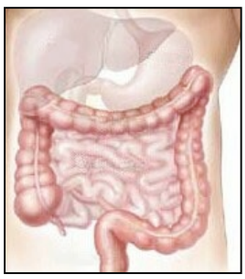
Colorectal Cancer Association of Canada

COLORECTAL CANCER RESEARCH UPDATES

Month Ending January 15th, 2016



The following colorectal cancer research update extends from September 19th, 2015 – January 15th, 2016 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. U.S. Task Force Recommends Aspirin for Colorectal Cancer Prevention (Sept.21/15)

Aspirin has been recommended for the prevention of colorectal cancer in people aged 50–59 years by the US Preventive Services Task Force. The recommendation follows several large studies that have suggested aspirin can reduce the risk of colorectal cancer, especially in patients with a genetic predisposition to the disease. In a draft recommendation that is out for consultation, the US task force

recommends low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer for patients who have a 10% or greater 10-year CVD risk, are not at increased risk of bleeding, have a life expectancy of at least ten years, and are willing to take low-dose aspirin daily for at least ten years. This is the first time that aspirin has been officially recommended for the prevention of cancer by a US national agency. The US task force has not recommended aspirin for prevention of colorectal cancer in patients under 50 years or older than 70 years. For patients aged 60–69 years, the decision over whether or not to take aspirin should be an "individual one", it recommends. Long-term aspirin use is associated with an increase in the risk of gastrointestinal bleeding and haemorrhagic stroke.

The Pharmaceutical Journal, 26 September 2015, Vol 295, No 7881, online | DOI: 10.1211/PJ.2015.20069366
http://www.pharmaceutical-journal.com/news-and-analysis/news-in-brief/us-task-force-recommends-aspirin-for-colorectal-cancer-prevention/20069366.article

2. FDA Approves Trifluride Plus Tipiracil for Advanced CRC (Sept. 2215)

The U.S. Food and Drug Administration (FDA) has approved trifluride plus tipiracil (Lonsurf), a combination oral medication, for the treatment of patients with advanced colorectal cancer who have been previously treated with chemotherapy and biologic therapy. Approval is based on the findings of an international, double-blind study that evaluated the efficacy and safety of trifluride plus tipiracil in 800 patients with previously treated metastatic colorectal cancer. Results showed that average overall survival was 7.1 months with trifluride plus tipiracil compared with 5.3 months with placebo. On average, time to disease progression was 2 months for those receiving trifluride plus tipiracil vs 1.7 months for those receiving placebo. The median overall survival in the Lonsurf-treated group was 7.1 months compared to 5.3 months in the placebo-controlled group, which was statistically significant. In regard to safety, the most common adverse events associated with the combination pill are anemia, neutropenia, thrombocytopenia, physical weakness, fatigue, nausea, decreased appetite, diarrhea, vomiting, abdominal pain, and fever.

http://www.cancertherapyadvisor.com/gastrointestinal-cancers/fda-approval-colorectal-cancer-trifluride-tipiracil-treatment/article/440088/

3. Response After Angiogenesis or EGFR Inhibitors in Metastatic Colorectal Cancer Depend on Chemotherapy Backbone (Oct.25/15)

Optimal preoperative treatment before colorectal cancer metastases (CRCM) resection remains unclear. This study evaluated pathological responses (pR) in colorectal cancer metastases resected after chemotherapy alone or combined with angiogenesis (i.e. Avastin) or epidermal growth factor receptor (EGFR) inhibitors (i.e. Erbitux). Pathological response was retrospectively evaluated on 264 resected metastases from 99 patients. The proportion of responding metastases after different preoperative treatments was reported and compared. Patient's progression-free survival (PFS) and overall survival (OS) were compared based on pathological responses. The combination of anti-angiogenics with **oxaliplatin-based chemotherapy** resulted in more pathological responses than when they were combined with irinotecan-based chemotherapy (80% vs 50%). Inversely, the combination of EGFR inhibitors with oxaliplatin-based chemotherapy seemed to induce fewer pathological responses than when they were combined with irinotecan-based treatment (53% vs 72%). Overall survival at 5 years was improved for patients with a pathological response in all resected metastases compared with those who did not achieve a pathological response (68.5% vs 32.6%) and this response was the only factor predicting overall survival in a multivariate analysis. The chemotherapy partner combined with angiogenesis or EGFR inhibitors influenced pathological response in resected colorectal cancer metastases. In the exploratory analysis anti-angiogenic/oxaliplatin-based regimens and anti-EGFR/irinotecan-based regimens were associated with the highest pathological response. Prospective randomized trials should be performed to validate these observations.

