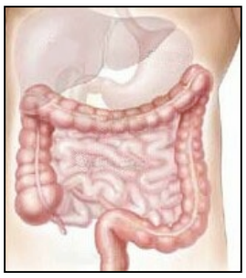
Colorectal Cancer Association of Canada

COLORECTAL CANCER RESEARCH UPDATES

Month Ending May 24th, 2015



The following colorectal cancer research update extends from March 16th, 2015 – May 24th, 2015 inclusive and is intended for informational purposes only.

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23. **Researchers reiterate benefits of exercise for cancer survivors**
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DRUGS / SYSTEMIC THERAPIES

1. No Non-Inferiority in Discontinuing Bevacizumab in Colorectal Cancer (Mar. 20/15)

Chemotherapy plus bevacizumab is a standard first-line treatment in metastatic colorectal cancer (mCRC) patients. Researchers in Switzerland assessed whether no continuation is non-inferior to continuation of bevacizumab after completing first-line chemotherapy. An open-label, phase III multicenter trial looking at 262 mCRC patients was conducted. After 4 to 6 months of standard first-line chemotherapy, patients were randomized to either continuation of bevacizumab at standard dosage or no treatment. Researchers performed CT scans every 6 weeks until disease progression. They found no non-inferiority in patients who did not continue with bevacizumab treatment. Median overall survival was 25.4 months in the continuation group versus 23.8 months in the no continuation group. The authors have concluded that based on no impact on overall survival and increased treatment costs, bevacizumab as a single agent is of no meaningful therapeutic value.

Koeberle, D., et al. "Bevacizumab continuation versus no continuation after first-line chemotherapy plus bevacizumab in patients with metastatic colorectal cancer: a randomized phase III non-inferiority trial (SAKK 41/06)." Annals of Oncology. doi: 10.1093/annonc/mdv011. [epub ahead of print]. January 20, 2015.

http://www.cancertherapyadvisor.com/gastrointestinal-cancers/colorectal-cancer-bevacizumab-continuation-treatment-chemotherapy/article/404565/

2. BCM-95 Curcumin reduces Chemoresistance in Colorectal Cancer Study (Mar. 23/15)

Resistance to chemotherapy is a major cause of death in colorectal cancer (CRC) patients. The process by which a cancer cell no longer responds to the cancer-killing effects of chemotherapy is termed chemoresistance. BCM-95 Curcumin has been shown to improve the effectiveness of chemotherapy in cell studies, though the molecular mechanisms underlying this phenomenon remained unclear. The present study demonstrates that cells treated with BCM-95 Curcumin and chemotherapy (5-flurouracil or 5-FU) lost their chemoresistance, enabling 5-FU to once again be effective. A unique mechanism of action was also identified via curcumin's influence on micro-RNA (miRNA). miRNAs are small molecules in the body that greatly influence patterns of gene expression. By targeting miRNAs, systems of many genes are controlled or modulated, which can play a crucial role in killing cancer cells, and preventing its recurrence and spread. The miRNAs that are affected by curcumin treatment control a process called epithelial to mesenchymal transition (EMT) by which cancer cells metastasize. The BCM-95 Curcumin used in the study influenced the expression of miRNA to prevent EMT which may have a profound impact on tumor growth suppression. As such, this study highlights the potential therapeutic usefulness of curcumin as an adjunct in patients with chemoresistant advanced CRC.

Toden S, Okugawa Y, Jascur T, et al. Curcumin mediates chemosensitization to 5-flurouracil through miRNA-induced suppression of epithelial-to-mesenchymal transition in chemoresistant colorectal cancer. Carcinogenesis. 2015;36(3):355-67.

http://www.chiroeco.com/bcm-95-curcumin-reduces-chemoresistance-in-colorectal-cancer-study/?redirect

3. Capecitabine Plus Bevacizumab Effective as Maintenance for Colorectal Cancer (Apr. 15/15)

The optimum duration of first-line treatment with chemotherapy in combination with bevacizumab in mCRC patients is unknown. The CAIRO3 study was designed to determine the efficacy of maintenance treatment with capecitabine plus bevacizumab versus observation. In this open-label, phase III, randomised controlled trial, researchers recruited 558 previously untreated mCRC patients with stable disease or better after induction treatment with six 3-weekly cycles of capecitabine, oxaliplatin, and bevacizumab (CAPOX-B). These patients were then assigned to either maintenance treatment with capecitabine and bevacizumab (maintenance group) or observation (observation group). Results showed that at a median follow-up of 48 months, the median duration to second progression was 11.7 months in the maintenance group compared with 8.5 months in the observation group. Researchers found that maintenance treatment was well tolerated, though 23% of patients in the maintenance group experienced hand-foot syndrome. The study also showed no deterioration in global quality of life during maintenance treatment.

