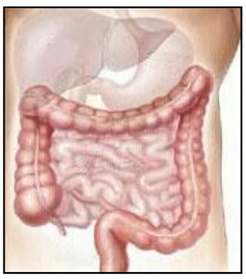
COLORECTAL CANCER RESEARCH

Month Ending February 18th, 2011



The following colorectal cancer research update extends from January 15th, 2011 – February 18th, 2011 inclusive and is intended for informational purposes only.

CONTENT

NUTRITION / HEALTHY LIFESTYLE

DRUGS / SYSTEMIC THERAPIES

1. New Phase I Study from Lorus Therapeutics (Jan. 16/11)

The biotech company Lorus has announced the enrollment of the first cancer patient in a Phase I clinical study evaluating its small molecule anticancer drug candidate ***LOR-253***. The open-label, dose escalation study will enroll patients with advanced or metastatic solid tumors for which no effective therapy is currently available, or whose cancer has not responded to conventional or standard therapies. The primary objectives of the study are to determine the maximum tolerated dose and recommended Phase II dose of LOR-253. Additional study objectives include the safety profile, anti-tumor activity, and pharmacokinetics of LOR-253. The study will be conducted under the direction of Dr. Andrea Cercek and Dr. Leonard Saltz in New York City at the Memorial Sloan Kettering Cancer Center, which is a recognized world leader in the investigation of novel cancer therapies. The study plans to enroll approximately 22-37 patients during the dose escalation stage. In addition, up to 10 patients will be added at the recommended Phase II dose level for assessment of tumor biomarkers related to the anticancer mechanism of LOR-253. Preference will be given to enrolment of patients with colorectal cancer and non-small cell lung cancer in this expanded treatment group, based on the strong anticancer efficacy of LOR-253 against these cancer types in preclinical studies. LOR-253 is a first in class drug, being the first clinical-stage compound to stimulate KLF-4 (Kruppel-like factor 4), a tumor suppressor factor which is characteristically deficient in a variety of cancers, including colorectal cancer and lung cancer, and so represents a new approach to cancer therapy. The study is listed in clinicaltrials.gov and can be accessed by clicking the following: http://clinicaltrials.gov/ct2/show/NCT01281592 .

http://www.marketwire.com/press-release/Lorus-Therapeutics-Enrolls-First-Patient-Phase-I-Clinical-Study-Anticancer-Drug-LOR-TSX-LOR-1379848.htm

2. Gene Discovered Hindering Oxaliplatin Action (Jan. 16/11)

The drug, oxaliplatin, is widely used in the treatment of colorectal cancer. It is used in early disease, following surgery in those cancers that are likely to recur. It is also used in advanced disease to slow progression of the cancer where it has spread to other parts of the body. However, a significant number of patients experience serious side effects, including prolonged damage to the nervous system, creating an urgent need to identify genes that are responsible for drug sensitivity or resistance, which results in directing therapy to those most likely to benefit. Nerve damage, or neurotoxicity, associated with oxaliplatin is most commonly manifested as pain or a loss of sensation in the hands and feet and can severely affect a patient's quality of life and ability to work. These symptoms are experienced in some form by the majority of patients receiving this drug and, for some patients, can be permanent. Researchers examined the role of individual cancer genes to influence the sensitivity or resistance of colon cancer cells grown in laboratory culture. According to the study, researchers identified 27 genes that, when silenced, altered the sensitivity of colon tumor cells to oxaliplatin, causing damage to the cancer cells' DNA and inhibiting the cancer cells' ability to reproduce and survive. This study has also shown that diverse gene networks also play a role in the ability of the drug to impact colon tumors. These 27 genes, whose loss of function significantly affect the effectiveness of oxaliplatin, may be promising therapeutic biomarkers for oxaliplatin.

Pelham, Robert J, et al., Functional Genomics Reveals Diverse Cellular Processes that Modulate Tumor Cell Response to Oxaliplatin. Molecular Cancer Research, online publication. **doi: 10.1158/1541-7786.MCR-10-0412**

3. Erbitux Shows Long Term Survival Benefit When Administered with Folfox (Jan. 19/11)

Results of the Phase II OPUSa study demonstrate an association between early tumor shrinkage and long-term median overall survival (OS) of more than 2 years for patients with KRAS wild-type metastatic colorectal cancer (mCRC) treated with erbitux (cetuximab) plus FOLFOX standard chemotherapy. This correlation was not seen in the chemotherapy-alone arm of the study. The study was presented at the annual Gastrointestinal (GI) Cancers Symposium of the American Society of Clinical Oncology (ASCO). This latest data shows that the majority of patients (69%) with KRAS wild-type mCRC demonstrated tumor shrinkage of 20% or more in the first 8 weeks of 1st line treatment with Erbitux and FOLFOX. These patients experienced a long-term median OS of ***26.2 months***. Patients treated with FOLFOX chemotherapy alone whose tumors shrank by 20% or more in the same period (46%) experienced median OS of only ***21.8 months***. These results support recent findings from the Phase III CRYSTALb trial, which found that early tumor shrinkage achieved with Erbitux in combination with FOLFIRI standard chemotherapy led to a long-term median OS of 2.4 years (28.3 months). The OPUS and CRYSTAL studies show, for the first time in colorectal cancer, that there is a correlation between early tumor shrinkage during the first weeks

of treatment and extended survival. This effect seems to be unique to treatment with chemotherapy and Erbitux since a similar association was not observed with chemotherapy alone in this analysis, nor has it been proved for any other colorectal cancer treatment, according to the investigators. The result is medically relevant for improving patient care through the personalized medicine approach with Erbitux. Further Erbitux data to emerge from ASCO GI came from the randomized Phase II CORE.1.2.002 study that included 152 patients. The results showed that administration of Erbitux every second week in combination with FOLFOX resulted in sustained efficacy and safety in the treatment of mCRC patients with KRAS wild-type tumors, which were equivalent to the results demonstrated with the weekly administration. Response rates of 51% and 63% were seen in the weekly administration group and in the group where Erbitux was given every second week, respectively. There was no significant difference between the two groups.

Piessevaux H, et al., ASCO GI, Abstract No. 398 and Ciuleanu T, ASCO GI, Abstract No. 494

4. New Phase I/II Trial Initiated for Kras-Mutant Patients (Jan. 20/11)

4SC AG, a drug discovery and development company, has announced the dosing of their first patient in the Phase I/II SHORE study with the oral pan-histone deacetylase, or HDAC, inhibitor called **resminostat** as a second-line treatment for patients with advanced and metastatic colorectal KRAS-mutant cancer. SHORE is a randomized, open-label, multi-centre, two-arm Phase I/II study in 70 patients that will evaluate the efficacy, safety and pharmacokinetics of resminostat, in combination with FOLFIRI, a chemotherapy regimen for the treatment of colorectal cancer, versus FOLFIRI alone in the control arm. In the combination arm of the study patients will be treated with the maximum tolerated dose of resminostat in combination with FOLFIRI, which will be determined through an initial dose-escalation phase, evaluating 200mg, 400mg, 600mg and 800mg of resminostat together with FOLFIRI in approximately 20 patients. The primary endpoint of the study is to determine the progression free survival (PFS). The secondary endpoints include progression free survival rate (PFSR) after eight weeks and every eight weeks thereafter, the analysis of time-to-progression (TTP), overall survival (OS), analysis of drug safety, tolerability, pharmacokinetics and the investigation of biomarkers, the company added. By evaluating the efficacy of resminostat in patients carrying KRAS-mutant tumours, investigators hope to open a second-line treatment option for this colorectal cancer patient population where there is an increased unmet medical need since they cannot be treated with current EGFR targeting agents. More information may be found by clicking on the following link:
http://www.clinicaltrials.gov/ct2/show/NCT01277406?term=resminostat&rank=1

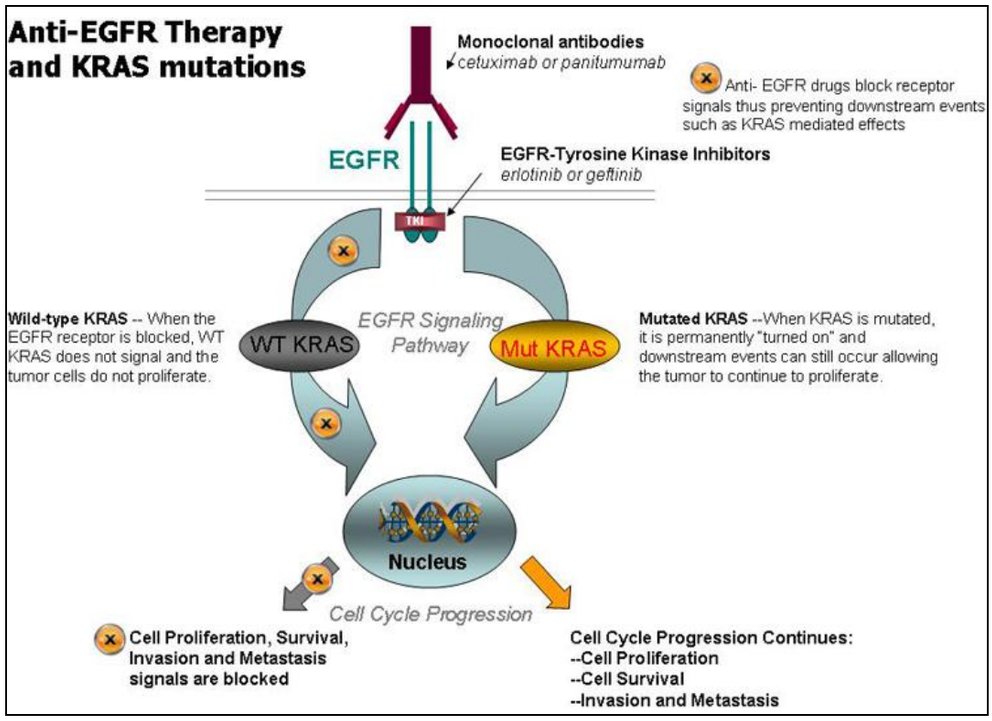


Figure 1: Studies evaluating KRAS mutation status in colorectal cancer patients demonstrate that KRAS mutations are strongly correlated with lack of response to cetuximab and panitumumab (anti-egfr therapies), shorter progression-free survival (PFS) and shorter overall survival, thereby requiring additional approved therapies for third line treatment of advanced colorectal cancer.

