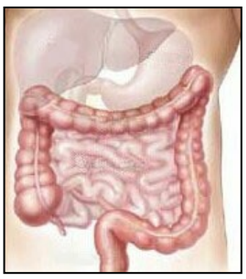
COLORECTAL CANCER RESEARCH UPDATES

Month Ending October 18th, 2013



The following colorectal cancer research update extends from August 20, 2013 – October 18th, 2013 inclusive and is intended for informational purposes only.

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DRUGS / SYSTEMIC THERAPIES

1. Discovery of New Predictive Biomarkers for Vectibix (Sept.11/13)

Amgen announced the publication of a biomarker analysis of Vectibix® (panitumumab) in combination with FOLFOX, a type of oxaliplatin-based chemotherapy, for the first-line treatment of patients with metastatic colorectal cancer (mCRC). The analysis found that ***RAS*** mutations, beyond the known *KRAS* exon 2 mutations, predict lack of response to Vectibix in combination with FOLFOX. *RAS* mutations are mutations occurring in exons 2, 3 and 4 of *KRAS* and *NRAS*. "While the *KRAS* exon 2 biomarker is well-known and has facilitated selection of patients more likely to respond to anti-EGFR treatment, we found that there were still some patients who didn't benefit from treatment," said Jean-Yves Douillard, M.D., Ph.D., professor of medical oncology, Centre R Gauducheau, France and PRIME trial lead investigator and study author. "This analysis is important as it furthers our understanding of tumor genetics and allows physicians to more accurately match patients to effective treatments." This predefined retrospective subset analysis of the PRIME study assessed the safety and efficacy of Vectibix plus FOLFOX, compared to FOLFOX alone based on *RAS* or *BRAF* mutation status. By more precisely narrowing the pool of patients treated with Vectibix plus FOLFOX to those with wild-type *RAS,* greater improvements in overall survival (OS) and progression-free survival (PFS) were observed. Specifically, previous data found that

- OS was improved by 4.4 months in patients with wild-type *KRAS*. By further narrowing to patients with wild-type *RAS*, an improvement in OS of 5.8 months was observed.
- In patients with wild-type *RAS*, OS was 26.0 months and 20.2 months and PFS was 10.1 months and 7.9 months in the Vectibix plus FOLFOX arm compared to the FOLFOX alone arm, respectively.
- *BRAF* mutations were not observed to have predictive value. Conversely, in the patients with *RAS* mutations, inferior OS and PFS were observed in the Vectibix plus FOLFOX arm compared to the FOLFOX alone arm.

Vectibix is not currently approved in Canada for use in combination with oxaliplatin.

About *KRAS* and *RAS*
Results from studies performed over the last 30 years indicate that *KRAS* plays an important role in cell growth regulation. In mCRC, EGFR transmits signals through a set of intracellular proteins. Upon reaching the nucleus, these signals instruct the cancer cell to reproduce and metastasize, leading to cancer progression. Anti-EGFR antibody therapies (such as Vectibix) work by inhibiting the activation of EGFR, thereby inhibiting downstream events that lead to malignant signaling. However, in patients whose tumors harbor a mutated *KRAS* gene, the KRAS protein is always turned "on," regardless of whether the EGFR has been activated or therapeutically inhibited. Common *KRAS* mutations occurring in exon 2 (codons 12/13) are present in approximately 40 to 50 percent of mCRC patients. Additional *RAS* mutations occurred in approximately 17 percent of patients with wild-type *KRAS* exon 2 tumors.

http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1854028

Douillard J-Y, et al., Panitumumab Folfox4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013; 369: 1023-1034

2. Colon Cancer Discovery Could Take Treatment Up a Notch (Sept.22/13)

Scientists have made an exciting discovery which may lead to more effective chemotherapy treatments of colorectal cancer patients. The study examined colorectal tumour tissues from 441 consenting patients undergoing surgery and chemotherapy to treat their cancers at Sir Charles Gairdner Hospital. The researchers found that genes involved in a process called "Notch signaling" caused tumours to grow quickly when switched on by the colorectal cancers, leading to a lower survival rate for patients. Researcher Dr Patrick Candy said Notch signaling in the colon was normally at low levels in healthy adults but studies on colon cancer cell-lines revealed that when tumours learned how to switch it on, they became much more resistant to chemotherapy. "The WAIMR team looked for the first time at Notch signaling in human colon cancer patients and we saw a very dramatic result," Dr Candy said. "For example, one protein we studied (SOX9) showed patients had an eight-fold higher risk of death when it was found at high levels." "Our work is leading to the point where medical professionals may be able to test levels of these Notch proteins and use it to decide whether Notch inhibitory drugs might be helpful in making chemotherapy treatment work better."

http://www.news.uwa.edu.au/201308075939/research/colon-cancer-discovery-could-take-treatment-notch

