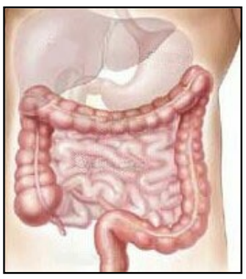
COLORECTAL CANCER RESEARCH UPDATES

Month Ending May 23rd, 2014



The following colorectal cancer research update extends from March 15th, 2014 – May 23rd, 2014 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. PEAK Study: Comparing Vectibix + Folfox to Avastin + Folfox (Mar 18/14)

The purpose of this study was to evaluate panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated wild-type (WT) KRAS. A prespecified secondary objective was to assess treatment effects in an extended RAS analysis that included exons 2, 3, and 4 of KRAS and NRAS, two genes which determine candidacy for anti-egfr therapies such as panitumumab (vectibix). Patients with WT KRAS (or nonmutated KRAS) exon 2 tumors were randomly assigned at a one-to-one ratio to panitumumab plus mFOLFOX6 or bevacizumab plus mFOLFOX6. The primary end point was progression-free survival (PFS); secondary end points included overall survival (OS) and safety. Median OS was 34.2 and 24.3 months in the panitumumab and bevacizumab arms. In the WT RAS subgroup (WT exons 2, 3, and 4 of KRAS and NRAS), PFS favored the panitumumab arm. Median OS was 41.3 and 28.9 months in the panitumumab and bevacizumab arms, respectively. PFS was similar and OS was improved with panitumumab relative to bevacizumab when combined with mFOLFOX6 in patients with WT KRAS exon 2 tumors. Investigators concluded that patients with WT RAS tumors seemed to experience more clinical benefit with anti-epidermal growth factor receptor therapy that included panitumumab.

Schwartzberg, Lee S., et al., PEAK: A Randomized, Multicenter Phase II Study of Panitumumab Plus Modified Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) or Bevacizumab Plus mFOLFOX6 in Patients With Previously Untreated, Unresectable, Wild-Type KRAS Exon 2 Metastatic Colorectal Cancer. J Clin Onc. 2014 Apr 21. [Epub ahead of print]

2. Certain Colon Cancer Patients Might Benefit From Aspirin (Mar.31/14)

A new study suggests that only certain patients may gain a survival benefit by taking aspirin after diagnosis. The study of about 1,000 patients found that people whose tumor cells give off a specific antigen, or defense mechanism, gained most from adding aspirin to their regular treatment. The findings aren't conclusive, and patients who develop colon cancer while already taking aspirin may not get any benefit. Also, aspirin, while inexpensive, comes with its own risks. Experts asked if colon cancer patients should begin taking aspirin as a result of these findings were divided. "Absolutely not," said study lead author Dr. Marlies Reimers, a doctoral student at Leiden University Medical Center in the Netherlands. She believes more research is necessary. But the author of a commentary accompanying the study, Dr. Alfred Neugut, said he now plans to recommend aspirin therapy for specific patients. The study adds to growing evidence that aspirin is helpful for certain colon cancer patients, said Neugut, an oncologist and epidemiologist at Columbia University Medical Center in New York City. In his commentary, Neugut writes he himself would add aspirin to his chemotherapy treatment regimen if he had a stage III colon cancer tumor, and he's ready to recommend that patients do, too. Stage III means the cancer has spread to nearby lymph nodes, but has not yet spread to other parts of the body. Together, this research and other recent studies "paint a very sound picture that warrants a change in standard of care -- that aspirin can and should be recommended for use for stage III patients," he said in an interview. But what about aspirin's well-known risks, especially the possibility of bleeding in the digestive system? "Stage III patients have a 40 percent to 70 percent chance of dying. I don't think the possibility that 1 percent to 2 percent will have some significant bleeding should deter aspirin's use, given a potential 20 percent to 30 percent improvement in survival," Neugut said. Aspirin is a "much easier and safer drug than chemotherapy, which we use without reservation," he added. Neugut said, however, that he doesn't recommend aspirin as a way to *prevent* colon cancer. The study examined tissue samples of 999 patients in the Netherlands who had surgery for colon cancer, mostly stage III or lower. Researchers then compared death rates for patients who were prescribed low-dose aspirin after diagnosis to those without the prescription, which is required in the Netherlands. The death rate was 38 percent among those who took low (80-milligram) doses of aspirin after diagnosis compared to 49 percent among the non-aspirin users, the study found. Survival rates were notably higher among aspirin-taking patients whose tumor cells gave off what's called **HLA class I antigen** -- a type of substance that alerts the immune system to defend the body. About two-thirds of 963 patients whose tumors were analyzed fell into this category. Aspirin had no apparent effect on the other patients who took it, the researchers said. It's unclear why aspirin might help some colon cancer patients but not others. Reimers said researchers believe aspirin may affect a process involving tumor cells and the components of blood known as platelets. What's next? Neugut said researchers have launched studies to get a better understanding of aspirin's perceived effect on colon cancer. But the results won't be available for at least 10 years, he noted. "There is a good chance that aspirin may also prove effective for other cancers in the future," Neugut said, "but there is much less data for any cancer other than colon." Patients are not routinely tested for HLA class I antigens, but Reimers said it wouldn't be expensive to do so.