http://www.clinicaltrials.gov/ct2/show/NCT01277406?term=resminostat&rank=1

5. Clinical Trial Involving Tivozanib Yielded Positive Results at ASCO GI (Jan. 21/11)

Aveo Pharmaceuticals announced that previously reported positive data from its Phase 1b clinical trial evaluating **tivozanib**, its lead product candidate designed to optimally block the VEGF pathway by inhibiting all three VEGF receptors, in combination with FOLFOX6, a standard chemotherapy regimen, in patients with advanced gastrointestinal (GI) cancers was presented at the American Society of Clinical Oncology (ASCO) 2011 Gastrointestinal Cancers Symposium. Results from this study showed the combination was tolerable and safe at the full recommended tivozanib dose (1.5 mg/day) and schedule and standard FOLFOX6 dose; and, partial responses in more than a third (35%) of patients evaluated and

disease control in 82% of patients. Tivozanib's unique characteristics allow it to be combined with other anti-cancer agents at full dose and schedule. Tivozanib, an investigational new drug, is designed to optimally block the VEGF (vascular endothelial growth factor) pathway by inhibiting all three VEGF receptors. Each of the three receptors of the VEGF pathway play an important role in angiogenesis (the formation of new blood vessels), which is critical in cancer cell growth. Tivozanib's high level of potency across VEGF receptors 1, 2 and 3 is designed to provide the most complete blockade of the VEGF pathway. Tivozanib's high level of selectivity for VEGF receptors 1, 2 and 3 is designed to minimize off-target toxicities, and its oral, one capsule, once-daily administration may enhance convenience for patients. Tivozanib has also demonstrated the ability to be combined with both targeted therapies and chemotherapies at the full dose. More information may be found at http://www.clinicaltrials.gov/ct2/show/NCT01210846?term=tivozanib&rank=8

Jac, Jaroslaw, et al., A Phase Ib, open-label, dose-escalation study of tivozanib and folfox6 in patients with advanced gastrointestinal (GI) tumors. ASCO 2011 GI Symposium. Abstract #549

6. AVANT Study Finds No Benefit From Avastin in Stage III Colon Cancer (Jan. 24/11)

A second randomized clinical trial has confirmed what the first one found — adding Avastin to standard chemotherapy *does not reduce recurrences* after surgery for stage III colon cancer. The AVANT trial compared standard FOLFOX chemotherapy to either FOLFOX plus Avastin (bevacizumab) or XELOX plus Avastin. Chemo was given for 6 months, and Avastin was added during that time and for another 6 months after chemo ended. Nearly 2,870 stage III patients took part in the study. Much like the C-08 trial, there was a temporary benefit during the year that patients received Avastin, but it didn't last. By the end of three years the percentage of people who were alive and cancer-free was slightly less in the two Avastin arms. At three years, disease-free survival was:

- 76% in the FOLFOX only arm
- 73% in the FOLFOX plus Avastin arm
- 75% in the XELOX plus Avastin arm

FOLFOX chemotherapy combines oxaliplatin with leucovorin and continuous infusion 5-FU. XELOX combines oral Xeloda (capecitabine) with oxaliplatin. Although it is too early to be certain, there was a trend toward poorer survival in those patients who received Avastin with their chemotherapy. It is not clear why this might be. There was no serious additional toxicity due to Avastin. When cancer did recur, the sites of recurrence weren't different among the three arms, with most initially in the liver, leading researchers to believe that there wasn't a "rebound" after Avastin was stopped. AVANT included collecting tissue and studying a number of biomarkers to see if there might be some subgroups where adding Avastin to chemo might be beneficial. Those results are not yet complete. In presenting the trial results at the 2011 GI Symposium, Aimery De Gramont concluded,

- The addition of bevacizumab to FOLFOX4 or XELOX did not improve disease-free survival in the adjuvant treatment of Stage III colon cancer.
- Immature overall survival data suggest a potential detriment. Continued follow-up is ongoing.
- Bevacizumab treatment effect was not constant over time.
    - In the first year, there was a transient favorable effect, consistent with what was found in C-08.
    - The treatment effect became unfavorable after one year, which is different than what C-08 discovered. In C-08 there was no difference between arms after one year.
- Bevacizumab is the third agent, after irinotecan and cetuximab, with proven efficacy in metastatic colorectal cancer and no observed benefit in the adjuvant treatment of colon cancer.

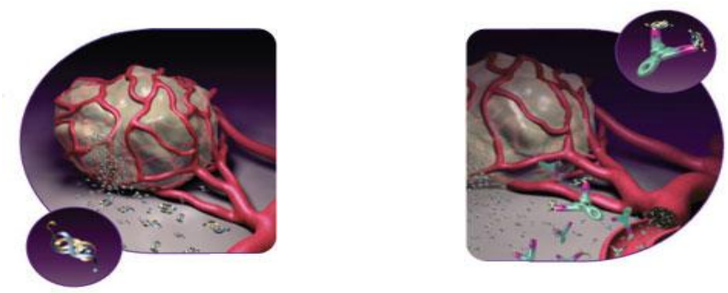


Figure 2*: Avastin consists of** *a group of large proteins called* ***monoclonal antibody (Mab)*. These agents are similar to the antibodies the body's own immune system normally makes when we have a bacterial or viral infection but, in this case, it has been made in a laboratory and attacks specific targets on cancer cells. In the case of Avastin, the target (otherwise called the antigen) is a protein called* ***V****ascular* ***E****pidermal* ***G****rowth* ***F****actor (VEGF). Avastin binds to VEGF, rendering it unable to then bind with its receptor which in turn by blocking the formation of new blood vessels then interferes with the growth of the tumour (see image above). When cancer cells spread to another part of the body they try to form a lump or tumour mass. In order to do this, they need to rapidly stimulate the local blood vessels and capillaries to grow into the tumour mass in order to nourish the cancer cells with food and oxygen (a process called angiogenesis). They achieve this by releasing a chemical into the surrounding tissues called* ***V****ascular* ***E****pidermal* ***G****rowth* ***F****actor (see image above). Avastin, being a monoclonal antibody which attaches to circulating VEGF, effectively blocks its ability to bind to its receptors in the tissues of the body, most importantly those surrounding tumours. Avastin, therefore, interferes with the tumour's ability to recruit new blood vessels reducing their ability to grow and spread to other areas of the body. As this process is universal to most bowel tumours, there is no requirement to perform extra laboratory tests on the cancer cells prior to Avastin therapy. There is also evidence that Avastin enhances the effect of chemotherapy. It is thought they make tumour vessels less "leaky" and so allows chemotherapy to reach the tumour more effectively.*

DeGramont et al., AVANT: results from a randomized, thre-arm multinational phase III study to investigate bevacizumab plus either xelox or Folfox4 versus folfox4 alone as adjuvant treatment for colon cancer, 2011 GI Cancers Symposium, Abstract 362.

7. Chemo Delay Puts Lives at Risk in Colon Cancer (Jan. 24/11)

The results of this study suggest that delaying adjuvant (post-operative) chemotherapy for colon cancer by more than four weeks increases the mortality risk, beginning with a 12% increase at eight weeks. The results of the analysis indicate a significant adverse association between time to adjuvant chemotherapy and survival in colorectal cancer. The level of evidence from the study, with knowledge that this relationship will not be subjected to prospective assessment, provides sufficient proof of an adverse association, according to the lead investigator. Two types of factors can contribute to delays in the onset of chemotherapy: patient-related factors — such as postoperative complications and variations in recovery — and logistical issues, including institution-specific delays and inefficiencies. To characterize the impact of delays in chemotherapy on outcomes in colorectal cancer, researchers performed a systematic review of the medical literature and a meta-analysis (a method designed to increase the reliability of research by combining and analyzing the results of all known trials of the same product or experiments on the same subject) of relevant data. The reviewers identified studies that had a clearly defined measure of the time from surgery to initiation of adjuvant chemotherapy for patients with colorectal cancer and that evaluated the impact of the time interval on overall and disease-free survival. Moreover, they included only those studies that adequately described the relevant prognostic factors in the groups compared. All nine studies showed an increase in the hazard for overall survival with increasing delays to the start of adjuvant chemotherapy. Similar associations were seen in an overall analysis and a separate analysis of the incremental impact per each four-week delay.

Biagi JJ et al. "Time to adjuvant chemotherapy in colorectal cancer: Systematic review and meta-analysis" ASCO GI 2011; Abstract 364.

8. Phase I Results of ARQ 197 c-MET Inhibitor (Jan. 24/11)

Phase 1 results of a clinical trial among patients with metastatic colorectal cancer (CRC) treated with ARQ 197, a selective small molecule inhibitor of the c-MET receptor tyrosine kinase, in combination with irinotecan and cetuximab were presented at ASCO 2011 Gastrointestinal Cancers Symposium showing that this combination was well tolerated and demonstrated encouraging anti-tumor activity in patients with relapsed metastatic CRC. Among nine patients treated, one had a complete response, two had partial responses and five had stable disease. The systemic exposure of ARQ 197 with this combination regimen was consistent with previous observations, and no dose-limiting toxicities were observed. These results provide important support for the ongoing Phase 2 randomized study of this combination. The ongoing Phase 2 study of ARQ 197 in CRC is enrolling patients with the **wild-type form of the KRAS gene** who have received front-line systemic therapy. The primary objective of the trial is progression-free survival. Secondary objectives include overall survival and objective response rate. Approximately 150 patients will be enrolled at clinical trial sites in the U.S. and Europe. The trial is being conducted by Daiichi Sankyo Pharma Development, the global development arm of Daiichi Sankyo, the co-developer with ArQule of ARQ 197 outside of certain countries in Asia. ARQ 197 is an orally available, selective inhibitor of c-Met, a receptor tyrosine kinase that is currently in Phase 2 and Phase 3 clinical trials and is not yet approved for commercial sale. In healthy adult cells, c-Met is present in normal levels to support natural cellular function, but in cancer cells, c-Met is inappropriately and continuously activated for unknown reasons. When abnormally activated, c-Met plays multiple roles in aspects of human cancer, including cancer cell growth, survival, angiogenesis, invasion and metastasis.