Simkens LH, van Tinteren H, May A, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group.Lancet. 2015. [Epub ahead of print]. doi: 10.1016/S0140--6736(14)62004-3.

http://www.cancertherapyadvisor.com/gastrointestinal-cancers/colorectal-cancer-capecitabine-bevacizumab-maintenance-treatment/article/409151/

4. Second-Line Ramucirumab/FOLFIRI Improves Survival in Metastatic CRC (Apr. 17/15)

According to the results of the phase III RAISE trial, mCRC patients whose disease progressed during or after first-line bevacizumab, oxaliplatin, and fluoropyrimidine, had about a 1.5-month increase in overall survival when treated with second-line ramucirumab plus FOLFIRI compared with FOLFIRI alone. In this study, 1,072 patients were randomly assigned to 8 mg/kg intravenous ramucirumab plus FOLFIRI or placebo plus FOLFIRI every 2 weeks until disease progression, unacceptable toxicity, or death. The trial was designed to address whether continuation of VEGF inhibition, with the VEGF receptor 2 inhibitor ramucirumab, into the second-line would benefit patients treated in the first-line with the VEGF inhibitor bevacizumab. Patients assigned to ramucirumab/FOLFIRI had a median overall survival of 13.3 months compared with 11.7 months for patients assigned to placebo/FOLFIRI. Median progression-free survival was also significantly longer in patients assigned ramucirumab/FOLFIRI compared with FOLFIRI alone (5.7 months vs 4.5 months). However, researchers noted several grade 3 or worse adverse events in patients assigned to ramucirumab/FOLFIRI and placebo/FOLFIRI, including neutropenia (38% and 23%), febrile neutropenia (3% and 2%), hypertension (11% and 3%), diarrhea (11% and 10%) and fatigue (12% and 8%). In view of these results, the authors conclude that the combination of ramucirumab with FOLFIRI is an effective second-line treatment for mCRC patients. It has, however, been pointed out that the regimen used in the RAISE trial may not necessarily represent standard practice, as many patients do not regularly receive bevacizumab as part of their first-line treatment, and there is increased use of anti-EGFR therapies in the first line.

Tabernero, Josep et al. "Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study." The Lancet Oncology. 2015; 16(5):499 -508. DOI: http://dx.doi.org/10.1016/S1470-2045(15)70127-0.

http://www.cancernetwork.com/colorectal-cancer/second-line-ramucirumab-folfiri-improves-survival-metastatic-crc

5. Novel Anticancer Small Molecule Could Overcome Treatment Resistance in Colorectal Cancer (May 6/15)

Irinotecan is a drug currently used in clinical practice to treat advanced CRC. However, acquired resistance mediated by the drug efflux pump ABCG2 is a prevalent problem. Researchers have recently reported on an analogue compound, FL118, which shows anticancer activity superior to that of irinotecan and might be able to overcome treatment resistance. Unlike irinotecan, FL118 activates p53, a tumor-suppressor protein, independently of the ataxia-telangiectasia mutated protein kinase (ATM). As such, FL118 can successfully avoid treatment resistance resultant from an overexpression of ABCG2. These findings open up the highly attractive prospect of developing FL118 as an orally administered treatment for cancer. In this study, FL118 was also found to extend the time to progression in lung as well as colorectal xenograft tumor models by more than 50%, compared to irinotecan. Researchers surmise that FL118 might be efficient against various liquid and solid tumors, and have been assessing its role as a potential compound for controlling pancreatic, colorectal and ovarian cancers as well as chronic lymphocytic leukemia and melanoma. The results of this initial study support the development of FL118 as a therapeutic option for patients with drug-refractory cancers resulting from high expression of ABCG2.

Westover, D., et al. "FL118, a novel camptothecin derivative, is insensitive to ABCG2 expression and shows improved efficacy in comparison with irinotecan in colon and lung cancer models with ABCG2-induced resistance." Molecular Cancer, 2015; 14:92. doi:10.1186/s12943-015-0362-9.

http://coloncancernewstoday.com/2015/05/06/novel-anticancer-small-molecule-overcome-treatment-resistance-colorectal-cancer/

6. Drug extends Survival of Patients with Metastatic Colorectal Cancer (May 13/15)

An international clinical trial led by scientists at the Dana-Farber Cancer Institute has showed that TAS-102 lengthened the lives of mCRC patients who had exhausted available standard treatments. The phase III study enrolled 800 patients with mCRC that was progressing despite previous treatment. Participants were randomly assigned to receive TAS-102 or a placebo pill. The drug combination not only extended patients' overall survival, but also delayed the advance of disease with very few side effects. The median survival period for patients receiving TAS-102 was 7.1 months, compared to 5.3 months for patients taking a placebo. The median time before the disease worsened was 5.7 months for the TAS-102 group and 4.0 months for the placebo group. According to the study authors, these results are especially impressive because half of these patients had just finished treatment with the standard class of chemotherapy agents - fluoropyrimidines (e.g. 5-fluorouracil [5-FU] or capecitabine [Xeloda]) but had failed to benefit from them. The fact that TAS-102 temporarily halted the disease in many of these patients suggests that it operates through a different biochemical pathway than 5-FU, and therefore may serve as an alternative to standard therapy. 5-FU works by blocking an enzyme (thymidylate synthase) that cancer cells need for survival. The cancer cell-killing component of TAS-102, a drug known as trifluridine, by contrast, integrates into cancer cell DNA and prevents the cells from metabolizing nutrients. The next step will be to test TAS-102 in combination with other drugs that are customarily used in conjunction with 5-FU, and compare results.