3. Aspirin, NSAID Use Mitigates GI Cancers (Sept.17/13)

Inflammatory processes are a leading cause of discomfort that affects the productivity and normal functioning of an individual. Likewise, chronic inflammatory processes increase the risk of developing malignancy in the long term. Anti-inflammatory drugs like aspirin are considered somewhat controversial,

due to gastric irritation; however the latest research suggests **aspirin** plays a very important role in the prevention of malignant lesions in the gut. Research conducted by investigators from the Department of Gastrointestinal Medical Oncology Cancer Center at **MD Anderson** analyzed the latest evidence-based research to study the role of non-steroidal anti-inflammatory drugs in the management and treatment of gut cancers like hepatocellular carcinoma, **colorectal carcinoma**, esophageal, pancreatic and gastric (stomach) carcinoma. Stomach cancer and colorectal cancer together are a leading cause of morbidity and mortality. Unfortunately, the screening tests are only available for colorectal cancers leading to high morbidity and mortality of other gut cancers due to advanced and widespread disease at the time of diagnosis. The MD Anderson-based research suggested that most inflammatory processes in the gut are initiated by **COX-2** (and ongoing inflammation increases the risk of malignancy many folds). It has been observed that COX- 2 inhibitors can control the inflammation and thereby may help in the prevention of different cancers. The team of researchers at MD Anderson identified somewhat controversial results when assessing previous literature on studies regarding the preventive role of NSAIDs on **esophageal cancer**. While many studies indicated a clear-cut benefit of NSAID therapy, other research revealed no significant correlation. MD Anderson researchers concluded that NSAID consumption is linked to a significant decrease in the overall incidence of **gastric cancer**. However, more aggressive study is needed to stratify the benefits. Likewise, the chemopreventive benefits of COX-2 inhibitors for the prevention of hepatic and pancreatic cancer are also mixed. However, ***clear-cut evidence of colorectal cancer prevention and management was observed with COX-2 inhibitor therapy***. The research team concluded that more research is needed to determine the therapeutic and preventive benefits of COX-2 inhibitor therapy (NSAIDs and aspirin) in the management of hepatic, esophageal and pancreatic cancers.

http://bionews-tx.com/news/2013/09/17/does-nsaid-use-impact-gi-cancers/

4. PI3KCA Could Predict Aspirin Response in Colorectal Cancer (Sept.26/13)

A new study, by researchers from the VICTOR trial, tested whether treatment with rofecoxib (Vioxx) or aspirin was effective for colorectal patients whose tumors harbored a mutation in the gene PIK3CA, finding that PIK3CA may be a predictive biomarker of aspirin therapy. Patients with PIK3CA-positive colorectal cancer who took aspirin had a lower colorectal cancer recurrence compared with those with a wild-type PIK3CA gene (no genetic mutation). No evidence of a greater benefit for PIK3CA-positive patients from rofecoxib treatment was found compared with placebo. Patients in the VICTOR trial had stage II or III colorectal cancer and were randomized to either rofecoxib or placebo. All patients had previously been treated with therapy that included surgery and may have included radiotherapy and chemotherapy. Patients took rofecoxib for a median of 7.4 months before study treatment was discontinued and rofecoxib was removed from the market. Patients who had been taking aspirin during randomization or those who started aspirin daily at follow-up were classified as aspirin users in the study. Of 896 patients in the VICTOR trial for whom *PIK3CA* mutation status was known, 792 patients had *PIK3CA* wild-type colorectal cancer and 104 (11.6%) had *PIK3CA*-mutated colorectal cancer. Among patients in the *PIK3CA*-mutated tumor group, 23 of 90 patients who did not use aspirin had a recurrence of disease. Zero of the 14 patients who took aspirin regularly had a recurrence. Among patients who were *PIK3CA* wild-type, 151 of 681 non-aspirin users (22.1%) recurred while 22 of 111 aspirin users recurred (19.8%). Among *PIK3CA*-mutated patients, those who were aspirin users had better survival compared with those who did not use aspirin regularly, but the results did not reach statistical significance. No difference in colorectal cancer recurrence was found in *PIK3CA*-mutated patients treated with rofecoxib compared with placebo, and no effect on recurrence-free survival was shown.

Domingo, Enric, et al., Evaluation of* PIK3CA *Mutation As a Predictor of Benefit From Nonsteroidal Anti-Inflammatory Drug Therapy in Colorectal Cancer. J of Clin Onc. Published online before print September 23, 2013.

5. Early Tumour Shrinkage in Colorectal Cancer Suggests Long-Term Cetuximab (Erbitux) Benefit
(Sept. 27/13)

Colorectal cancer patients who have early tumor shrinkage after first-line treatment with chemotherapy plus cetuximab (erbitux) may be more likely to have long-term response to therapy, according to an analysis of two large clinical trials. Researchers show that a more robust tumor response at 8 weeks after start of therapy was associated with improved progression-free and overall survival. An early tumor shrinkage of 20% or more could identify patients, receiving a combination of chemotherapy plus cetuximab, who had both longer progression-free and overall survival. For patients who received chemotherapy alone, there was only a weak association between early tumor shrinkage and progression-free and overall survival. The results provide evidence that tumor shrinkage can be used as a prognostic biomarker. The patients analyzed for the study included the 1,289 patients compiled from two randomized first-line colorectal cancer trials of cetuximab whose tumors could be analyzed for KRAS mutation status. "If confirmed in a prospective trial, [early tumor shrinkage] may be useful to guide on-treatment decisions including continuation or discontinuation of therapy," conclude the authors. While colorectal tumors with a mutation in the KRAS gene generally do not benefit from EGFR-targeted therapy such as cetuximab, there are no current biomarkers to select patients who are more likely to respond. In their study, researchers analyze the data from the CRYSTAL (Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) phase III trial and the OPUS (Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer) phase II trial that accrued patients between 2004 and 2006. A previous single-arm colorectal cancer trial with cetuximab suggested that

early tumor shrinkage could predict the long-term response to the antibody-chemotherapy combination treatment. The current results provide further evidence that early tumor shrinkage is an indication that a patient with wild-type KRAS colorectal cancer is not only sensitive to cetuximab but is likely to have a long-term response from therapy.