Marlies Reimers, M.D., Leiden University Medical Center, the Netherlands; Alfred Neugut, M.D., Ph.D., oncologist and epidemiologist, professor, Columbia University Medical Center, and co-director, Cancer Prevention Program, New York Presbyterian Hospital, New York City; March 31, 2014, JAMA Internal Medicine

http://consumer.healthday.com/general-health-information-16/aspirin-news-46/only-certain-colon-cancer-patients-might-benefit-from-aspirin-study-says-686312.html

3. Erbitux + Chemo Before Liver Surgery May Not Be Helpful (May2/14)

The new EPOC study evaluated whether the drug cetuximab (erbitux) and chemotherapy together worked better than chemotherapy alone as a treatment in addition to surgery for people with colorectal cancer that had spread to the liver but could be surgically removed. In the trial patients either received chemotherapy on its own or chemotherapy combined with cetuximab. Patients received their specified treatment for 12 weeks. They then had surgery and followed by their specified treatment for another 12 weeks. Patients were then monitored via CT or MRI scans. The researchers found that adding cetuximab to chemotherapy did not help this group of people. Analysis looked at how long people in each group were living without any sign of their cancer getting worse. They found this was on average **14.1 months** in the group having chemotherapy and cetuximab compared to **20.5 months** in the group having chemotherapy alone. John Primrose, Professor of Surgery at the University of Southampton, comments: "These results were unexpected. Cetuximab is already approved by NICE in the UK alongside chemotherapy for people who had bowel cancer that had spread to the liver if the oncologist and liver surgeon thought this would enable the patient to have a liver operation. The cetuximab and chemotherapy combination is also used successfully in patients whose disease cannot be operated on at all. Our trial tested it in people who had cancer spread to the liver who were suitable for surgery from the outset, a similar group, but for these patients it seems to have an adverse effect. More research is needed to understand this surprising result."

Primrose, John et al., Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. **The Lancet Oncology*, 2014; DOI*: *10.1016/S1470-2045(14)70105-6***

RADIOTHERAPY/INTERVENTIONAL RADIOLOGY

4. Radiotherapy Before Immunotherapy for CRC Tumours (Mar.26/14)

Radiation therapy fights cancer in more ways than one. Not only does it force cancer cells to self-destruct, but several studies demonstrate that it also activates the immune system to attack tumour cells. This activation can be used to boost current immunotherapies, such as anti-tumor vaccines, to produce better clinical results. What's less clear, however, is exactly how to combine the two therapies to get the best bang for the therapeutic buck. To address this question, researchers at Thomas Jefferson University tested an experimental cancer vaccine in combination with radiation therapy in mice with colorectal cancer. Investigators showed that the vaccine was most effective when tumors were irradiated first and then vaccinated a week later. "Prior to these experiments, we didn't appreciate the impact that sequencing of these treatments had on their combined ability to generate immune and clinical responses," says Thomas Jefferson University radiation oncologist Matthew Witek M.D., first author of the study. "Remarkably, immune activation and tumor regression only occurred when radiation was given prior to vaccination." When mice received either treatment alone, the researchers noticed only a modest reduction in tumor size. However, when radiation was given first, the investigators saw a six-fold increase in cancer-fighting immune cells, and impressively, complete remission of the majority of tumors. Although the work will need to be reproduced in humans to determine if the same holds true for cancer patients, the finding is exciting, says lead researcher Adam Snook, Ph.D., an instructor in the department of Pharmacology and Experimental Therapeutics. "In a patient population that will undergo radiation therapy as standard treatment, these results provide a roadmap to amplifying the effects of immunotherapies like the one we're developing for colon cancer."