Mayer, Robert J. et al. « Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer."N Engl J Med 2015; 372:1909-1919. May 14, 2015. DOI: 10.1056/NEJMoa1414325.

http://medicalxpress.com/news/2015-05-drug-survival-patients-metastatic-colorectal.html

7. Regorafenib Improves Survival in Treatment-Refractory Colorectal Cancer (May 18/15)

A recent double-blind, placebo-controlled, parallel-group, phase III trial assessed regorafenib in a broad population of Asian patients with refractory mCRC. Researchers enrolled 204 participants with progressive mCRC who had received at least two previous treatment lines or were unable to tolerate standard treatments. Participants were randomly assigned to receive oral regorafenib 160mg once daily or placebo plus best supportive care. Compared with placebo, regorafenib improved overall survival in patients with refractory mCRC. After a median follow-up of 7.4 months, median overall survival was 8.8 months in the regorafenib group and 6.3 months in the placebo group. Drug-related adverse events occurred in 97% of participants treated with regorafenib compared with 46% of those treated with placebo. The most common grade 3 or worse adverse events in the regorafenib group were hand-foot skin reaction, hypertension, hyperbilirubinemia, hypophosphatemia, elevated ALT/AST, elevated lipase concentration, and macropapular rash. These findings suggest that regorafenib is an important treatment for patients with mCRC whose disease has progressed after standard treatments, which may or may not include targeted treatments.

Li, J., et al. "Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial." The Lancet Oncology. DOI: http://dx.doi.org/10.1016/S1470-2045(15)70156-7. 13 May 2015.

http://www.cancertherapyadvisor.com/gastrointestinal-cancers/colorectal-cancer-regorafenib-better-survival-treatment/article/415215/

8. High dose Vitamin D supplementation in Stage 4 Colorectal cancer patients

A large body of evidence suggests that high blood levels of Vitamin D decreases the risk of developing cancer, especially CRC. Very little is known about what role optimum blood levels of Vitamin D can play in the treatment of cancer. The purpose of this clinical trial is to study the therapeutic effect and the safety of high-dose vitamin D supplementation in stage 4 (metastatic) CRC patients. Anyone who has a stage 4 CRC diagnosis, living in Ontario or British Columbia, may be eligible to participate. All participants need to have access to a Lifelabs facility for blood and urine collections. This 40 month study involves regular lab tests and follow-up phone calls. Participation is fully voluntary and participants can withdraw at any time. Participants will be randomized into either a high-dose vitamin D treatment group or a control group. Participants in the treatment group receive daily oral high-dose Vitamin D supplementation provided through the clinical study. Participants in the control group will not receive vitamin D through the clinical study, but may take their usual dose of vitamin D if they wish to. Participants in both groups may continue all other cancer treatments including chemotherapy.

If you have any further questions regarding this study or you are interested in participating in this study, please contact:
British Columbia: 604-734-7125, toll free 1- 888-734-7125 or vitDstudy@inspirehealth.ca
Ontario: 613-792-1222, toll free 1-855-546-1244 or research@oicc.ca

http://www.colorectal-cancer.ca/en/research-trials/studies-participate/

SURGICAL THERAPIES

9. Surgical Management of Patients with Colorectal Cancer and Simultaneous Liver and Lung Metastases (Mar. 18/15)

The management of CRC patients with simultaneously diagnosed liver and lung metastases (SLLM) remains controversial. In this study, the LiverMetSurvey registry was used to assess outcomes after resection of SLLM, and the factors associated with survival. SLLM was defined as liver and lung metastases diagnosed 3 months or less apart. Survival was compared between patients with resected isolated liver metastases (group 1, control), those with resected liver and lung metastases (group 2), and patients with resected liver metastases and unresected (or unresectable) lung metastases (group 3). Adjusted overall 5-year survival was similar for groups 1 and 2 (51.5% and 44.5% respectively), but worse for group 3 (14.3%). As such, patients who had resection of liver and lung metastases had similar overall survival to those who had undergone removal of isolated liver metastases.

Andres, A., Mentha, G., Adam, R., Gerstel, E., Skipenko, O. G., Barroso, E., Lopez-Ben, S., Hubert, C., Majno, P. E. and Toso, C. "Surgical management of patients with colorectal cancer and simultaneous liver and lung metastases." Br J Surg. 2015; 102: 691–699. doi: 10.1002/bjs.9783.

http://onlinelibrary.wiley.com/doi/10.1002/bjs.9783/abstract;jsessionid=DB92BCB9B885C2100D8F42686A0A78B0.f04t01

10. Treatment Options for Peritoneal Carcinomatosis Associated with Colorectal Cancer (Apr. 8/15)

Peritoneal carcinomatosis (PC) is one of the most serious complications of gastrointestinal malignancies. The peritoneum is the lining within the abdominal cavity and covers the intra-abdominal organs. It has several components including the outer (parietal) and inner (visceral) layers as well as the greater and lesser omentum. The peritoneum supports the structure and metabolism of the intra-abdominal organs by providing an important source of blood and lymph circulation. The peritoneum therefore has a significant immunological role in localizing and attacking certain infections. As the peritoneum is a relatively vascular and lymphoid structure, it can be a potential site of metastases from numerous malignancies, which leads to the diagnosis of PC.

There are several proposed mechanisms of how patients can develop PC. There can be direct extension of the intra-abdominal malignancy into the peritoneum or direct seeding of the peritoneum following tumor rupture. The peritoneum can also be seeded during surgery when the abdomen is exposed to the contents of the lymph nodes or blood vessels during surgical exploration. It may be extremely difficult to ascertain when the peritoneum is seeded with malignant cells, as there may be a minute amount of cells that remain relatively undetectable by conventional means. PC has been reported in up to 40% of patients with CRC at any time point within their clinical course. Older, more traditional treatments in patients with PC secondary to CRC include removal of the omentum, systemic and/or palliative chemotherapy, and palliative surgery. Newer treatment options include cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC), and intraperitoneal chemotherapy. Older, systemic chemotherapy regimens such as 5-flurouracil (5FU) and leucovorin provide a limited survival benefit of around 7 months while additional agents like oxaliplatin and irinotecan are able to extend survival to approximately 23 months. Newer treatment regimens (CRS and HIPEC) have shown survival benefit of up to 63 months, with a 5-year survival near 50%.

