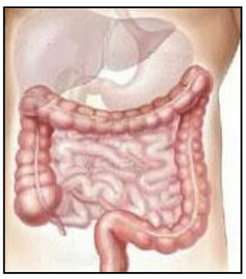
COLORECTAL CANCER RESEARCH UPDATES

Month Ending June 22nd, 2012



The following colorectal cancer research update extends from May 19th, 2012 – June 22nd, 2012 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Avastin After Failure of First Line Chemo Improves Second Line Survival Time (Jun.3/12)

Combined second-line treatment with Avastin® (bevacizumab) and standard chemotherapy extends survival in patients with advanced colorectal cancer who have received first-line combined Avastin treatment, according to the results of a large phase III study presented at the 2012 annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago, Illinois. Avastin is an anti-angiogenic targeted therapy that blocks a protein known as VEGF. VEGF plays a key role in the development of new blood vessels. By blocking VEGF, Avastin deprives the cancer of nutrients and oxygen and inhibits its growth. Avastin's effects on blood vessels may also improve the delivery of chemotherapy to the tumor. Multiple studies have shown that the addition of Avastin to standard chemotherapy improves outcomes among patients with metastatic colon cancer—and now, the results of this study confirm what physicians have long suspected, that extended Avastin treatment provides significant benefit for patients with advanced colorectal cancer. Avastin (used in combination with standard chemotherapy) is already approved for first- and second-line treatment of advanced colorectal cancer, but this is the first randomized trial to evaluate the regimen in the second-line setting in patients who have previously been treated with it in the first-line setting. The study included 820 patients with metastatic, inoperable colorectal cancer who were treated with standard first-line chemotherapy and Avastin. After disease progression, patients were randomized to receive a different chemotherapy drug plus Avastin or chemotherapy plus placebo. The group that received Avastin experienced improved survival—overall survival was 11.2 months in the Avastin group, compared to 9.8 months in the placebo group and progression-free survival was 5.7 months in the Avastin group compared to 4.1 months in the placebo group. Treatment was well tolerated by patients in both arms. The researchers concluded that extended Avastin treatment improves survival in patients with advanced colorectal cancer. They speculated that the results indicate that even when tumors become resistant to chemotherapy, they may not develop resistance to anti-angiogenic therapy—so switching chemotherapy drugs when the cancer progresses and continuing Avastin could make second-line treatment more effective.

Arnold D, Andre et al. Bevacizumab (BEV) plus chemotherapy (CT) continued beyond first progression in patients with metastatic colorectal cancer (mCRC) previously treated with BEV plus CT: Results of a randomized phase III intergroup study (TML study). Presented at the 2012 annual meeting of the American Society of Clinical Oncology, June 1-5, 2012, Chicago, IL. Abstract CRA3503.

2. Study Involving Ramucirumab Presented at ASCO (May 19/12)

New late-stage clinical trial data on Lily's multipurpose cancer therapy ramucirumab was presented at the American Society of Clinical Oncology (ASCO) 2012 annual meeting. Data from three of six phase III studies of the fully human IgG1 monoclonal antibody receptor antagonist was showcased at the Chicago event, highlighting its performance against **metastatic colorectal cancer**, metastatic gastric adenocarcinoma and hepatocellular cancer. This will be supported by data from a phase II study that evaluated the drug among persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma patients. Ramucirumab is involved in one of the largest clinical programs currently underway at Lilly, with six global phase III trials being carried out, spanning breast, colorectal, hepatocellular, lung and gastric cancer. Stay tuned as we learn more about this new agent.

http://www.zenopa.com/news/801366250/Lilly_to_present_new_ramucirumab_data_at_ASCO_2012

3. Zaltrap (Aflibercept) Can Be Used In Patients Who Have Previously Received Avastin (May 24/12)

A promising treatment approach for metastatic colorectal cancer can be used safely in patients previously treated with bevacizumab (Avastin), researchers reported. In the placebo-controlled, phase III VELOUR trial of aflibercept (Zaltrap) plus the FOLFIRI chemotherapy combination, patients who had previously received bevacizumab showed similar side-effect profiles as other patients. Median overall survival time with the combination was slightly shorter in patients with a bevacizumab history (12.5 months versus 13.9 months). Moreover, in the past-bevacizumab patients, overall survival with this regimen did not differ significantly from that seen with placebo plus FOLFIRI (median 11.7 months). But median progression-free survival with aflibercept plus FOLFIRI was nearly the same irrespective of prior bevacizumab treatment (6.7 months with previous bevacizumab versus 6.9 months without). It was also significantly longer than when placebo was substituted for aflibercept (3.9 months with and 5.4 months without previous bevacizumab). Both bevacizumab and aflibercept target vascular endothelial growth factor (VEGF). Bevacizumab, the angiogenesis-promoting growth factor, binds to and disables VEGF receptors. Aflibercept is a synthetic fusion protein that acts as a decoy receptor for VEGF, preventing two forms of the protein, as well as placental growth factor, from triggering angiogenic signaling. The latter agent has generated excitement in the oncology community because relatively few new drugs have shown promise for advanced colorectal cancer. Top line results from the VELOUR trial were greeted warmly since it demonstrated a statistically significant, if clinically modest, improvement in overall and progression-free survival with the addition of aflibercept to FOLFIRI. FOLFIRI is the current standard of care, combining leucovorin, fluorouracil, and irinotecan. But there have been questions as to whether aflibercept would be of any use in patients whose disease had previously progressed while on bevacizumab, and part of the VELOUR trial was a pre-specified subgroup analysis comparing outcomes in patients who had previously received bevacizumab with those who didn't. VELOUR was a large trial, with 1,226 patients

with metastatic colorectal cancer, including 373 with prior bevacizumab treatment, whose last unsuccessful treatment regimen was based on oxaliplatin. In addition to showing that the aflibercept-FOLFIRI combination extended progression-free survival in the bevacizumab-treated patients, the results also indicated no special safety problems in such patients.

Allegra, C, et al., Effects of prior bevacizumab (B) use on outcomes from the velour study: a phase III study of aflibercept (afl) and folfiri in patients (pts) with metastatic colorectal cancer (mcrc) after failure of an oxaliplatin regimen. ASCO 2012; Abstract #3505.

