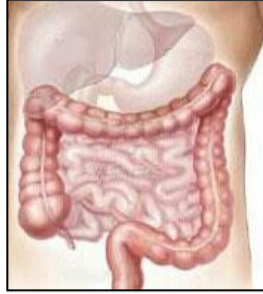


COLORECTAL CANCER RESEARCH Month Ending August 19th, 2011



The following colorectal cancer research update extends from July 18th, 2011 – August 19th, 2011 inclusive and is intended for informational purposes only.

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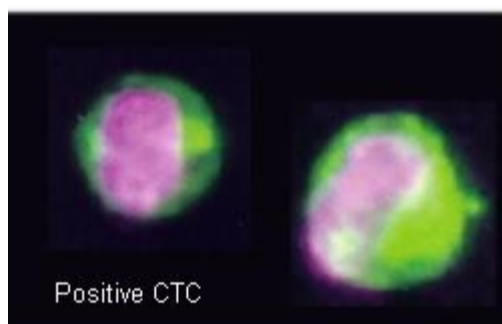
1. Intermittent vs. Continuous Oxaliplatin and 5FU Combination Chemo for First Line Treatment of Advanced Colorectal Cancer (Jul. 18/11)

According to the authors of this study, when cure is impossible, cancer treatment should focus on both length and quality of life. Maximization of time without toxic effects could be one effective strategy to achieve both of these goals. The COIN trial assessed preplanned treatment holidays in advanced colorectal cancer to achieve this aim. COIN was a randomized controlled trial in patients with previously untreated advanced colorectal cancer. Patients received either continuous oxaliplatin and 5FU combination (arm A), continuous chemotherapy plus cetuximab (arm B), or intermittent (arm C) chemotherapy. In arms A and B, treatment continued until development of progressive disease, cumulative toxic effects, or the patient chose to stop. In arm C, patients who had not progressed at their 12-week scan started a chemotherapy-free interval until evidence of disease progression, when the same treatment was restarted. Investigators compared arms A and C, with the primary objective of establishing whether overall survival on intermittent therapy was non-inferior to that on continuous therapy. After analyzing the results, investigators concluded that chemotherapy-free intervals remain a treatment option for some patients with advanced colorectal cancer, offering reduced time on chemotherapy, reduced cumulative toxic effects, and improved quality of life. Subgroup analyses suggest that patients with normal baseline platelet counts could gain the benefits of intermittent chemotherapy without detriment in survival, whereas those with raised baseline platelet counts have impaired survival and quality of life with intermittent chemotherapy and should not receive a treatment break.

Adams, RA, et al., Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first line treatment of advanced colorectal cancer: results of the randomized phase 3 mrc coin trial. Lancet Oncol. 2011 Jul 1; 12(7): 642-653.

2. Blood Test Can Help With Oncology Treatment (Jul. 20/11)

Oncology clinicians are testing a new tool to help determine patients' response to treatment, evaluate prognosis and make better-informed decisions — **The CellSearch Circulating Tumor Cell Test**. The data to date that's been presented indicates changes in CTC count can predict overall survival and the patient's response to a particular treatment. CellSearch CTC from Veridex, a Johnson & Johnson Co., is a blood test that captures and counts circulating tumor cells, which are cells that have detached from the tumor and are traveling in the bloodstream. It is the only CTC test cleared by the U.S. Food and Drug Administration for use with breast, prostate and colorectal cancers. The CellSearch assay detects certain cell markers expressed by tumors of epithelial cell origin, called adenocarcinomas. A blood sample drawn from the patient is treated in the laboratory with a CellSearch kit. Tiny, protein-coated magnetic balls mark the cancer cells, which are then stained with fluorescent markers. A magnetic field is applied, forcing magnetically marked cells to move to the surface where they are analyzed, counted and verified by a pathologist.



Source: http://www.pathology.ucla.edu/news/item?item_id=66729

The test is capable of detecting one circulating tumor cell among approximately 40 billion blood cells. The greater number of cells present, the worse the prognosis. In metastatic breast or prostate cancer, fewer than five circulating cancer cells predicts better survival than a count of five or more. In colorectal cancer, three is the cutoff point. Physicians may use the CellSearch CTC test as an independent predictor of survival. The test also may be used as an adjunct to other tests and imaging studies. CTC counts can predict treatment response earlier than imaging studies or prostate-specific antigen levels. Providers may begin checking for CTC at diagnosis and retest as early as following the first round of chemotherapy to monitor changes in prognosis. In the beginning, oncologists were utilizing it for patients who were on chemotherapy for a while, through a second or possibly a third regimen, to see the effectiveness of the therapy. Now it appears to be more readily utilized on just about everybody from the beginning, on patients who have never been treated, to see where the circulating tumor cells are, as noted by an RN at Florida Cancer Specialists. When oncologists at Florida Cancer Specialists start noting higher levels of circulating tumor cells, they may re-evaluate the therapeutic regimen and try a different approach. On the other hand, if the circulating tumor cell counts are declining, it indicates the therapy is effective.

3. Phase III Trial Involving Perifosine Completes Patient Enrollment (Jul. 27/11)

Aeterna Zentaris Inc. announced the completion of patient recruitment for the ongoing Phase 3 trial with **perifosine** in refractory advanced colorectal cancer (colorectal cancer patients who have exhausted standard treatments). The trial, involving over 430 patients, is being conducted pursuant to a Special Protocol Assessment (SPA) with the Food and Drug Administration (FDA) and with Fast Track Designation. It is sponsored by Keryx Biopharmaceuticals, Inc., (Keryx), Aeterna Zentaris' licensee for perifosine in North America. Perifosine is a novel, potentially first-in-class, oral anticancer drug candidate that inhibits Akt activation in the phosphoinositide 3-kinase (PI3K) pathway. For more information about perifosine, please see below. The Phase 3 trial, entitled the "X-PECT" (**X**eloda[®] + **P**erifosine **E**valuation in **C**olorectal cancer **T**reatment) trial, is a randomized (1:1), double-blind trial comparing the efficacy and safety of perifosine + capecitabine vs. placebo + capecitabine in over 430 patients with refractory advanced colorectal cancer. Patients must have failed available therapy including 5-fluorouracil (5-FU), oxaliplatin (Eloxatin[®]), irinotecan, bevacizumab (Avastin[®]) and, if KRAS wild-type, failed prior therapy with cetuximab (Erbix[®]) and/or panitumumab (Vectibix[®]). The primary endpoint is overall survival, with secondary endpoints including overall response rate (complete + partial responses), progression-free survival and safety.