Witek, M, et al., "Tumor radiotherapy creates therapeutic vaccine response to the colorectal cancer antigen GUCY2C" International Journal of Radiation Oncology, 2014.

SCREENING

5. Home Stool DNA Test Detects Colorectal Tumours (Mar. 19/14)

Results of a clinical trial of Cologuard show unprecedented rates of precancer and cancer detection by a noninvasive test. The detection rates are similar to those reported for colonoscopy. Cologuard is a noninvasive sDNA test for the early detection of colorectal precancer and cancer. The Cologuard test is based on a stool sample that is analyzed for DNA signatures of precancer or cancer. The samples are easily collected, mailed from home, requires no bowel preparation, medication restriction or diet change. The clinical trial, called the **DeeP-C study**, included 10,000 patients and was designed to determine how well Cologuard detects precancer and cancer. The study also compared Cologuard to the fecal immunochemical test for occult blood (FIT). The study was conducted at 90 medical centers throughout the United States and Canada. In the study, all patients received Cologuard, FIT and colonoscopy. Colonoscopy was the reference method. Major findings reported in the study include:

- Sensitivity of Cologuard for cancer was 92% overall, and 94% for the earliest and most curable cancer stages (stages I and II).

- Sensitivity was 69% for precancerous polyps at greatest risk to progress to cancer (i.e., those containing high-grade dysplasia).

- Cologuard detected significantly more cancers and significantly more precancerous polyps than did FIT.

"The most important finding of the study is the high sensitivity of Cologuard for curable stage colorectal cancer, which represents the highest sensitivity of any noninvasive test to date," says Thomas Imperiale, M.D., a Professor of Medicine at Indiana University Medical Center in Indianapolis and a study author. "It is also significant to note that these results were achieved in a robustly conducted multicenter study." Cologuard works by testing a patient's stool for altered DNA shed during digestion. Altered DNA is known to occur within colorectal cancers and precancerous polyps. The test also examines the stool for the presence of blood, another possible indicator of colorectal cancer. Combining the data from the stool DNA test and the blood test into a single result provides a comprehensive, powerful screening approach, which is reflected in the study results. Because of its accessibility and ease of use, researchers hope the test will increase the number of people who will choose to be screened for colorectal cancer. Screening is important because, if cancer is detected early, removing polyps during a colonoscopy can prevent the cancer.

***Imperiale, Thomas F, et al., Multitarget Stool DNA Testing for Colorectal-Cancer Screening*. New England Journal of Medicine*, 2014; 140319083230003 DOI*: 10.1056/NEJMoa1311194**

6. Colon Cancer Rates Decreasing Among Older Americans (Mar.19/14)

According to a new report from the American Cancer Society, rates of colorectal cancer are decreasing steeply among older people in the US because of increasing use of colonoscopy screening, which can detect and remove precancerous growths**.** Over the last 10 years in the US, colon cancer incidence rates have fallen by 30% among people aged 50 and over, with the largest fall in those over 65. Meanwhile, use of colonoscopy screening has nearly tripled among those aged 50 to 75 - from 19% in 2000 to 55% in 2010. These were the key findings of the latest issue of Colorectal Cancer Statistics 2014, which was published in the March/April issue of *CA: A Cancer Journal for Clinicians*, and for which a companion report is available on the Society's website. They are being released as part of a new initiative to push colon cancer screening rates up to 80% by 2018.

