall quality of life, lessens fatigue, and helps decrease inflammation in the body. Qigong is gentle and can be practiced by most people, and so offers a unique way to better manage cancer treatment side effects, and possibly even establish healthy coping habits for the long-term. If you want to learn more about Qigong, ask your cancer treatment center for information on this form of meditation. You can also learn about Qigong from the Qigong Association of America and Qigong USA.

Oh, B., et al., Impact of medical qigong on quality of life, fatigue, mood and inflammation in cancer patients: a randomized controlled trial. Annals of Oncology. Advance Access published online on October 30, 2009. doi: 10.1093/annonc/mdp479

30. Exercise Can Prevent Colon Cancer (Nov. 14/09)

An important study shows that exercise is a powerful intervention for colorectal cancer prevention, and is underutilized for health maintenance. According to the study from Dutch researchers, exercise is an intervention that can prevent colon cancer. The researchers provide information that colon cancer is repeatedly shown to stem from lack of exercise and poor diet that leads to obesity. The authors looked at colon cancer risk in 150,000 people over a period of six years. They found that exercise reduces risk of colon cancer by 40% in individuals who exercised more than seven hours per week. The findings also show that the effects of exercise for preventing colon cancer are direct. Previous levels of physical activity were taken into account. Exercise was not found to prevent polyps of the colon, but was protective for the development of colon cancer. The authors write, “The recurrence of colonic polyps seems not to be prevented, however, suggesting that the protective effect of exercise and sport is exerted only after the development of adenoma [a type of colon polyp] in the adenoma-carcinoma sequence.” The study also suggests a vicious cycle that occurs during cancer treatment that leads to physical inactivity following surgery and during cancer treatment. Fatigue makes exercise seemingly impossible. The authors write, “Physical training can counteract these symptoms. Exercise is therefore an essential component of treatment for CRF” (cancer related fatigue). Many patients who develop colon cancer were not found to modify lifestyle to follow exercise guidelines and other healthy lifestyle guidelines. Just 23% of patients exercised, 12% continued to smoke, and 16% drank moderate to large amounts of alcohol. Study participants recruited between 1990 and 1994 were questioned about vigorous and less intensive exercise levels, then classified into “no activity” and “activity once or more per week” – 41,528 study participants were examined for exercise levels and incidence and survival of colon cancer and observed for ten to fourteen years. Among the group, 526 developed colon cancer - 229 who actively exercised, and 297 classified as “no activity”. Both groups received the same treatment, but patients who exercised regularly had higher survival rates after five and a half years. For stage II and stage III colon cancer, mortality decreased overall rates of death by 39% and disease-specific mortality by 51%. Additional findings revealed that death from colon cancer was associated with a 45% mortality decline among those who exercised for at least three times 45 minutes weekly. The power of exercise for disease prevention deserves attention and promotion by clinicians.

http://www.eurekalert.org/pub_releases/2009-11/dai-tbo111309.php

31. Fruits & Vegetables Promote Healthy Colon (Nov. 20/09)

This study from the Netherlands maintains that eating fruits and vegetables, and drinking tea and red wine may offer overweight men and normal weight women some protection from colon and rectal cancers. Plant-based foods contain flavonoids, compounds thought to interfere with cancer-causing processes. Researchers estimated the intake of specific flavonoids in 120,852 men and women, 55 to 69 years old, who filled out dietary surveys as part of a large study designed to assess ties between diet and cancer. Over about 13 years, 1,444 men and 1,041 women developed colon or rectal cancer. Specific flavonoid intake did not seem to influence the risk for colorectal cancer when the investigators allowed for multiple factors potentially tied to the development of colorectal cancer, including age, family history, smoking, drinking alcohol, physical activity, and eating habits overall, plus estrogen use among women. But when they allowed for weight, it seems "there may be protective effects of some of these compounds in subgroups of overweight men and normal weight women.” Compared with the least intake, the greatest intake of catechins -- common in berries, grapes, black chocolate, tea, red wine, and some beans -- seemed to be associated with lower colorectal cancer risk among both overweight men and normal weight women. The researchers observed a similar trend for flavonols -- found in onions, kale, apples, pears, tea, wine, and fruit juices -- in normal weight women. "The fact that the inverse trend was observed for most of the specific catechins and flavonols argues against the associations being spurious," claimed the lead investigator. She and colleagues, therefore, call for further investigations to shed more light on the how these compounds alter colon and rectal cancer risk and how weight modifies this impact.