Perifosine: Perifosine is a novel, oral anticancer treatment that inhibits Akt activation in the phosphoinositide 3-kinase (PI3K) pathway. The product works by interfering with membranes of cancer cells thereby inhibiting Akt signaling which then affects cell death, growth, differentiation and survival. Perifosine, in combination with chemotherapeutic agents, is currently being studied for the treatment of multiple myeloma, colorectal cancer and other cancers, and is the most advanced anticancer agent of its class. Perifosine, as monotherapy, is being explored in other indications. The FDA has granted perifosine orphan-drug designation in multiple myeloma and neuroblastoma, and Fast Track designations in both multiple myeloma and refractory advanced colorectal cancer. Additionally, an agreement was reached with the FDA to conduct the Phase 3 trials in both of these indications under a Special Protocol Assessment. Perifosine has also been granted orphan medicinal product designation from the European Medicines Agency (EMA) in multiple myeloma. Furthermore, perifosine has received positive Scientific Advice from the EMA for both the multiple myeloma and advanced colorectal cancer programs, with ongoing Phase 3 trials for these indications expected to be sufficient for registration in Europe. Perifosine rights have been licensed to Keryx for North America, to Yakult Honsha for Japan and to Handok for Korea.

<http://www.abc12.com/story/15155496/aeterna-zentaris-announces-completion-of-patient-recruitment-for-phase-3-trial-with-perifosine-in-refractory-advanced-colorectal-cancer>

4. TAS-102 May Be Promising for Treatment of Advanced Colorectal Cancer (July 26/11)

A phase II clinical trial in Japan showed improved survival time for TAS-102 when compared to a placebo in patients whose cancer had progressed on standard treatments. Median survival was 9 months for patients who received oral TAS-102 compared to 6.6 months on placebo. Taiho Pharmaceutical says that they are proceeding with a larger Phase III trial. In a randomized, double-blinded clinical trial 172 patients received either TAS-102 (114 patients) or a placebo (58 patients.) All had previously had at least two other regimens that included a fluoropyrimidine, irinotecan, and oxaliplatin. The trial was conducted in 20 medical institutions in Japan between August 2009 and April 2010. Results were reported as an abstract at the 9th Annual Meeting of the Japanese Society of Medical Oncology held in Yokohama on July 21, 2011. Grade 3 or higher side effects reported in more than 10% of patients were limited to neutropenia (low white blood cell counts). While early results from a Phase II trial in Japan show promise for a new treatment with a drug called TAS-102, it is too soon to make any conclusions about its value. The trial was done in patients with *refractory* colorectal cancer. They had already had at least two different treatment regimens including 5-FU or Xeloda, oxaliplatin, and irinotecan. There is no information about whether they had received Avastin, Erbix, or Vectibix. Compared to no chemotherapy at all, a placebo, there was an improvement of about two and a half months in survival time. There was also serious neutropenia or low white blood cell counts. Some patients, less than 1 in 10, also had serious nausea, diarrhea, and fatigue. It is important to wait for the results of a randomized Phase III clinical trial including more specific information about survival time and side effects before evaluating the drug.

<http://www.taiho.co.jp/english/news/20110722.html>

5. Hand Foot Syndrome Indicative of Xeloda Effectiveness (Aug. 11/11)

Developing tender swelling or rash on the hands and feet may actually be good news for patients being treated with Xeloda[®] (capecitabine). During a recent clinical trial, colorectal cancer patients with hand-foot syndrome lived longer, and it took longer for their cancer to get worse. Researchers comparing two Xeloda-based chemotherapies for people with advanced colorectal cancer, studied skin side effects from

both Xeloda and Erbitux® (cetuximab). They found that about a third of patients experienced at least some hand-foot syndrome, and these patients lived almost 10 months longer than patients without skin changes. As part of a Phase II clinical trial, the German AIO Colorectal Study Group randomized 185 patients in 35 cancer centers across Germany to receive either CAPOX-C (capecitabine, oxaliplatin, and cetuximab) or CAPIRI-C (capecitabine, irinotecan, and cetuximab). Their primary goal was to see if there was a difference in objective response rate — the percentage of complete and partial tumor shrinkage. They also looked at time to cancer progression, overall survival time, safety, and side effects. In studying side effects, they analyzed skin toxicity known to be associated with capecitabine: hand-foot syndrome and nail changes. Hand-foot syndrome or palmar-plantar erythrodysesthesia (PPE) ranges from mild redness and swelling on the palms of the hands and soles of the feet to severe and painful cracking and sores that can interfere with walking or using hands and fingers. It appears to get worse with heat and friction.



Source: <http://www.handresearch.com/news/cancer-patient-no-fingerprints-hand-foot-syndrome.htm>

Patients are told to avoid hot water and aerobic exercise like running and jumping. Using hand tools can also create friction and make hand-foot syndrome worse. Comparing patients with no capecitabine-related skin toxicity (grade 0) with those with mild to severe symptoms (grades 1 to 3):

- 32.2% of all patients had some skin toxicity: 31% had hand-foot syndrome, 8% had nail changes. Only 2% had nail changes without hand-foot syndrome as well.
- Patients with skin toxicity had longer time before cancer got worse (*progression-free survival*): median 9.9 months vs. 5.6 months.
- Skin toxicity also meant longer median survival time (*overall survival*): 32.8 months vs. 22.4 months.
- Disease control (complete or partial tumor shrinkage or stable disease) was greater in those with skin changes: 97.9% vs 86.1%.
- Dose reductions were necessary more often in patients with skin toxicity: 45.1% required them compared to 29.3% without skin changes.

There were more skin problems in the CAPOX regimen (39.4%) than the CAPIRI plan (25.6%), although the research team attributes this to a higher dose of capecitabine used with CAPOX. Hand-foot syndrome began to be diagnosed after a median of three treatment cycles and reached its maximum at five cycles. The research team concluded: *In the setting of first-line chemotherapy with CAPIRI with cetuximab or CAPOX with cetuximab, capecitabine skin toxicity appears to be an early indicator of treatment efficacy. Capecitabine-induced skin toxicity is predictive for a longer progression-free survival and overall survival. The percentage of hand-foot syndrome is associated with higher dosing, so that patients not showing any HFS might be treated with higher doses.*

Stintzing, S, et al., Correlation of capecitabine-induced skin toxicity with treatment efficacy in patients with metastatic colorectal cancer: results from the German AIO KRK-0104 trial. British J of Cancer (2011) 105, 206-211.