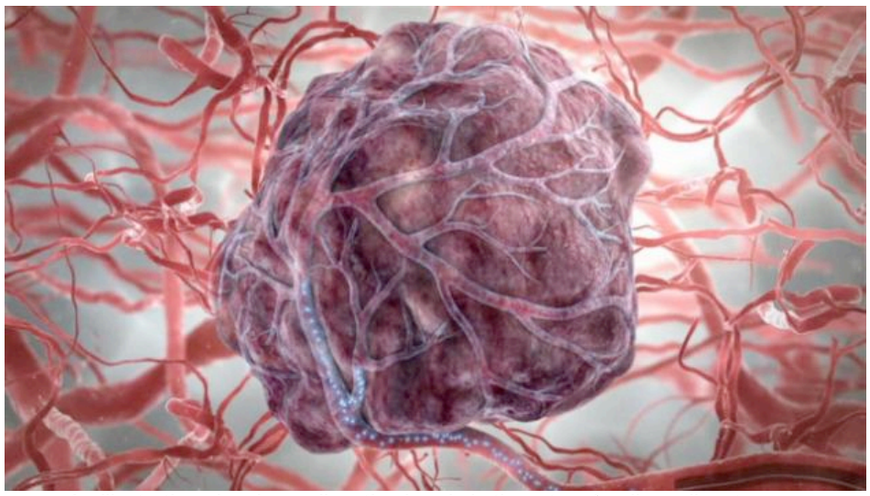
There are several scales that rate the extent of PC and provide a prognostic estimate that can help stratify patients for potential treatments. These scales include the Peritoneal Cancer Index (PCI) and the Peritoneal Surface Disease Severity Score (PSDSS). The scales can include information regarding the patient's symptoms as well as the location and size of the patient's PC tumor. Certain patients who have a poor prognosis based on these scales may not be the ideal candidates for more aggressive surgery or chemotherapy. For example, the 5-year survival rates of patients with CRC who have PC based on the PCI include: 50% with PCI 10 or less, 20% with PCI of 11 to 20, and 0% with PCI more than 20. Therefore, patients with a PCI of more than 20 are typically not considered candidates for newer, more aggressive therapies. Many patients with extensive liver metastases and intra-abdominal lymphadenopathy may also be considered to have relative or absolute contraindications to the newer treatments secondary to poor prognosis. As with many new and upcoming oncology treatments, additional clinical data is needed to ascertain survival benefit in CRC patients with PC.

http://www.cancertherapyadvisor.com/gastrointestinal-cancers/colorectal-cancer-peritoneal-carcinomatosis-treatment-options/article/408012/

RADIATION/INTERVENTIONAL RADIOLOGY

11. 'Glass Beads' in Bowel Cancer Fight (Apr. 27/15)

Tiny radioactive glass beads will form the basis of a radical form of treatment to be tested on patients with bowel cancer that has spread to the liver. At least 20 patients with cancer that has become resistant to chemotherapy will undergo the therapy starting this month in Oxford. In about 60% to 70% of CRC cases, the cancer spreads or metastasises to the liver. Surgery offers the greatest chance of a cure, but for some patients, chemotherapy is the only available option. These microscopic beads offer a new radiotherapy treatment option to patients when chemotherapy has not worked. The glass "microspheres" are about a third of the width of a human hair and contain the radioactive isotope yttrium-90. Using a flexible catheter inserted via the groin, they are delivered directly into cancer-affected parts of the liver through the tumours' own network of blood vessels. The microspheres become permanently lodged in the small blood vessels surrounding a tumour and destroy the cancer while having a minimal impact on surrounding healthy tissue. They continue to generate radiation for weeks after treatment. The trial will compare the new therapy combined with conventional chemotherapy with drug treatment alone. Side effects may include flu-like symptoms, mild to moderate fatigue, and the possibility of some pain and nausea. This Oxford study will form part of a global trial of internal radiotherapy treatment for bowel cancer that has spread to the liver called Epoch. The therapy is already approved in the European Union for treating certain types of liver cancer.



An illustration showing radioactive beads in the artery feeding a liver tumour

https://uk.news.yahoo.com/glass-beads-bowel-cancer-fight-160533637.html#eGcHaIL

PSYCHOSOCIAL

12. Psychosocial Impact of Lynch Syndrome on Affected Individuals and Families (Mar. 19/15)

Lynch syndrome (LS) is the most common hereditary CRC syndrome, conferring a heightened risk of colon cancer and various extracolonic tumors. Studies in hereditary breast cancer have shown a negative psychological impact for patients testing positive for BRCA1 or BRCA2 mutations, but there is little literature looking at psychosocial impact of Lynch Syndrome testing for families. A literature review shows that LS mutation carriers, whether or not they have had cancer, suffer a transient increase in depression and anxiety scores post-disclosure, which seems to normalize by 6–12 months. Younger patients with higher CRC risk perception, higher education level, married, and employed are more likely to accept genetic testing. Major motivators for testing are predicting one's own risk of cancer and risk to offspring. Carrier status also influences family planning, and there is growing interest for preimplantation genetic diagnosis. This review leads the authors to conclude that the psychosocial impact of LS testing need to be explored further.