Simons, Colinda, et al., Dietary flavonol, flavone and catechin intake and risk of colorectal caner in the Netherlands Cohort Study. International J of Cancer. Vol. 125, Issue 12, pp. 2945-2952

32. Folic Acid Is Helpful with Recurrent Colorectal Adenoma (Nov. 20/09)

Researchers affiliated with the Health Professional Follow-Up Study and the Nurses' Health Study have reported that folic acid supplementation in patients with recurrent colorectal adenoma was not protective or harmful in most patients. However, patients who were **folate deficient** had a significant 39% decrease in adenoma recurrence. The role of micronutrients in relationship to cancer incidence has become a major focus among researchers. Some dietary choices have been shown to reduce the risk of developing certain types of cancers; however, newer research has also shown exogenous vitamins do not lower the incidence of cancer and, in some instances, they may increase cancer risks. Thus, there is evolving evidence that exogenous vitamin supplementation is no substitute for micronutrients in food. Retrospective and randomized trials have shown that colorectal cancer is increased in persons with the lowest dietary intake of folic acid compared with persons with a high intake of dietary folic acid. In one study the risk of colon cancer was reduced by 27% in persons with the highest folic acid intake compared with the lowest intake. This study also found that men who consume higher amounts of alcohol combined with inadequate intakes of folate and methionine are at a higher risk of developing rectal carcinoma. Recently, researchers involved in a multicenter U.S. trial have reported that folic acid supplementation in patients did not prevent, and may have increased, the incidence of recurrent colorectal adenomas. Researchers affiliated with the Aspirin/Folate Polyp Prevention Study have also reported that supplementation with folic acid significantly increases the risk of prostate cancer. Researchers from Norway have also shown that folic acid and B12 supplements in patients with ischemic heart disease increase the risk of cancer and all-cause mortality in a population that does not fortify food with folic acid. The current study involved 338 patients with recurrent colorectal adenoma who received folic acid supplementation and 334 patients who received a placebo. For the entire cohort, the incidence of recurrent adenomas was not affected by folic acid supplementation. However, persons who had a baseline folate level of 7.5 ug/mL or less and received folic acid supplementation had a 39% decreased risk of recurrent colorectal adenoma. In persons with a folate level over 7.5 ug/ml, folic acid supplementation had no effect on recurrent colorectal adenomas. These authors concluded: "Our results do not support an overall protective effect of folic acid supplementation on adenoma recurrence. Folic acid supplementation may be beneficial among those with lower folate concentrations at base line."

Understanding the role of folic acid in the development of cancer (carcinogenesis) is made even more complex by the fact that genetic factors may modify the way the body metabolizes folate. In one recent study, researchers from Sweden reported that postmenopausal women with high plasma folate levels associated with the 677T allele of the folate-metabolizing enzyme (methylenetetrahydrofolate reductase [MTHFR]) gene had an increased risk of developing breast cancer. It's possible that genetic variation of the MTHFR gene could influence the results of the various clinical trials being carried out to determine the effect of supplemental folate in cancer prevention.

Wu, Kana, et al., A randomized trial of folic acid supplementation and risk of recurrent colorectal adenoma. American Journal of Clinical Nutrition [early online publication]. October 28, 2009.

Ebbing, M., et al., Cancer Incidence and mortality after treatment with folic acid and vitamin B12. J of the American Medical Association. 2009; 302: pp. 2119-2126

Ecricson UC, Ivarsson Mi, Sonestedt E, et al. Increased breast cancer risk at high plasma folate concentrations among women with the MTHFR 677T allele. American Journal of Clinical Nutrition. 2009;90:1380-1389.