6. Oxaliplatin Not Helpful in Neoadjuvant Therapy for Rectal Cancer (Aug. 17/11)

This study sought to investigate oxaliplatin combined with fluorouracil-based chemoradiotherapy as preoperative treatment for locally advanced rectal cancer. Seven hundred forty-seven patients with resectable, locally advanced adenocarcinoma of the mid-low rectum were randomly assigned to receive pelvic radiation and concomitant infused fluorouracil (5FU) either alone or combined with oxaliplatin. Overall survival was the primary end point to be measured. Investigators noted that grade 3 to 4 adverse events during preoperative treatment were more frequent with oxaliplatin plus fluorouracil and radiation than with radiation and fluorouracil alone (24% v 8% of treated patients). In arm B, 83% of the patients treated with oxaliplatin had five or more weekly administrations. Ninety-six percent versus 95% of patients underwent surgery with similar rates of abdominoperineal resections (20% v 18%, arm A v arm B). The rate of pathologic complete responses was 16% in both arms. Twenty-six percent versus 29% of patients had pathologically positive lymph nodes (arm A v arm B), 46% versus 44% had tumor infiltration beyond the muscularis propria, and 7% versus 4% had positive circumferential resection margins. Intra-abdominal metastases were found at surgery in 2.9% versus 0.5% of patients (arm A v arm B).

Investigators concluded that adding oxaliplatin to fluorouracil-based preoperative chemoradiotherapy significantly increases toxicity without affecting primary tumor response. Longer follow-up is needed though to assess the impact on efficacy end points.

Aschele, C, et al., Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. *J Clin Oncol.* 2011 Jul 10; 29(20): 2773-2780.

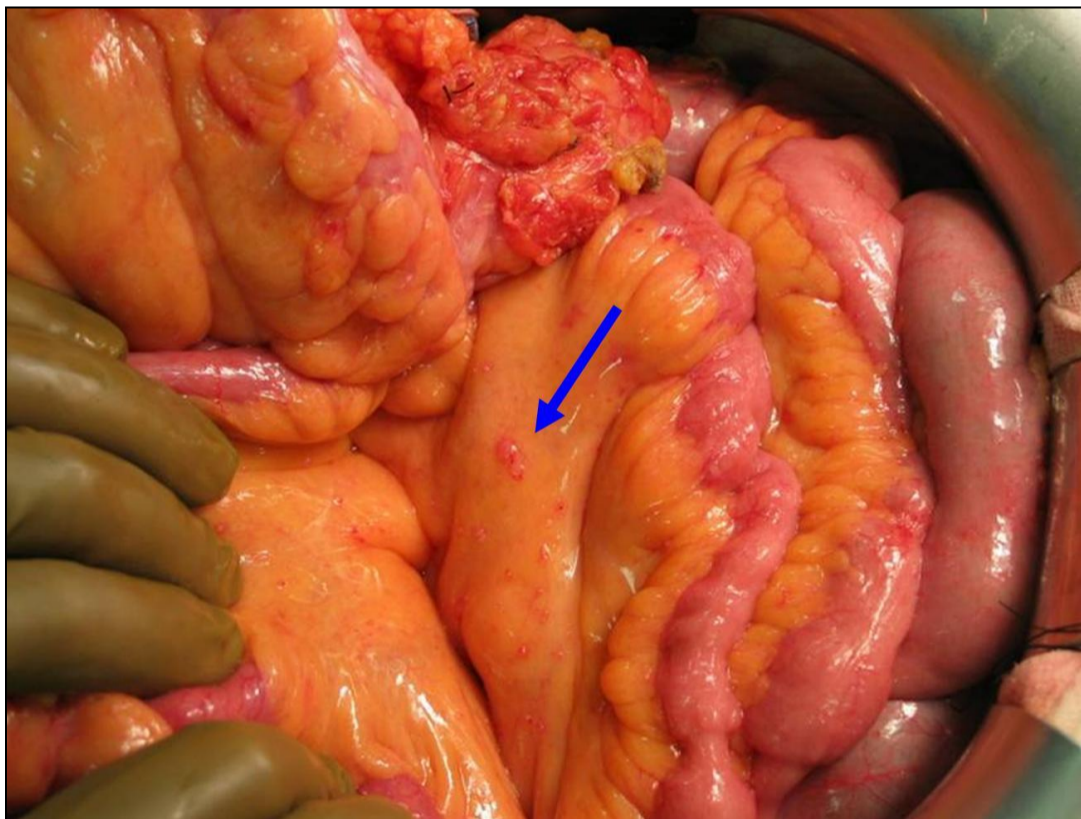
SURGICAL THERAPIES

7. The Elderly May Also Qualify for Peritoneal Carcinomatosis Surgery

(Aug.11/11)

According to the results of this study, old age alone should not be a barrier to surgery for colorectal cancer patients with peritoneal carcinomatosis (see below for explanation), experts say, after finding an acceptable safety profile in selected elderly patients. Of 24 patients aged 70 years and older who underwent cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy (PIC), none died during the surgery, Australian and Dutch surgeons report. Furthermore, the median duration of post-operative survival (35 months) appeared to be comparable with results in younger patients, they wrote, although median follow-up was only 10 months to date (range: 1-52 months). The authors concluded that CRS and PIC “should not be withheld for elderly patients in whom a potential to prolong a good quality of life is to be expected”. Their study included patients from St George Hospital in Sydney and Catharina Hospital in the Netherlands, and surgery was carried out by specialized surgical teams. Patients were a highly selected group, who were considered fit for major surgery and did not have any absolute contraindications for general anaesthetics. The authors wrote that while many surgeons were currently reluctant to offer CRS and PIC to patients over 70s, their finding that it could be done safely was consistent with results from other surgical studies. CRS and PIC couples extensive abdominal surgery with blasts of heated chemotherapy to the abdominal cavity and its organs for patients whose colorectal cancer has spread to the peritoneum: the lining of the abdomen. The benefit of adding heated chemo: it has long been known that cancerous cells are unable to withstand as much heat as healthy cells and putting the chemotherapy on top of tumors should be more effective than systemically delivering it through the bloodstream.