Eng, C. et al., Phase I results of the randomized, placebo controlled, phase I/II study of the novel oral c-MET inhibitor, ARQ 197, irinotecan and cetuximab in patients with wild type kras metastatic colorectal cancer who have received front line systemic therapy. 2011 GI Cancers Symposium, Abstract No. 527

9. Bone Drugs Reduce Risk of CRC (Jan. 25/11)

Postmenopausal women taking oral bisphosphonates for osteoporosis had almost a 50% reduction in the risk of colorectal cancer, according to data from a large cohort study. The case-control study, conducted among over 1,800 Israeli women, found that the magnitude of the risk reduction increased with length of time women were on antiresorptive therapy — topping out at almost 80% with more than three years of bisphosphonate use. The findings add to the growing body of evidence of a chemopreventive potential for bisphosphonates. The same group previously reported a reduction in the risk of breast cancer among women taking the bone-friendly drugs. The importance of these findings is that the colon is a tumor site that is less hormonally driven [compared with breast cancer] and therefore there is a better chance that what we actually see, in this association study, is a true effect of the drug, according to the researchers. To examine the association between bisphosphonate use and colorectal cancer, investigators analyzed data from the Molecular Epidemiology of Colorectal Cancer (MECC) study, an epidemiologic study of newly diagnosed colorectal cancer in northern Israel from 1998 to 2004. The analysis included 933 postmenopausal women who developed colorectal cancer and 933 matched female controls. The analysis identified several factors that had significant associations with a reduced risk of colorectal cancer, including:

- Aspirin use for more than three years
- Statin use for more than a year
- Postmenopausal hormone therapy

- Use of bisphosphonates for more than a year

Any use of bisphosphonates was associated with a 33% reduction in the risk of colorectal cancer. The magnitude of the benefit ranged from no benefit for less than a year of use to 50% for a year or more of treatment, 49% for more than two years, and 61% for more than three years.

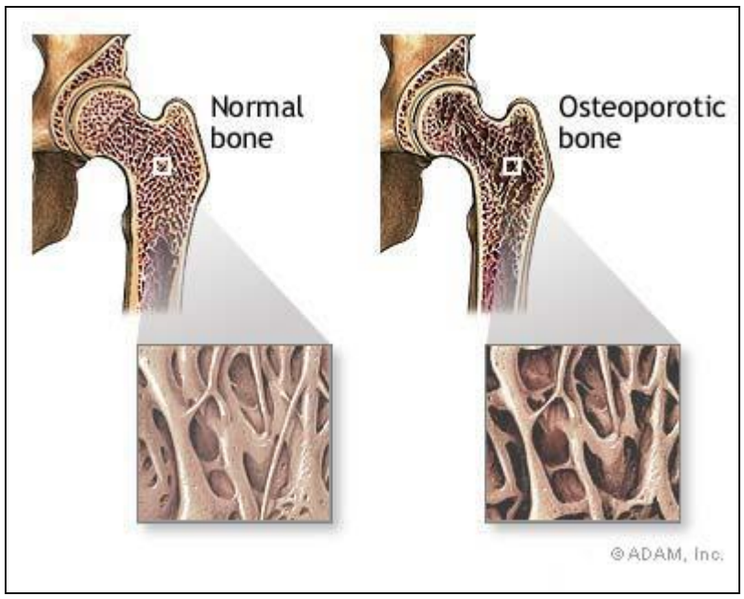


***Figure 3*:** Biphosphonates are a class of drugs that prevent the loss of bone mass, used to treat osteoporosis and similar diseases, as depicted in the image above.

Rennert G, et al., Association of bisphosphonate use and risk of colorectal cancer. ASCO GI 2011; Abstract 371.

10. Reducing Hypersensitivity Reactions from Oxaliplatin Therapy (Jan. 26/11)

Oxaliplatin is a third-generation platinum compound and a key agent for the management of colorectal cancer, both in early and late stage disease. Patients treated with oxaliplatin are at risk for hypersensitivity reactions (allergic reactions). Researchers designed a modified premedication regimen to prevent oxaliplatin-related hypersensitivity reactions and assessed if this approach was effective. A retrospective cohort study of patients with advanced colorectal cancer who received modified FOLFOX6 (mFOLFOX6) was performed. Patients received routine premedication with dexamethasone 8 mg and granisetron 3 mg for the first five cycles of mFOLFOX6. From the sixth cycle onward, cohort (group) 1 received the same premedication, and cohort 2 received modified premedication (diphenhydramine 50 mg orally, followed by dexamethasone 20 mg, granisetron 3 mg, and famotidine 20 mg). Researchers compared the incidence of hypersensitivity reactions, duration of treatment, and reasons for treatment withdrawal between the two cohorts. A total of 181 patients were studied (cohort 1, 81; cohort 2, 100). Hypersensitivity reactions developed in 16 patients (20%) in cohort 1 and 7 (7.0%) in cohort 2. The median number of cycles increased from 9 in cohort 1 to 12 in cohort 2. Apart from progressive disease, neurotoxicity was the reason for discontinuing treatment in 20% of the patients in cohort 1, as compared with 53% in cohort 2. Researchers concluded that increased doses of dexamethasone and antihistamine significantly reduced oxaliplatin-related hypersensitivity reactions. This effective approach should be considered for all patients who receive FOLFOX, allowing treatment to be completed as planned.

Kidera, Yasuhiro, et al., High dose dexamethasone plus antihistamine prevents colorectal cancer patients treated with modified Folfox6 from hypersensitivity reactions induced by oxaliplatin. International J of Clinical Oncology. Doi: 10.1007/ss10147-010-0170-6

11. KRAS Mutation May Promote Lung Mets in Patients with Curatively Resected Colorectal Cancer (Jan. 31/11)

Analyzing KRAS mutation status has become routine clinical practice in the management of advanced colorectal cancers to determine if patients have a chance to benefit from therapy with EGFR monoclonal antibodies, such as cetuximab (erbitux) and panitumumab (vectibix). The identification of KRAS mutations as a negative predictive factor for cetuximab and panitumumab therapy, however, does not appear to be the end of the story for KRAS. Results from this study suggest that KRAS mutations are associated with *a higher propensity of colorectal cancers to form lung and brain metastases*, a finding which could eventually help gain insight into the biology of site-specific metastases. In addition, it has to be pointed out that, potentially, not all KRAS mutations have the same biologic effect with regard to their value as negative predictive biomarkers. Results of a recent retrospective analysis of several trials conducted with cetuximab suggested that a specific KRAS mutation at codon 13 (G13D) might not be associated with resistance to EGFR antibodies (as summarized in the January Clinical Research Updates).

Tie, Jeanne, et al., Kras mutation is associated with lung metastasis in patients with curatively resected colorectal cancer. Clin Cancer Res., Jan. 14, 2011.

12. IROX Not Superior to Folfiri In First Line Therapy for Advanced Colorectal Cancer (Jan. 31/11)

According to the results of this study, a new regimen of irinotecan plus oxaliplatin (mIROX) failed to demonstrate superior activity over high-dose 5FU/folinic acid and irinotecan (Folfiri) in patients with advanced colorectal cancer. Nor was the IROX regimen tolerated as well as Folfiri, which remains the standard of care.

Fischer Von Weikersthal, L., et al., Phase III trial of irinotecan plus infusional 5FU/Folinic Acid versus irinotecan plus oxaliplatin as first-line treatment of advanced colorectal cancer. Eur J Cancer, 2011 January. 47(2): 206-214.

13. Avastin Increases the Number of Fatal Events (Feb.1/11)

A team of researchers at Stony Brook University School of Medicine in New York published a paper in JAMA showing that patients who receive Avastin (bevacizumab), in combination with chemotherapy are at increased risk of side effects that may lead to death. Lead author Dr. Vishal Ranpura and his colleagues reported that the risk of fatal adverse events varied according to the type of chemotherapy agents used in conjunction with Avastin. There were also suggestions that the risk might vary by tumor type and dose of Avastin, but results were not definitive. The randomized trials reviewed in this analysis involved more than 10,200 patients. Overall fatal events in patients who received Avastin was low--2.5% compared to 1.7% of patients who did not receive it. However, the increased risk was more than three times higher in patients who received Avastin in combination with platinum or taxane chemotherapy agents such as carboplatin and paclitaxel. The most common fatal event, accounting for nearly one-quarter of the total, was hemorrhage. This finding will most likely affect overall usage of Avastin. Because the most significant benefits from Avastin are seen, thus far, in colorectal cancer, it may be that the drug is used with less frequency for treating lung or breast cancers, where the risk may not outweigh the benefits.