Galiatsatos, P., Rothenmund H., Aubin S., Foulkes WD. "Psychosocial Impact of Lynch Syndrome on Affected Individuals and Families." Digestive Diseases and Sciences. DOI: 10.1007/s10620-015-3626-8. 19 March 2015.

SCREENING

13. Biomarker set forms the basis for new blood test to detect colorectal cancer (Mar. 27/15)

Researchers from various European oncology centers have identified biomarkers that can be incorporated into a new diagnostic test for CRC. This should make it possible to detect CRC at an early stage using a simple blood test. When affected by cancer, the immune system responds by trying to remove cancer cells from the body. A specific role in this process is assigned to a type of white blood cell called the peripheral blood monocyte. From the moment that CRC cells are present in the body, peripheral blood monocytes respond to the substances secreted by these cells. These substances activate specific genes in the monocytes. Researchers have identified these genes so that they can be used to diagnose CRC through blood collection by using standard techniques. This new test will be more sensitive because it detects tumor-induced changes directly, and not merely blood in the stool. An additional benefit is that this process takes place at a point when the tumor is forming, the earliest stage of tumor development. Since this test is based on how the body reacts to the presence of CRC cells, it may also be used to detect distant metastasis even after the primary tumor has been removed. This unique potential makes it a valid tool for patient follow-up after removal of the primary tumor. The challenge facing the investigators now is to develop a test using a minimal set of bio-markers.

Hamm, P., et al. Tumour-Educated Circulating Monocytes are Powerfule Candidate Biomarkers for Diagnosis and Disease Follow-up of Colorectal Cancer. Gut 2015. doi:10.1136/gutjnl-2014-308988.

http://www.vib.be/en/news/Pages/Bio-marker-set-forms-the-basis-for-new-blood-test-to-detect-colorectal-cancer.aspx

http://medicalxpress.com/news/2015-03-biomarker-basis-blood-colorectal-cancer.html

14. Does Colonoscopy Cut Colon Cancer Rates in Seniors? (Apr. 1/15)

Lowered CRC rates with surveillance colonoscopy in the elderly is disputed. Surveillance colonoscopy is defined as any colonoscopy occurring within 10 years of the diagnostic colonoscopy that followed the abnormal results of the initial screening test (flexible sigmoidoscopy, FSG). The Study of Colonoscopy Utilization (SCU), using a subset of CRC screening participants from the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial, failed to replicate findings from an earlier retrospective cohort study performed at Kaiser Permanente Southern California (reported 2014). The original study showed a 15-fold reduced risk of CRC among older (75+) versus younger (50-74) subjects undergoing surveillance colonoscopy. Despite the fact that the SCU trial had relatively small numbers of CRCs (n=21), it showed that, among those undergoing surveillance, older subjects had higher risk compared with younger subjects (relative risk for ages 70-80 compared with 55-69 was 1.5). In addition, increasing CRC incidence with age is a well-known trend. As such, there is some concern that the specific environment of the study performed at Kaiser Permanente Southern California may have influenced results. The authors have emphasized that physicians should view the original findings of reduced risk with older age with some scepticism.

Pinsky PF and Schoen RE. Colorectal Cancer Incidence by Age Among Patients Undergoing Surveillance Colonoscopy. JAMA Intern Med. 2015;175(5):858-860. doi:10.1001/jamainternmed.2015.0344.

http://www.medpagetoday.com/HematologyOncology/ColonCancer/50772

OTHER

15. Utility of postoperative CEA for surveillance of recurrence after resection of primary colorectal cancer (Mar. 11/15)

Researchers have evaluated the use of CEA as a prognostic marker in CRC. Over a 56 month period, 569 patients with measured CEA levels underwent curative resection for CRC. The median follow up was 40 months, during which period recurrence occurred in 149 patients. Serum CEA levels were measured at regular intervals starting from 3 months post resection. Investigators found that elevated CEA levels were more frequent in patients with an aggressive primary CRC (grade, T stage and nodal disease). In patients found to have colorectal recurrence, a significantly higher proportion of patients were resectable in the group with a non-elevated CEA. The median interval between CEA elevation and diagnosis of recurrence (diagnostic interval) was 4 weeks. CEA elevation led to a change in the routine surveillance program by bringing imaging forward by 2 months. CEA levels were a significant predictor of survival following resection of colorectal primary (CEA ≤5–38months, CEA >5–27 months). The authors conclude postoperative CEA levels are useful in the surveillance of CRC patients. It is a predictor of recurrence, resectability and survival following resection of CRC. Furthermore, an elevated CEA has a short diagnostic interval for detecting recurrent disease and therefore should mandate adjustment of the routine surveillance program with the next planned imaging being brought forward (2 months).