Carrasco, J., et al., Pathological responses after angiogenesis or egfr inhibitors in metastatic colorectal cancer depend on the chemotherapy backbone. British J of Cancer 113, 1298-1304

4. Will Lower-Dose Regorafenib (Stivarga) Be Safer for Colorectal Cancer? (Oct.29/15)

Regorafenib is a tyrosine kinase inhibitor indicated for the treatment of patients with metastatic colorectal cancer (mcrc) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor receptor (VEGF) therapy (avastin), and, if KRAS wild-type positive, an anti-epidermal growth factor receptor (EGFR) therapy (erbitux or vectibix). The recommended dose is 160 mg orally once daily for the first 21 days of each 28-day cycle. Although effective at this dose for mCRC, a pivotal trial comparing regorafenib with placebo showed that at 160 mg daily, regorafenib caused asthenia/fatigue in 64% of patients, hand–foot skin reactions in 45% of patients, hypertension in 30% of patients, and rash in 26% of patients treated with the drug. Lower doses of regorafenib are also acceptable in patients who develop toxicities at the 160 mg dose. Reducing the dose of regorafenib to 120 mg is recommended for the first occurrence of grade 2 hand–foot skin reactions of any duration, after recovery of any grade 3 or 4 adverse reaction, and for grade 3 AST/ALT elevation as long as potential benefit outweighs the risk of liver toxicity. The dose can be further reduced to 80 mg after re-occurrence of grade 2 hand–foot skin reactions at the 120 mg dose and after recovery of grade 3 or 4 adverse reactions except liver toxicity at the 120 mg dose.

http://www.cancertherapyadvisor.com/gastrointestinal-cancers/colorectal-cancer-lower-regorafenib-dose-safer-treatment/article/449917/2/

5. Keytruda for Advanced Colorectal Cancer (Nov.3/15)

The FDA has granted a breakthrough therapy designation to pembrolizumab (Keytruda) as a potential therapy for patients with microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC), according to a statement from the company developing the PD-1 inhibitor, Merck. The designation was based on findings from an ongoing phase II study, which demonstrated high response rates with pembrolizumab in patients with heavily pretreated CRC with mismatch repair (MMR) deficiency, a condition that causes MSI. In the findings presented at ASCO, the objective response rate (ORR) was 62% with pembrolizumab in MMR-deficient mCRC compared with 0% in patients with MMR-proficient tumors. Median progression-free survival (PFS) and overall survival (OS) were not reached, with many patients responding to treatment for longer than 12 months in the MMR-deficient arm. In the 3-arm study that was the basis for the new designation, pembrolizumab was administered at 10 mg/kg every 2 weeks to patients with CRC who were MMR-deficient (n = 13) and MMR-proficient (n = 25). Additionally, a separate arm looked at pembrolizumab in patients with MMR-deficient non-CRC malignancies (n = 10). Defects in MMR commonly lead to microsatellite instability, which can be found in most cancers, including a majority of patients with hereditary nonpolyposis CRC (Lynch syndrome). Without this repair mechanism, the mutational burden is generally higher, suggesting a higher likelihood of developing cancer. In total, more than 80% of patients in the MMR-deficient arm were positive for Lynch syndrome. The primary endpoint of the study was immune-related PFS and response rate at 20 weeks. Secondary endpoints focused on OS, PFS, and disease control rate (DCR; complete response, partial response, plus stable disease). In the 48 patients analyzed from the study for the ASCO presentation, those with MMR-deficient CRC experienced a DCR of 92% compared with 16% in MMR-proficient tumors. After a median treatment duration of 5.9 months, no patients in the MMR-deficient group who responded had progressed. In patients with MMR-deficient non-CRC tumors, the ORR was 60% and the DCR was 70%.OS and PFS were not reached in the MMR-deficient group versus a median PFS of 2.3 months (HR, 0.10; 95% CI, 0.03-0.37; P <.001) and an OS of 7.6 months in the MMR-proficient group. In the analysis published in NEJM, which contained data from fewer patients, the ORR with pembrolizumab was 40% in patients with MMR-deficient mCRC (n = 10). In this same group, the PFS rate with pembrolizumab at 20 weeks was 78%. Interestingly, patients with Lynch syndrome (n = 11) were less likely to respond compared with those with other forms of MMR, according to the data published in NEJM. In those with Lynch syndrome, the ORR was 27% with pembrolizumab compared with 100% in those with MMR that was unrelated to Lynch syndrome (n = 6).

Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch repair deficiency. J Clin Oncol. 2015;(suppl; abstr LBA100).

Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015; 372:2509-2520.

http://global.onclive.com/web-exclusives/pembrolizumab-granted-breakthrough-status-for-microsatellite-instability-high-mcrc

6. Expanded Genetic Testing Should be Standard for Metastatic Colorectal Cancer (Nov.25/15)

ASCO released a provisional clinical opinion update recommending that all patients with metastatic colorectal cancer who are candidates for anti-EGFR antibody therapy (such as Erbitux or Vectibix) undergo *KRAS* and *NRAS* expanded genetic testing. The report indicated that an analysis of outcomes from 15 phase 2 and 3 trials showed patients with *RAS* mutations are unlikely to benefit from anti-EGFR monoclonal antibody therapy alone or in combination with chemotherapy. Thus, patients should undergo expanded testing, or assessment of KRAS and *NRAS* exon 2 (codons 12 and 13), exon 3 (codons 59 and 61) and exon 4 (codons 117 and 146). *RAS* testing is necessary before initiating treatment of patients who are considered candidates for anti-EGFR monoclonal antibody therapy because *RAS* mutations in exon 2, 3 or 4 are associated with lack of benefit from this treatment and may, in fact, be associated with worse outcomes when added to chemotherapy. Restricting cetuximab [Erbitux] or panitumumab [Vectibix] administration to patients whose tumors have no *RAS* mutations detected will help further tailoring of therapy to maximize patient benefit while minimizing harm.

Allegra CJ. J Clin Oncol. *2015;doi:10.1200/JCO.2015.63.9674.*
Douillard JY, et al. N Engl J Med. *2013;doi:10.1056/NEJMoa1305275.*
Van Cutsem E, et al. J Clin Oncol. *2015; doi:10.1200/JCO.2014.59.4812.*

SURGICAL

7. Colorectal Cancer With Liver Metastases: Synchronous vs. Sequential Resection (Sept.23/15)

In approximately 20% of cases, colorectal cancer has metastasized beyond the colon at the time of diagnosis. The liver is the most common site for these metastases. Although the approach to treating primary tumors within the colon and metastatic tumors in the liver continues to evolve, treatment typically

involves chemotherapy plus surgical removal of both types of tumors. However, experts continue to debate whether surgical resection of primary tumors and metastatic tumors should be performed at the same time (synchronously) or in separate operations (sequentially). The authors, all from the Mayo Clinic in Rochester, Minnesota, explained that the study results provide procedure-specific national benchmarks for postsurgical outcomes that will facilitate comparisons for quality improvement. Analyzing data from patients within specific risk categories, the study also found that major complications after synchronous liver and colorectal resections vary and are related to the extent of liver resection performed and the type of colorectal surgery performed. The risk for poor patient outcomes increases as the risk of each component surgical procedure increases. In other words, regardless of surgery timing, patients who require higher-risk procedures, such as a major liver resection due to the presence of larger or multiple metastatic tumors or high-risk colorectal resections, have poorer outcomes than those who underwent more minor surgery. ***Synchronous resection of primary colorectal tumors and metastatic liver tumors is safe and effective in patients who require only minor liver resections***. "Our findings also show that performing preoperative risk assessments on patients who require both liver and colorectal resections could allow surgeons to more accurately predict patient outcomes and assist in preoperative planning and counseling these patients," said lead author David Nagorney, MD, a general surgeon at Mayo Clinic. In designing the study, the researchers used a large, multi-institutional database to identify a pool of **43,408 patients** who underwent colorectal and liver resections for stage IV colorectal cancer. Before this study was conducted, only limited surgical outcomes data was available for these patients. "Our primary aim was to establish the magnitude of risk that each component operation, both liver and colon, contributed to synchronous resections in order to determine which combination of colon and liver operations were most safe to be performed at the same time," said Nagorney. The researchers also reviewed the type or location of colorectal resection, whereas past studies only considered the extent of liver resection performed. "We wanted to test the hypothesis that both the extent of the liver resection and the location or type of colorectal resection influence the overall risk and patient outcomes associated with these operations," said the article's first author, Christopher Shubert, MD, who is also a surgeon and Kern Scholar at Mayo Clinic. The researchers assigned risk categories to each of the operations performed in the data pool, including colorectal and liver resections, and then compared 30-day postsurgical outcomes among patients within similar risk groups. They also compared outcome data between two groups of patients within each risk category: those who underwent synchronous colorectal and liver resections and those whose surgeries were performed sequentially.