33. Soy May Prevent & Treat Colon Cancer (Nov. 25/09)

Researchers have found agents in soy that have the ability to prevent and possibly treat colon cancer. These agents, called sphingadienes, may prove helpful in fighting this type of cancer. Colon cancer is a disease of the large intestine, and usually begins as small, noncancerous clumps of cells called adenomatous polyps. Eventually, some of these polyps become colon cancer. Previous studies have shown that soy may possess properties that protect against cancer, **including colon**, prostate, and breast cancer. This benefit is usually associated with soy protein and soy isoflavones, including genistein. In this latest study, Saba and her team made the groundbreaking discovery that sphingadienes found in soy may underlie the health advantages provided by soy foods. A fruit fly served as the launching point for this study, after Dr. Saba and her team first identified sphingadienes in this organism. They soon discovered that high levels of sphingadienes caused mutant cells in the fly to die. The scientists then connected this finding with the knowledge that soy is a rich source of sphingadienes, and they believed they had found a natural way to help prevent colon cancer. Dr. Saba notes that they are "encouraged to find a natural molecule that could be consumed through soy products as a strategy to help prevent colon cancer." She also indicates that the findings of their study can help toward eventually developing new drug treatments for people who already have colon cancer. Further research is needed to find the best way to provide sphingadienes for individuals and to determine their toxicity when used for a prolonged time and with other agents. Dr. Saba has received two grants toward that end, and also hopes to determine whether sphingadienes can prevent other cancers as well.

http://dietary-supplements.info.nih.gov/Funding/abstract.aspx?q=1R21AT005336-01+

34. Wholegrain and Cabbage May Protect Against Colorectal Cancer (Nov. 29/09)

This study shows that women with high concentrations of enterolactone in their blood have about 40% lower risk of getting colon cancer. Enterolactone is a plant estrogen, which is formed in the intestine. Oat, rye bread, cabbage, nuts, seeds (eg. Linseed), and leafy vegetables are good sources of enterolactone. It seems that enterolactone has an effect on colon cancer. For each doubling of the concentration of enterolactone women decreased risk of getting colon cancer by 24% and by 42% if you have not taken antibiotics within the past year.

Johnsen, Nina F., et al., Plasma enterolactone and risk of colon and rectal cancer cohort study of Danish men and women. Cancer Causes Control. 2009, Oct. 21, Epub ahead of print.

35. Meat and Colon Cancer (Nov. 30/09)

Studies have shown that eating meat is linked with colon cancer risk, but what kind, how much, and how the meat is prepared are important parts of the story. Different types of meat appear to have different effects on the colon. Some types of meat cause more damage, damage that can lead to cancer development, to the cells in the colon than other types of meat. And when it comes to colon cancer risk, fresh is best. This means that in terms of colon cancer risk, freshly prepared chicken, other poultry, fish, lean beef, and pork are "safer" than processed meats. Processed means smoked, cured, and salted meats, such as hot dogs, sausages, salami, bologna, bratwurst, bacon, salt pork, cold cuts and lunch meat, ham, pastrami, pepperoni, smoked fish, corned beef, and jerky. It turns out that when processed, cancer-causing (carcinogenic) chemicals are created in meat. These chemicals, when eaten, increase colon cancer risk. How meat is prepared and cooked also has an impact on how much the meat increases colon cancer risk. The higher the temperature at which the meat is cooked, and the more well-done the meat is, the more likely it is to increase colon cancer risk. Just as with processing of meat, cooking meat at high temperatures until very well-done creates carcinogens (cancer-causing compounds). More well-done meat contains higher levels of carcinogens, called heterocyclic aromatic amines (HAAs) and polycyclic aromatic hydrocarbons (PAHs) than less well-done meat. HAAs and PAHs are formed when the protein and/or fat in the meat gets very hot. Think of the black, char-grilled exterior that a piece of grilled meat can have. This is a source of carcinogens, the chemicals that can increase colon cancer risk. As for how much meat to eat, kindly keep the following in mind: When studying diet and colon cancer, health experts have found that people regularly eating the most red meat have up to 50% greater colon cancer risk compared with people eating the least red meat. Eating more than 3-5 ounces of meat per day significantly increases the risk of death from any cause, including death due to colon cancer, other cancers, and heart disease. Eating more than an ounce and a half of processed meat per day, such as hot dogs and lunch meat, significantly increases the risk of death due to colon cancer, other cancers, and heart disease. Simply eating a roast beef sandwich for lunch and a burger or hot dog for dinner will put you over the daily limit for meat intake that research tells us will increase your risk of colon cancer, other cancers, heart disease, and death. If you enjoy meat, but want to keep your risk for colon cancer in check, keep the following in mind:

- **Focus on Quality, Not Quantity**. You don't need to skip meat altogether, as long as the rest of your diet is based around healthy, cancer-fighting foods such as vegetables, fruit, whole grains, legumes (beans and peas), nuts, and seeds. Enjoy good-quality, fresh meat in 3-ounce servings, 3-4 times per week.

- **Cook Slow & Low**. Even if two pieces of meat are cooked to the same "level of done-ness", the one that was cooked at a lower temperature for longer will contain fewer carcinogenic (cancer-causing) compounds than meat that is cooked very hot and fast.

- **Raise the Flavor with Spices and Herbs**. Marinade your meat in mixtures that contain spices and herbs such as rosemary, thyme, oregano, basil, fennel, or anything you enjoy. Believe it or not, marinating meat in spice and herb mixtures actually reduces the amount of carcinogens that are formed during cooking.

- **Use the Right Tools**. When grilling, use tongs to flip the meat rather than a fork. Piercing the meat causes fat and juices to drip onto the coals. This, in turn, causes the formation of carcinogens that coat the meat when smoke rises back up from the grill.

- **Cook with Plants**. You can heat up vegetables, fruit, or any other plant-based food as hot as you want. This does not create the hazardous compounds that are formed when meat is cooked. Try kabobs with plenty of vegetables on them.

Sinha R, et al., "Meat Intake and Mortality: A Prospective Study of Over Half a Million People." Archives of Internal Medicine 2009 169:562-571.

Wei EK, et al., "Cumulative risk of colon cancer up to age 70 years by risk factor status using data from the Nurses' Health Study." American Journal of Epidemiology 2009 170:863-872.

36. Calcium and Vitamin D Can Protect Against Colorectal Cancer (Dec. 2/09)

This study suggests that supplements of calcium and vitamin D may promote the health of the cells in the colon and rectum, offering potential protection from tumour development. The mineral-vitamin combination was found to normalize the health of cells in the colon and rectum. Researchers from Emory University, the University of Minnesota, and the National Cancer Institute and the National Institutes of Health conducted a pilot, randomized, double-blind, placebo-controlled, clinical trial in 92 men and women with a history of benign colorectal tumours. Led by Veronika Fedirko, the researchers randomly assigned the participants to receive daily calcium (2.0 g) and/or vitamin D3 supplements (800 IU), or placebo for six months. Markers of the health of cells were found to increase by 201, 242, and 25% in the calcium, vitamin D, and calcium plus vitamin D groups relative to the placebo, said the researchers. *"These results indicate that calcium and vitamin D promote colorectal epithelial cell differentiation and may 'normalize' the colorectal crypt proliferative zone in sporadic adenoma patients, and support further investigation of calcium and vitamin D as chemopreventive agents against colorectal neoplasms,"* wrote Fedirko and her co-workers. The potential benefits for the vitamin-mineral combination in relation to colorectal cancer is somewhat controversial, with some studies reporting benefits while others report null results. Indeed, back in 2006 results from the Women's Health Initiative (WHI) stated that daily supplements of vitamin D and calcium 'had no effect' on the risk of colorectal cancer. The results were questioned however and independent cancer experts said at the time that the claims should be interpreted in the light of the complexities of the study. Michele Forman and Bernard Levin from the MD Anderson Cancer Center at the University of Texas, noted that the WHI trial had three overlapping components, with 69% of the women enrolled on the Dietary Modification trial, 54% enrolled on the Hormone Therapy trial, and 14% enrolled on both. "The enrolment in three overlapping trials maximized the participation and size of the WHI trial but created a complex approach with potential confounders for biological interpretation," said Forman and Levin.