http://www.medicalnewstoday.com/articles/274134.php

7. Colonoscopy Misses 6% of Cancers According to Utah Researchers (Mar..30/14)

Not all colon cancers are recognized immediately following a colonoscopy, according to new research from the Huntsman Cancer Institute. A Utah population-based study reveals that about 6 percent of colorectal cancers are diagnosed within three to five years after a patient gets a clean colonoscopy report. But that means that colonoscopies catch 94 percent of colon cancers," said Dr. Jewel Samadder, lead author of the study and a Huntsman Cancer Institute investigator. He said that "for a long time, the screening mechanism has been thought to be 100 percent effective at eliminating the risk of colon cancer, but there is a small risk within three to five years of getting a colonoscopy." Colonoscopy is very good, but it is not perfect," Samadder said. The "missed" cancers are either overlooked at the time of the colonoscopy or develop rapidly before the next colonoscopy is ordered, which is typically between five and 10 years later." "The study also helped researchers discover a number of factors associated with the missed cancers", Samadder said. He said the condition — involving possibly flatter and faster growing polyps that are unseen during a colonoscopy — arises most in patients over age 65, in patients with a family history of colorectal cancer and patients in whom polyps were found during previous colonoscopies. The majority of missed cancers were also more likely to appear in the right side of the colon, at the far end of the colonoscope's reach. "Our first thought was that perhaps doctors did not view the entire colon, or that preparation for the procedure was not complete, which would obscure their view," Samadder said. "However, the medical records of the patients with missed cancers showed these problems were seldom present." The two-year study included results from nearly 127,000 colonoscopies performed at University of Utah Health Care and Intermountain Healthcare facilities between 1995 and 2009, as well as data from the Utah Population Database, which combines genealogical, medical and demographic data with cancer records from the Utah Cancer Registry.

http://www.deseretnews.com/article/865599116/Utah-researchers-Colonoscopy-misses-6-percent-of-cancers.html?pg=all

OTHER

8. Scientists Identify Protein That Spurs Spread of Colon Cancer (Apr.4/14)

PLAC8, a protein that until now has been poorly understood, appears to play a key role in the spread - or metastasis - of colorectal or colon cancer. Previous research has already found that PLAC8 is linked to colon cancer. Now, in a new study published in the *Journal of Clinical Investigation*, researchers from Washington University School of Medicine in St. Louis, MO, and Vanderbilt University Medical Center in Nashville, TN, reveal that the protein triggers normal cells lining the colon to change into a state that helps colon cancer to spread. We knew levels of this protein are elevated in colon cancer. Now we've shown what PLAC8 could be doing - causing the cells to transition to a state that allows them to spread." Vanderbilt is also where senior author Robert Coffey, the Ingram Professor of Cancer Research, and his group have been developing ways of growing colon cancer cells in three dimensions instead of the more conventional two-dimensional flat dish culture. **When they managed to get the colon cancer cells to grow in three dimensions, the group found they grew into one of two shapes: either hollow balls or spiky clumps with the spiky bits protruding into their surroundings.** Then, upon injecting these two types of colon cancer cells into mice, they found the spiky clumps formed tumors that spread more rapidly. When the team compared the genetic signatures of the two types of three-dimensional cancer cells, they found the spiky clumps, which formed the more aggressive tumors, had very much higher levels of expression of PLAC8. This is where the zebrafish come in. They are an ideal lab model - for instance they are versatile, small and easy to breed - for studying many of the biological processes that are common across vertebrate species. In this case, the team used them to study PLAC8 to see exactly how it influences different types of tissue and cells, as Prof. Solnica-Krezel explains: "We looked at this protein in zebrafish and saw that it was also expressed in the gut. In normal zebrafish, PLAC8 is present on the inner lining of the gut. We also noticed PLAC8 is heavily expressed in the early embryos of zebrafish." The team also found that when there is too much PLAC8, the zebrafish embryos develop abnormally - the cells move more slowly resulting in abnormal body shapes and other defects.