Bhatti, I., et al.Utility of postoperative CEA for surveillance of recurrence after resection of primary colorectal cancer. International Journal of Surgery. 2015; Volume 16 (part A): 123 – 128. DOI: http://dx.doi.org/10.1016/j.ijsu.2015.03.002.

http://www.journal-surgery.net/article/S1743-9191(15)00080-1/abstract?rss=yes

16. Metformin And Vitamin D3 Combined Show Promise In Preventing Colorectal Cancer (Mar. 26/15)

A recent study showed that the combined use of metformin and vitamin D3 may represent a novel strategy for CRC prevention. Both have been shown to have chemopreventive effects against various tumors. The anti-diabetic drug metformin plays a key role in suppressing the proliferation of colon epithelial cells and aberrant crypt foci (ACF), frequent precursors to CRC. Vitamin D3 is important in cancer mechanisms such as cell differentiation, proliferation and apoptosis. It also inhibits the activation of the Wnt/β-catenin pathway, a process linked to CRC cell proliferation. This study was designed to investigate the combined preventative effects of vitamin D3 and metformin against the development of early colon neoplasia in two animal models. Compared with either vitamin D3 or metformin alone, the combined use of vitamin D3 and metformin showed significantly improved outcomes (fewer colon neoplasias) in both models, using only very discrete amounts. According to investigators, on average, there was a 40% decrease in the development of polyps in all animals receiving both drugs in combination compared to control groups.

If these results can be translated to humans, this may represent a significant strategy in CRC prevention. Current options for clinical testing in humans include:

- testing the combination of metformin-vitamin D3 to address treatment for colorectal cancer as a neo-adjuvant therapy;
- testing the combination to prevent colon cancer in those with familial adenomatous polyposis (FAP);
- assessing the outcomes of administering the combination in those with colon cancer before their surgery.

Patients with a 10 mm or larger adenoma polyp or high-grade neoplasia have a 50% chance of recurrence within 4 years. These individuals can be screened with colonoscopies every few years, but preventative measures do not presently exist. This metformin-vitamin D3 combo may provide an opportunity to prevent recurrence.

Li, W., et al. "Combined Use of Vitamin D3 and Metformin Exhibits Synergistic Chemopreventive Effects on Colorectal Neoplasia in Rats and Mice." Cancer Prev Res. 2015; 8; 139. doi: 10.1158/1940-6207.CAPR-14-0128.

http://coloncancernewstoday.com/2015/03/26/metformin-and-vitamin-d3-combined-show-promise-in-preventing-colorectal-cancer/

NUTRITION & HEALTHY LIFESTYLE

17. Vitamin D Protects Against Colorectal Cancer

A study by Dana-Farber Cancer Institute investigators demonstrates that vitamin D can interact with the immune system to raise the body's defenses against CRC. This represents the first time that a link between vitamin D and the immune response to cancer has been shown in a large human population. It is already known that individuals with high levels of vitamin D in their bloodstream have a lower overall risk of developing CRC. Laboratory research also suggests that vitamin D boosts immune system function by activating T cells that recognize and attack cancer cells. In this study, investigators wanted to determine if these two phenomena were related: Does vitamin D's role in the immune system account for the lower rates of CRC in people with high circulating levels of the vitamin? Researchers compared groups of 318 CRC patients and 624 individuals free of cancer. All 942 participants had blood samples drawn before any developed cancer, which were tested for 25-hydroxyvitamin D, (abbreviated 25(OH)D), a substance produced in the liver from vitamin D. It was found that patients with high amounts of 25(OH)D had a lower-than-average risk of developing colorectal tumors that were enriched with immune system cells. In the future, it may be possible to predict how increasing an individual's vitamin D intake and immune function can reduce his or her risk of CRC.

Song, M. et al. "Plasma 25-hydroxyvitamin D and colorectal cancer risk according to tumour immunity status. Gut. 2015 Jan 15. pii: gutjnl-2014-308852. doi: 10.1136/gutjnl-2014-308852. [Epub ahead of print]

http://egpnews.com/2015/03/vitamin-d-protects-against-colorectal-cancer/

18. The Best Diet to Lower Your Colon Cancer Risk (Mar. 25/15)

Research shows that what you eat can impact your risk for developing CRC. A recent study shows that a diet of mostly fruits, vegetables and a moderate amount of fish (pesco-vegetarian diet) appears to offer the most protection against developing CRC. Researchers analyzed the diets of nearly 78,000 people and compared them to cancer incidence rates to estimate the number of people who might develop CRC. They found that vegans- who do not eat any foods derived from animals, including dairy products such as cheese, milk and eggs- had a 16% lower risk for CRC compared to non-vegetarians. In addition, vegetarians had a 22% lower risk of CRC compared to meat-eaters. However, researchers found that a pesco-vegetarian diet appears to offer the most protection against CRC. This type of diet is associated with a 45% reduced risk for CRC compared to people whose diets include meat.

Previous studies have linked red meat, especially processed meat, to increased risk of CRC. This is especially true for processed meat, which is meat preserved by smoking, curing, salting, or adding chemical preservatives. Examples of processed meat include bacon, ham, sausage and hot dogs. Conversely, foods that contain high amounts of fiber have been linked to decreased risk of CRC. This may be because fiber tends to add bulk to the digestive system, shortening the amount of time that wastes travel through the colon. As this waste often contains carcinogens, a high amount of fiber decreases the opportunity for carcinogens to affect the intestinal cells.

This study noted that a Mediterranean-style diet, with its emphasis on fish and fresh fruits and vegetables, was a good example of a pesco-vegetarian diet. A Mediterranean-style diet lowered CRC risk by 43%, compared to a non-vegetarian diet. The Dietary Guidelines Advisory Committee has recommended that all Americans eat a Mediterranean-style diet, or a diet that provides about 30% of its calories from fat. In addition to seafood, fruits and vegetables, the Mediterranean diet emphasizes whole grains, beans, nuts and olive oil.