Ranpura, Vishal, et al., Treatment related mortality with bevacizumab in cancer patients. JAMA: 2011; 305(5): 487-494

14. Comparing Preoperative and Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer (Feb.17/11)

Although many trials have shown the efficacy of preoperative chemoradiotherapy (CRT) or postoperative CRT compared with surgery alone, the optimal sequence of radiotherapy and surgery for the treatment of locally advanced rectal cancer is unclear. The authors of this study reported the final results of this randomized phase 3 trial comparing preoperative CRT with postoperative CRT using the oral chemotherapeutic agent capecitabine (better known as xeloda) in survival, local control, sphincter preservation, and toxicity for the treatment of locally advanced rectal cancer. Patients with locally advanced rectal cancer (cT3, potentially resectable cT4 or N+) were randomly assigned to receive preoperative or postoperative CRT. CRT consisted of 50 Gy/25 fractions and concurrent capecitabine (1,650 mg/m^2/day). Patients then went on to receive surgery - total mesorectal excision. From March 2004 to April 2006, 240 patients were enrolled. After a median follow-up time of 52 months, the 3- and 5-year disease-free survival, overall survival, and cumulative incidence of local recurrence were **similar** between both arms. However, for the patients with low-lying tumors, the preoperative CRT arm had a higher rate of sphincter preservation (68% v.s. 42%). Acute and late complication rates were similar between both arms. According to the authors of the study, although significant benefit of preoperative CRT in local control and survival was not demonstrated, the data showed that increased rate of sphincter preservation was possible in low-lying tumors without jeopardizing local control and surgical complication by preoperative CRT

Park, Jin-hong, et al., Randomized phase III trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. Cancer. Article first published online: 15 FEB 2011 DOI: 10.1002/cncr.25943

SURGICAL THERAPIES

15. Cure Still Possible with Liver Mets (Jan. 24/11)

Hepatic resection of colorectal liver metastases (CLM) is now regarded the standard of care. Evaluation of true long-term survivors will demonstrate the curative potential of this therapy with cure being defined as actual 10-year survival versus a satisfactory cancer outcome of 5-year survival. According to the study authors, limited data exists on outcomes of patients beyond 5 years. Studying the rates of cure and predictive factors for cure are essential to define the true benefit of this therapy. This research paper shares the latest data on survival after colon cancer has spread to the liver. It gives reason for hope, and shows that people can be cured, even after having colon cancer that has spread to the liver. The study showed that of the people with liver metastasis (no spread to bone or other organs) who undergo surgery to remove the colon cancer growths from the liver, 34% will live at least five years. Even more encouraging is that of the 34% of people who live at least five years after surgery, half will go on to live 10 or more years and be cured of colon cancer liver metastasis. These numbers may sound dismal to anyone who doesn't have colon cancer, and certainly, we need more and better treatments to bring that

cure rate to 100%. But the fact that a significant portion of people survive a disease that was once considered a death sentence is incredibly encouraging.

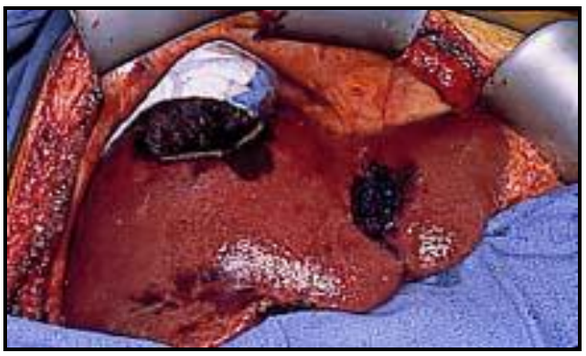


Figure 4: photograph showing the liver after the tumor has been removed leading to a potential cure of the disease.

Chua, Terence C. et al., Predictors of cure after hepatic resection of colorectal liver metastases: An analysis of actual 5- and 10-year survivors. J of Surg Onc; doi: 10.1002/jso.21864

16. Resection of Liver Mets & Survival (Jan. 27/11)

Two-stage resection (TSR) is associated with good outcomes for patients with advanced colorectal liver metastases (CLM) compared to those treated non-surgically, according to the results of this study. Antoine Brouquet, M.D., from the University Of Texas M.D. Anderson Cancer Center in Houston, and colleagues analyzed data from 890 patients undergoing resection after chemotherapy and 879 patients who received only chemotherapy for CLM. Intent-to-treat analysis was used to evaluate survival of patients who underwent TSR. The non-surgically treated controls were selected to match the TSR population: colorectal metastases with liver-only disease, objective response to chemotherapy, and survival for at least one year after initiation of chemotherapy. The investigators identified 65 patients who underwent the first stage of TSR, whose outcomes were compared with 62 patients who were included in the nonsurgical group. Of the patients who completed the first stage of TSR, 47 patients went on to complete the second stage. After an average follow-up of 50 months, the five-year survival rate was 51% in the TSR group, compared with 15% in the nonsurgical group. Non-completion and major postoperative complications were both independently associated with poorer survival in patients who underwent TSR. Researchers concluded that this study showed that complete TSR is associated with excellent outcome in patients with advanced bilateral (two sided) CLM who respond to chemotherapy.

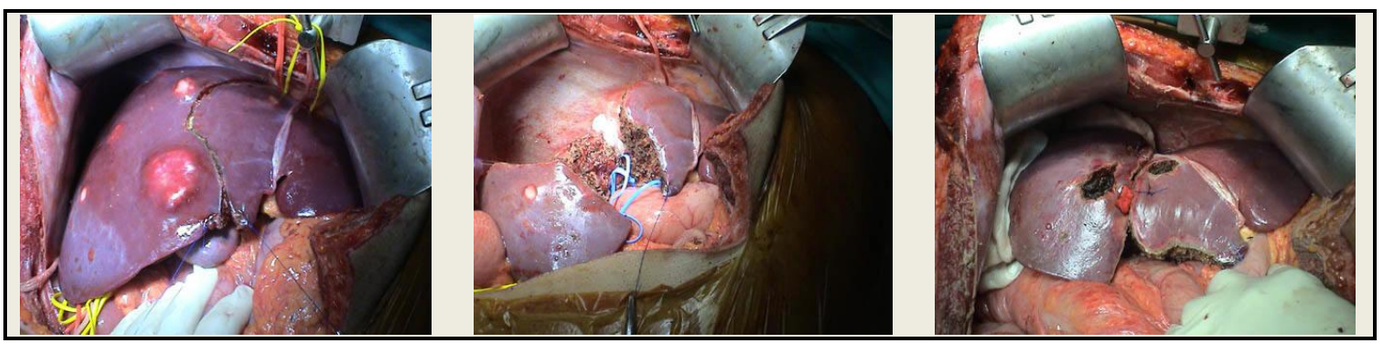


Figure 5: Showing colonic mets *Figure 6: Showing extent of liver resection* *Figure 7: Showing liver after complete resection*

Brouquet, Antoine, et al., High survival rate after two stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. J Clin Oncol. Published online before print January 24, 2011, doi: 10.1200/JCO.2010.32.6132

17. Fast Track Management of Colorectal Surgery (Feb. 8/11)

The concept of a fast track rehabilitation program has been recently introduced in colorectal surgery. It is basically a multidisciplinary perioperative care strategy for patients after resection of colorectal cancer. A research article addresses this particular issue. The authors compared the complications, restoration of gastrointestinal functions, and hospital stay time of postoperative colorectal cancer patients after fast-track rehabilitation program and conventional care. The results indicate that fast-track rehabilitation program can significantly accelerate the restoration of gastrointestinal function and reduce the postoperative complications as well as hospital stay time of patients after resection of colorectal cancer.

Wang G, et al., Fast track rehabilitation program vs. conventional care after colorectal resection: a randomized clinical trial. World J of Gastroenterol 2011; 17(5): 671-676

18. Palliative Care for Colorectal Obstructions in Patients with Unresectable Metastatic Disease

(Feb. 8/11)

Self-expandable metal stents (SEMSs) provide a promising alternative for initial symptom relief of malignant large bowel obstruction. However, data on the long-term outcomes of SEMSs are limited. The aim of this retrospective study was to compare the long-term outcomes of endoscopic stenting with those of surgery for symptom relief (palliation) in patients with incurable obstructive colorectal cancer. From January 2000 to December 2008, patients with incurable obstructive colorectal cancer who were treated with SEMSs (n = 71) or palliative surgery (n = 73) were reviewed. SEMS placement was accomplished by using either through-the-endoscope method or through surgery. Early success rates in the SEMS group and those in the surgery group were not different (95.8% vs 100%), and the SEMS group had fewer early complications than the surgery group (15.5% vs 32.9%). Although the duration of the first stent in the SEMS group was shorter than that in the surgery group, the median duration after a second stenting was comparable to that of the surgery group. There were more late complications in the SEMS group than in the surgery group, but the rates of major complications did not differ between the 2 groups. Researchers concluded that SEMSs were not only an effective and acceptable therapy for initial palliation of malignant colorectal obstruction, but they also showed long-term efficacy comparable to that with surgery.

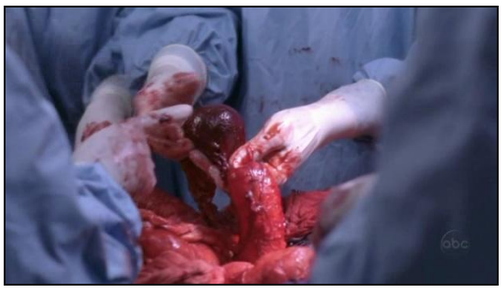


Figure 8: Showing surgical removal of colonic obstruction

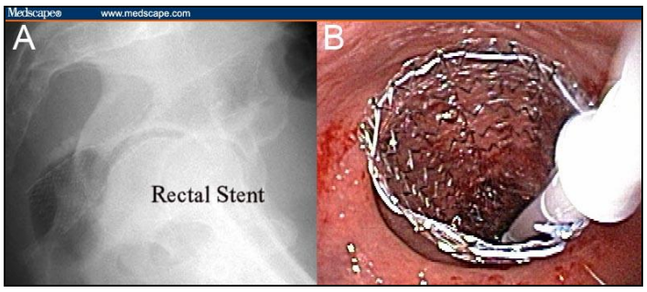


Figure 9: Insertion of colonic stent to manage colonic obstruction

Lee, Hyun Jung, et al., Long term outcome of palliative therapy for malignant colorectal obstruction in patients with unresectable metastatic colorectal cancers: endoscopic stenting versus surgery. Gastro Endos. January 2011.

19. Liver Surgeries for the Elderly (Feb.7/11)

Aging of the population - global graying - is occurring rapidly, with significant effects on epidemiology (medical study of the causes of a disease like cancer), treatment and outcomes for cancer patients. In colorectal cancer, outcomes for the elderly are worse than those for younger patients, partially driven by treatment disparities between the two groups. Nonetheless, standard-of-care treatment for the elderly results in equivalent long-term outcomes to those observed in the younger population; and available data supports the use of aggressive surgery and adjuvant (post-operative) therapies in well-selected patients. Data evaluating epidemiology, treatment patterns and outcomes in elderly patients with colorectal cancer liver metastasis are lacking. Liver resection offers the only curative approach, but it is rarely offered to older adults. Researchers concluded that current data support the use of hepatectomy (liver surgery) for well-selected elderly colorectal cancer patients with liver metastasis; however, this and other evolving therapies need to be assessed in the elderly to better define their role, indications, safety and outcomes.