4. Adjuvant Chemo in Stage III Colon Cancer Patients After Age 75 (June 4/12)

Few patients 75 years of age and older participate in clinical trials, thus whether adjuvant chemotherapy for stage III colon cancer (CC) benefits this group is unknown. A total of 5,489 patients ≥ 75 years of age with resected stage III CC, diagnosed between 2004 and 2007, were selected from four data sets containing demographic, stage, treatment, and survival information. Researchers found that use of adjuvant therapy (chemo administered post surgery) declined with age and comorbidity. Chemotherapy receipt was associated with a survival benefit of comparable magnitude to clinical trials results. The incremental benefit of oxaliplatin over non–oxaliplatin-containing regimens was also of similar magnitude to clinical trial results in two of three examined data sources. However, statistical significance was inconsistent. The non-investigational experience suggests patients with stage III CC ≥ 75 years of age may anticipate a survival benefit from adjuvant chemotherapy. Oxaliplatin offers no more than a small incremental benefit. Use of adjuvant chemotherapy after the age of 75 years merits consideration in discussions that weigh individual risks and preferences.

Sanoff, Hanna K., et al., Effect of adjuvant chemotherapy on survival of patients with stage iii colon cancer diagnosed after age 75 years. J of Clin Onc. Doi: 10.1200/JCO.2011.41.1140

5. Kras, Braf and PIK3CA Mutations in Patients Undergoing Erbitux or Vectibix Therapy (Jun.6/12)

Anti-epidermal growth factor receptor (EGFR) antibodies, cetuximab (Erbitux) and panitumumab (Vectibix), are established as a new treatment option for metastatic colorectal cancer (mCRC). The mutation in the KRAS gene, which is present in 30-45 % of CRC patients, has shown to be a predictive biomarker of resistance to anti-EGFR antibody therapy. Those who do not harbor the mutation in the kras gene may demonstrate a response to the therapies. There are two other genes whose mutation may affect response to these anti-egfr therapies: BRAF and PIK3CA. In this study, 43 chemotherapy-refractory Japanese patients with mCRC were treated with cetuximab monotherapy or cetuximab plus irinotecan. KRAS, BRAF, and PIK3CA mutational status of tumors was assessed. The association between mutational status and treatment outcome was evaluated. Of 43 tumors, KRAS, BRAF, and PIK3CA mutations were identified in 12 (27.9 %), 2 (4.7 %), and 2 (4.7 %) tumors, respectively. The wild-type (no mutation) KRAS subgroup showed better clinical outcomes than the mutant KRAS subgroup in terms of response rate (RR) (31.3 % vs. 0 %) and progression-free survival (PFS) (5.1 vs. 3.0 months). No response to treatment was shown in 16 (37.2 %) patients with tumors harboring mutations in any one of the three genes (KRAS, BRAF, and PIK3CA). The ***wild-type subgroup without any mutations in KRAS, BRAF, and PIK3CA had a better RR (37.0 %)*** and PFS (6.4 months) than did the wild-type KRAS subgroup. The data indicated that KRAS status is predictive of cetuximab response in the Japanese population. The additional analysis of BRAF and PIK3CA genes in wild-type KRAS patients could improve selection of patients who are most likely to benefit from anti-EGFR antibody therapy.

Soeda, Hiroshi, et al., Clinical usefulness of kras, braf, and pik3ca mutations as predictive markers of cetuximab efficacy in irinotecan- and oxaliplatin- refractory Japanese patients with metastatic colorectal cancer. Inter J of Clin Onco. 2012. Doi: 10.1007/s10147-012-0422-8

6. Study Examining the Neuroprotective Effects of Neurotropin on Oxaliplatin-Induced Neurotoxicity (Jun.8/12)

Oxaliplatin is effective in adjuvant and first-line colorectal cancer chemotherapy. Oxaliplatin-induced severe chronic neurotoxicity is the main dose-limiting side effect. No standard treatment for oxaliplatin-induced chronic neurotoxicity has been identified. Researchers conducted a prospective pilot clinical trial to explore whether ***neurotropin*** has neuroprotective effects on chronic neurotoxicity. From May 1, 2010 to May 1, 2011, 80 stage II and III colorectal cancer patients who were eligible to receive oxaliplatin-based chemotherapy voluntarily enrolled in the trial. The patients were randomly divided into two groups:

- one in which patients received neurotropin treatment along with oxaliplatin therapy
- the other receiving placebo along with oxaliplatin therapy

The patients in the control group experienced significantly ≥ grade 2 and ≥ grade 3 neurotoxicity than those in the neurotropin group (60.9 vs. 21.1 %, for at least grade 2 neurotoxicity; 39 vs. 2.7 % for at least grade 3 neurotoxicity). If neurotoxicity was assessed by oxaliplatin-specific neurotoxicity grading, the patients in the control group also experienced significantly more ≥ grade 2 neurotoxicity (51.2 vs. 12.5 %). Neurotropin was the only factor that affected the incidence of ≥ grade 2 neurotoxicity. Researchers concluded that neurotropin combined with oxaliplatin decreases chronic neurotoxicity effectively and safely.

7. **Early Tumor Shrinkage With Erbitux Correlates With Prolonged Survival in mCRC** (Jun.11/12)

Early tumor shrinkage in patients with metastatic colorectal cancer treated first line with the EGFR inhibitor cetuximab (Erbitux) is associated with prolonged survival. Patients with metastatic colorectal cancer taking part in the AIO KRK0104 trial were randomized to capecitabine (xeloda) plus oxaliplatin (CAPOX) or irinotecan (CAPIRI) as first-line treatment. A total of 121 patients were evaluated for early tumor shrinkage (defined as a relative change of 20% or more in the sum of the longest diameters of target lesions) at six weeks. Results showed that just over half (63 patients) had early tumor shrinkage. Early tumor shrinkage correlated with prolonged progression free survival (8.9 vs 4.7 months) and overall survival (31.6 vs 15.8 months). Further results showed that early tumor shrinkage was also associated with cetuximab-induced skin toxicity. A further study reported at ASCO found that patients with KRAS wild type colorectal cancer metastases not limited to the liver (non-LLD) gained greater benefit in overall survival from adding cetuximab to chemotherapy than those with liver limited disease (LLD). A pooled analysis of the CRYSTAL and OPUS studies showed that overall survival was increased by 24% with cetuximab in non-LLD (median OS 22.0 vs 17.3 months) compared to 19% in LLD. "The finding strengthens the value of cetuximab in palliative treatment in addition to its already established role in the first-line treatment of KRAS wild-type mCRC". "Early tumor shrinkage facilitates potentially curative resection".

http://www.medicalnewstoday.com/articles/246403.php

8. Preoperative Chemoradiotherapy and Postoperative Chemotherapy with Folfox vs. 5FU Alone in Locally Advanced Rectal Cancer (Jun.11/12)