Shubert, Chrisjtopher, et al., Journal of Gastrointestinal Surgery 2015; 10.1007/s11605-015-2895-z

8. Survival Benefit of Repeat Resection of Successive Recurrences After the Initial Hepatic Resection for Colorectal Liver Metastases (Oct.16/15)

Relapse is common after the resection of colorectal liver metastases; however, the optimal treatment for such recurrent disease remains uncertain. Researchers investigated whether repeat resections for successive recurrences of colorectal liver metastases provide survival benefit on the postrecurrence survival. They reviewed patients who underwent upfront, curative resection for colorectal liver metastases at our center during a 15-year period. Of these, 263 patients who had not received any other perioperative treatment for the metastases were eligible for their analysis. The recurrence-free survival (RFS0) after the initial hepatic resection and after the first (n = 108), second (n = 43), and third (n = 15) repeat resections for recurrent disease were assessed (RFS1-3). The overall survival after the initial hepatic resection and the postrecurrence survival (n = 198) also was assessed. The median RFS0 was 0.8 years, and RFS1, RFS2, and RFS3 were 1.3, 1.1, and 2.0 years, respectively. The 5-year and 10-year OS rates were 54.6% and 42.2%, and the 5-year and 10-year postrecurrence survival was 34.3% and 28.6%, respectively. Researchers concluded that repeat resection in patients with recurrent disease after colorectal liver metastases resection is beneficial, offering the potential for cure in a small proportion of patients with recurrent disease.

Oba, Masaru, et al., Survival benefit of repeat resection of successive recurrences after the initial hepatic resection for colorectal liver metastases. Surg Feb 2016 Vol 159, Issue 2, pp 632-640.

9. Watch and Wait Approach Versus Surgical Resection After Chemoradiotherapy for Rectal Cancer (Dec.16/15)

A substantial proportion of patients with rectal cancer managed by the watch-and-wait approach avoided a major operation and averted permanent colostomy without differences in 3-year non-regrowth disease-free survival compared with patients who underwent surgical resection, a new study published online ahead of print in the journal *The Lancet Oncology* has shown. Although a watch-and-wait approach has emerged as a management strategy for patients with rectal cancer after they have achieved a clinical complete response with chemoradiotherapy, there is limited evidence evaluating the safety of this approach. Therefore, researchers sought to compare oncological outcomes between patients managed by watch and wait who achieved a clinical complete response and those who underwent surgical resection. For the ONCORE cohort analysis study, researchers included 259 patients diagnosed with rectal adenocarcinoma without distant metastases who had received preoperative chemoradiotherapy consisting of fluoropyrmidine-based chemotherapy. Patients who achieved a complete clinical response were offered watch-and-wait management and patients who did not have a clinical complete response were offered surgical resection. A total of 129 patients were managed by watch and wait. Of those, 34%

had local regrowths and 88% of 41 patients with non-metastatic local regrowths were salvaged. Researchers found no differences in 3-year non-regrowth disease-free survival between the watch-and-wait group and the surgical resection group. There was also no difference in the 3-year overall survival rate between the 2 groups. The study demonstrated that patients managed by watch and wait had significantly better 3-year colostomy-free survival compared with those who had undergone surgical resection. "These findings should inform decision making at the outset of chemotherapy," the investigators concluded.

Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis [published online ahead of print December 16, 2015]. Lancet Oncol. doi: 10.1016/S1470-2045(15)00467-2.