http://www.medicalnewstoday.com/releases/271908.php

9. What Keeps Tumour Cells in Place (Mar.25/14)

Researchers at the University of Freiburg have found switches that colorectal cancer cells use to migrate away from the primary tumor site and to invade neighboring tissue. This migration is the first step in metastasis, the process by which the cancer forms secondary tumors in other organs. The researchers hope to develop new diagnostic and therapeutic approaches for colorectal cancer on the basis of the newly discovered signaling events. Colorectal cancer is one of the most common forms of cancer worldwide. Principally, tumors in the intestine can be removed and initially the disease poses a limited threat. This changes dramatically when the tumor cells begin to spread beyond the gut and migrate via blood vessels into further tissues to form metastases. These secondary tumors are often difficult to find and to remove and can lead to organ failure or even death. In order to prevent a tumor from forming these dangerous metastases, it is necessary to understand how cancer cells manage to break the chains that hold normal cells in place in the body. Proteins on the surface of healthy intestinal cells, so-called ephrin receptors, are responsible for instructing specific cell types like secretory cells or stem cells which position to occupy in the tissue. They perform this task when activated through contact with adjacent cells. The ephrin receptors thereby inform cells about their neighborhood: Depending on whether the neighborhood suits the cell, it stays or moves on. In cancer cells, it is known that ephrin receptors control a signaling pathway that prevents the cells from going astray. In order to break free from the primary tumor cell mass, the tumor cells shut down the production of the receptors, particularly that of the proteins ***EPHB2*** and ***EPHB3***. How they do this was previously unclear. The researchers found DNA regions in the ephrin receptor genes that regulate the amount of EPHB2 and EPHB3 on cells. These so-called enhancers are switched off in intestinal tumor cells that form metastases. One of the causes is an error in regulatory networks of tumor cells involving the protein Notch. The researchers also showed that the Notch signaling pathway is deactivated in tumors that have a poor prognosis. Determining whether the Notch signaling pathway and EPHB regulation are intact provides an indication as to how dangerous the tumor might be and could thus help doctors to make a more precise diagnosis.

Jagle, S, et al., Silencing of the EPHB3 tumor-suppressor gene in human colorectal cancer through decommissioning of a transcriptional enhancer. **Proceedings of the National Academy of Sciences*, 2014; DOI*: *10.1073/pnas.1314523111***

10. NCCN: Test All Colorectal Cancers For Lynch Syndrome (Mar.14/14)

The National Comprehensive Cancer Network (NCCN) now recommends that patients with colorectal cancer (CRC) be tested for Lynch syndrome. The syndrome is the most common inherited form of CRC, accounting for 2% to 4% of all cases. This translates to roughly 1 of every 35 CRCs. The universal testing recommendation includes an optional age-related consideration: for CRC patients younger than 70 years, test everyone; for CRC patients 70 years and older, test only those who meet the Bethesda criteria. The NCCN is housing this new recommendation in the Genetic/Familial High-Risk Assessment: Colorectal Cancer guideline. The guidance was formerly part of the Colorectal Screening Guideline. The primary way to detect Lynch syndrome in CRC tissue that is either biopsied or surgically resected is with immunohistochemistry (IHC) or microsatellite instability (MSI) testing. The new guideline says that genetics counseling "is not required prior to *routine* tumor [tissue] testing" at a center. If there is no tumor tissue available, certain patients can undergo genetics testing. In such cases, pretest counseling should be performed by a professional genetics counselor. Tumor testing is a win for CRC patients; there is virtually no downside. The outstanding risk is for insurance discrimination. A 2008 federal law prohibits employment and healthcare insurance discrimination on the basis of genetic information. Still, this law, known as the Genetic Information Nondiscrimination Act, does not cover life insurance discrimination. This is one of the reasons that counseling is advised when a person who has an immediate relative with Lynch syndrome considers undergoing genetic testing.

http://www.medscape.com/viewarticle/821981

11. Researchers Discover Involvement of Common Gut Bacterium in CRC (Apr.2/14)

New evidence that a common gut bacterium is involved in bowel cancer has been discovered by researchers from the Department of Physiology and Medical Physics in RCSI (Royal College of Surgeons in Ireland). The HRB funded research, led by Dr David Hughes at the Department of Physiology and Medical Physics, RCSI found a significantly increased presence of a common microbe Fusobacterium nucleatum (*Fn*) in tissue and stool samples of patients with colorectal cancers and colorectal benign tumours. Additionally Fn infection levels were related with benign tumour progression from early to advanced stages and the transition from a benign tumour to cancer. Commenting on the research, Dr David Hughes, said “Our research found that cancer patients with low bacterial levels had significantly longer survival times than patients with moderate and high levels of the bacterium. Also, for patients with