Anaya, AD, et al., Global Graying, Colorectal Cancer and Liver Metastasis: New implications for surgical management. Crit Rev Oncol Hematol. 2011 Feb. 1; 77(2): pp. 100-108

RADIATION / INTERVENTIONAL RADIOLOGY

20. Response to Radiation Therapy Found to be Linked to a Gene (Jan. 6/11)

Australian researchers have identified a defective gene which explains why some colorectal cancer patients respond very well to radiotherapy but others not at all. They examined the role played by the gene MCC which was found earlier to be awry in approximately half of all cases of colorectal cancer. MCC is known as a potential tumour suppressor gene, and is believed to be involved in responding to DNA damage within cells. If an individual has low expression levels of MCC, their cells have a reduced ability to respond to DNA damage. According to researchers, the defective gene is a “double-edged sword”, as it appears to encourage a tumour to develop but also to make these tumours less resistant and easier to kill off with radiotherapy. Those patients with a defective gene were found to have an improved response to radiotherapy, and some types of chemotherapy, as their tumours were much less resistant to treatment. The researchers have already developed a test that can identify MCC defects in tissue. The study is important for colon cancer, but even more important for rectal cancer, because rectal cancer has a real disparity when it comes to radiotherapy, which is not well explained. Some patients respond very well and others don’t respond at all. The results of this study have the potential to provide a scientific explanation as to why some patients respond to treatment better than others and a practical test to identify those patients who are likely to respond.

Pangon, Laurent, et al., The mutated in colorectal cancer protein is a novel target of the UV-Induced DNA damage checkpoint. Genes & Cancer, Vol. 1, 9: pp. 917-926

SCREENING

21. OnkoSure by Radient Pharma Undergoing Clinical Trial Phase (Jan. 18/11)

Onko-Sure is a cancer diagnostic test and is currently in clinical trials in the U.S., with plans to complete the trial in the first quarter of this year. The study, conducted with the Mayo Clinic, is looking to validate the test as a tool in the detection of colorectal cancer in all stages, especially early ones. Approximately 1,000 colorectal cancer patients in various stages are being tested to compare the efficiency of the Onko-Sure test with another type that is reported to misdiagnose a disproportionate number of early stage cancers. Manufacturer RPC's (Radient) executive team has been aggressively cultivating relationships across a broad base of oncology and healthcare practitioners and the consistent feedback they have received in regards to the long-term potential of Onko-Sure test has been overwhelmingly positive. The company's Onko-Sure is a non-invasive in vitro diagnostic (IVD) test used to detect and monitor treatment for various types of cancer. This is done by measuring the accumulation of Fibrin and Fibrinogen Degradation Products (levels that rise dramatically with the progression of cancer) in the blood. The test has been cleared in the US for the detection of colorectal cancer and by Health Canada for the detection of lung cancer.

http://www.proactiveinvestors.com/companies/news/11544/radient-pharmaceuticals-to-complete-clinical-trial-for-cancer-diagnostic-test-in-first-quarter-11544.html

22. Stage II Colon Cancer Risk Test (Jan. 19/11)

Most stage II colorectal cancer patients do not relapse after surgical removal of their primary tumour. However, one in five stage II colorectal cancer patients will have cancer spread beyond their colon after resection of their primary tumour. Better information about which patients will relapse could spare many from the risks of chemotherapy that is administered after surgery. A new gene test announced at the 2011 Gastrointestinal Cancer Symposium helps provide answers to which patients are at highest risk and could help patients and their doctors make better decisions about follow-up chemotherapy after surgery. ***ColoPrint***, an 18 gene tumor tissue signature, found that three out of four patients with stage II colon cancer had only about a 5% risk of recurrence, very similar to stage I patients. For the remaining high risk patients, one in five (20%) had cancer return. In a series of 135 patients with stage II colon cancer, ColoPrint identified

- 73% at low risk of recurrence. After a median 97 months of follow-up, only 5% experienced a relapse.
- 27% at high risk. During the 97 month follow-up, 20% had cancer return.

ColoPrint was developed by searching the whole genome for a fingerprint of genes that predicted recurrence from colon cancer. The study reported at the GI Symposium is the second one to validate the test. A third validation study of 600 patients is now underway at MD Anderson Cancer Center in Houston, with results expected later this year. According to researchers, the ColoPrint gene expression test was the only significant factor that predicted the development of distant metastasis in a patient series. In this validation study, the performance of ColoPrint seemed to be independent of known clinical factors. ColoPrint was able to predict outcome in stage II patients, and this facilitates the identification of patients who may be safely managed without chemotherapy.

Rosenberg R, et al., Independent validation of a prognostic genomic profile (ColoPrint) for stage Ii colon cancer patients. Abstract #358, 2011 Gastrointestinal Cancers Symposium

23. GCC Assay Can Predict Risk of Colon Cancer Recurrence (Jan. 20/11)

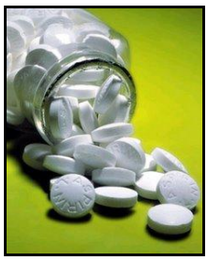
DiagnoCure Inc. has announced positive initial results of a multi-center clinical study of 241 stage II colon cancer patients, a population categorized as low risk by traditional methods yet with an average recurrence rate of 20%. In this population, the study demonstrated that DiagnoCure's Previstage™ GCC Colorectal Cancer Staging Test can stratify patients into high and low risk of recurrence groups, thereby providing relevant and more accurate clinical information for physicians to make more personalized treatment decisions. The new study demonstrates the prognostic value of the Previstage™ GCC assay (analysis). In a group of patients currently thought at low risk of recurrence, the test discriminates between those who have a very low risk of recurrence similar to a stage I cancer, and patients who have a higher risk of recurrence similar to a stage III cancer. Researchers believe that the Previstage™ GCC test has the potential to significantly improve the treatment decisions by identifying patients whom likelihood of colon cancer recurrence is very low and could be safely managed without chemotherapy. The first phase of the study, called VITAR (Validating Indicators to Associate Recurrence Risk), included 241 stage II colon cancer patients from six North American clinical sites. All patients had surgery in the prior ten years and had at least three years of follow-up; none received adjuvant (post-operative) chemotherapy. In a subset of 181 patients with traditionally favorable prognostic factors (T3 tumor and 12 or more lymph nodes examined), the Previstage™ GCC test classified 1/3 of patients as having a high risk of recurrence following surgery and 2/3 of patients at low risk of recurrence. In this subset, the high risk group had a 6 times greater likelihood of recurrence than the low risk group (27% versus 4%). These results are promising and very relevant. Prognostic risk stratification in stage II colon cancer remains a very clinically important issue in 2011, as researchers continue to face the challenge of attempting to identify those patients most likely to benefit from adjuvant chemotherapy. The initial VITAR study results were presented by the Principal Investigator, Daniel Sargent at the American Society of

Clinical Oncology (ASCO) 2011 Gastrointestinal Cancers Symposium. DiagnoCure intends to pursue the second phase of the study to further validate these positive initial results. The Previstage™ GCC Colorectal Cancer Staging Test evaluates lymph nodes removed during the colorectal cancer surgery. Whereas traditional microscopic examination of a lymph node assesses less than 1% of the lymph node and can detect 1 cancer cell in 200 normal cells, Previstage™ GCC evaluates **at least 50%** of each node and uses technology with a sensitivity of 1 cancer cell in 10 million normal cells. The test measures the Guanylyl Cyclase C (GCC) biomarker, which is exclusively expressed within the intestinal lining. When GCC is found in the lymph nodes nearing the tumor, it indicates that the cancer has escaped the intestine. To date, results of published studies totaling over 1,000 patients have shown that the GCC biomarker is a better predictor of disease recurrence in early stage colorectal cancer patients. The Previstage™ GCC test is a laboratory-developed test offered and performed by *DiagnoCure Oncology Laboratories* (Pennsylvania, USA).

Sargent, Daniel, et al., VITAR Study Results. Abstract #369. GI Cancers Symposium 2011.

24. Aspirin Boosts Accuracy of FOBT (Jan. 31/11)

Fecal Occult Blood Test (FOBT) detects subtle blood loss in the gastrointestinal tract and is commonly used in population-based screening programs across Canada. The test does not directly detect colon



cancer and shows positive in case of any kind of gastrointestinal bleeding. This results in many false positives. A positive test for gastrointestinal bleeding can also result from jaundice, sickle cell anemia or a bleeding peptic ulcer. According to researchers, of all the patients testing positive with FOBT, only 2-10% are detected with cancer later. Researchers at the German Cancer Research Centre in Heidelberg, Germany, have found that giving low-doses of aspirin prior to FOBT helps in better detection of colorectal cancer. The risk of colon cancer rises with age, with more than 90% of cases occurring in people over the age of 50. It was believed that aspirin leads to increased bleeding and false results. People who underwent FOBT were advised to go off the drug. Aspirin's blood-thinning properties prompt doctors to prescribe its low-doses to those at risk of cardiovascular diseases. Investigators assessed the association between low-doses of aspirin and performance of FOBTs in a sample of 1,979 patients with an average age of 62 years. The study was conducted over a period of four years (2005-2009). They were divided according to aspirin usage (regular users and non-users). The study found the sensitivity of FOBTs was twice for low-dose aspirin users as compared to that of non-users in both the tests. The results were more accurate as well. The study suggests that use of low-dose aspirin does not hamper testing of the cancer; on the contrary, it enhances test performance.

Brenner, Hermann, et al., Low-Dose Aspirin Use and Performance of Immunochemical Fecal Occult Blood Tests, JAMA 2010; 304: 2513-2520.