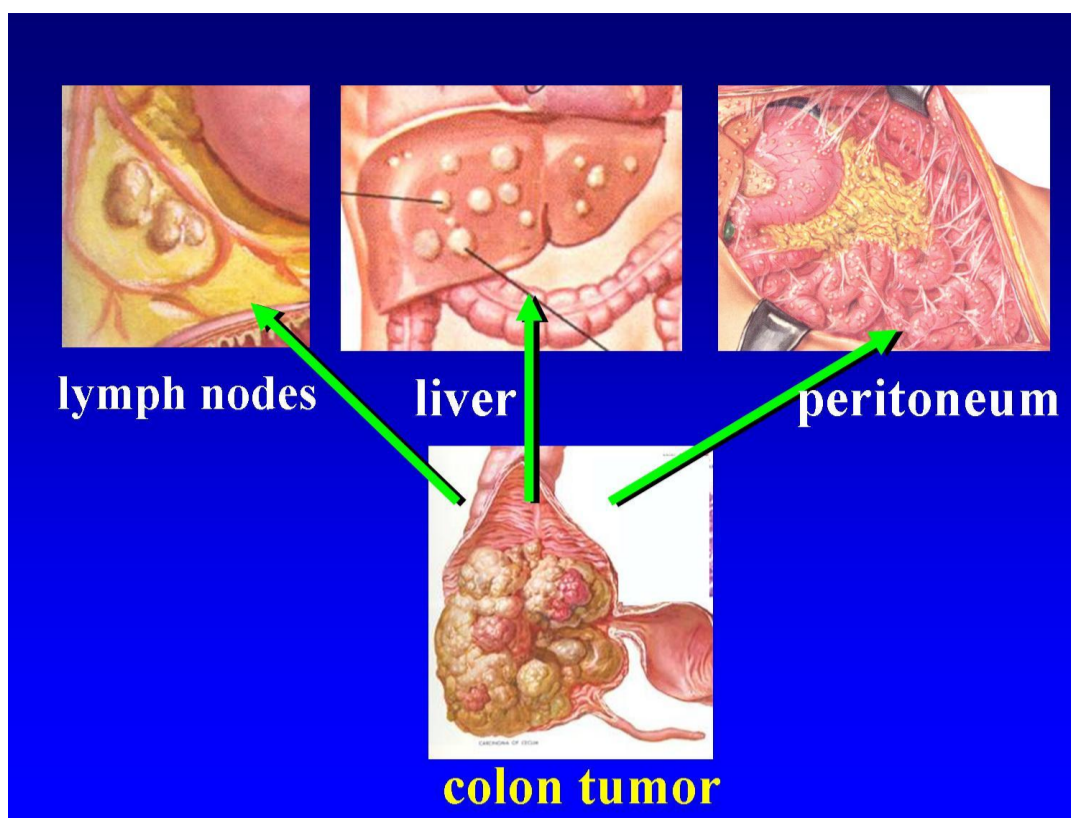
The peritoneum is a glistening membrane which covers all abdominal organs. It secretes the peritoneal fluid, which enables the bowels to move smoothly during the propagation of food. Its surface is as large as the skin surface, 2 square meters. Peritoneal carcinomatosis means the widespread presence of cancer cells on the peritoneum. Below you can see the small bowel, covered by the glistening peritoneum, with several small pink implants of cancer cells (blue arrow).



Source: <http://www.drmulier.com/3%20en%20pat%20info%20hipec.html>

Tumors of the large bowel (colon) can spread (seed) in three ways (see image below):

- via the lymphatic vessels to the lymph nodes
- via the blood vessels to other organs such as to the liver or the lungs
- via the abdominal cavity to the peritoneum



Source: <http://www.drmulier.com/3%20en%20pat%20info%20hipec.html>

Klaver, Yvonne, et al., *Outcomes of elderly patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy for colorectal cancer peritoneal carcinomatosis.* *J of Surg Oncology.* DOI: 10.1002.js0.22019.

SCREENING

8. Screening Tumors for Lynch Syndrome is Cost Effective (Jul. 21/11)

Screening all new colon and rectal cancer tumors for markers that might indicate Lynch syndrome not only saves future lives, it is cost effective according to a new study. In order for tumor screening to be cost-effective, not only should new tumors be tested, but family members need to follow through with genetic testing after a new Lynch mutation is found. Finally people with Lynch syndrome mutations need to follow surveillance guidelines to prevent cancer or find it early. Testing both tumors and at least three to four family members could cost as little of \$36,000 per life year saved — well within the value of preventive health strategies. Researchers used a computer model to predict costs of testing tumors using several strategies, upper age limits, and assumptions about family members following up with genetic testing. In order to fall beneath the \$50,000 per life year saved threshold for cost-effectiveness, three to four family members needed to follow up with DNA testing for an identified Lynch syndrome mutation. Women with Lynch syndrome could improve their life expectancy by about four years if they had their uterus and ovaries removed and followed the colorectal cancer surveillance guidelines, the study found. The researcher team said that the ideal testing strategy was for pathologists to:

1. Use immunohistochemistry (IHC) tumor tests to look for missing protein expression related to Lynch syndrome (MLH1, MSH2, MSH6, PMS2).
2. If IHC is positive, followup with tumor tests for a BRAF V600E mutation. (Inherited Lynch mutations don't have BRAF mutations.)
3. If IHC is positive and BRAF is negative, do DNA blood tests for an inherited germline Lynch syndrome mutation.

Once an individual is identified with an inherited Lynch syndrome mutation, it is critical to inform close family members — siblings, children, and parents — of their own potential risk. Since Lynch syndrome is passed directly from parent to child (autosomal dominant), children of an affected parent have a 50-50 chance of inheriting the gene. When they know they are at risk, family members should also have DNA testing. However, they only need to be tested for the gene discovered in their family — a much less expensive process. Genetic counseling after their test can help them understand what the test results mean and, if positive, what steps they can take to protect themselves against cancer. Study principal investigator, Uri Ladabaum, M.D., from Stanford University, said:

A systematic approach to identify families with Lynch syndrome makes sense clinically, because it can save lives, and economically, because its costs are comparable to other things we choose to spend our health-care dollars on. We advocate establishing similar tumor-screening systems on a national level.

The study team, led by Dr. Ladabaum, included members from Stanford, University of California, Baylor University, and Memorial Sloan Kettering Cancer Center. They concluded,

Widespread colorectal tumor testing to identify families with the Lynch syndrome could yield substantial benefits at acceptable costs, particularly for women with a mutation associated with the Lynch syndrome who begin regular screening and have risk-reducing surgery. The cost-effectiveness of such testing depends on the participation rate among relatives at risk for the Lynch syndrome.

Although family history can help identify individuals and families that may carry a Lynch syndrome mutation, it is not foolproof. About half of families with mutations don't meet the criteria and another half who do have histories that meet Amsterdam criteria don't have one of the identified Lynch mutations. In an editorial accompanying the study report in *Annals of Internal Medicine*, Dr. Randall Burt from the University of Utah and the Huntsman Cancer Center points out:

The Amsterdam criteria were developed to identify persons and families who are likely to have the syndrome. The criteria include the following:

- *3 relatives in a family must have colorectal cancer, and 2 of them must be first-degree relatives of the third;*
- *at least 2 generations must be affected;*
- *and 1 of the cases must be diagnosed at an age younger than 50 years.*

These criteria have been successfully used to identify families with the Lynch syndrome but have also proven to be insensitive. At least 50% of families with the condition do not meet the criteria. About one half of families meeting the criteria will have a disease-causing mutation in one of the mismatch repair genes (MLH1, MSH2, MSH6, or PMS2).