Fedirko, V., et al., "Effects of Vitamin D and Calcium on Proliferation and Differentiation In Normal Colon Mucosa: a Randomized Clinical Trial" . Cancer Epidemiology, Biomarkers & Prevention November 2009, Volume 18, Pages 2933-2941 , doi:10.1158/1055-9965.EPI-09-023

37. Cigarette Smoking Increases Risk of Colorectal Cancer (Dec. 3/09)

This new study results strengthen the evidence that cigarette smoking over a long period of time increases risk for developing colorectal cancer, even after adjusting for other risk factors. "This provides one more reason not to smoke, or to quit smoking as soon as possible," claim the researchers. "Colorectal cancer should be added to the list of cancers caused by smoking." Researchers tested the association between long-term cigarette smoking and colorectal cancer after adjusting for multiple other factors that are generally associated with risk, including screening. From 1992 through 2005 the researchers followed almost 185,000 participants aged 50 to 74 years old; participants described their behaviours and medical conditions. Smoking cigarettes for 40 or more years or participants who did not quit before age 40, had a 30% to 50% increased risk of developing colon or rectal cancer during the follow-up, even in analyses that adjusted for 13 other potential risk factors. After 13 years of follow-up, the researchers identified 1,962 cases of invasive colorectal cancer. While previous large studies conducted in long-term smoking showed similar results, the lead investigator stated that this study is the first to control for screening and all of the suspected risk factors for colorectal cancer, such as alcohol consumption, physical inactivity and consumption of red or processed meat. "These findings contributed to the evidence recently reviewed by the International Agency for Research on Cancer (IARC) in October of this year. IARC upgraded the evidence that smoking causes colorectal cancer from 'limited' to 'sufficient'." This IARC reclassification brings the number of cancer organ sites causally related to cigarette smoking to 17, which includes cancers of the oral cavity, pharynx, nasopharynx, nasal cavity and paranasal sinuses, larynx, lung, esophagus (both squamous cell and adenocarcinoma), stomach, colorectum, liver, pancreas, kidney (both renal cell and transitional cell carcinoma), urinary bladder and lower urinary tract, uterine, cervix, and myeloid leukemia.

Thun, Michael J., et al., The association between cigarette smoking and risk of colorectal cancer in a large prospective cohort from the United States. Cancer Epidemiology Biomarkers Prevention. December 2009: 18: pp. 3362-3367

38. Mirtoselect (Bilberry Extract) Aids Colon Cancer Patients (Dec. 3/09)

Mirtoselect is the original standardized bilberry extract. It is produced from bilberry fruits (*Vaccinium myrtillus* L.), containing 36% anthocyanins**.** Pharmacological and clinical data for colorectal carcinoma chemoprevention on Indena's standardized bilberry extract Mirtoselect were presented at the 51st Annual Meeting of the Italian Cancer Society (SIC) in Sesto San Giovanni, Milan, on Nov. 23 to 24, during the session of "Dietary Supplements and Nutraceuticals in the Management of Cancer". A total of 25 patients with colorectal cancer (and scheduled to undergo resection of primary tumor or liver metastasis) received Mirtoselect 1.4, 2.8 and 5.6 g/d for seven days before surgery. Anthocyanins and metabolites were measured in blood work and colorectal tissue. Results indicate that Mirtoselect reduced tumor proliferation in colorectal tumor samples taken from all patients who received the product by 7% compared with pre-intervention values. For more information on Mirtoselect, please click on the link below.