Piessevaux, Hubert, et al., Use of Early Tumor Shrinkage to Predict Long-Term Outcome in Metastatic Colorectal Cancer Treated With Cetuximab. J of Clin Onc. Published online before print September 16, 2013.

6. Overall Survival Results Comparable for Vectibix and Erbitux (Sept.28/13)

Panitumumab (Vectibix) proved noninferior to cetuximab (Erbitux) in extending overall survival (OS) in patients with chemorefractory KRAS wild-type metastatic colorectal cancer (mCRC), according to the results of the international ASPECCT trial. ASPECCT is the first head-to-head, randomized phase III study evaluating the two EGFR-targeted monoclonal antibodies in patients with mCRC. At the time that ASPECCT was initiated, cetuximab had prospectively demonstrated an OS benefit, while single-agent panitumumab had not. Researchers explained that, in a pivotal trial, the lack of OS benefit with panitumumab may have been due to a 70% cross-over rate from the control arm to the panitumumab arm. The crossover potentially diluted the overall survival benefit, and this has often been a discussion point between the two drugs. ASPECCT, therefore, was designed as a non-inferiority trial to determine if the two anti-EGFR agents provide a comparable survival benefit. The study enrolled 999 *KRAS* wild-type mCRC patients who had previously received irinotecan-, oxaliplatin-, and fluorouracil-based treatment for metastatic disease, but no prior anti-EGFR regimens; about 25% of patients had received prior bevacizumab (avastin). Patients were randomized 1:1 to receive panitumumab or cetuximab. Although crossover between the arms was not allowed, a small proportion of patients did cross over, but it was well balanced between the arms. The primary endpoint was OS. Noninferiority was determined if panitumumab preserved at least 50% of the cetuximab OS effect compared with best supportive care. At a median follow-up of >9 months, panitumumab proved noninferior to cetuximab. Median OS was 10.4 months with panitumumab and 10.0 months with cetuximab. “It is quite evident that the primary outcome—the overall survival curves—essentially mirror each other, with no obvious differences,” note researchers. Median progression-free survival was also similar: 4.1 months with panitumumab and 4.4 months with cetuximab. The objective response rates were 22.0% and 19.8%, respectively. The safety profiles between the two arms were consistent with previously reported studies for both agents. Serious adverse events were observed in 30.4% of the panitumumab arm and 33.6% of the cetuximab arm, with 13.9% and 12.1%, respectively, discontinuing the drug. Skin toxicity grade 3 or 4 was more common with panitumumab (12.5% vs. 9.5%), as was hypomagnesemia (7.2% vs. 2.6%), but infusion reactions were more common with cetuximab (1.8% vs 0.2%).

Price T, et al. ASPECCT: a randomized, multicenter, open-label, phase 3 study of panitumumab (pmab) vs cetuximab (cmab) for previously treated wild-type (WT) KRAS metastatic colorectal cancer (mCRC). Presented at: European Cancer Congress 2013; September 27-October 1, 2013; Amsterdam, The Netherlands. Abstract LBA18.

SURGICAL THERAPIES

7. HIPEC Procedure Targets Cancers Inside Abdomen (Sept.1/13)

Surgeons at Saint Louis University Hospital have a new option for cancer patients with spread of disease inside the abdomen, offering a procedure called cytoreductive surgery with or without hyperthermic intraperitoneal chemoperfusion (HIPEC). Peritoneal surface malignancies describe a subset of cancers that spread inside the abdomen. They are diseases that in the past have had few medical or surgical options. Cytoreductive surgery involves removing all visible tumors and HIPEC involves circulating chemotherapy heated up 107 degrees Fahrenheit to directly target cancer cells. “We make a midline incision in the abdomen and remove every tumor growth visible to the naked eye,” says Jula Veerapong, MD, surgical oncologist at Saint Louis University Hospital and a SLUCare physician. “We then temporarily close the incision and insert inflow and outflow tubes for heated chemotherapy which targets microscopic disease. “ As the chemotherapy is applied, Dr. Veerapong and his colleagues physically massage or agitate the patient’s abdomen for up to 90 minutes as the chemotherapy is circulating from the perfusion machine. “Current thinking is that heat enhances the tumor killing activity of the chemotherapy itself,” says Dr. Veerapong. The theoretical benefits of HIPEC include

- increased tissue penetration for enhanced tumor destruction,
- treatment of microscopic disease and floaters, and
- more favorable pharmacokinetics.

Moreover, advantages include

- optimal treatment timing (chemotherapy can be delivered at the time of surgery as opposed to waiting for wound healing),
- direct cytotoxic effects of administering chemotherapy to cancer cells,

- the ability to safely deliver higher concentrations of chemotherapy compared to intravenous delivery, and
- the ability to break down scar tissue (from prior surgery) to ensure that all peritoneal surfaces are treated.