25. Missed Polyps During Colonoscopy Studied (Jan.31/11)

Because many colorectal cancers (crc) develop as a result of missed lesions during an earlier colonoscopy, researchers assessed the rate and predictors of colorectal cancer diagnosed within three years of a colonoscopy, according to a study published in the *American Journal of Gastroenterology.* The researchers studied 4,883 CRC patients. Of those, 7.9% or 388 cases were early or missed CRC, defined as cases diagnosed 6-36 months after a colonoscopy. This finding suggests that approximately 1 in 13 CRC cases may be due to early or missed CRC. Independent risk factors for early or missed CRC include prior colonoscopy, performance of index colonoscopy by family physicians, recent year of CRC diagnosis and proximal (right sided) site of CRC. The results also suggest women are more likely to have early or missed CRC. The researchers claim that this is unclear and may be related to differences in procedure difficulty, bowel preparation issues, or tumour biology between men and women.

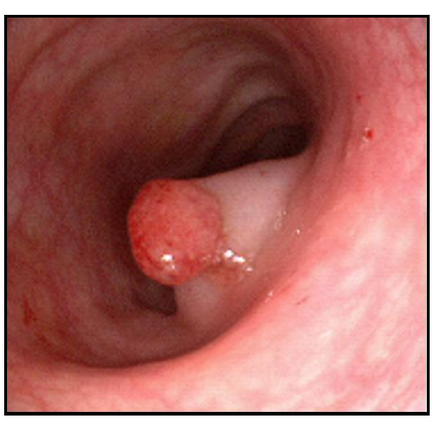


Figure 10: A colon polyp is a small growth of tissue that can best be compared to a wart or mole. Small colon polyps typically aren't dangerous; however, some of the larger polyps can eventually lead to cancer, which is why they are removed during a colonoscopy

Singh, Harminder, et al., Rate and predictors of early/missed colorectal cancers after colonoscopy in Manitoba: a population-based study. Am J Gastroenter 2010; 105: 2588-2596

26. Colorectal Cancer Screening Recommendations for First Degree Relatives (Feb.1/11)

Colorectal screening recommendations for first-degree relatives of individuals diagnosed with an adenoma before age 60 may be too aggressive, researchers argue in this study. The American Cancer Society, U.S. Multi-Society Task Force on Colorectal Cancer and the American College of Radiology recommend first-degree relatives (sibling, parent or child) of individuals diagnosed with an adenoma before age 60 undergo a colonoscopy every five years starting at age 40. However, researchers point out that there is not sufficient evidence to support the recommendation. Because not all adenomas portend the same cancer risk in the individual that has the adenoma, they would not be expected to portend the same risk in their first-degree relatives, according to the authors. For this very reason, the U.S. Preventive Services Task Force does not recommend such aggressive screening of first-degree relative of individuals with adenomas. Authors argued that more evidence and data is needed to justify such aggressive screening recommendations.

Austin, Gregory L., et al., Are colorectal cancer screening recommendations for first-degree relatives of patients with adenomas too aggressive? Clin Gastro & Hepatology. Published online January 18, 2011.

27. Colorectal Cancer Screening Using Dogs (Feb.5/11)

Early detection and early treatment are of vital importance to the successful treatment of various cancers. The development of a novel screening method that is as economical and non-invasive as the fecal occult blood test (FOBT) for early detection of colorectal cancer (CRC) is needed. In this study, canine scent detection was used to determine whether odour material can become an effective tool in CRC screening. Exhaled breath and watery stool samples were obtained from patients with CRC and from healthy controls prior to colonoscopy. Each test group consisted of one sample from a patient with CRC and four control samples from volunteers without cancer. These five samples were randomly and separately placed into five boxes. A Labrador retriever specially trained in scent detection of cancer and a handler cooperated in the tests. The dog first smelled a standard breath sample from a patient with CRC, then smelled each sample station and sat down in front of the station in which a cancer scent was detected. 33 and 37 groups of breath and watery stool samples, respectively, were tested. Among patients with CRC and controls, the sensitivity of canine scent detection of breath samples compared with conventional diagnosis by colonoscopy was **0.91 and the specificity was 0.99**. The sensitivity of canine scent detection of stool samples was 0.97 and the specificity was 0.99. The accuracy of canine scent detection was high even for early cancer. Canine scent detection was not confounded by current smoking, benign colorectal disease or inflammatory disease. According to the study investigators, this study shows that a specific cancer scent does indeed exist and that cancer-specific chemical compounds may be circulating throughout the body. These odour materials may become effective tools in CRC screening. In the future, studies designed to identify cancer-specific volatile organic compounds will be important for the development of new methods for early detection of CRC.

Sonoda, Hideto, et al., Colorectal cancer screening with odour material by canine scent detection. Gut (2011) online publication. Doi: 10.1136/gut.2010.218305

28. Colonoscopy Effective Screening Tool (Feb.11/11)

A large, well-designed study gives more support to the notion that when it comes to colon cancer, nothing saves lives like getting everyone screened. The study included over 2 million, 50-90 year old men and women living in Ontario, Canada. This group was followed for 14 years to determine the connection between colon cancer screening rates where people lived and the likelihood of dying of colon cancer in those areas. The researchers found that for every 1% increase in colon cancer screening rates in a given geographic area, the population in that area experienced a 3% decrease in the risk of dying of colon cancer. Screening works for the simple reason that it catches colon cancer early, before it has spread beyond the colon. When caught early, or even better, when pre-cancerous colon growths are removed before they become cancer, this disease is very preventable. Nearly everyone diagnosed with early stage colon cancer will be cured. Study authors concluded that increased colonoscopy use was associated with mortality reduction from colorectal cancer at the population level.

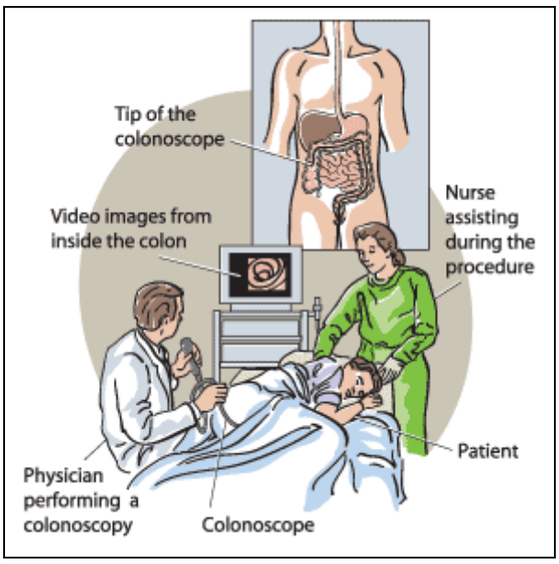


Figure 11: The Colonoscopy Procedure. A colonoscopy allows doctors to ***view the inner lining of the entire colon.*** *A long, thin, flexible tube with a tiny camera and light, called a colonoscope, is used to conduct this procedure. Looking at a video monitor, your doctor can check for problems such as bleeding, inflammation, or abnormal growths (polyps).*

Rabeneck, Linda et al., Association between colonoscopy rates and colorectal cancer mortality. Am J Gastroenterol 2010; 105: pp. 1627-1632.

PSCHYCOSOCIAL

29. Better Communication Urged in Advanced Cancer (Jan. 30/11)

The American Society of Clinical Oncology (ASCO) has issued a policy statement urging cancer doctors to communicate better with their advanced cancer patients. While people can live many years with advanced cancer, it is not considered curable in most cases. The ASCO paper states that all available treatment and cancer care options should be discussed with patients up front, before treatment begins. When seeing advanced cancer patients for the first time, many cancer doctors present one or two possible treatment options and then discuss the possible outcomes of those treatments. Doctors often discuss palliative care or other options only *after* there are signs that treatments are not working well to contain the cancer. Many people think palliative care means end-of-life care. It is not the same. Palliative care is a growing specialty focused on symptom control and maintaining quality of life – according to the patient's goals. Experts say it should be initiated, along with disease-directed treatments, soon after diagnosis – especially in patients having aggressive disease or severe symptoms or side effects. (Hospice, or end-of-life care begins when the patient is expected to live less than six months and when disease-directed treatments are discontinued) Palliative care focuses on increasing comfort through prevention and treatment of suffering. It encompasses the whole self, caring for the physical, emotional, and spiritual needs of patients and their families. Palliative care is designed to prevent and relieve symptoms so a person can get on with daily life. ASCO president George Sledge, MD summed up the new approach: "While improving survival is the oncologist's primary goal, helping individuals live their final days in comfort and dignity are one of the most important responsibilities of our profession". He also indicated that, "Oncologists must lead the way in discussing the full range of curative and palliative therapies to ensure that patients' choices are honored." This strong statement about honest and open communication between doctors and advanced cancer patients is important for many reasons. By sharing full information up front, doctors can make sure patients understand the pros and cons of each possible cancer management plan. And by discussing all options up front, doctors can lessen the chances of giving patients false hope about their situation. It's always important to be hopeful and to cope with cancer as one sees fit, but if doctors delay discussions of what happens when treatments don't work as well as hoped, this can lead to added stress and grief for everyone in the long run. By offering all options up front, doctors can help patients make decisions that are best for them. Sometimes the decision to treat advanced cancer aggressively makes sense and can give people many months and even years of life. At other times, aggressive treatments can actually shorten life and make people miserable in the mean time. A lead author on the new paper states: "Instead of viewing the whole process as fighting, fighting, fighting, and then giving up, having these conversations as an ongoing dialogue may lead to better outcomes for the patients."

Peppercorn JM, et al., American Society of Clinical Oncology statement: toward individualized care for patients with advanced cancer. J Clin Oncol. 2011 Jan 24. Epub ahead of print.

30. Chemobrain or Chemofog is Real (Feb.11/11)

In recent years, there is growing evidence in the medical literature to support an association between administration of commonly used chemotherapeutic agents and an increased risk for cognitive impairment, or what is commonly referred to as "chemobrain". This study sought to summarize data relating to the mechanisms by which chemotherapy may induce cognitive impairment (CICI) in patients

surviving from solid tumors. References for this review were identified by from 1995 until December 2009. Findings indicate that CICI is a relatively common event that, in most of the cases, remains under diagnosed, thereby adversely affecting the quality of life of patients with cancer. Researchers also discovered that effective pharmacological interventions toward the symptomatic or prophylactic management of CICI are also lacking. Either called "chemobrain" or "chemofog," the long-term CICI in cancer survivors is real. The need for multidisciplinary care interventions toward a timely diagnosis and management of CICI is clearly warranted, according to the researchers.