Orlich MJ, Singh PN, Sabaté J, et al. Vegetarian Dietary Patterns and the Risk of Colorectal Cancers. JAMA Intern Med. 2015;175(5):767-776. doi:10.1001/jamainternmed.2015.59.

http://health.clevelandclinic.org/2015/03/the-best-diet-to-lower-your-colon-cancer-risk/

19. Does Aspirin Prevent Colorectal Cancer? Depends on your DNA (Mar. 17/15)

It has been known for a while that aspirin and non-steroidal anti-inflammatory drugs, or NSAIDs, can protect against some CRCs, though not used as a preventive agent due to the uncertainty of the risk-benefit ratio. What was not known, however, was why some individuals seemed to benefit while others did not. Researchers at Fred Hutchinson Cancer Research Center have discovered that the benefits of using aspirin and NSAIDs, like ibuprofen, to cut CRC risk actually hinge on a person's particular DNA. Investigators compared genetic and lifestyle data from 8,624 people who developed CRC with that of 8,553 people who did not. While regular use of aspirin and NSAIDs was associated with an overall reduced risk of CRC, there was no such protective effect among about 9% of participants who carried an uncommon genetic variation on chromosome 15. Furthermore, about 4% of participants who carried 1 or 2 even rarer alleles on chromosome 12 had a higher risk of CRC with aspirin or NSAID use. These findings suggest that medications do not have the same effects on all individuals. It is important to identify what factors exist that distinguish why some individuals may benefit and some will not. Investigators have also said that it is far too early for people to have genetic testing done to see if they could conceivably benefit from NSAID/aspirin as a preventive agent against CRC. The above results need to be validated in other populations first. Ideally, these findings support the fact that physicians should take a personalized approach to risk prediction and guidance for lifestyle, screening and interventions when counselling patients.

Nan H, Hutter CM, Lin Y, et al. Association of Aspirin and NSAID Use With Risk of Colorectal Cancer According to Genetic Variants. JAMA. 2015;313(11):1133-1142. doi:10.1001/jama.2015.1815.

http://www.fredhutch.org/en/news/center-news/2015/03/does-aspirin-prevent-colorectal-cancer.html

20. Fitness Level Associated With Lower Risk Of Colorectal Cancer In Men (Apr. 2/15)

A recent study showed that middle aged men with high fitness levels have lower risks of developing CRC. Furthermore, higher fitness levels are associated with lower death rates in men diagnosed with cancer in older age. The association between cardiovascular disease (CVD) and cardiorespiratory fitness (CRF) has been well-established, but the value of CRF as a predictor of primary cancer has received less attention. As such, investigators looked at the connection between incident cancer, midlife CRF and survival after a cancer diagnosis at the age of 65 and older. The study enrolled 13,949 men who underwent a baseline fitness exam and had their CRF values assessed. Fitness levels and cancer incidence were studied at regular intervals during the study period. Researchers found that high CRF values in midlife were related to lower chances of developing CRC. This is the first such study to demonstrate that CRF is predictive of site-specific cancer incidence, as well as risk of death from cancer or CVD following a cancer diagnosis. These findings provide further support for the effectiveness of CRF assessment in preventive health care settings. Future studies are required to determine the absolute level of CRF necessary to prevent site-specific cancer as well as evaluating the long-term effect of cancer diagnosis and mortality in women.

Lakoski SG, Willis BL, Barlow CE, et al. Midlife Cardiorespiratory Fitness, Incident Cancer, and Survival After Cancer in Men: The Cooper Center Longitudinal Study. JAMA Oncol. 2015;1(2):231-237. doi:10.1001/jamaoncol.2015.0226.

http://coloncancernewstoday.com/2015/04/02/fitness-level-associated-with-lower-risk-of-colorectal-cancer-in-men/

21. Excess Weight Early in Life linked to Colon Cancer Risk in Women (Apr. 2/15)

Women who were overweight as children and teens may be at a greater risk for CRC regardless of their current weight, a new study cautions. As part of this study, researchers analyzed data from more than 75,000 American women and 34,000 men. Their results showed that compared to women who were lean in childhood, those who were overweight had a 28% higher risk of developing CRC. Women who were overweight in their teens had a 27% higher risk of CRC than women who were lean during their teen years. This association was not observed in men. However, investigators stress that it is too early to conclude that the association does not in fact exist in men. Investigators feel that their study supports the growing evidence that early life body size can influence risk of CRC many decades later. It is already a well-known fact that overweight kids often become overweight adults who are at risk for many cancers. This study emphasizes how important it is for parents and caregivers to help children choose healthy habits.

http://medicalxpress.com/news/2015-04-excess-weight-early-life-linked.html

22. Can Vitamin C kill Cancer? (Apr. 13/15)

Research at the University of Iowa Hospitals and Clinics (UIHC) is reintroducing a controversial idea: using high doses of vitamin C to treat cancer. Researchers want to find out if they can fight cancer by injecting patients with large amounts of vitamin C while also using traditional cancer treatments such as radiation and chemotherapy. Preclinical trials started in 2008, testing the vitamin C treatment on cancer cells and mice. During these trials, researchers successfully slowed tumor growth. High-dose vitamin C seems to work by creating hydrogen peroxide that kills cancer cells without harming other cells. Phase I

trials currently underway are focused on whether intravenous, high-dose vitamin C is safe and well-tolerated in human patients. Trials so far have shown the treatment is safe and tolerable for patients with pancreatic cancer. Researchers also are testing its safety in patients with cancers of the brain and lungs. Researchers hope to test the treatment's efficacy in humans during a second phase of research in late 2015 or early 2016.