Preoperative chemoradiotherapy, total mesorectal excision surgery, and adjuvant chemotherapy with fluorouracil (5FU) is the standard combined modality treatment for rectal cancer. With the aim of improving disease-free survival (DFS), this phase 3 study (CAO/ARO/AIO-04) integrated oxaliplatin into standard treatment. This was a multicentre, open-label, randomized, phase 3 study in patients with rectul cancer with clinically staged T3—4 or any node-positive disease. Between July 25, 2006, and Feb 26, 2010, patients were randomly assigned to two groups:

- a control group receiving standard fluorouracil-based combined modality treatment, consisting of preoperative radiotherapy of 50.4 Gy plus infusional fluorouracil (1000 mg/m^2 days 1—5 and 29—33), followed by surgery and four cycles of bolus fluorouracil (500 mg/m^2 days 1—5 and 29; fluorouracil group);
- and an experimental group receiving preoperative radiotherapy of 50.4 Gy plus infusional fluorouracil (250 mg/m^2 days 1—14 and 22—35) and oxaliplatin (50 mg/m^2 days 1, 8, 22, and 29), followed by surgery and eight cycles of adjuvant chemotherapy with oxaliplatin (100 mg/m^2 days 1 and 15), leucovorin (400 mg/m^2 days 1 and 15), and infusional fluorouracil (2400 mg/m^2 days 1—2 and 15—16; fluorouracil plus oxaliplatin group).

DFS was the primary endpoint. Secondary endpoints included toxicity and compliance. Of the 1265 patients initially enrolled, 1236 were evaluable (613 in the fluorouracil plus oxaliplatin group and 623 in the fluorouracil group). Preoperative grade 3—4 toxic effects occurred in 140 (23%) of 606 patients who actually received fluorouracil and oxaliplatin during chemoradiotherapy and in 127 (20%) of 624 patients who actually received fluorouracil chemoradiotherapy. Grade 3—4 diarrhea was more common in those who received fluorouracil and oxaliplatin during chemoradiotherapy than in those who received fluorouracil during chemoradiotherapy (73 patients [12%] vs 52 patients [8%]), as was grade 3—4 nausea or vomiting (23 [4%] vs nine [1%]). 516 (85%) of the 606 patients who received fluorouracil and oxaliplatin-based chemoradiotherapy had the full dose of chemotherapy, and 571 (94%) had the full dose of radiotherapy; as did 495 (79%) and 601 (96%) of 624 patients who received fluorouracil-based chemoradiotherapy, respectively. A pathological complete response was achieved in 103 (17%) of 591 patients who underwent surgery in the fluorouracil and oxaliplatin group and in 81 (13%) of 606 patients who underwent surgery in the fluorouracil group. In the fluorouracil and oxaliplatin group, 352 (81%) of 435 patients who began adjuvant chemotherapy completed all cycles (with or without dose reduction), as did 386 (83%) of 463 patients in the fluorouracil group. The investigators concluded that inclusion of oxaliplatin into modified fluorouracil-based combined modality treatment was feasible and led to more patients achieving a pathological complete response than did standard treatment. Longer follow-up is needed to assess DFS.

Rodel, C. et al., Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer. Lancet Oncol. 2012 May 23; Epub Ahead of Print.

9. KRAS Mutations in Primary Tumours & Metastatic Lesions (Jun. 11/12)

Kras mutations are predictive markers for the efficacy of anti-EGFR antibody therapies in patients with metastatic colorectal cancer. Although the mutational status of kras is reportedly highly concordant between primary and metastatic lesions, it is not clear whether toxic chemotherapies might induce additional mutations. In this study, a total of 63 lesions (23 baseline primary, 18 metastatic and 24 post-

treatment metastatic) from 21 patients who were treated with FOLFOX as adjuvant therapy for stage III/IV colorectal cancer following curative resection were examined. The DNA samples were inspected for KRAS, NRAS, BRAF and PIK3CA mutations. The numbers of primary lesions with wild-type and mutant KRAS codons 12 and 13 were 8 and 13, respectively. The mutational status of KRAS remained concordant between the primary tumours and the post-FOLFOX metastatic lesions, irrespective of patient background, treatment duration and disease-free survival. Furthermore, the mutational statuses of the other genes evaluated were also concordant between the primary and metastatic lesions. Because the mutational statuses of predictive biomarker genes were not altered by FOLFOX therapy, specimens from both primary tumours and post-FOLFOX tumour metastases might serve as valid sources of DNA for known genomic biomarker testing.

Kawamoto, Y, et al., Kras mutations in primary tumours and post-folfox metastatic lesions in cases of colorectal cancer. Br J Cancer. 2012 May 22; Epub Ahead of Print.

10. Advanced Cancers Can Recur After Treatment with Single Targeted Agents (Jun.11/12)

Targeted cancer cell therapies using man-made proteins dramatically shrink many tumors in the first few months of treatment, but new research from Johns Hopkins scientists finds why the cells all too often become resistant, the treatment stops working, and the disease returns. In a study of 28 advanced colon cancer patients treated with the monoclonal antibody **panitumumab (vectibix)**, the Johns Hopkins Kimmel Cancer Center team reports that drug-resistance tumor cell mutations appear in the blood of patients five to seven months later, and that low levels of these mutations exist in nearly all tumors before the therapy begins, making the cancers predestined to recur. These resistance mutations develop by chance as cancer cells divide so that tumors always contain thousands of resistance cells. The Johns Hopkins scientists analyzed blood samples taken from 28 patients with advanced colorectal cancers. These patients were enrolled in a clinical trial of panitumumab, one of a new and growing class of monoclonal antibodies, or synthetic proteins that hones in on cancer cells' vital growth pathways. In the case of panitumumab, the agent targets a growth-factor receptor called EGFR. Patients most likely to respond to the drug also have normal copies of the KRAS gene in their tumors. Twenty-four of the 28 patients in the study had normal KRAS gene copies in their tumors, and four had mutations in KRAS, serving as a control group. Blood samples were taken before beginning the therapy and at four-week intervals during the therapy, for a total of 169 combined blood draws. Virtually all cancers shed DNA material into the blood, according to the researchers, and provide an easy route to collecting molecular evidence from lesions typically inaccessible for surgical biopsy. "The amount of tumor DNA found in the blood is akin to tests used to determine HIV viral load," said the lead investigator. In their analysis, the scientists found that 9 of the 24 patients with normal KRAS genes (38%) exhibited KRAS mutations detectable in the blood within five to seven months of beginning therapy. KRAS mutations were detected in three patients before imaging scans showed metastatic tumor growth. Then, the investigators used mathematical models to calculate when KRAS mutations likely originated. They determined that KRAS mutations were present prior to the initiation of treatment with panitumumab. "The probability that the mutations were absent at the beginning of treatment is exceedingly low," claimed researchers, leading the team to conclude that the development of drug-resistance is a fait accompli. The time it takes for cancers to recur is determined simply by how long it takes cancer cells with mutant genes to multiply. The research team says that combination therapies are the best chance for longer remissions. "The good news is that there is a limited number of pathways that go awry in cancer, so it should be possible to develop a small number of agents that can be used in a large number of patients". However, they hope this research will help stimulate the testing of new drugs as combination therapies much earlier in the drug approval process than the current norm.