This study looked at how costly a testing strategy to identify people with Lynch syndrome was for a large population. The cost isn't for one individual or one family, but for everyone in a national health care system. However, it does support the idea that people who have surgery for colon or rectal cancer should have simple, inexpensive tests done on their tumor tissue to see if they *might have* Lynch syndrome. This is not a definitive test for Lynch syndrome. It will also be positive for people who don't have Lynch, but it will also screen and find those who do. About 15 out of 100 people with colon or rectal cancer will have tumors that *suggest* Lynch syndrome, but only 3 to 5 of them will actually carry a Lynch mutation. Many of these people with Lynch mutations *won't have strong family cancer histories*, so tumor testing is the only way the syndrome would be uncovered. If you have had surgery to remove a colon or rectal tumor, check with your doctor to see if testing for *microsatellite instability (MSI)* has been done. It will be part of the pathology report from the surgical specimen. Many hospitals are now doing this test automatically after surgery at the same time they look for lymph nodes and other tumor information. If it wasn't done, you might wish to request it. The tumor block saved by the pathology department should still be available for the test. If testing does indicate you might carry a Lynch mutation, you'll want to talk to a genetic counselor about DNA testing to either confirm or rule out Lynch syndrome. The test can save your life by changing the way your cancer is followed up. And it can save the lives of your brothers, sisters, and children if they also have the mutation.

Ladabaum, Uri, et al., Strategies to identify the Lynch syndrome among patients with colorectal cancer. Annals of Internal Medicine. Vol. 155, Number 2, July 19, 2011.

9. Aggressive Bowel Preps Don't Improve Long Term Outcomes After Colon Surgery (Jul.22/11)

More evidence has emerged that strong laxatives before bowel surgery don't reduce complications after surgery, nor do they improve survival. Traditionally, doctors prescribed laxatives to completely remove all feces from the colon before surgery, a process known as mechanical bowel preparation (MBP). However, a study in Scotland that looked at 1,730 colon cancer surgeries performed between 2000 and 2005 found no differences in surgical complications 30 days after surgery whether patients got mechanical bowel preps or not. In addition, during 3 to 5 years of follow-up there was no difference in survival. A research team in the West of Scotland Cancer Surveillance Unit at the University of Glasgow looked at records for 1,730 patients who had surgery for colon cancer between 2000 and 2005. More than 8 out of 10 (84.4%) had mechanical bowel preparation before their operation. However, after a median follow-up period of 3.5 years, an analysis showed:

- There was no statistical difference in complications in the 30 days after surgery between the groups of patients who had mechanical bowel preparation and those who didn't.
- After adjustments for other factors that affect outcomes after colon surgery, mechanical bowel preparation had no impact on death from all causes.

G.A. Nicholson and his team concluded: *Neither postoperative complications nor long-term survival are improved by MBP before colonic cancer surgery.* A Cochrane Review updated in 2009 looked at 14 clinical trials including 4,921 patients. They showed: ". . .no statistically significant differences in how well the two groups of patients (mechanical bowel preparation group and the no preparation group) did after surgery in terms of leakage at the surgical join of the bowel, mortality rates, peritonitis, need for

reoperation, wound infection, and other non-abdominal complications. Consequently, there is no evidence that mechanical bowel preparation improves the outcome for patients.”

Comparing 13 randomized clinical trials where 2,390 patients had some form of mechanical bowel preparation and 2,387 didn't, the Cochrane Review found:

- Leakage at the place where the two pieces of intestine were joined (*anastomosis*) was 4.2% in patients with mechanical bowel preparation (MBP) and 3.4% in those without it.
- Surgical infections happened in 9.6% of patients with MBP and 8.3% of those who didn't have it.

The differences weren't statistically significant. In addition, the Cochrane Review summarized: “*Preoperative bowel preparation is time-consuming and expensive, unpleasant to the patients, and even dangerous on occasion (increased risk for inflammatory processes).*”

Nicholson, GA, et al., Mechanical bowel preparation does not influence outcomes following colonic cancer resection. British J of Surgery. Vol. 98, Issue 6: pp. 866-871.

10. Single Flexible Sigmoidoscopy Can Reduce Colorectal Cancer (Aug. 19/11)

According to the results of this study, a single flexible sigmoidoscopy screening between the ages of 55-64 years is linked with a reduced level of colorectal cancer (CRC) incidence and mortality.



Flexible Sigmoidoscope

Source: <http://www.edoctor.co.in/tag/flexible-sigmoidoscopy>

Several randomized controlled investigations have revealed that fecal occult blood testing (FOBT) in CRC screening of patients diagnosed with CRC can reduce the mortality rate. Observational studies and an earlier randomized trial from the U.K., known as SCORE, have shown a decrease in incidence and mortality for cancer in the rectum and sigmoid colon (distal CRC) among patients who had undergone endoscopy. Which suggests long-term protection against the development of distal CRC can be provided by the removal of adenomas at screening. To find out if the flexible sigmoidoscopy is a useful prevention method in CRC screening, the investigators in this study mailed a survey investigating subjects in FS screening to a random population sample of men and women who were aged between 55 and 64 years old. Responders who were interested and eligible were randomly designated to either the control group (N= 17148 - no further contact) or intervention group (N=17144 - invitation for flexible sigmoidoscopy). Flexible sigmoidoscopy was carried out on 9,991 subjects, of which, 9,387 (94.71%) were discharged, while 55 (0.55%) were referred for surgery, 395 for follow-up surveillance colonoscopy, and the 74 patients who remained did not comply with the recommended total colonoscopy evaluation. For CRC incidence, the median follow-up period was 10.5 years and 11.4 years for all-cause and CRC specific mortality. 557 people (including those detected at initial screening) were diagnosed with CRC and 148 people died of the disease during this period. The investigators discovered that CRC incidence and mortality were reduced by **18% and 22%** respectively. For those who were screened (per protocol analysis) CRC incidence was reduced by **31%, and 46%** for advanced CRC cases. In addition, CRC mortality was statistically significantly reduced by 38% in screened subjects in comparison to the control group. The researchers write that the reported discoveries, which are consistent with the observed reduction of CRC incidence and mortality among people screened in the recently published UK Flexible Sigmoidoscopy Screening Trial, support the theory that Flexible sigmoidoscopy screened offered only one time, represents a safe and effective method for CRC screening and ensures a long lasting reduction of CRC risk. A longer follow-up is necessary to fully evaluate the impact on mortality and to estimate the duration of the protective effect, according to the researchers.

Segnan, Nereo, et al., RESPONSE: Re: Baseline Findings of the Italian Multicenter Randomized Controlled Trial of “Once-Only Sigmoidoscopy”—SCORE. J National Cancer Institute. Vol. 95, Issue 14: pp. 1090.