"There is retrospective data to support the use of HIPEC in certain diseases like pseudomyxoma peritonei, appendiceal cancer, and mesothelioma. There are also randomized control trials in the use of HIPEC in colorectal cancer," says Dr. Veerapong. "The data for HIPEC in ovarian cancer patients is evolving. The best outcomes are in those patients who have had their tumors completely removed," he says. "There are ongoing randomized trials. This represents the start of treatment for patients with carcinomatosis." Cancer that has spread to the lining surfaces of the peritoneal (abdominal) cavity from appendiceal cancer, primary colorectal cancer, mesothelioma, ovarian cancer, primary peritoneal cancer, certain sarcomas, and pseudomyxoma peritonei – often grouped under the moniker of peritoneal carcinomatosis – are examples of such types that are treated at Saint Louis University Hospital. Historically, treatment for some of these conditions has not been good, with low cure rates and adverse side effects from traditional chemotherapy. With HIPEC, Dr .Veerapong feels it is an alternative for patients who otherwise may not have many options.

http://interact.stltoday.com/pr/lifestyle/PR080813105413887

8. New Direction in Surgery for Rectal Cancer (Sept.1/13)

Surgeons at the University of California, San Diego School of Medicine are evaluating a new, combined surgery technique to remove cancerous tumors from the rectum. The hybrid technique uses the body's natural opening to remove malignancies and diseased tissue while also performing reconstruction. UC San Diego Health System's surgical team is the first in the United States – in a clinical trial setting – to integrate two novel minimally invasive techniques to treat rectal cancer. "By operating through the rectum, and with one small abdominal incision, we are able to perform an effective operation to remove the cancer, and to visualize and identify pelvic structures that are vital to normal bladder and sexual function," said Elisabeth McLemore, MD, colorectal surgeon at UC San Diego Health System and principal investigator of the study. "With this advanced approach, we reduce the number of incisions from six to one. This can result in less blood loss, less pain and a shorter hospital stay for the patient." This clinical trial surgery combines a technique called natural orifice translumenal endoscopic surgery (NOTES) with laparoscopic total mesorectal excision (TME), a form of rectal surgery. The NOTES technique allows the surgeons to operate through the rectum to remove tumors and TME ensures that a section of normal tissue around the tumor is also safely removed to reduce the chance of cancer recurrence. "This study is evaluating both the safety and efficacy of the surgery, as well as pain levels, cosmetic outcomes, operative costs and logistical outcomes. "Our goal is to expand the range of minimally invasive techniques that can be performed for patients with any form of digestive cancer." The surgical team utilizes special tools designed to allow simultaneous access through the rectum and abdomen. The rectal cancer is removed from below while the colon is mobilized from the abdomen. The remaining colon is then used to re-construct the rectum. The procedure is 5 hours in comparison to the average six to eight hours of operating room time using the traditional surgical approach. McLemore added that the tools used by the surgical team were less expensive than the current tools she uses for laparoscopic and robotic procedures. "Up until now, new technologies and techniques have taken longer to perform in the operating room and were associated with increased cost," said McLemore, a national leader in transanal minimally invasive surgery. "This is the first technique using a new technology to perform minimally invasive rectal cancer surgery that may result in improved visibility, and lower costs and procedure time. If successful, the new technique could create a better experience, value and long-term results for the patient."

http://www.newswise.com/articles/new-direction-in-surgery-for-rectal-cancer

9. Laparoscopic Surgery May Benefit Seniors (Oct.8/13)

Seniors who have minimally invasive laparoscopic surgery for colon cancer are much less likely to end up in a nursing home after being discharged from the hospital than those who have open surgery, a new study finds. One expert not connected to the research said the study adds valuable information for patients. "Laparoscopic surgery offers many advantages when compared to similar procedures performed through a large open incision," said Dr. Jerald Wishner, director of colorectal surgery at Northern Westchester Hospital in Mount Kisco, N.Y. "Patients undergoing a laparoscopic approach experience less pain, earlier return of intestinal function, earlier ambulation [walking ability], shorter hospital stays and earlier return to their baseline activities," he said. "These advantages can be particularly important to the elderly." In the new study, a Canadian team of researchers reviewed data on more than 9,400 patients over the age of 70 who had colon cancer surgery in the United States between 2009 and 2010. Of those patients, more than 5,700 had open surgeries, while about 3,700 had less-invasive laparoscopic procedures. Patients who had open surgery were much more likely than those who had laparoscopic surgery to be sent to a nursing home after leaving the hospital, the team found, at 20% versus 12.5%, respectively. "There is evidence that laparoscopic surgical treatment for colon cancer is similar to an open operation in terms of outcomes from a cancer treatment point of view," study author Dr. Richard Liu, a general surgery resident at Dalhousie University in Halifax, Nova Scotia, said in

a college news release. According to the U.S. National Cancer Institute, three-year survival and cancer recurrence rates are comparable for patients who have laparoscopic or open surgery for any stage of colon cancer. Age also affected the risk of ending up in a nursing home after colon cancer surgery. The lowest risk was for those aged 70 to 75, while the risk was four times higher among those aged 80 to 85 and eight times higher among those over 85, the researchers said. Liu's team also found that patients who had other diseases -- such as diabetes, high blood pressure or heart disease -- were more likely to require nursing home care after leaving the hospital. For colon cancer patients in their early 70s who do not have advanced cancer or other major health problems, laparoscopic surgery may help prolong their lives and also preserve their quality of life, the researchers concluded.

http://www.webmd.com/colorectal-cancer/news/20131008/laparoscopic-surgery-for-colon-cancer-may-benefit-seniors

RADIATION THERAPY/INTERVENTIONAL RADIOLOGY

10. Study Involving SRT To Help Treat 5 or Fewer Mets Underway at PMH (Oct.1/13)

A phase II study involving the delivery of SBRT (Stereotactic Body Radiation Therapy) to 5 or fewer metastases originating from colorectal cancer is underway at Princess Margaret Hospital in Toronto. The purpose of the study is to monitor the side effects and treatment outcomes of delivering higher doses of radiation therapy to the tumour, while limiting the dose of radiation to the normal tissues. This will be done using a 5 day treatment schedule. All patients will be treated with SBRT 1-2 weeks after radiotherapy planning scans. Therapy will be given once daily, over 5 consecutive working days according to standard practice. The trial identifier is NCT01761929 and additional information may be accessed at http://clinicaltrials.gov/show/NCT01761929

http://clinicaltrials.gov/show/NCT01761929

SCREENING

11. Mailed Screening Outreach Improves Screening Rates (Sept.1/13)

Among underserved patients whose colorectal cancer (CRC) screening was not up to date, mailed outreach invitations appear to result in higher CRC screening compared with usual care, according to this study. A total of 5,970 participants were randomly assigned to one of three groups:

- 1,593 to fecal immunochemical test (FIT) outreach,
- 479 to colonoscopy outreach, and
- 3,898 to usual care.