The idea of using vitamin C to kill cancer gained popularity in the late 1970s. Cameron and Pauling used a mix of orally-ingested and intravenous vitamin C against cancer and found that the treatment showed promise. However, a Mayo Clinic study in the early 1980s contradicted these findings, indicating that oral vitamin C was ineffective against cancer. The UIHC study is different from the Mayo Clinic study in that it focuses on intravenous vitamin C, a method that allows doctors to administer the nutrient at much higher and more effective levels than with oral ingestion.

http://www.press-citizen.com/story/news/local/2015/04/12/can-vitamin-kill-cancer-uihc-seeking-answer/25672883/

23. Researchers reiterate benefits of exercise for cancer survivors (Apr 20/15)

The benefits of walking for patients who have survived CRC have been emphasised in a Dutch study. CRC survivors often experience chemotherapy-induced peripheral neuropathy caused by nerve damage, including a tingling or burning sensation in their hands and feet, itching, muscle weakness or a loss of reflexes. The study, which followed 1,648 CRC survivors, showed that patients who did at least 150 minutes of moderate to vigorous exercise per week experienced fewer of these symptoms 2 to 11 years after being diagnosed with cancer. Those who were less active not only had more such symptoms, but also experienced a subsequent lower quality of life. This leads investigators to conclude that regular physical activity plays an important role in CRC prevention, recurrence and mortality.

Mols, F., et al. "Chemotherapy-induced peripheral neuropathy, physical activity and health-related quality of life among colorectal cancer survivors from the PROFILES registry." Journal of Cancer Survivorship. DOI: 10.1007/s11764-015-0427-1. 16 April 2015.

http://www.nursingtimes.net/nursing-practice/specialisms/cancer/researchers-reiterate-benefits-of-exercise-for-cancer-survivors/5084333.article

24. Healthy Lifestyle Before Colorectal Cancer Diagnosis Could Improve Survival Rate

Following lifestyle guidelines about diet, physical activity and maintaining a healthy weight is associated with an improved likelihood of survival when a patient is diagnosed with CRC. This is based on findings from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Researchers developed a healthy lifestyle index (HLI) composed of five potentially modifiable lifestyle factors to explore the association of lifestyle with CRC incidence in 520,000 participants. A six-point score was constructed for men based on national and international lifestyle guidelines about body weight, physical activity, food and drinks that promote weight gain, plant foods (which includes vegetable, fruit, legumes and grains), meat-based food, and alcoholic drinks. Women had a seven-point score based on the previous six recommendations and whether or not they had breastfed. Points were allocated based on meeting these recommendations. It was found that men who had a lifestyle score of 3 or more points were more likely to survive CRC. For women, a score of 4 or above was associated with increased survival; in both cases, the higher the score, the lower the risk of mortality after CRC. When individual recommendations were studied, it was found that having a healthy weight and high plant foods consumption had the strongest associations with survival. There was also an association seen with women who breastfed and survival of CRC. The results of this study demonstrate that a healthy lifestyle in your adult life, in line with recommendations on diet, physical activity and body weight for cancer prevention, not only prevent CRC but improves survival in those who eventually develop it. It is important to note that due to the study design, it was not possible for this study to demonstrate what would happen if these lifestyle habits were acquired after cancer diagnosis. Also, lifestyle was measured only once so it is not possible to know if lifestyle habits changed during follow-up or after cancer diagnosis. Further studies are needed to understand the association of a healthy lifestyle before and after cancer diagnosis and CRC survival.

Aleksandrova, K., et al. "Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study." BMC Medicine 2014, 12:168 doi:10.1186/s12916-014-0168-4.

http://www.endonurse.com/news/2015/05/healthy-lifestyle-before-colorectal-cancer-diagno.aspx

25. New Research finds Walnuts May help Slow Colon Cancer Growth (May 11/15)

A new animal study indicates that a diet containing walnuts may slow colorectal tumor growth by causing beneficial changes in cancer genes. This is the first such study to evaluate whether walnut consumption can cause changes to miRNA. Researchers conducted the randomized study with two groups of mice. One group was fed the equivalent of two servings (2 ounces) per day of walnuts for humans, while the second group received a similar control diet with no walnuts. After 25 days, researchers found that in walnut-fed mice, key miRNA that may affect cancer cell inflammation, vascularization (blood supply) and proliferation were positively engaged. The tumors of mice fed the walnut-containing diet were found to have 10 times the amount of total omega-3 fatty acids, including plant-based alpha-linolenic acid (ALA), in the tissue compared to the mice fed the control diet. The study results found that a smaller tumor size

was associated with greater percentage of omega-3s in tumor tissues, suggesting that ALA may provide a protective benefit. Tumor growth rate was also significantly slower in the walnut group compared to the control group. As this study was conducted on animals, results cannot yet be implied for humans.

Tsoukas, MA., et al. Dietary walnut suppression of colorectal cancer in mice: Mediation by miRNA patterns and fatty acid incorporation. Journal of Nutritional Biochemistry. DOI: http://dx.doi.org/10.1016/j.jnutbio.2015.02.009. 1 April 2015.

http://medicalxpress.com/news/2015-05-walnuts-colon-cancer-growth.html