11. Less Costly Process May Save Lives of Lynch Syndrome Patients (Aug. 18/11)

People who are at risk for a certain form of colon and other types of cancer may soon have a better chance at surviving or even avoiding the diseases. Scientists at the Intermountain Healthcare group used sophisticated computer modeling to develop a reliable and cost-effective way to identify patients who may have Lynch syndrome, an inherited cancer syndrome that occurs in people who carry a genetic mutation in one of the DNA mismatch repair genes. The mismatch repair (MMR) genes usually help to repair DNA damage that happens to all of us as a part of daily life. But patients who have genetic mutations in these genes have a substantially increased risk of developing **colon**, uterine, pancreatic and urologic cancers. For some patients, the lifetime risk approaches 80%. Being able to identify people who carry a gene change is profoundly important because earlier and more frequent screening - not just for colon cancer, but also for other cancers - could save their lives. It could also save the lives of relatives who have no idea that they may share the increased risk for cancer. A national report on colon cancer a few years ago recommended screening all patients with colon cancer for Lynch syndrome, but stopped short of outlining the best way to do it. There are many tests available that can be used in different combinations to diagnose Lynch syndrome, but there's little clarity about what's the most effective and efficient approach according to the investigators. Doing full genome sequencing on all colorectal cancer patients would uncover virtually all MMR mutations, but the majority of these patients don't have them. Sequencing costs \$4,000 to \$6,000 per person, so it would be incredibly costly and inefficient to test everyone. The Intermountain team set out to determine if they could develop a system for screening colon cancer patients with existing tests that could keep costs down, but also ensure accurate results. The team gathered information from a variety of sources, including Intermountain patient data, published literature and outside groups to define the best approach to screening. They came up with a plan that relies on two relatively inexpensive tests to eliminate possible Lynch patients before doing full genome sequencing. So far, 272 colon cancer patients have been screened according to the group's system, with 261 individuals ruled out as carriers of the abnormal genes. That left only 11 patients who they would recommend going forward with the full genome sequencing test. This represents the wisest use of the expensive resource of full sequencing. The benefits extend not only to the colon cancer patients, but also to members of their extended families, who may also have the MMR mutation. Confirming the Lynch diagnosis changes the way physicians treat the disease. This form of colon cancer has a generally better prognosis than sporadic colon cancer, but it doesn't respond as well to certain kinds of chemotherapy. It can also make patients more alert to other forms of cancer, triggering earlier and more frequent screenings.

<http://www.medicalnewstoday.com/releases/232867.php>

PSYCHOSOCIAL

12. Colorectal Cancer and Quality of Life (Jul. 27/11)

The German Cancer Research Center (DKFZ) in Heidelberg has reported the results of a long-term study showing that even ten years after diagnosis bowel cancer patients still suffer from health limitations. However, their impact varies depending on the age of those affected. Investigators surveyed 117 colorectal cancer patients over a period of ten years. Study subjects were questioned at regular intervals about their health status and the data obtained were compared with those of controls of the same age. They found that colorectal cancer and its treatment leave traces. All of those affected reported long-term handicaps, particularly digestive problems such as diarrhea and constipation. Effects on the quality of life in cognitive, social and emotional respects, however, were dependent on people's age at first diagnosis. In the youngest patient group, comprising patients whose tumor was discovered under age 60, quality of life tended to be restricted most by mental and social problems. Many cited work, hobbies and everyday activities to be affected by limitations. Subjects also complained about problems concentrating, fatigue and sleeping disorders. Although such symptoms improved during the first years following diagnosis, they were still present ten years after. By contrast, the eldest patients, who had been diagnosed with cancer after age 70, reported that their health status during the first few years after diagnosis was comparable or even better than that of persons of the same age not affected by bowel cancer. However, five to ten years after diagnosis, they reported similar health limitations as younger patients, including shortness of breath in many cases. However, despite these particular limitations, bowel cancer survivors rate their general health and quality of life as comparable to that of control persons. The researchers surmise that elderly patients have better strategies for coping with a sudden diagnosis of bowel cancer. They also consider it possible that different treatment methods during the first years play a role, since elderly patients receive less chemotherapy and radiotherapy. The researchers now consider it particularly important to investigate which factors besides age have an impact on the long-term effects of cancer. Moreover, it is mandatory to continue care of cancer survivors after treatment has ended. Volker Arndt: "From our point of view, psychological care of patients is of particular importance, because most limitations appear in the psycho-social sphere."

Jansen, Lina et al., Health-Related Quality of Life During 10 Years After Diagnosis of Colorectal Cancer: A Population-Based Study. Journal of Clinical Oncology 18 July 2011; DOI: 10.1200/JCO.2010.31.4013

OTHER

13. Greater Cancer Risk Among Taller Women (Jul. 20/11)

Taller women may have an increased risk of developing certain cancers. Overall, cancer risk increases by 16% for every 4-inch increase in height. Greater insight into height and cancer risk may help researchers expand their understanding of basic mechanisms that cause cancer. Previous studies have indicated that taller people have a greater general risk of developing cancer. Less has been known, however, about how height is associated with risks for specific types of cancer and whether other factors such as smoking and socioeconomic status affect this association. To better understand cancer risks associated with height, researchers in the UK evaluated more than 1 million women. During roughly nine years of follow-up, more than 97,000 cancers were diagnosed among study participants. Seventeen different types of cancer were included in the evaluation.

- Height was associated with 10 of the 17 types of cancer studied. These 10 cancer types were breast, lung, **colon**, endometrium (uterus), ovary, kidney, and rectum, as well as leukemia, non-Hodgkin's lymphoma, and melanoma.
- The association between height and cancer risk was not affected by socioeconomic status.
- Among current smokers, height had relatively little effect on the risk of smoking-related cancer.
- When these results were compared with data from other regions in the world, the association between height and cancer risk was similar across populations.

Greater height appears to be linked with an increased risk for many cancer types—a finding that suggests a basic common mechanism behind cancer development. The researchers note, however, that taller women should not worry excessively about their cancer risk, and that shorter women should remain vigilant. In short, all women, regardless of height, may benefit from cancer-preventive lifestyle choices and regular screening.

Green J, et al. Height and cancer incidence in the Million Women Study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk. The Lancet Oncology [early online publication]. July 21, 2011.

14. **More Genetic Mutations Lead to Colon Cancer Than Previously Thought** (Jun. 21/11)

Based on this study, there may be at least 70 genetic mutations involved in the formation of colon cancer, far more than scientists previously thought. Researchers are suggesting a new approach to colon cancer treatments targeting multiple genes and pathways simultaneously. Current cancer treatments target just one or two known cancer-driven genes believing this would be beneficial to patients. While patients may get transient tumor burden reduction, almost universally tumor growth returns. It contradicts previous thinking that only a few mutated genes are important in the development of cancerous tumors. The ways we've been treating patients up to now is to just go after one target when we should be going after three to four different pathways simultaneously. Under the old model, scientists believed there were 151 candidate genes and that mutations in just eight to 15 of them would lead to cancer. There were 700 other genes classified as passenger genes whose mutations were incidental to cancer growth. According to UT Southwestern's research, there are 65 candidate genes and at least five passenger genes whose mutations play significant roles in cancer development. Inactivating the function of any of these tumor-suppressing genes led to a key step in cancer development called anchorage-independent growth, meaning cells piled up on top of each other rather than aligning neatly. The next step is further research to classify more accurately which genes drive cancer and which are merely passengers.