http://www.mirtoselect.info/

39. Omega-3s Help Prevent Colon Cancer (Dec. 8/09)

Long-chain omega-3 fatty acids may prevent colorectal cancer, according to these results. "Experimental data have shown benefits of long-chain omega-3 fatty acids in colorectal carcinogenesis, ranging from reduced tumor growth, suppression of angiogenesis and inhibition of metastasis," claimed the lead investigator. "Our finding of inverse association between dietary intakes of long-chain omega-3 fatty acids and distal large bowel cancer in white participants adds additional support to the hypothesis." Kim and colleagues studied the link between polyunsaturated fatty acid intake and distal (left sided) large bowel cancer using data from a population-based control study. They recruited 1,509 white participants (716 cancer cases and 787 controls) and 369 black participants (213 cancer cases and 156 controls). 19 polyunsaturated fatty acids were assessed using a validated food frequency questionnaire, which collect information on the frequency and amount of foods typically consumed in the past 12 months. Patients who consumed more long-chain omega-3 fatty acids had a reduced risk of distal large bowel cancer. Compared to the lowest quartile, fat intake in the highest quartile was linked with a 39% reduced risk of cancer. The researchers detected these associations in white participants, but not in black participants.

www.aacr.org/home/scientists/meetings--workshops/frontiers-in-cancer-prevention-research/abstracts.aspx

40. Antioxidant Compound Reduces Incidence of Colorectal Adenomas (Dec. 8)

This study indicates that supplementation with a selenium-based antioxidant compound decreased the risk of developing new polyps of the large bowel called colorectal metachronous adenomas in people who previously had colorectal polyps removed. The study is the first intervention trial specifically designed to evaluate the efficacy of the selenium-based antioxidant compound on the risk of developing metachronous adenomas. Adenomatous polyps (or adenoma) are benign lesions of the large bowel that, in time, could progress to cancer. Even though only a small proportion of adenomas will develop into cancer, almost 70% to 80% of colorectal cancer stems from an adenoma. Adenomas are common in people aged 60 years or older; one in four people will have at least one adenoma. Participants in this study were aged 25 to 75 years and had already had one or more colorectal adenomas removed, but did not have any other diagnosis of colorectal diseases, cancer or life-threatening illnesses and did not use vitamins or calcium supplementations. The researchers randomized 411 participants to the placebo group or to receive an antioxidant compound specifically selenomethionnine **200 µg, zinc 30 mg, vitamin A 6,000 IU, vitamin C 180 mg and vitamin E 30 mg.** Researchers report: "Our results indicated that individuals who consumed antioxidants had a 40% reduction in the incidence of metachronous adenomas of the large bowel and it is noteworthy that the benefit observed after the conclusion of the trial persisted through 13 years of follow up." The researchers are currently conducting a study to evaluate the role of genetic alterations as predictors of metachronous adenomas in participants who received the antioxidant compound compared with those in a placebo group.

Bonelli, Luigina, et al.,National Institute for Cancer Research, Genoa, Italy; presentation, Dec. 7, 2009, Frontiers in Cancer Prevention Research Conference, American Association for Cancer Research, Houston

http://www.aacr.org/home/public--media/aacr-press-releases.aspx?d=1681

41. Insulin Resistance and Colorectal Cancer (Dec. 12/09)

Two studies have been recently published documenting the link between insulin resistance and colorectal cancer. Insulin was higher and adiponectin (see definition below) lower with colorectal cancer, and both correlated with the stage of the disease. The authors of the second study claim that in addition to cardiovascular disease, individual components of the metabolic syndrome have been linked to the development of cancer, particularly to colorectal cancer. The physiopathological mechanism that links **metabolic syndrome** (combination of one or more of the following conditions: increased blood pressure, diabetes, and increased cholesterol) and colorectal cancer is mostly related to abdominal obesity and insulin resistance.

[Adiponectin is a protein hormone produced and secreted exclusively by adipocytes (fat cells) that regulates the metabolism of lipids and glucose. Adiponectin also influences the body's response to insulin. And adiponectin also has antiinflammatory effects on the cells lining the walls of blood vessels. Low levels of adiponectin are found in people who are obese (and who are at increased risk of a heart attack).]