Argyriou, Andreas, et al., Either called chemobrain or chemofog, the long term chemotherapy induced cognitive decline in cancer survivors is real. J of Pain and Symptom Management. Vol. 41, Issue 1: pp. 126-139

31. Depression, Anxiety and Adjustment Disorder in Cancer (Feb.16/11)

Substantial uncertainty exists about prevalence of mood disorders in patients with cancer, including those in oncological, hematological, and palliative-care settings. Researchers aimed to quantitatively summarize the prevalence of depression, anxiety, and adjustment disorders in these settings. They identified 24 studies with 4007 individuals across seven countries in palliative-care settings. Interview-defined depression and anxiety was less common in patients with cancer than previously thought, although some combination of mood disorders occurs in 30–40% of patients in hospital settings without a significant difference between palliative-care and non-palliative-care settings. Researchers maintained that clinicians should remain vigilant for mood complications, not just depression.

Mitchell, AJ, et al., Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 95 interview-based studies. Lancet Oncol. 2011 Feb.1; 12(2): pp. 160-174

OTHER

32. Anemia May Be An Indicator for Colon Cancer (Jan. 18/11)

For healthy men and post-menopausal women, the risk of iron deficiency anemia is very low. In fact, iron deficiency anemia is so uncommon in men and older women that when it does occur, it is oftentimes a warning of something more disconcerting. And it should not be ignored. A new study on iron deficiency anemia and colon cancer points to a problem during medical care and follow up. Researchers considered 628,882 patients, 40 years of age or older, who were screened for iron deficiency anemia as part of routine medical care. They found that 3.1%, or 19,349 patients, had iron deficiency anemia. More notably, 3% of the patients with iron deficiency anemia, or 578 people, were later found to have colon cancer. The length of time that it took to arrive at a diagnosis, though, varied widely in the group. In the patients later found to have colon cancer as a cause of iron deficiency anemia, the time to diagnosis ranged from 2.5 to 31.9 months. That means some people received a diagnosis of colon cancer within a couple of months of finding out they had anemia. For others, it took nearly three years to receive a colon cancer diagnosis. The biggest determinant of how long it took to get a colon cancer diagnosis was the type of health care specialist a person saw for follow up. This study took place in Great Britain, which has a different system of health care than the United States or Canada. This implies, according to researchers, that if this study were conducted here the results may be somewhat different. However, it is quite likely that there would be delays in colon cancer diagnosis stateside as well. If a patient receives any type of test for which the results aren't completely normal, they need to ensure follow up with their health care provider. Request that your doctor assist you carefully and systematically to rule out all of the conditions that may be causing anemia, or any other condition or abnormal blood tests received.

Damery, Sarah, et al., Iron deficiency anemia and delayed diagnosis of colorectal cancer: a retrospective cohort study. Colorectal Disease. Online edition: DOI: 10.1111/j.1463-1318.2010.02488.x

33. Online Calculator Tool For CRC Treatment Decisions (Jan. 31/11)

More treatment is not always better. Cancer patients and their doctors often face difficult decisions about how much chemotherapy and/or radiotherapy is the best course for the individual. For colon cancer diagnosed at stage I, II, or III, surgery is the first line treatment. Adjuvant, meaning additional, treatment with chemotherapy is believed to be beneficial for stage III cancer, but not for stage I. For stage II, the use of chemotherapy is still a topic of debate. Each individual is different, and the optimum treatment depends on many factors. Two research groups have developed computer models to predict the results of chemotherapy. Both are available online. The Numeracy calculator is provided by the Mayo Clinic, based on data from 3,302 patients from seven randomized trials. It has four inputs:

1. Lymph nodes (none, 1 – 4, or 5+)
2. Tumor stage (T1/T2, T3, or T4)
3. Grade (low or high)
4. Age (49 or younger, 50 – 59, 60 – 69, or 70+)

Thus, there are 72 different combinations. The Adjuvant! calculator is based on data from the U.S. Surveillance Epidemiology and End Results (SEER) tumor registry, and provides additional inputs:

1. Gender (male or female)
2. Comorbidity (perfect health, minor problems, average for age, or major problems)
3. Number of examined lymph nodes (0, 1 – 3, 4 – 10, >10)

The chemotherapy regimens are 5-FU (5-fluorouracil plus leucovorin) and FOLFOX (5-fluorouracil plus leucovorin plus oxaliplatin). Researchers at Johns Hopkins University, the Mayo Clinic, Creighton University in Nebraska, and the University of British Columbia performed a comparison of these two calculators. They chose 192 hypothetical patient scenarios, using characteristics of individuals who could be chemotherapy candidates. The results indicated small but statistically significant differences between the two calculators. Thus, when you see small differences between survival rates with different treatment options, it is important to understand that these could be numerical artifacts. Both websites encourage users to have a health care provider help with entering data and interpreting results, since the patient may not be as familiar with all the input options. However, researchers claim the Numeracy calculator appears fairly simple for the average user.

- To access the Numeracy calculator online, please click on the following link: www.mayoclinic.com/calcs/
- To access the Adjuvant! Calculator online, please click on the following link: http://adjuvantonline.com/index.jsp

Bardia, A, et al., Adjuvant chemotherapy for resected stage Ii and III colon cancer: comparison of two widely used prognostic calculators. Semin Oncol. 2011 Feb; 37(1): pp. 39-46

34. Treating Metastatic Colorectal Cancer – Expert Opinion (Feb.7/11)

A recent article was published about how one doctor treats advanced, or metastatic, colon cancer. Metastatic refers to cancer that has spread beyond the colon, to other areas of the body, such as the liver or lungs. Dr. Alex Grothey, MD, a professor of oncology at the Mayo Clinic, details how he works with patients who have been diagnosed with metastatic colon cancer. Dr. Grothey begins by identifying goals of treatment. He then goes through each option that might be considered as part of a possible treatment plan. He suggests which might or might not be appropriate for advanced colon cancer patients with different medical situations. About.com offers the following points that should be kept in mind throughout the article:

- There is no one standard way to treat advanced colon cancer. This is why an article by a noted expert in the colon cancer field can be helpful to anyone recently diagnosed with the disease.
- You can use this article as a way to start a conversation with your doctor about what your best treatment options are.
- As new research emerges, new treatment options, new medications and surgical techniques, and new ways of combining existing treatments become available.
- What your cancer doctor offers you right now as the best treatment, may not be the best treatment six months from now. This is not because your doctor is clueless, it is because science moves forward. Your doctor can only offer you what is available at the time of your diagnosis.
- The options discussed in the article are one doctor's opinion of the best way to proceed when someone is diagnosed with metastatic colon cancer. Your doctor may have a different opinion about what is best in any one situation.
- To make sure you get the best treatment for you, ask your doctor to explain to you, in a way that you can understand, why he or she favors a particular treatment plan.
- It's perfectly normal for doctors to have differences of opinion about the best way to treat a disease as complex as advanced colon cancer. If you understand why your doctor favors a particular treatment approach, you can feel good about moving forward and know that you are getting what is best for you!

To access the article, please click on the following link: http://journals.lww.com/oncology-times/Fulltext/2011/01250/How_Do_I_Treat_a_Patient_with_Metastatic.1.aspx

http://coloncancer.about.com/b/2011/02/07/whats-the-best-way-to-treat-metastatic-colon-cancer.htm

Grothey, Alex, How Do I treat a patient with metastatic colorectal cancer? Oncology Times. 25 January 2011; Vol 33, Issue 2: pp. 8, 10-11. Doi: 10.1097/01.COT.0000394480.09588.32

35. Reduced Inflammation Lowers Colon Cancer Risk (Feb.10/11)

The results of this study have added to our understanding of the connection between inflammation and colon cancer. This study looked at colon cancer risk in a large group of people who had not had the disease before. Between 1987 and 1989, researchers collected blood samples and medical information from 13,414 adults. The blood samples were analyzed for CRP (C-Reactive Protein - a substance in the blood that measures inflammation) and several other substances that indicate inflammation at the beginning of the study and again later, in the mid-1990s. Each person was assigned an inflammation score based on their blood values of inflammation markers. A higher inflammation score meant more

inflammation in the body. This group was tracked for approximately 18 years to see who developed colon cancer. After 18 years, the researchers analyzed the information they had collected and found that the higher a person's inflammation score at the beginning of the study, the more likely he or she was to later develop colon cancer.

- People with the highest inflammation scores had 65% higher risk of developing colon cancer compared with people with the lowest scores.
- People with the highest blood levels of CRP were 97% more likely to develop colon cancer compared with people with the lowest scores.

The message from this research is clear: more inflammation is associated with higher colon cancer risk. The results imply that inflammation is linked with colon cancer risk. Additionally, inflammation is linked with heart disease, diabetes, and other chronic conditions as well. Reducing inflammation seems to help prevent colon cancer in the first place, and prevent it from returning if you've had it.