Eskicok, U, et al., Functional Parsing of Driver Mutations in the Colorectal Cancer Genome Reveals Numerous Suppressors of Anchorage-Independent Growth. Cancer Research, 2011; 71 (13): 4359 DOI: [10.1158/0008-5472.CAN-11-0794](https://doi.org/10.1158/0008-5472.CAN-11-0794)

15. **Bisphosphonates May Reduce CRC Risk** (Aug. 6/11)

Bisphosphonates (used to treat osteoporosis) appear to reduce a patient's risk of colorectal cancer by 16%, with risedronate reducing it by up to 50%, a Canadian trial concludes. If the findings are confirmed in other research, risedronate may turn out to be the drug of choice in people with osteoporosis and a high risk of colorectal cancer.

<http://www.gastroenterologyupdate.com.au/news/some-bisphosphonates-may-halve-crc-risk--study>

16. **Patients Under 40 May Have Lower Survival** (Aug.16/11)

Colorectal cancer patients aged under 40 with no family history of the disease have lower survival rates and are less likely to recover than those over 40, according to a surgeon at Tainan's Chi Mei Medical Center. These patients also suffer from more malignant tumors and are often diagnosed at a later stage, citing a 10-year study. This is because younger patients tend to have a higher tolerance for pain and are more likely to overlook the warning signs of colorectal cancer, such as blood in the stool and abdominal pain. Moreover, patients and doctors are more likely to mistake the cancer for other diseases and delay diagnosis if the patient does not have a family history of colorectal cancer. The study spanned 10 years and covers 322 colorectal cancer patients at the Taipei Veterans General Hospital from 2001 to 2006. A total of 69 of the research subjects were under 40 years old, with no family history of the cancer. The rest were mostly aged over 80. 80% of the young patients needed chemotherapy after surgery and as much as 40% of these young patients were diagnosed in the latter stages of the disease. Even after surgery

and chemotherapy, the five-year survival rates of some of these young patients was still lower than those of the older patients. What was also noted: Statistics from the national health insurance program's research database show that the average age of colorectal cancer patients in Taiwan has hiked from 1998 to 2005, while the rate among the under 40 group has remained stable.

http://focustaiwan.tw/ShowNews/WebNews_Detail.aspx?Type=aALL&ID=201108160044

NUTRITION & HEALTHY LIFESTYLE

17. Cancer Patients & Survivors Are Bothered by Sleeping Problems (Jul.18/11)

According to the results of this study, nearly one in three people with cancer, both those with active cancer and cancer survivors, report having trouble falling asleep, staying asleep, or sleeping too much. Pain and emotional distress were often associated with sleep problems. When researchers in Scotland asked 2,862 patients "Over the last two weeks, how often have you been bothered by trouble falling or staying asleep or sleeping too much?"

- 34.5% with active cancer said yes.
- 28.0% of cancer survivors also answered yes.

In addition, patients who said they had sleep problems were almost three times as likely to have pain and nearly five times as likely to have emotional distress. The team at the Universities of Edinburgh and Glasgow concluded: "Sleep problems are common in cancer outpatients and are strongly associated with pain and emotional distress. A combined approach to the management of sleep, pain and emotional distress is indicated."

Sharma, Neelom, et al., Sleep problems in cancer patients: prevalence and association with distress and pain. Psycho-Oncology. Early view: doi: 10.1002/pon.2004

18. Vegetarians Less Likely To Develop Colorectal Cancer (Jul.21/11)

According to the results of this study, vegetarians are a third less likely to get a common bowel disorder (diverticular disease) than their meat eating counterparts.



Source: <http://www.sciencedaily.com/releases/2009/04/090401101747.htm>

Diverticular disease has been termed a "disease of western civilization" because of the higher numbers of cases in countries like the UK and the US compared with parts of Africa. The condition affects the large bowel or colon and is thought to be caused by not consuming enough fibre. Typical symptoms include painful abdominal cramps, bloating, wind, constipation and diarrhea. Previous research has suggested that a low fibre diet could lead to diverticular disease, and that vegetarians may have a lower risk compared with meat eaters, but there is little evidence to substantiate this. Researchers set out to examine the link between a vegetarian diet and intake of dietary fibre with the risk of diverticular disease. Their findings are based on 47,033 generally health conscious British adults who were taking part in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Oxford study. Of those recruited, 15,459 reported consuming a vegetarian diet. After an average follow-up time of 11.6 years, there were 812 cases of diverticular disease (806 admissions to hospital and six deaths). After adjusting the factors such as smoking, alcohol and body mass index (BMI), vegetarians had a lower risk of diverticular disease compared with meat eaters. Furthermore, participants with a relatively high intake of dietary fibre (around 25g a day) had a lower risk of being admitted to hospital with or dying from diverticular disease compared with those who consumed less than 14g of fibre a day. Consuming a vegetarian diet and a high intake of dietary fibre are both associated with a lower risk of diverticular disease, say the authors. The 2000-1 UK National Diet and Nutrition Survey showed that 72% of men and 87% of women were not meeting the recommended average intake for dietary fibre of 18 g per day and so the proportion of cases of diverticular diseases in the general population attributed to a low fibre diet could be considerable, they

add. These findings lend support to the public health recommendations that encourage the consumption of foods high in fibre such as wholemeal breads, wholegrain cereals, fruits and vegetables, they conclude. In an accompanying editorial, researchers from Nottingham University Hospital discuss the implications for the health of the population and the individual. Based on these findings, David Humes and Joe West estimate that "about 71 meat eaters would have to become vegetarians to prevent one diagnosis of diverticular disease." They add: "Overall the opportunity for preventing the occurrence of diverticular disease and other conditions, such as colorectal cancer, probably lies in the modification of diet, at either a population or an individual level." However, they stress that "far more evidence is needed before dietary recommendations can be made to the general public."