Researchers measured for screening participation in any CRC test within one year after outreach was conducted. Screening participation was significantly higher for both FIT (40.7%) and colonoscopy outreach (24.6%) than for usual care (12.1%). In stratified analyses, screening was higher for FIT and colonoscopy outreach than for usual care, and higher for FIT than for colonoscopy outreach among whites, blacks, and Hispanics, according to the study results. "This prospective, randomized, comparative effectiveness trial demonstrated that organized mailed outreach efforts substantially increased CRC screening participation among underserved patients. FIT outreach tripled CRC screening rates, and colonoscopy outreach doubled the rates compared with usual care," the study concludes. "For underserved populations, our findings raise the possibility that large-scale public health efforts to boost screening may be successful if noninvasive tests, such as FIT, are offered over colonoscopy," the study concludes.

Gupta, Samir, et al., Comparative Effectiveness of Fecal Immunochemical Test Outreach, Colonoscopy Outreach, and Usual Care for Boosting Colorectal Cancer Screening Among the Underserved: A Randomized Clinical Trial. JAMA Intern Med. 2013;():-. doi:10.1001/jamainternmed.2013.9294

12. Colon Cancer Detected Earlier with New Method (Sept.5/13)

Researchers have found new techniques to spot certain gene variations that have been linked to colon cancer, and they say their new findings may soon allow doctors to identify the disease in the very first stages, potentially saving patients' lives. According to the researchers, two genes are most frequently mutated in patients with colorectal cancer; 60% of patients have a mutated **APC gene** and 40% of patients have a mutated **KRAS gene**. Until now, however, finding these mutations has been tricky, as lead investigator Scholtka explains: "Tumor cells are released into stool from the surface of precancers and early-stage colon cancers, but detecting a cancer-initiating genetic mutation among a large quantity of normal DNA from a patient's stool is like looking for a needle in a haystack." Because precancer cells carrying the genetic mutations are regularly passed through the stool, Scholtka says detecting these cells in stool samples is better than in blood. She notes that the cells can only be detected in blood once the

cancer has reached a later stage. To test their method, the researchers used a combination of two techniques to analyze genetic variations within 80 cancerous and precancerous human colon tissue samples:

- **Locked nucleic acid (LNA)-based, wild-type blocking (WTB) polymerase chain reaction**, which suppressed normal DNA present in large quantities, and
- **High-resolution melting (HRM)**, which enhanced the detection of genetic variations.

Through these methods, the researchers detected APC variations in 41 of the 80 samples and also identified previously unknown variations in APC. The currently used technique - direct sequencing - only detected variations in 28 of the samples. When the researchers then analyzed 22 stool samples from patients with APC variations in their colon tissues (and nine control stool samples without APC variations), they successfully detected APC variations in 21 out of the 22 samples. Additionally, the team was able to detect KRAS variations in 20 human colon tissue samples, demonstrating that their technique can also identify variations in non-APC genes.

http://www.medicalnewstoday.com/articles/265682.php

OTHER

13. New Biomarker Could Help Predict if Disease Will Spread (Sept.1/13)

Scientists have identified a protein that could play a crucial role in recognizing whether colorectal cancer patients need chemotherapy as there is a high risk of their cancer spreading, according to a new study[1] published. Scientists found that patients with low levels of the protein, known as **FOXO3**, had an increased risk of their cancer spreading to other parts of the body. By comparing levels of FOXO3 in tissue samples from patients with different stages of colorectal cancer the researchers found the protein was a good predictor of how aggressive a tumour is – decreasing levels of the protein were linked to more aggressive cancers. Mr Marc Bullock, MRC Clinical Research Training Fellow, said: "We see and operate on a lot of patients with advanced and recurrent colorectal cancer. Our findings suggest that looking at levels of FOXO3 could help single out which patients need extra treatments to help stop their cancer from coming back, as well as being a good potential target for drug development. Although other studies have looked at the role of FOXO3 in stopping tumours growing, this is the first time that such a clear link between levels of the protein and tumour growth has been identified." Mr Alexander Mirnezami, the study's senior author, a Cancer Research UK scientist and bowel cancer surgeon at University Hospital Southampton, said: "As our research continues, we hope to identify lots of other new biomarkers that can help us adapt treatments based on individual patients' tumour characteristics as part of a personalized approach to cancer treatment." Dr Julie Sharp, senior science communications manager at Cancer Research UK, said: "This fascinating new finding could help doctors tackle the problem of bowel cancer spread. Although levels of FOXO3 alone are not enough to accurately predict whether a patient's cancer will return, the authors highlight several other potential biomarkers that, alongside FOXO3, could offer a powerful new tool to help doctors decide the best way to treat patients."