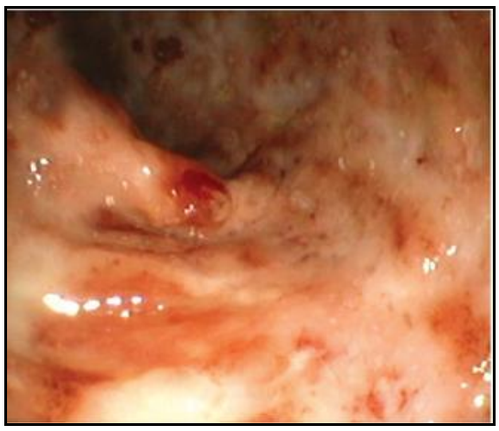


Figure 12: Colonoscopic Picture of Inflammation of Colonic Wall

Prizment, Anna, et al., Association of Inflammatory Markers with Colorectal Cancer Incidence in the Atherosclerosis Risk in Communities Study. Cancer, Epid, Biomar Prev; Published OnlineFirst January 7, 2011; doi: 10.1158/1055-9965.EPI-10-1146

NUTRITION & HEALTHY LIFESTYLE

36. School Milk Can Help to Prevent Colorectal Cancer (Jan.17/11)

The results of this study found that the risk of bowel cancer was 30% lower in people who drank school milk daily. The reduction in risk was greatest in those who drank 1200 or more half-pint bottles of milk while at school. The researchers believe that the calcium provided by the free milk-in-schools program from 1937 to 1967 may be responsible for the dramatic reduction in risk of bowel cancer that has occurred in New Zealand for people born between 1938 and 1953. Studies in adults have suggested that calcium consumption may reduce bowel cancer risk but very few studies of consumption in childhood have been done.

The results of this study, if confirmed, would provide a means of reducing the very high rates of bowel cancer in New Zealand. Researchers also suggest that “the study should encourage a greater focus on factors in childhood that affect the risk of bowel cancer and health overall.” The research team is currently planning further research which, if funding can be obtained, could confirm that the provision of milk at school can significantly reduce the risk of bowel cancer in future generations. The study involved obtaining information from people newly diagnosed with bowel cancer and people of a similar age without bowel cancer selected from the general electoral roll. Responses about drinking milk when at school corresponded to the historical reports of participation

37. Obesity & C Reactive Protein Affect Survival After Colon Cancer (Jan. 26/11)

Many studies have linked obesity with colon cancer. Health experts note that being obese, or significantly overweight, increases the risk of colon cancer. And carrying extra pounds makes it more likely that colon cancer will return (recurrence) if you've already had it. This new study points to why obesity increases the risk of colon cancer and its recurrence. Researchers invited 344 colon cancer patients to participate in a study on obesity and survival after colon cnacer. They measured each person's height and weight to determine whether or not they fell into the obese category. They also collected blood to analyze for markers of inflammation. This included two substances, ***called c-reactive protein (CRP) and Ang-2***. The researchers found that patients who had the highest amounts of CRP and Ang-2 in their blood were significantly more likely to die of colon cancer. They also noted that CRP blood levels were inversely associated with survival in stage 2 colon cancer patients, meaning that the higher the CRP level, the less likely someone is to survive. The study authors concluded that it is obesity-related inflammation, rather than obesity itself, that is linked with poorer survival after a colon cancer diagnosis. The obvious thing most people draw from this is that if you are obese, it may be important to think about aiming for a healthier body weight once you have completed colon cancer treatment. There is no proof that weight loss will translate into better survival, but it's a good place to start.

Volkova, E., et al., Association of angiopoietin-2, C-reactive protein and markers of obesity and insulin resistance with survival outcome in colorectal cancer. British Journal of Cancer (2011) 104, 51–59. doi:10.1038/sj.bjc.6606005

38. Smoking Can Be a Source of Stress for Cancer Patients (Jan. 28/11)

This study speaks to the issue of someone with cancer and his or her caregiver being on different pages when it comes to smoking. New research looked at people with cancer and their main caregivers having a difference of opinion. The biggest problems seem to arise when only one of two people in this relationship smoke. It doesn't seem to matter much which person smokes; it can be the person with cancer or the person who's helping out. But either way, smoking seems to come between people and make it harder to cope with the stresses of cancer when only one of the two smoke. Even without cancer in the picture, people often argue about smoking habits. If only one person smokes, he or she might feel "nagged" to quit smoking. For the person who doesn't smoke, he or she might feel that their partner cares more about smoking than them. A little empathy can go a long way toward helping people cope with differences in smoking habits - putting yourself in the other person's shoes. If you are providing care and support to someone with cancer, and you also smoke, consider taking your smoking outdoors on the days when your loved one doesn't feel well. Smells that normally don't bother a person can become very strong and even nauseating during cancer treatment. If your loved one is not feeling well and you do your best to limit his or her exposure to smoke, they will appreciate it more than you know. If you have cancer and you smoke, but your caregiver does not smoke, consider that he or she may be "nagging" you about smoking out of love and concern. It may come across as mean and aggressive when he or she urges you to quit smoking, but take a moment to consider *why* he or she keeps bringing this up. That person loves you, he or she wants you to live, and only wants the best for you in terms of how to best fight your cancer. When you know that love is behind a seemingly nagging request, it makes it a little easier to cope. If you or a loved one smokes and are willing to consider trying to quit, seek help. Attending a quit smoking support group or chat room (online), using nicotine replacement products, and trying prescription medications, if appropriate, all increase the chances of successfully quitting tobacco. Quitting by yourself, cold turkey, is very difficult. The old adage, "If at first you don't succeed, try, try again," is certainly appropriate for anyone who's trying to quit smoking. Health experts note that to successfully quit tobacco, most people need to try several times. Each time you try to quit, you learn a little more about what works for you in terms of coping with the cravings and the habit of smoking. After enough tries, you'll find the magic mix of things that work for you, and you'll quit for good.

http://coloncancer.about.com/b/2011/01/28/emotional-toll-of-smoking-on-cancer-patients-and-caregivers.htm

Weaver, Kathryn, et al., Smoking concordance inlung and colorectal cancer patient – caregiver dyads and quality of life. Cancer, Epidem Biomark & Prev. Published OnlineFirst December 21, 2010; doi: 10.1158/1055-9965.EPI-10-0666

39. Vitamin D Linked to Colon Cancer Protection (Feb.7/11)

High blood levels of vitamin D are associated with a reduced risk of colorectal cancer, according to a new meta-analysis of observational studies from an international team of researchers. Analysis of data from nine studies revealed that, for every 10 nanograms per millilitre increase in levels of vitamin D (25-hydroxyvitamin D) the associated risk of colorectal cancer **decreased by 15%**. On the other hand, no association was observed between vitamin D levels and the risk of breast or prostate cancer. Vitamin D refers to two biologically inactive precursors - D3, also known as cholecalciferol, and D2, also known as ergocalciferol. Both D3 and D2 precursors are transformed in the liver and kidneys into 25-hydroxyvitamin D (25(OH)D), the non-active 'storage' form, and 1,25-dihydroxyvitamin D (1,25(OH)2D), the biologically active form that is tightly controlled by the body. The link between vitamin D intake and protection from cancer dates from the 1940s when Frank Apperly demonstrated a link between latitude and deaths from cancer, and suggested that sunlight gave *"a relative cancer immunity".* Since then, there have been numerous studies suggesting associations between vitamin D and lower risks of certain cancers. There is growing evidence that 1,25(OH)2D has anticancer effects, but the discovery that non-

kidney cells can also hydroxylate 25(OH)D had profound implications, implying that higher 25(OH)D levels could protect against cancer in the local sites. The new meta-analysis study adds to the subject, while also showing the relationship between vitamin D and cancer is ambiguous, depending on the type of cancer. Researchers analyzed data from 35 epidemiological studies of 25(OH)D levels and colorectal, breast and prostate cancer. The analysis showed that for every 10 nanograms per milliliter increase in 25(OH)D levels, the associated risk of colorectal cancer decreased by 15%, while the risk of breast cancer was associated with an 11% decrease. However, when the researchers restricted their analysis to prospective studies only, the breast cancer risk was decreased by only 3%, whereas data from case-control studies indicated a risk reduction of 17%. No association between vitamin D levels and prostate cancer were observed at all. *"To assess whether vitamin D status is a risk factor or a risk marker for colorectal cancer, it is likely that new randomized trials will need to be organized to test whether increasing the 25-hydroxyvitamin D level changes the risk of colorectal cancer, and to determine how much of an increase is required to change the risk of cancer sufficiently to be useful as a public health measure,"* researchers concluded.

Gandini, S et al., Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. International Journal of Cancer. 15 March 2011, Volume 128, Issue 6, pages 1414–1424

40. Lack of Sleep is Identified as A Risk Factor For CRC (Feb.8/11)

The results of this study found that individuals who averaged less than six hours of sleep at night had an almost 50% increase in the risk of colorectal adenomas compared with individuals sleeping at least seven hours per night. Adenomas are a precursor to cancer tumors, and left untreated, they can turn malignant. This appears to be the first study to report a significant association of sleep duration and colorectal adenomas. According to researchers, a short amount of sleep can now be viewed as a new risk factor for the development of colon cancer. In the study, patients were surveyed by phone prior to coming into the hospital for scheduled colonoscopies at UH Case Medical Center. They were asked demographic information as well as questions from the Pittsburg Sleep Quality Index (PSQI), which obtains information about the patient's overall sleep quality during the past month. The PSQI asks for such information as how frequently one has trouble sleeping and how much sleep one has had per night. Of the 1,240 patients, 338 were diagnosed with colorectal adenomas at their colonoscopy. The patients with adenomas were found in general to have reported sleeping less than six hours compared to those patients without adenomas (control) patients, and the association between amount of sleep and adenomas remained even when adjusted for family history, smoking, and waist-to-hip ratio (a measurement of obesity). The researchers also found a slightly stronger association of sleep duration with adenomas with women compared to men, but the difference was not statistically significant. Researchers said the magnitude of the increase in risk due to fewer hours of sleep is comparable to the risk associated with having a first-degree relative (parent or sibling) with colon cancer, as well as with high, red meat intake. Short sleep duration is a public health hazard leading not only to obesity, diabetes and coronary heart disease, but also, as they now have shown in this study, colon adenomas. Effective intervention to increase duration of sleep and improve quality of sleep could be an under-appreciated avenue for prevention of colorectal cancer. Researchers don't truly understand why fewer hours of sleep may lead to colon cancer, but some of the theories may include that less sleep may mean less production of melatonin, a natural hormone that in animals has been linked to DNA repair, or that insulin resistance may underlie the link between sleep disturbance and cancer development.

Cheryl L. Thompson, Cheryl L., et al., Short duration of sleep increases risk of colorectal adenoma.* Cancer*, 2011; 117 (4): 841 DOI: 10.1002/cncr.25507