http://www.hopkinsmedicine.org/news/media/releases/advanced_cancers_destined_to_recur_after_treatment_with_single_drugs_

11. Cetuximab-Induced Skin Reactions Suppressed by Cigarette Smoking (Jun.13/12)

Smoking is widely accepted as the most important risk factor for cancer in the modern world. Several constituents of cigarette smoke are known to interact with drug-metabolizing enzymes, potentially affecting the outcomes of drug treatment. Cetuximab (Erbitux(®) is indicated for the treatment of colorectal cancer with respect to restoring chemosensitivity to irinotecan in irinotecan-resistant patients. The purpose of this study was to determine whether cigarette smoking adversely affects the actions of cetuximab in the treatment of colorectal cancer. Researchers studied 56 patients with colorectal cancer who were treated with cetuximab in their hospital during the time period from 2009 through 2010. They compared the adverse reaction rates of 16 patients who smoked (smokers) with those of 38 patients who did not smoke (non-smokers, including 16 patients who never smoked and 22 patients who were former smokers). The incidence of skin reactions after cetuximab treatment was lower in the smokers than in the non-smokers. In addition, the incidence of anorexia was higher in the smokers than in the non-smokers. Within the group of non-smokers, no statistically significant differences were observed between the never smokers and the former smokers with regard to adverse reactions. Their findings suggest that cigarette smoking during anticancer treatment with cetuximab-based regimens reduces the skin reaction, ***which leads to a reduction in the benefit of the treatment***; therefore, patients should quit smoking, at least while receiving cetuximab-based treatment.

Kajizono, Makoto, et al., Cetuximab-induced skin reactions are suppressed by cigarette smoking in patients with advanced colorectal cancer. Inter J of Clin Onc. 2012, doi: 10.1007/s10147-012-0427-3

SURGICAL THERAPIES

12. Stent Placement or Surgery for Obstructive Primary Tumour in Stage IV Patients (May 25/12)

It is still a matter of debate as to whether palliative resection of obstructive primary tumors may prolong the survival of patients with obstructive colon cancer and unresectable synchronous metastases. The main goal of this retrospective study was to compare the use of self-expanding metallic stents (SEMS) with open surgery for the palliation of patients with respect to survival, morbidity, and the time to start chemotherapy. Between January 2000 and January 2008, 88 consecutive patients (52 who underwent surgery and 36 who underwent SEMS insertion) with obstructive colon cancer and unresectable synchronous metastases were retrospectively evaluated. The median hospital stay for all admissions was 7.2 days (range, 3–29 days) in the SEMS group and 12.3 days (range, 6–45 days) in the surgery group. The incidence of stoma formation was significantly lower in the SEMS group than in the surgery group (16.7% vs 38.5%, respectively). The median time to starting chemotherapy was significantly shorter in patients who underwent SEMS insertion compared with those who underwent surgery (8.1 vs 21.7 days, respectively). The 1-year and 2-year survival rates were 44.2% and 21.27% in the surgery group and 16.7% and 2.8% in the SEMS group, respectively. The median survival for all patients was 15 months from the initiation of treatment (6.0–19 months). Researchers concluded that both procedures can be safely performed, but the choice of treatment should be individualized and discussed with a multidisciplinary team.

Lee, Won-Suk, et al., The outcome after stent placement or surgery as the initial treatment for obstructive primary tumor in patients with stage iv colon cancer. Amer J of Surgery. Vol. 203, Issue 6: pp. 715-719

13. Two Stage Liver Resection for Bilobar Liver Mets (May 25/12)

The aim of this study was to analyze the feasibility and early outcomes of 2-stage liver resection for bilobar metastases (metastatic disease identified on both lobes of the liver). Data from 39 consecutive patients undergoing 2-stage hepatectomy (liver resection) between 2004 and 2010 were prospectively collected. The median age was 59 years (range, 33–79 years), and the ratio of men to women was 1.8:1. Metastases originated from

- colorectal carcinoma (n = 33),
- neuroendocrine tumors (n = 3),
- gastrointestinal stromal tumor (n = 1),
- ocular melanoma (n = 1), and
- salivary gland carcinoma (n = 1).

Presurgical chemotherapy was given to 32 patients (82%). Twenty-nine patients (74%) underwent portal vein embolization. Radiofrequency ablation was used in 8 patients (21%). Twenty-seven patients (69%) successfully completed clearance. For the 1st and 2nd stages, the median lengths of stay were 11 days (range, 6–53 days) and 13 days (range, 6–44 days), and morbidity rates were 23% and 56%. Liver insufficiency occurred in 2 (5%) and 6 (22%) patients. Overall mortality was 2.6%. For **colorectal metastases, median survival in successes versus failures was 24 versus 10 months, and 3-year survival was 30% versus 0%**. Researchers concluded that two-stage hepatectomy is feasible, with 69% of patients achieving clearance with low mortality.

Bowers, Kaye A, et al., Feasibility study of two stage hepatectomy for bilobar liver metastases. Amer J of Surg. Vol. 203, Issue 6: pp. 691-697

14. Progression While Receiving Preoperative Chemo Should Not Rule Out Liver Resection (May 25/12)

Tumor progression while receiving neoadjuvant chemotherapy (Progression of Disease - PD) has been associated with poor outcome and is commonly considered a contraindication to liver resection (LR). This study attempted to clarify in a large multicenter setting whether PD is always a contraindication to LR. Patients undergoing LR for colorectal metastases without extrahepatic disease (disease outside the liver) after neoadjuvant chemotherapy between 1990 and 2009 were reviewed. Among 2143 patients, PD occurred in 176 (8.2 %). Risk of progression was increased after 5-FU or irinotecan (22.7 % vs. 6.8 % after other regimens; 14.9 % vs. 7.2 %), while it was reduced after oxaliplatin (5.6 % vs. 12.0 %) and still diminished among patients receiving targeted therapies (2.6 %). In the PD group, 3 independent prognostic factors were identified:

- carcinoembryonic antigen (CEA) ≥200 ng/mL ,
- >3 metastases , and
- tumor diameter ≥50 mm.