Crowe, Francesca L., et al., Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians. BMJ, 2011; 343:d4131 DOI: [10.1136/bmj.d4131](https://doi.org/10.1136/bmj.d4131)

David J Humes and Joe West. Diet and risk of diverticular disease. BMJ, 2011; 343:d4115 DOI: [10.1136/bmj.d4115](https://doi.org/10.1136/bmj.d4115)

19. Body Mass Index Affects Survival in Patients Receiving Chemo (Jul. 28/11)

According to the authors of this study, obesity has been associated with an increased risk of development and recurrence of colorectal cancer. However, the role of obesity in advanced colorectal cancer (ACC) patients is unknown. Researchers investigated the effect of body mass index (BMI) on overall survival (OS) in ACC patients receiving systemic treatment in two large phase III studies (CAIRO and CAIRO2). Treatment data were obtained and analyzed from 796 ACC patients who were treated with chemotherapy in the CAIRO study, and from 730 ACC patients who were treated with chemotherapy plus targeted therapy in the CAIRO2 study. Baseline height and weight were used to assign patients to one of the following BMI categories:

Category A (BMI < 18.5 kg/m²),
 Category B (BMI = 18.5–24.9 kg/m²),
 Category C (BMI = 25.0–29.9 kg/m²) and
 Category D (BMI ≥ 30.0 kg/m²).

In 796 patients of the CAIRO study, ***a high BMI was associated with better median OS*** (8.0, 14.9, 18.4 and 19.5 months for BMI categories A, B, C, and D, respectively). BMI was not associated with OS in 730 patients who participated in the CAIRO2 study, although a trend was observed. The researchers concluded that ***these results show that BMI is an independent prognostic factor for survival in patients receiving chemotherapy***, but not in patients receiving chemotherapy and targeted therapy. The possible decreased efficacy of bevacizumab (avastin) in obese patients may explain this discrepant result. The role of BMI in patients receiving targeted therapy should be further tested.

Calculating BMI:

$$\text{BMI} = \frac{\text{weight (lb)} * 703}{\text{height}^2 \text{ (in}^2\text{)}}$$

OR

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height}^2 \text{ (m}^2\text{)}} \quad \text{(metric)}$$

Simkens, Lieke, et al., Influence of body mass index on outcome in advanced colorectal cancer patients receiving chemotherapy with or without targeted therapy. European J of Cancer. Published online August 2011.

20. Fatty Livers and Colon Cancer (Aug. 5/11)

People who have a common liver disease are more likely to develop colon cancer - a study has shown. Given the higher chances of developing colorectal cancer, Chinese University researchers recommend that people with non-alcoholic fatty liver disease undergo colonoscopy starting from the age of 40. From 2008 until last year, researchers from the Center for Liver Health at CUHK performed colonoscopies on 380 people aged between 40 and 70 years old. That comprised 199 people having non-alcoholic fatty liver disease and 181 healthy individuals as a control group. The study found that those with a fatty liver had a 60% chance of getting colorectal polyps and were three times more likely to develop cancer. Colorectal cancer is preventable as the polyps are benign. If the polyps are removed before they transform into cancerous cells, cancer and death can be prevented. One in four adults in Hong Kong has a fatty liver. It takes five to ten years for colorectal polyps to become cancerous and polyps tend to be

advanced and located in the right side of the colon, perhaps because this part is more prone to inflammation, a symptom of colon cancer.

http://www.thestandard.com.hk/news_detail.asp?pp_cat=11&art_id=113862&sid=33285370&con_type=1&d_str=20110805

21. Beans May Help Reduce Risk of Colorectal Cancer (Aug. 5/11)

According to the results of a new study, eating pulses on a regular basis can reduce the risk of bowel cancer by up to a third. Californian researchers found that having brown rice just once a week cut the risk by 40%, while eating cooked green vegetables every day reduced the danger by 24%. The team reviewed data from 2,818 people collected in the 1970s and then carried out a follow-up survey to identify cases of rectal polyps. Around a sixth of people in the study developed polyps, which are a precursor to the disease. People who regularly ate foods such as lentils, brown rice and vegetables had less risk of developing the polyps.



Pulses, dried fruits, and brown rice all have a high content of fibre, known to dilute potential carcinogens. Additionally, cruciferous vegetables, such as broccoli, contain detoxifying compounds, which would improve their protective function. Eating these foods is likely to decrease the risk for colon polyps, which would in turn decrease the risk for colorectal cancer. While a majority of past research has focused on broad food groups, such as fruits and vegetables, in relation to colon cancer, this study focused on specific foods, as well as more narrowed food groups, in relation to colon polyps, a precursor to colon cancer.

<http://www.tandf.co.uk/journals/titles/01635581.asp>

23. Vitamin D Deficiency Can Increase Aggressiveness of Colon Cancer (Aug. 18/11)

A study conducted by VHIO researchers confirms that a lack of vitamin D increases the aggressiveness of colon cancer. The indication that vitamin D and its derivatives have a protective effect against various types of cancer is not new. In the field of colon cancer, numerous experimental and epidemiological studies show that vitamin D3 (or cholecalciferol) and some of its derivatives inhibit the growth of cancerous cells. Researchers at the Vall d'Hebron Institute of Oncology (VHIO), in collaboration with the Alberto Sols Institute of Biomedical Research (CSIC-UAB), have confirmed the pivotal role of vitamin D, specifically its receptor (VDR), in slowing down the action of a key protein in the carcinogenic transformation process of colon cancer cells. These results are being published in the journal PLoS One. This protein, known as beta-catenin, builds up in large quantities when the tumour transformation begins. As a result of these changes, the protein is retained in the cell nucleus, where it facilitates the carcinogenic process, and this is the point at which vitamin D intervenes, or rather, the vitamin D receptor (VDR). The researchers also analyzed the effect of the VDR on human colon cancer cell cultures and observed that the concentration of the altered protein, beta-catenin, increased in cells without the VDR. These findings were repeated in the three types of colon cancer cells studied, and confirmed the results observed in the mice. In two-thirds of advanced colon cancer tumours there was a lack of VDR in the cancer cells, and this circumstance leads them to believe that this loss may contribute to speeding up the growth of the tumour. The findings of this study confirm this supposition. **Vitamin D: essential in the initial phases of colon cancer. In light of these findings, chronic vitamin D deficiency represents a risk factor in the development of more aggressive colon tumours. Patients in the initial stages of colon cancer, the time when the VDR still has a substantial presence in the cells, could benefit from being treated with vitamin D3.** However, this would not be useful in the advanced stages of the disease when the presence of the VDR is very much reduced. The study data support the development of anti-tumour medicines based on the structure of vitamin D, although their use in patients will require further research in the next few years. The body not only obtains vitamin D from food, especially milk and fish oils, but also manufactures it from exposure to sunlight. Prolonged exposure is not necessary; just 10 minutes in the sun every day when it is not at its peak is sufficient to stimulate its production. During the summer, when we are more likely to sunbathe, it is important to use the appropriate protective measures against sunburn to avoid future sun damage. Use high-factor solar protection products and do not expose the skin to the sun in the middle of the day to protect against skin cancers.

Larriba, Maria Jesus, et al., *Vitamin D Receptor Deficiency Enhances Wnt/ β -Catenin Signaling and Tumor Burden in Colon Cancer*, PLoS ONE 6(8): e23524. doi:10.1371/journal.pone.0023524.