a benign tumour, we found that the presence of *Fn* may be a risk factor for disease progression from tumour to cancer. This is a significant finding because it highlights the potential of Fn detection as a possible indicator of colorectal cancers." The research highlights that screening for *Fn* levels may be used as a new bowel cancer detection method or to further inform existing screening strategies. Efforts to combat Fn infection could be considered for colorectal cancer patients with high levels of the bacterium to improve the survival prospects for these patients. For patients with benign tumours, *Fn* levels may be used to classify the tumours that may have a higher risk of disease progression to colorectal cancers with implications for increasing follow-up and at the possible use of anti-microbial treatments. Dr Hughes continued "Potentially, any impact of *Fn* infection on benign tumour development and progression to more serious stages will be considerable, because 95% of all bowel cancers arise from benign tumours, but only a small number of them become cancerous. Currently, there are no reliable predictive markers of whether a benign tumour will advance to cancer."

http://www.rcsi.ie/index.jsp?n=110&p=100&a=4457

NUTRITION & HEALTHY LIFESTYLE

12. Obesity Primes the Colon For Cancer (Apr. 2/14)

Obesity, rather than diet, causes changes in the colon that may lead to colorectal cancer, according to a study in mice by the National Institutes of Health. The finding bolsters the recommendation that calorie control and frequent exercise are not only key to a healthy lifestyle, but a strategy to lower the risk for colon cancer, the second leading cause of cancer-related death in the United States. A large body of scientific literature says people who are obese are predisposed to a number of cancers, particularly colorectal cancer. To better understand the processes behind this link, investigators fed two groups of mice a diet in which 60 percent of the calories came from lard. The first group of mice contained a human version of a gene called NAG-1, which has been shown to protect against colon cancer in other rodent studies. The second group lacked the NAG-1 gene. The NAG-1 mice did not gain weight after eating the high-fat diet, while mice that lacked the NAG-1 gene grew plump. The researchers noticed another striking difference between the two groups of animals. "The obese mice exhibited molecular signals in their gut that led to the progression of cancer, but the NAG-1 mice didn't have those same indicators," Eling said. The researchers looked for molecular clues, by isolating cells from the colons of the mice and analyzing a group of proteins called histones. Histones package and organize DNA in a cell's nucleus, and sometimes undergo a process known as acetylation, in which chemical tags bind to their surface. The pattern of acetylation varies depending on the chemical processes taking place in the cell. Wade explained that the acetylation patterns for the obese mice and the thin NAG-1 mice were drastically different. Patterns from the obese mice resembled those from mice with colorectal cancer. The additional weight they carried also seemed to activate more genes that are associated with colorectal cancer progression, suggesting the obese mice are predisposed to colon cancer. "Any preexisting colon lesions in these animals are more likely to evolve rapidly into malignant tumors," Wade said. "The same thing may happen in humans." Wade and Eling want to find out exactly how obesity prompts the body to develop colorectal cancer. Wade said that the likely candidates for triggering tumor growth in the colon are fat cells, but there are many more possibilities. Finding these cellular switches may give rise to production of medications to keep people from getting colorectal cancer. "Once we identify the signaling pathways and understand how the signal is transduced, we may be able to design ways to treat colorectal cancer in obese patients," Wade said.

Wade, PA. et al., Obesity, rather than diet, drives epigenomic alterations in colonic epithelium resembling cancer progression. Cell Metab; doi:10.1016/j.cmet.2014.03.012 [Online 1 April 2014].