The data showed that patients without any risk factors had 5-year survival rates of 53.3 %; good survival results were still observed if metastases were >3 or ≥50 mm (29.9 and 19.1 %, respectively). On the contrary, survival was less than 10 % at 3 years in the presence of >1 prognostic factor or CEA of ≥200

ng/mL. Researchers concluded that PD is a negative prognostic factor, but it is **not** an absolute contraindication to LR. Patients with PD could be scheduled for LR except for those with >3 metastases and ≥50 mm, or CEA ≥200 ng/mL in whom further chemotherapy is recommended.

Vigano, Luca, et al. Progression while receiving preoperative chemotherapy should not be an absolute contraindication to liver resection for colorectal metastases. Annals of Surgical Oncology. Online first: May 24, 2012.

15. Liver Resection May Be Possible With Hepatic Arterial Infusion (HAI) And Systemic Therapy (Jun. 10/12)

Previously, the authors of this study showed that HAI with FUDR + dexamethasone (Dex) plus systemic therapy produced a **47 % resectability rate** in a retrospective study of 49 patients with unresectable colorectal liver metastases. In this study, the researchers prospectively evaluated unresectable colorectal liver metastases patients in a new protocol combined with the above protocol (n=105 pts) and all were treated with HAI + FUDR/Dex + Systemic therapy. Unresectability was defined as diffuse bilateral metastases, involvement of all hepatic/portal veins, and/or inability to preserve remaining liver with adequate function. 61 of the 105 patients had prior systemic theapy (56% with prior Oxaliplatin) and 45 (74%) were progressing at the time of pump placement. In previously treated patients, 44% underwent resection, with a median OS of 45 months. Of 44 chemo-naïve patients, 57% underwent liver resection, with a median OS of 68 mos. The following were significantly associated with resection conversion:

- lesion number
- baseline CEA
- females and
- clinical risk score (CRS)

In the analysis, gender and CRS remained predictive of resectability. Median PFS was 12 mos for all patients. Researchers concluded that even in previously treated patients, HAI + SYS is an approach to convert unresectable colorectal liver metastases to resection. Gender and CRS are associated with conversion to resectability.

Kemeny, N, et al., Is conversion to resection possible with hepatic arterial infusion (HAI) and systemic (sys) even in previously treated patients with unresectable colorectal liver metastases? Abstract No: 3577. Citation: J Clin Oncol 30, 2012 (suppl; abstr 3577)

SCREENING

16. Sigmoidoscopy OK For Screening Colorectal Cancer (May 20/12)

In a large trial of more than 150,000 older U.S. adults, those who were randomly assigned to get screened using flexible sigmoidoscopy on two different occasions were 21% less likely to get colon cancer than those not offered the screening. They were also 26% less likely to die of cancer, probably because screening picked up pre-cancerous lesions and early-stage cancers before they could cause serious harm. Flexible sigmoidoscopy is one of three colon cancer screening methods recommended by the U.S. Preventive Services Task Force, a government-backed body that sets screening guidelines. The Task Force says that annual fecal occult blood testing, flexible sigmoidoscopy every five years with fecal testing every three years or colonoscopy every 10 years are all options for adults aged 50 to 75 at **average risk** of cancer. But many Americans in that age group still don't get screened -- and one of the reasons may be the discomfort of preparing to get a colonoscopy, including taking laxatives, and the inconvenience and invasiveness of the procedure itself. The new findings provide more evidence that sigmoidoscopy as an initial test -- followed by colonoscopy only in the case of positive findings -- may be a valid alternative, researchers said. The data come from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which compared new cases of cancer and cancer-related deaths in adults who did or didn't get different types of screening. This analysis, led by Dr. Robert Schoen from the University of Pittsburgh Medical Center, involved 154,900 adults age 55 to 74 who were offered either two sigmoidoscopies, three or five years apart, or no colon cancer screening. Over the next 12 years, there were 1,012 new cases of colon cancer in the screening group and 1,287 in the unscreened group. In addition, there were 252 related deaths among people offered sigmoidoscopy, compared to 341 in the unscreened group. The lower mortality in the screening group seemed to be attributable entirely to fewer deaths from so-called distal colon cancer, which occurs in the part of the intestines closer to the rectum. There was no difference between the two groups in deaths from proximal colon cancer, which is cancer higher up in the intestines and beyond the reach of the sigmoidoscopy scope. The screening tests were not without their limitations. One in five men and one in eight women had a false-positive sigmoidoscopy, which resulted in more invasive testing that ultimately found no pre-cancers or cancers. In addition, 22 people suffered a bowel perforation either from the initial sigmoidoscopy or a follow-up colonoscopy. A limitation of the trial itself is that the two study groups weren't as different as the researchers initially intended: almost half of people in the group assigned to no screening ended up getting a sigmoidoscopy or colonoscopy on their own during the study.

Schoen, RE, et al., Colorectal cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med. 2012; 366: pp. 2345-2367

17. Middle-Aged Diabetics May Need Earlier Colon Checks (May 24/12)

Researchers who say they've linked type 2 diabetes with earlier development of precancerous colon lesions recommend people with the blood sugar disorder start colorectal screenings at a younger age than others. "Based on our data, it implies that people with diabetes should get screenings earlier, possibly at age 40, rather than at age 50," said Dr. Hongha Vu. However, another expert said more research is needed before making that recommendation. Also, the researchers cautioned that they can't say for sure that diabetes by itself raises the risk of the precancerous lesions and further study is required. Experts know that diabetes is linked with an increased risk of colon and other cancers. Vu's team set out to determine if people with diabetes develop precancerous lesions, also called polyps or adenomas, earlier than people without diabetes. The researchers compared the incidence of polyps in three groups of patients: those 40 to 49 with and without diabetes and those 50 to 59 without diabetes. Each group had 125 people. All had colonoscopies between June 2005 and June 2011. In a colonoscopy, a doctor examines the large intestine with a long, thin tube that has a camera at the end. Any polyps found are removed so they can't progress to cancer. The younger men and women with diabetes had a rate of polyps similar to the older people without diabetes. "We found that between the three groups, the adenoma detection rate in those 40 to 49 without diabetes was 14.4%, whereas it was significantly higher in those with diabetes in the same age range -- at 30.4 percent". "This is a similar rate as those 50 to 59 without diabetes." The 50- to 59-year-olds had a rate of 32%. Vu took into account other risk factors, such as race, obesity and smoking, and still found that those in their 40s with diabetes had a higher rate of polyps.