Bullock, M D. et al (2013-07-04) FOXO3 expression during colorectal cancer progression: biomarker potential reflects a tumour suppressor role. DOI: 10.1038/bjc.2013.355

http://www.cancerresearchuk.org/cancer-info/news/archive/pressrelease/2013-07-24-new-biomarker-bowel-cancer-help-predict-spread

14. Attitudes Toward Genetic Testing for Colon Cancer (Sept.1/13)

Only half of those with a family history of colon cancer chose to go for genetic testing and counseling, according to a study. Hereditary nonpolyposis colorectal cancer (HNPCC) accounts for between one and five per cent of all colon cancers. This inherited condition imposes a 90 per cent or more chance of developing the disease in those who carry the relevant gene mutation. It is now possible to test for the HNPCC mutation – but is this option welcomed by all at risk? To find out, researchers at the National Human Genome Research Institute in the US studied a group of 111 first degree relatives of 104 adults with HNPCC. They found that only around half chose to have genetic testing and counseling. Many were worried about the effect a positive result would have on their health insurance, and chose not to have the test. Many of those who did consider the test said they wanted to know the result for the sake of their children. It emerged that concern about the psychological impact of the test result on the family was a deciding factor in many cases. These issues must be thoroughly explored by all those taking part in testing for HNPCC.

http://www.newsfix.ca/2013/06/18/attitudes-towards-genetic-testing-for-colon-cancer/

15. New Phase III Trial (Sept.2/13)

Colorectal cancer is recognized as a common cancer and is the third leading cause of cancer mortality. As with many other types of cancer, people who have been treated for colon cancer are at increased risk for developing a new colon cancer. To explore if colorectal cancer recurrence can be reduced after initial treatment, the National Cancer Institute, Southwest Oncology Group, and Cancer Prevention Pharmaceuticals, Inc., recently announced a phase III trial called the Preventing Adenomas of the Colon with Eflornithine and Sulinidac (PACES) trial. The primary objective is to assess whether eflornithine 500

mg or sulindac 150 mg (or both) are effective in reducing the 3-year event rate, defined as high risk adenoma or 2nd primary colorectal cancer, in patients with Stage 0, I, II, and III colon cancer. Both drugs work to lower levels of polyamines, which are naturally-formed molecules that play a role in the development of colorectal cancer. Eflornithine slows the body's production of polyamines and sulindac helps cells eliminate excess polyamines. The researchers chose these two drugs because of an earlier study that looked at their preventive effects in patients who already had at least one adenoma removed from their colon. In that study, participants who took the drug combination lowered their risk of developing another adenoma over the next three years to less than one third of what it was for those who did not take the drugs. They lowered their chances of developing high-risk adenomas or multiple adenomas during that time by 90%. Information about the trial and patient enrollment criteria are available at http://clinicaltrials.gov/ct2/show/NCT01349881.

http://www.onclive.com/social-media/nurses_blogs/0813/New-Phase-III-Trial

16. Colorectal Cancer May Be Triggered by Mouth Bacteria (Sept.5/13)

A type of gut bacteria found in the mouth may trigger colorectal cancer by influencing the immune response and switching on cancer genes. The researchers believe their findings may lead to more timely and improved ways of diagnosing, preventing, and treating colorectal cancer. Our gut contains trillions of bacteria, vastly outnumbering our own cells. These microbe communities maintain our health by training our immune system and helping us digest food. But they can also trigger disease. There is evidence that an imbalance between the "good" and the "bad" gut bacteria may promote colon cancer. The two new studies focus on a genus of bacteria called *Fusobacteria*, and the species *F. nucleatum* in particular. **Researchers have found *Fusobacteria* from the mouth are also abundant in tissues from colorectal cancer patients.** But until this latest research, it was not clear whether these gut microbes actually trigger tumors, and if so, how they do it. In the first study, the researchers found *Fusobacteria* in benign tumors that can become cancerous over time. This might suggest that they contribute to the early stages of tumour formation. Then, in mice bred to have a human-like form of colorectal cancer, the team found the bacteria sped up tumor formation by summoning a type of immune cell called myeloid cells, which penetrate tumors and trigger inflammations that can lead to cancer. In the second study, another team found that *Fusobacteria* use a molecule that lives on the surface of the bacterial cell to stick to and then invade human colorectal cancer cells. The molecule, called Fusobacterium adhesin A (FadA), switches on genes that spur cancer growth, triggers inflammation in the human cancer cells, and spurs tumor formation. The team also found that tissue from healthy individuals had much lower levels of FadA than tissue from patients with benign and cancerous colorectal tumors. Plus, they identified a compound that can stop the effects of FadA on cancer cells.

Kostic, Alexsandar, et al., Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor immune microenvironment. Cell Host & Microbe 14(2) pp.207-215

Rubinstein, Mara Roxana, et al., Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-Cadherin/B-Catenin Signaling via its FadA adhesin. Cell Host & Microbe. 14(2) pp.195-206

17. Cancer Risks Confirmed in Crohn's (Sept.22/13)

People with Crohn's disease are 50% more likely to develop cancer than the general population but there is no increased risk for those with ulcerative colitis (UC), a large Danish study finds. The increased risk of cancer in Crohn's was particularly associated with diagnosis at a young age, colonic disease, smoking, and the use of 5-ASA and thiopurines, data from over 2,300 patients with a median follow-up of 15 years showed. Crohn's patients also had a 15-fold higher risk of small bowel cancer whereas an increased risk of colorectal cancer was only evident in men.

http://www.gastroenterologyupdate.com.au/latest-news/cancer-risks-confirmed-in-crohn-s

18. Metformin and Colorectal Cancer Incidence (Sept.27/13)

The intake of metformin has been associated with a decreased incidence of colorectal cancer in patients with type 2 diabetes in several studies. However, other studies have presented contradictory results. Smiechowski et al used data on patients "newly-treated" with oral anti-diabetic medications from the United Kingdom Clinical Practice Research Datalink to conduct a nested case-control designed study. Researchers matched "incident cases of colorectal cancer occurring during follow-up" with a max of 10 controls. Adjusted rate ratios of colorectal cancer "associated with ever use, and cumulative duration of use of metformin" were then calculated. Results showed that metformin use and duration of use was not linked to incidence of colorectal cancer among patients. The authors conclude the study by recommending against the start of metformin randomized controlled trials for the prevention of colorectal cancer.