13. Scientists Find Key Steps Linking Dietary Fats And Colon Cancer Tumor Growth (Apr. 24/14)

Scientists have shown new genetic evidence that could strengthen the link between the role of dietary fats and colon cancer progression. The study, led by Arizona State University researcher and physician Raymond DuBois, has identified a molecular culprit, called peroxisome proliferator-activated receptor delta (PPAR delta), which, when deleted in a mouse model of colon cancer, stopped key steps required for the initiation and progression of tumor growth. "This study has shown without a doubt there is a new function for a key molecule, **PPAR delta**, in the initiation and progression of colon cancer," said DuBois, executive director of ASU's Biodesign Institute. "These results also provide a new rationale for developing therapeutics that could block PPAR delta to treat inflammatory bowel disease and colorectal cancer." The DuBois research team has been in pursuit of uncovering the links between inflammation and colon cancer for the past two decades. Colorectal cancer is the second leading cause of cancer deaths in the U.S. Evidence for this link comes from data showing that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) reduced the risk of developing colorectal cancer by 40-50 percent. NSAIDs target an enzyme called cyclooxygenase 2 (COX-2), which carries out steps to produce the pro-inflammatory molecule prostaglandin E2 (PGE2), found at high levels in colorectal tumors. DuBois' research team has long sought to uncover the key molecular steps regulating the COX-2/PGE2 pathway. According to the Centers for Disease Control and Prevention, dietary components high in saturated fats such as red meat are thought to be risk factors for colon cancer. Other known epidemiological risk factors are family

history, inflammatory bowel disease, smoking and type-2 diabetes. The cell's garbage pail for dietary fat is called the peroxisome. PPARs are central players in regulating the breakdown and storage of fats within a cell, and the DuBois team wanted to investigate the role one molecule, called PPAR delta, had on chronic inflammation and colorectal cancer progression. In a mouse model of colon cancer, the team "knocked out" the gene to make PPAR and found that the mice showed no clinical or cellular signs of chronic inflammation. Furthermore, when looking at the immune response, they found none of the usual immune cells associated with inflammation. They also measured the levels of COX-2 and found that loss of PPAR had no effect on COX-2 expression. They found that PPAR required for induction of COX-2 expression and high levels of PGE2 production that are associated with inflammation and colon cancer. "We found that both PPAR and COX-2-derived PGE2 signaling coordinately promote tumorigenesis. This is likely to be clinically relevant because the elevation of both PPAR delta and COX-2 in tumor tissues correlates with poor prognosis in colorectal cancer patients," said DuBois. "This provides us with an important new clue in designing and developing a therapeutic arsenal to stop the initiation and progression of colon cancer."

https://asunews.asu.edu/20140421-dietary-fats-colon-cancer-study

14. Vitamin D May Increase Survival Rates For those with Breast and Colon Cancer (Apr.29)

Cancer patients who have higher levels of vitamin D when they are diagnosed tend to have better survival rates and remain in remission longer than patients who are vitamin D-deficient, according to a new study published. The body naturally produces vitamin D after exposure to sunlight and absorbs it from certain foods. In addition to helping the body absorb the calcium and phosphorus needed for healthy bones, vitamin D affects a variety of biological processes by binding to a protein called a vitamin D receptor. This receptor is present in nearly every cell in the body. "By reviewing studies that collectively examined vitamin D levels in 17,332 cancer patients, our analysis demonstrated that vitamin D levels are linked to better outcomes in several types of cancer," said one of the study's authors, Hui Wang, MD, PhD, Professor of the Institute for Nutritional Sciences at the Shanghai Institutes for Biological Sciences at the Chinese Academy of Sciences in Shanghai, China. "The results suggest vitamin D may influence the prognosis for people with breast cancer, colorectal cancer and lymphoma, in particular." The meta-analysis looked at the results of 25 separate studies that measured vitamin D levels in cancer patients at the time of diagnosis and tracked survival rates. In most of the research, patients had their vitamin D levels tested before they underwent any treatment for cancer. The study found a 10 nmol/L increase in vitamin D levels was tied to a 4 percent increase in survival among people with cancer. Researchers found the strongest link between vitamin D levels and survival in breast cancer, lymphoma and colorectal cancer. There was less evidence of a connection in people with lung cancer, gastric cancer, prostate cancer, leukemia, melanoma or Merkel cell carcinoma, but the available data were positive. "Considering that vitamin D deficiency is a widespread issue all over the world, it is important to ensure that everyone has sufficient levels of this important nutrient," Wang said. "Physicians need to pay close attention to vitamin D levels in people who have been diagnosed with cancer."

Hui Wang.et al., Review:The Impacts of Circulating 25-Hydroxyvitamin D Levels on Cancer Patient Outcomes: A Systematic Review and Meta-Analysis. **The Journal of Clinical Endocrinology & Metabolism*, 2014; jc.2013-4320 DOI*:** *10.1210/jc.2013-4320*