Vu, Hongha T. Digestive Disease Week, May 22, 2012, San Diego, Calif..

PSYCHOSOCIAL

18. How To Deliver the News of a Cancer Diagnosis to Family Members (May 30/12)

Receiving a diagnosis of colon cancer is probably some of the worst (if not the worst) news you can receive. What's almost as bad is that you now have to go home and state the words, "I have cancer" to your loved ones. The conversation is sure to be emotional fraught and probably the last thing your frazzled nerves need right now. The right way to tell your family is: *however you decide to do it*. You may break the information up into pieces and tell your spouse followed by your children, siblings and any other relatives, or you may choose to have a family meeting to discuss your prognosis with the entire family. Some people choose to tell only their spouse or partner - again, there is no right or wrong way to do this, just the way that works for you. Support, advice and assistance is available on many different professional networks as well as through survivorship workshops and support groups. The American Cancer Society suggests allowing yourself time to sort through your emotions before disseminating your news, whereas the American Academy of Family Physicians suggests informing young children that they are **not at fault** for your disease. Many Guides have shared tips and guidance on how to talk to your family, friends and even your employer about a diagnosis of cancer. Psychosocial support is available at most Cancer Centres for patients and caregivers requiring the assistance and help sharing the news with their loved ones. Please dialogue with your treating physician about being referred to an expert who can help you through this trying time.

http://coloncancer.about.com/b/2012/05/31/how-do-i-tell-my-family.htm

OTHER

19. Onco-Defender CRC Predicts Recurrence Risk for Early Stage Colorectal Cancer (Jun. 4/12)

Everist Genomics, a rapidly growing personalized medicine company, has announced the publication of positive results from an international validation study which demonstrated that the **OncoDefender-CRC** colorectal cancer test result is a significant independent predictor of recurrence in node-negative, invasive colorectal cancer (CRC) patients. The study, originally presented, in part, at the 2011 American Society of Clinical Oncology (ASCO) Annual Meeting, was published online on May 17 in *Cancer*, a journal of the American Cancer Society. The findings show that the OncoDefender-CRC test outperforms current National Comprehensive Cancer Network (NCCN) Guidelines in differentiating early stage CRC patients at high risk from those at low risk for cancer recurrence within 3 years after potentially curative surgery, making it the only molecular CRC assay that has been shown to outperform a complete set of standard clinico-pathologic prognostic criteria for early stage disease. The OncoDefender-CRC test measures the expression of 5 tumor genes, identified using the company's proprietary Evolver machine learning data analysis platform. Compared to other marketed tests in this area, it is applicable to more than twice as many early stage CRC patients and ***is better able to identify those tumors most likely to recur*** and, therefore, those patients most likely to benefit from adjuvant chemotherapy. As of May 2012, more than 6,000 OncoDefender-CRC specimen collection kits have been requested by physicians. "The findings of this study support the use of OncoDefender-CRC to personalize treatment planning for early stage CRC patients". "The need for such testing is apparent considering that 1 in 4 early stage CRC patients eventually develop a recurrence following resection of their tumors, and the vast majority of these recurrences prove fatal. Moreover, given the costs associated with administration of adjuvant therapy and management of patients with recurrences, OncoDefender-CRC testing can achieve significant cost savings for patients and insurers." The validation study used

OncoDefender-CRC to analyze tumor samples from 264 patients from 18 hospitals in 4 countries. The test correctly classified 62/92 cases that recurred and 87/172 cases that did not recur (sensitivity 67%, specificity 51%). “High-risk” patients had a significantly greater probability of 3-year recurrence (42%) than “low-risk” (26%) patients, independent of T-classification, the number of lymph nodes examined, histologic grade/subtype, anatomic location, age, sex or race. OncoDefender-CRC not only outperformed current NCCN Guidelines, but also was found to accurately differentiate the risk of recurrence in a subset comprised of only colon cancer patients. The test demonstrated advantage over existing clinico-pathologic prognostic criteria which will provide clinicians with an important key tool for optimizing the post-surgery medical management for all of their early stage CRC patients.

http://www.everistgenomics.com/blog/everist-genomics-announces-publication-validation-study-confirming-oncodefender-crc-independently-predicts-recurrence-risk-early-stage-colorectal-cancer-patients/

20. Younger Colon Cancer Patients Have Worse Prognosis at Diagnosis, Yet Better Survival (Jun.4/12)

Younger patients with colorectal cancer were more likely to present advanced stage tumors at diagnosis and metastasize much sooner, yet had better than or equal survival to patients 50 and older, according to data presented at the 2012 American Society of Clinical Oncology Annual Meeting in Chicago. (Abstract # 3621). Researchers are seeing more advanced tumors in this population because the cases aren't being caught early enough. Screening isn't recommended until age 50, and the younger a patient is, the more likely they are to ignore symptoms of more advanced stages of the disease. The objective of this study was to assess pathological features and outcomes of colorectal cancer in patients less than age 50. Researchers obtained data from the tumour registry of Thomas Jefferson University Hospital (TJUH) on 4,595 patients treated for colorectal cancer from 1988 to 2007. They compared those data with data obtained from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database on 290,338 patients with colorectal cancer treated from 1988 to 2004. The researchers collected data on location, stage and histologic grade of the cancer. Patients under age 50 with colorectal cancer presented with more advanced stage tumors in both data sets (SEER and TJUH), and had more poorly differentiated tumors than older patients, the researchers found. Patients under 50 also had more mucinous/signet ring cell tumors with 12% to 8.1% in the TJUH data and 13.2% to 10.3% in the SEER data, with younger males having the highest prevalence in both data sets. Younger patients had fewer right-side tumors than patients 50 and over, and a higher proportion of rectal tumors. Patients under age 50 were also more likely to have positive nodes at all stages relative to 50 and over, as well as more likely to develop peritoneal metastases, but less likely to have lung metastases than older patients. Despite their poor pathologic features, patients under age 50 had better than or equal survival to those 50 and older, which may in part be explained by their overall health. Early evidence suggests that younger patients are able to tolerate more aggressive cancer therapies because of fewer co-morbidities. "Ongoing studies will help clarify the survival disparity and assess differences in treatment and molecular features between younger and older colorectal cancer patients".

http://medicalxpress.com/news/2012-05-younger-colon-cancer-patients-worse.html

21. Risk of Colorectal Cancer in Patients with Ulcerative Colitis (Jun.6/12)

Patients with ulcerative colitis (UC) have an increased risk of developing colorectal cancer (CRC). Studies examining the magnitude of this association have yielded conflicting results. In this study, researchers performed a meta-analysis (review of multiple studies) of population-based cohort studies to determine the risk of CRC in patients with UC. They included 8 studies in the meta-analysis. Their results showed that an average of 1.6% of patients with UC was diagnosed with CRC during 14 years of follow-up. Men with UC had a greater risk of CRC than women. Young age was a risk factor for CRC (although this might have resulted from small numbers), as was extensive colitis. Researchers concluded that in population-based cohorts, UC increases the risk of CRC 2.4-fold. Male sex, young age at diagnosis with UC, and extensive colitis increase the risk.