Smiechowski B, et al. The use of metformin and colorectal cancer incidence in patients with type 2 diabetes mellitus. Cancer Epidemiol Biomarkers Prev. 2013.

19. Smokers Have Higher Complication Risk After Colon Surgery (Sept.25/13)

Smoking increases the risk of complications and death following colorectal surgery, a new study says. The study is based on an analysis of data from 47,000 patients in the United States who had major, non-emergency colorectal surgery. Researchers from the University of Rochester Medical Center in New York found that smoking raised the risk of complications such as pneumonia and other infections by about 30 percent. "Anecdotally, we know that many patients don't take the opportunity to quit or join a smoking cessation program before surgery," study lead author Dr. Fergal Fleming said in a university news release. "We want to find out what motivates patients, how can we make them a major player in their own care, and how can we as physicians do a better job of explaining issues like this to patients," Fleming explained. The study looked at 26,000 patients who had surgery for colorectal cancer, 14,000 operated on because of diverticular disease (small, inflamed pockets that form along the colon wall), and 7,000 who had surgery for inflammatory bowel disease. Twenty percent of the patients were current smokers, 19 percent were former smokers and the rest had never smoked. After taking age, body fat, alcohol use and other health conditions into account, the researchers concluded that current smokers still had an estimated 30 percent higher risk of dying or developing complications following colorectal surgery compared to those who never smoked. Current smokers -- who were younger than ex-smokers and never-smokers -- had the highest rates of pneumonia and infection, were more likely to require additional surgery and had much longer hospital stays, the researchers said. They also found the rates of all complications and the risk of death were significantly higher in patients who smoked two packs a day for more than 30 years.

http://consumer.healthday.com/cancer-information-5/colon-cancer-news-96/smoking-adds-to-complications-after-colorectal-surgery-study-finds-680510.html

20. Increased Primary Care Visits Tied to Lower Colorectal Cancer Incidence (Oct.1/13)

Higher utilization of primary care among Medicare beneficiaries reduces colorectal cancer (CRC) incidence and mortality, according to a study. Researchers utilized data to identify patients aged 67 to 85 years diagnosed with CRC between 1994 and 2005 and matched controls (205,804 participants for CRC incidence; 54,160 for CRC mortality; and 121,070 for all-cause mortality). Primary care visits in the four- to 27-month period before CRC diagnosis was assessed. The researchers found that persons with five to 10 primary care visits had lower CRC incidence compared to patients with no more than one primary care visit. For patients having late-stage CRC diagnosis, left sided lesions, and diagnosis in more recent years when there was greater Medicare screening coverage, the associations were even stronger. Ever having CRC screening and polypectomy reduced the association between primary care utilization with CRC incidence. "Increasing and promoting access to primary care in the United States for Medicare beneficiaries may help decrease the national burden of CRC," the authors write.

http://www.oncologynurseadvisor.com/increased-primary-care-visits-tied-to-lower-colorectal-cancer-incidence/article/314271/

NUTRITION & HEALTHY LIFESTYLE

21. Sugary Foods Increase Risk of Colorectal Cancer (Sept.1/13)

Sugary snacks increase the risk of colorectal cancer, according to this new study. It is the first study of its kind to find a positive link between colorectal cancer and high sugar and fat diets. Work from the University of Edinburgh in Scotland has found that the consumption of sodas, cakes, biscuits, snacks and desserts is linked to an increased risk in colorectal cancer. Conducted last year using data from the Scottish Colorectal Cancer Study, the study included 2,063 patients suffering from bowel cancer and 2,776 controls from Scotland. The study builds on previous research analyzing links between diet and bowel cancer, which identified two distinct eating patterns. One was a diet high in healthy foods, such as fruit and vegetables, and the other diet was high in meat, fat and sugar. The research team analyzed over 170 foods, including fruits, vegetables, fish and meat, as well as chocolate, nuts, crisps and fruit drinks. They also looked at links between some established risks of bowel cancer, such as family history of cancer, physical activity and smoking. Results revealed that the healthy diet was associated with a decreased risk of colorectal cancer, while the high fat and sugar diet is associated with an increased risk.

Theodoratou, Evropi, et al., Associations between dietary and lifestyle risk factors and colorectal cancer in the Scottish population. European J of Cancer Prev. July 12, 2013.