Gonullu, Guzin, et al., Association between adiponectin, resistin, insulin resistance, and colorectal tumours. International J of Colorectal Disease. Published online ahead of print. Doi:10.1007/s00384-009-0826-6

Pais, Raluca, et al., metabolic syndrome and risk of subsequent colorectal cancer. World J of Gastroenterology. 2009, November 7; 15 (41): pp. 5141-5148

42. Treatment of Neuropathy with Goshajinkigan (GJG) (Dec. 14/09)

One of the most frustrating side effects of certain colorectal cancer treatments is neuropathy. Neuropathy is characterized by burning and tingling in the hands and feet. It is caused by nerve damage due to some

types of chemotherapy such as oxaliplatin. New research suggests that a Japanese herbal medicine called Goshajinkigan (GJG), may help minimize, and possibly prevent, neuropathy. In the study, researchers in Japan examined rates of neuropathy in 90 patients with advanced (metastatic) colorectal cancer who had received chemotherapy that included the medication oxaliplatin. Oxaliplatin is one of the types of chemotherapy most likely to cause nerve damage that leads to neuropathy in metastatic colorectal cancer. The 90 patients had received their chemotherapy in one of four ways:

Group A: In combination with 7.5 grams per day of Goshajinkigan (GJG) herbal medication, taken orally (by mouth)

Group B: In combination with 1 gram each of calcium gluconate and magnesium sulfate, given intravenously, before each chemotherapy treatment

Group C: In combination with GJG and calcium gluconate and magnesium sulfate therapies

Group D: Alone, without either GJG or calcium gluconate and magnesium sulfate

The researchers reported the following results:

- 50% of the patients in Group A experienced neuropathy
- 100% of patients in Group B experienced neuropathy
- 78.9% of patients in Group C experienced neuropathy
- 91.7% of patients in Group D experienced neuropathy

Only the people who received their chemotherapy with GJG herbal medication alone, had a significantly lower overall rate of neuropathy compared with no herbal medication or calcium/magnesium therapy. The authors concluded that giving GJG herbal medication along with oxaliplatin can reduce the rate of neuropathy by as much as half, as noted in this study.

Kono, Toru, et al., Efficacy of Goshajinkigan for peripheral neurotoxicity of oxaliplatin in patients with advanced or recurrent colorectal cancer. Evidence-based Complementary and Alternative Medicine. Advance Access published online on December 1, 2009. doi: 10.1093/ecam/nep200

43. Greater Physical Activity Associated with Lower Risk of Colorectal Cancer Mortality in Men (Dec. 15/09)

To date, most studies reveal that physically active individuals have a lower risk of developing colorectal cancer but few studies have examined whether exercise benefits colorectal cancer survivors. In this study, researchers studied colorectal cancer–specific and overall mortality in a group of 668 men with a history of stage I to stage III colorectal cancer according to predefined physical activity categories after diagnosis. In this group of men with colorectal cancer and no apparent metastases at diagnosis, 50.4% exercised at least 18 metabolic equivalent task (MET) hours per week. (A metabolic equivalent in task is defined as a unit of measurement of heat production by the body. One MET is equal to 50 kcal per hour per square meter of body surface of a resting individual.) Increased physical activity was significantly associated with improved colorectal cancer–specific mortality and overall mortality. Men who engaged in more than 27 MET hours per week of physical activity had better outcomes compared with men who engaged in 3 or less MET hours per week of physical activity. The apparent benefit of physical activity was seen regardless of age, disease stage, body mass index, diagnosis year, tumor location, and prediagnosis physical activity. Researchers concluded that in a large cohort of men with a history of nonmetastatic colorectal cancer, more physical activity was associated with a lower risk of colorectal cancer–specific and overall mortality

Meyerhardt, Jeffrey, et al., Physical activity and male colorectal cancer survival. Archives of Internal Medicine. 2009; 169 (22): pp. 2102-2108