Jess, Tine, et al., Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population based cohort studies. Clin Gastr & Hep. Vol. 10, Issue 8: pp. 639-645

22. No Link Between Bone Drugs & Colon Cancer (Jun. 8/12)

Women who use certain bone-building drugs may not have a decreased risk of colon cancer, a new study finds -- despite prior evidence suggesting the drugs might offer some protection. The drugs, called bisphosphonates, include brands like Fosamax, Boniva, Reclast and Actonel, along with generic versions. They are used to prevent and treat the bone-thinning disease osteoporosis, which mainly strikes older women. The drugs can also be used to help treat cancer that has spread to the bone from other sites in the body. Bisphosphonates have been tied to both good and bad side effects. Research has found after years of use, the drug may, in rare cases, actually weaken the bones and lead to thighbone fractures or a painful breakdown of the jaw bone. On the other hand, several studies have suggested women who use bisphosphonates may have a decreased risk of developing breast or colon cancer. But this latest study, reported in the Journal of Clinical Oncology, found no evidence that women on the medications had lower odds of colon cancer. Of more than 86,000 U.S. nurses followed for over a decade as part of a large health study, 801 developed colon cancer. The risk was no different among women who didn't use bisphosphonates, versus users -- regardless of how many years they had been on the medications. It is not clear whether bisphosphonates have any role in treatment of colorectal cancer, and the data does not support its routine use as a (prevention) agent for colorectal cancer. Since

evidence suggests bisphosphonate users have a lower risk of certain cancers, researchers have been interested in whether the drugs might help prevent those tumors in people who are particularly at risk. In the case of colon cancer, risk factors include inflammatory bowel disease (ulcerative colitis or Crohn's disease) and having a strong family history of the cancer. According to the researchers, there is evidence women on bisphosphonates have a lower risk of breast cancer -- though that does not mean the drugs are the reason. This study followed a large group of initially cancer-free women over time. Thus, the researchers were able to collect information on women's health and lifestyle habits before their cancer diagnosis. That's important because women on bisphosphonates may, for example, be more likely than other women to get screened for colon cancer. Bisphosphonate users are also likely to be taking vitamin D and calcium to help protect their bones -- and those nutrients have been linked to lower colon cancer risk themselves. When the team first looked at its data, there was in fact some weak evidence that women on bisphosphonates might have a slightly lower colon cancer risk than non-users. But the link got even weaker when the researchers accounted for colon cancer screening and which women were taking calcium and vitamin D.

Khalili, Hamed, et al., A prospective study of bisphosphonate use and risk of colorectal cancer. Published online before print May 29, 2012.

NUTRITION & HEALTHY LIFESTYLE

23. Does Coffee Help to Ward Off Colorectal Cancer? (May 18/12)

The *New England Journal of Medicine* published outcomes from the NIH-AARP Diet and Health Study, which found drinking coffee was associated with living longer in both men and women. This is not only the largest study ever to look into this question, NIH-AARP is one of the largest prospective (forward-looking) studies ever performed on nutrition and disease, following more than a half million people for a dozen years. This follows on the heels of an editorial published last month in the *American Journal of Clinical Nutrition* entitled "Coffee Consumption and Risk of Chronic Diseases: Changing Our Views," which reviewed the growing evidence that for most people, the benefits of drinking coffee likely outweigh the risks. Though the NEJM study published found no significant relationship between coffee consumption and cancer, a recent analysis of the best studies published to date suggests coffee consumption may lead to a modest reduction in overall cancer incidence. Each daily cup of coffee was associated with approximately a 3% reduced risk of cancers, especially bladder, breast, mouth, colorectal, endometrial, esophageal, liver, leukemic, pancreatic, and prostate cancers. One of the reasons it's so difficult to study the relationship between diet and disease is because many dietary behaviors are associated with non-dietary behaviors. For example, people who drink coffee may be more likely to have a cigarette in the other hand, which can lead to spurious conclusions. When these considerations are factored in, though, the best available evidence suggests that coffee consumption is generally health-promoting. The benefits of caffeine have been reported to be:

1. increases energy availability,
2. increases daily energy expenditure,
3. decreases fatigue,
4. decreases the sense of effort associated with physical activity,
5. enhances physical performance,
6. enhances motor performance,
7. enhances cognitive performance,
8. increases alertness, wakefulness, and feelings of 'energy,'
9. decreases mental fatigue,
10. quickens reactions,
11. increases the accuracy of reactions,
12. increases the ability to concentrate and focus attention,
13. enhances short-term memory,
14. increases the ability to solve problems requiring reasoning,
15. increases the ability to make correct decisions,
16. enhances cognitive functioning capabilities and neuromuscular coordination, and
17. in otherwise healthy non-pregnant adults is safe.

Up to a thousand milligrams of caffeine is considered safe for most people, which translates into approximately 10 cups of coffee a day. New advice suggests that pregnant women, however, should restrict their caffeine consumption to under just 200 mg a day. There are a few other coffee caveats. Some health conditions may be worsened by coffee, such as insomnia, anxiety, grastroesophageal reflux (heartburn), high blood pressure, and certain heartbeat rhythm irregularities. There are also compounds in coffee that increase cholesterol levels, but are effectively removed when filtered through paper, so drip coffee is preferable to boiled, French press and espresso.