22. Body Mass Index and Smoking Affect Patient Outcomes (Sept. 22/13)

The impact of body mass index (BMI) on the prognosis of patients with colorectal cancer remains largely unknown, particularly in Asian populations. Therefore, the aim of this study was to examine the influence of BMI on the mortality of Chinese colorectal cancer patients. The study consisted of 525 patients who were diagnosed with colorectal cancer and underwent radical surgery between June 2004 and August 2011. Study participants were divided into two BMI categories: normal weight (BMI <23 kg/m2) and overweight (BMI >=23 kg/m2). Of 525 patients, 208 patients (39.6%) were included in the normal-weight group and 317 patients were included in the overweight group. During the mean follow-up period of 48.8 months, 89 patients had disease recurrence and 131 deaths occurred. High BMI was significantly correlated with younger age, presence of diabetes, alcohol consumption, distal (left sided) colon tumors, amount of lymph node harvested and pathological stage. No statistically significant correlation was found between high BMI and progression-free survival (PFS) or overall survival (OS) when the total group of patients was considered. Cigarette-smoking patients had significantly shorter OS than patients who had

never smoked. Cigarette-smoking patients did not have significantly different PFS compared with patients who had never smoked. Researchers concluded that there was no significant correlation between obesity and outcomes of patients with colorectal cancer. In addition, their findings support the claims that cigarette smoking may be partially responsible for the divergent mortality of patients with colorectal cancer.

Liu, Dan, et al., Association of body mass index and smoking on outcome of Chinese patients with colorectal cancer. World J of Surg Onc. 2013, 11:271.

23. Women Who Smoke Are More vulnerable to Colorectal Cancer (Oct.1/13)

Women who smoke are more vulnerable than male smokers to an increased risk of colorectal cancer. It is already known that smoking and drinking alcohol can increase the risk of developing colorectal cancer. Researchers at Evanston Northwestern Health Care have produced further evidence on how these risk factors affect women. They looked at a large database covering patients in 350 hospitals and found that age of onset of colorectal cancer is somewhat younger among men than among women in the non-smoking non-drinking group. Among current smokers, both men and women had a significantly lower age of presentation for colorectal cancer, compared to those who didn't drink or smoke. Alcohol use, too, was linked to a younger age of developing the cancer. When men were compared to women, it was found that women were more sensitive to tobacco as a risk factor for colorectal cancer. It's a risk worth emphasizing when supporting people giving up smoking. While many associate lung cancer with smoking, the risk of colorectal cancer is perhaps not as well known.

http://www.newsfix.ca/2013/06/20/women-more-vulnerable-to-colorectal-cancer-risk-of-tobacco/

24. Garlic Can Help Fight Colon Cancers (Oct.1/13)

According to a report, an analysis of 18 studies on garlic consumption shows a strong protective effect against gastrointestinal cancers. But this benefit only appears to come from eating fresh garlic – raw or cooked – and not garlic supplements, researchers at the University of North Carolina at Chapel Hill, N.C., found. Based on their analysis, high consumption of raw or cooked garlic, which averaged about 18.3 grams, or about six cloves per week, showed a 10 percent to 50 percent reduction in colorectal cancer. Stomach cancer risk was cut in half by high garlic consumption, researchers report. Garlic supplements did not decrease cancer risk at all, researchers say. More evidence suggests people can get cancer-protective benefits by eating whole foods rather than supplements. Scientists suspect there are many components working together in whole foods that provide this anti-cancer effect and are difficult to replicate in supplement or pill form.

http://www.newsfix.ca/2013/06/19/garlic-fights-stomach-colon-cancers/

25. Soy Foods May Protect Against Colon Cancer (Oct.1/13)

The link between eating soy-based foods, such as soy beans and tofu, and lower rates of **colon cancer** has long been known, but scientists didn't quite know the molecular reasoning behind the phenomenon. Now, in a **research paper** out of the University of Illinois, Professor Hong Chen and her graduate student Yukun Zhang reveal that a bioactive compound found in soy, called genistein, protects against colon cancer by repressing cell signals that normally push a cell to become cancerous. Genistein, in other words, can block cells from growing rapidly and developing into polyps and ultimately tumors. Researchers are maintaining that based on this evidence, colon cancer is an epigenetic disease, meaning that dietary and environmental factors can influence genes to be switched on or off so that there is a different pattern of gene expression, leading to a change in disease susceptibility. They reported: "The genetic information you inherit from your parents is not the whole story. Our dietary choices, our exposure to environmental toxins, even our stress levels, affect the expression of those genes."

Zhang Y, Li Q, Chen H. DNA methylation and histone modifications of Wnt genes by genistein during colon cancer development. **Carcinogenesis.** ***2013.***

26. Dietary Olive Oil May Be Protective (Oct.16/13)

Researchers from Oxford University, Institute of Health Sciences, Oxford, investigating the role of dietary factors in the development of colorectal cancer found that a diet rich in olive oil is associated with a decreased risk, and that this protective effect was irrespective of the amount of fruit and vegetables eaten. Information from the International Agency for Research in Cancer (IARC), detailing cancer rates, and food supply data from the Food and Agricultural Organization of the United Nations were combined and analyzed to calculate the correlation between colorectal cancer rates and ten dietary factors in 28 countries. Details of olive oil consumption were obtained from the International Olive Oil Council. Analysis of the data showed that 76% of the inter-country variation in colorectal cancer incidence rates was associated with the following factors:

- Meat and fish consumption combined were associated with increased colorectal cancer incidence
- Olive oil consumption was associated with decreased colorectal cancer incidence

The researchers hypothesized that a high meat intake would increase the production of bile acids and cause reduced enzyme diamine oxidase (DAO) activity leading to changes in the mucosal lining of the bowel, polyp formation, and adenoma/carcinoma. Olive oil seemed to have reduced the amount of bile acid produced and, consequently, allowed increased levels of DAO which maintained the integrity of the bowel lining.

http://www.newsfix.ca/2013/07/18/diet-and-colorectal-cancer-is-dietary-olive-oil-protective/