Freedman, Neal D. et al., Association of coffee drinking with total and cause specific mortality. N Engl J Med 2012; 366: pp. 1891-1904

24. Fish Should Be Added to Your Diet (May 20/12)

According to an analysis of international studies, people who eat fish often have a lower risk of colorectal cancer. Researchers pooled results from 41 studies that measured fish intake and tracked cancer

diagnoses. Studies included were from Canada, the United States, Britain, Australia, Italy, Japan, China, Norway, Finland, Sweden and the Netherlands. Over all, people who ate fish regularly were 12% less likely to be diagnosed with colon or rectal cancer even after accounting for family history, body weight, physical activity, smoking, alcohol use and other dietary factors. The protective effect of fish was stronger for rectal cancer. Compared to participants who consumed the least fish, those who ate the most had a 21% lower risk of rectal cancer. Whether the beneficial effects have to do with omega-3 fatty acids or other nutrients found in fish, such as selenium, is unclear. However, omega-3 fats have been demonstrated to reduce the size and number of colorectal cancer cells in experimental studies. Omega-3 fats might also reduce the formation of colon polyps through their anti-inflammatory actions. In a study published earlier this year, women who ate three servings (3.5 ounces each) of fish a week – versus less than half a serving – were one-third less likely to develop colorectal adenomas. (Adenomas in the colon are polyps that have the potential to become cancerous.) It's also possible that a diet plentiful in fish is one that's low in red and processed meat, two dietary factors known to increase colorectal cancer risk. How much fish should you eat to lower the risk of colorectal cancer? Based on the current analysis, it's impossible to say since the ranges of fish intake for low and high consumers varied considerably across studies. However, it's likely prudent to include at least **two servings a week**. Fish that offer the most omega-3 fatty acids include **salmon, herring, mackerel, trout, sardines and anchovies**. Whether a daily fish oil supplement offers the same benefit remains unclear. Evidence suggests the following recommendations will help guard against the disease:

Limit red and processed meat

It's well established that a high intake of red meat and processed meat increases the risk of colorectal cancer. Cooking meat at a high temperature forms heterocyclic amines (HCAs), compounds linked to precancerous colon polyps in humans. It's also thought that preservatives in processed meats called nitrites may form cancer-causing compounds. Limit red meat (beef, veal, pork, lamb, goat) to less than 18 ounces a week. Choose fish, chicken, turkey, legumes, tofu and soy foods more often than red meat. Eat very little, if any, processed red meat including ham, bacon, pastrami, salami, bologna, hot dogs and sausages.

Reduce alcohol

There's convincing evidence that consuming more than two alcoholic drinks a day is a cause of colorectal cancer, particularly in men. Alcohol may stimulate the growth of colon cancer cells, activate cancer-causing substances and help transform polyps into cancer. Alcohol also interferes with the body's use of folate, a B vitamin needed to repair DNA damage in cells. If consumed at all, limit alcoholic drinks to two a day for men and one a day for women.

Increase fibre

A high fibre intake, especially from cereals and whole grains, is linked to a lower risk of the disease. Every 10-gram increase in fibre has been estimated to lower colorectal cancer risk by 10%. Fibre-rich foods include oat bran, wheat bran, 100-per-cent bran cereals, amaranth, barley, buckwheat, oats, quinoa, wheat berries, bulgur and brown rice.

Meet calcium requirements

A greater intake of calcium from milk and supplements is associated with a lower risk of colorectal cancer. Calcium is thought to bind with toxic substances in the intestinal tract, preventing them from entering colon cells. Milk also contains bioactive substances, which may play a role. Adults aged 19 to 50 need 1,000 milligrams of calcium a day. After 50, women need 1,200 mg daily; men's calcium requirements increase from 1,000 to 1,200 mg at age 70. One cup of milk or a ¾ cup of plain yogurt contains roughly 300 mg of calcium.

Increase magnesium

A higher intake of magnesium has been linked to protection from colorectal cancer. The mineral is thought to reduce free radical damage, inhibit the growth of colon cancer cells and improve how the body uses insulin. (Insulin resistance, a condition in which the body produces insulin but does not use it properly, is considered a risk factor for colon cancer.) Magnesium-rich foods include almonds, cashews, peanuts, soybeans, tofu, lentils, kidney beans, Swiss chard, spinach, kale, brown rice, wheat bran and avocado.

Stay lean

Weight gain and obesity increase the risk of a number of cancers, including colorectal. Excess body fat triggers inflammation and affects levels of hormones, including insulin and estrogens, creating an environment that encourages cancer development. Maintain a body mass index of 18.5 to 25 throughout adulthood. Some research suggests a BMI between 18.5 and 22 is associated with the lowest risk of chronic disease. Avoid weight gain and increases in waist circumference.

Get regular exercise

There's plenty of evidence that higher levels of physical activity reduce colon cancer risk. Be moderately active, the equivalent of brisk walking, for 30 minutes every day. As your fitness level improves, aim for 60 minutes or more of moderate activity daily, or 30 minutes of vigorous activity (e.g. jogging, cycling, and walking uphill).

http://m.theglobeandmail.com/life/health-and-fitness/yet-another-reason-to-add-fish-to-your-diet/article4178854/?service=mobile

25. Safer Grilling Methods May Cut Cancer Risk (Jun.5/12)

A few simple changes in how people grill outdoors, such as avoiding too much beef or processed meats and not charring foods, can aid in cancer prevention. "Two aspects of the traditional American cookout, what you grill and how you grill it, can potentially raise cancer risk," Alice Bender, a dietitian with the American Institute for Cancer Research, said in an institute news release. "Diets that feature big portions of red and processed meat have been shown to make colorectal cancer more likely. Evidence that grilling itself is a risk factor is less strong, but it only makes sense to take some easy cancer-protective precautions," she added. One way to help prevent cancer is to avoid overcooking foods on the grill, Bender said. Charring, she explained, results in the formation of cancer-causing compounds called heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs). Bender offered four other ways to grill more safely:

- **Add color (but not red meat).** By cutting back on red meat and grilling a wider variety of colorful fruits and vegetables, people will increase their intake of phytochemicals. These naturally occurring compounds found in plants offer protection against cancer, Bender said. She suggested grilling vegetables like asparagus, onions, mushrooms, zucchini, eggplant and corn on the cob, which can be grilled whole, in chunks or in a basket. When grilling fruits, she noted, brush them with olive oil so they won't stick. Bender added that fruits should be grilled a day or two before they are completely ripe so they retain their texture.
- **Mix it up.** Opt for chicken or fish instead of hamburgers or hotdogs.
- **Marinate.** Marinating meat reduces the formation of HCAs, Bender advised. Marinating meats in seasoned vinegar or lemon juice for even just 30 minutes can be beneficial, she noted.
- **Pre-cook (partially).** Pre-cooking meat will reduce the amount of time it spends exposed to high heat on the grill and reduce the formation of HCAs. Bender cautioned that partially pre-cooked meats should be transferred from the kitchen to the grill right away.
- **Cook slowly.** By grilling meats slowly at a lower heat, they are less likely to burn or char. Bender said this will reduce the amount of HCAs and PAHs that end up on people's plates.

Bender added that visible fat should be trimmed off meats to avoid high flames or flare-ups, and that any charred portions of meat should also be cut off.

http://news.yahoo.com/safer-grilling-methods-might-cut-cancer-risk-130606004.html