SCREENING

10. Study Suggests IBD Patients Only Need to Undergo Colonoscopy Up To Every 5 Years (Sept.24/15)

There has been substantial debate on the issue of how often one should undergo surveillance colonoscopy procedures to detect colorectal cancer (CRC) at an early stage and improve survival. Recent studies and advice from disease authorities suggest that patients who are not considered high-risk can be allowed a few more years in between procedures. Now, a study led by University Medical Center Utrecht scientist Bas Oldenburg, MD, PhD, suggests that patients with active inflammatory bowel disease (IBD) who regularly have surveillance colonoscopy have a lower occurrence of interval CRC, meaning they can allow up to 5 years before having to undergo another surveillance colonoscopy. To arrive at this conclusion, Dr. Oldenburg and his fellow researchers conducted a retrospective analysis of IBD patient information. They gathered data on 1,273 IBD patients (34% Crohn's disease, 63% ulcerative colitis, 3% unclassified) who underwent a total of 4,327 surveillance colonoscopies between January 1, 2000 and January 1, 2014. Patients were monitored between their first and last surveillance colonoscopy, bearing in mind procedure-related factors that may be linked to any incidence of CRC, such as inadequate procedures, inadequate surveillance, or inadequate management of dysplasia. According to a news release, true interval CRCs were defined as those "detected within the appropriate surveillance interval, after an adequately performed surveillance colonoscopy." Researchers found that 1.3 percent of the studied patients developed CRC, with the median interval between the last colonoscopy procedure and CRC diagnosis being 22 months. This study shows that the incidence of crc among IBD patients enrolled in a surveillance program is low compared with previous studies, with only 17 cancers detected during 6,823 years of follow-up evaluation, the researchers wrote. This might support the longer surveillance interval of up to 5 years as recommended in the current [British Society of Gastroenterology] and European Crohn's and Colitis Organization guidelines, although the fact that one third of all CRC cases appear to be interval carcinomas underscores the need to further identify risk factors associated with the development of interval cancer, the researchers maintain.

Mooiweer, Erik, et al., Incidence of interval colorectal cancer among inflammatory bowel disease patients undergoing regular colonoscopic surveillance. Clin Gastro & Hep. Sept 2015 Vol 13, Issue 9, pp 1656-16661.

11. Shorter Colonoscopies Linked to Higher Cancer Intervals (Sept. 25/15)

Research by a Veterans Affairs team has confirmed that longer-lasting colonoscopies are associated with lower cancer rates. Experts already know about the link between colonoscopy withdrawal time and patient outcomes, but the new study provides some of the strongest evidence yet to back clinical guidelines covering this aspect of the procedure. In a colonoscopy, a doctor inserts a long, thin tube with a tiny camera fitted to the end into the patient's colon. After the tube is fully inserted, it is then slowly withdrawn. It is during this "withdrawal time" that the doctor carefully examines the lining of the colon, looking at a view of the colon on a monitor in the exam room. Any small growths, or polyps, are removed with the scope's snipping tool and sent for biopsy. These growths may grow into cancer within a few years. According to current guidelines, a "normal" colonoscopy--one in which there is no finding of cancer or pre-cancerous growths, and the doctor does not remove any snippets of tissue to be biopsied--should have a withdrawal time of at least six minutes. Shaukat's team looked at data on colonoscopies performed over six years by 51 gastroenterologists in a large community practice in Minnesota. The team calculated average withdrawal times for each doctor. The average for the practice on the whole was 8.6 minutes--well within guidelines. But about 10 percent of the doctors had individual averages of under six minutes. The researchers then checked the state's cancer registry to look for cases of colorectal cancer among patients who had been screened at the same practice during the study period. Patients who had been examined by doctors with shorter withdrawal times, on average, were more likely to have cancer. The rate was more than twice as high for patients whose doctors had average withdrawal times of under six minutes, compared with those whose physicians' average times were over six minutes. Withdrawal times of longer than eight minutes didn't seem to afford any extra reduction of risk. As such, the researchers say focusing quality-improvement efforts on withdrawal times of under six minutes would likely have the most impact. The study included cancers that occurred within about five years of the patient's last colonoscopy. The assumption is that such "interval cancers" might have grown from polyps that were present during the colonoscopy but not detected, or not fully removed. Shaukat says the reasons for sub-standard withdrawal times may vary, but "generally, every physician aims to do a complete inspection of the colon lining, regardless of their withdrawal time." Even the American College

of Gastroenterology acknowledges that not every colonoscopy withdrawal must take at least six minutes, as some colons can be examined effectively in under six minutes. Just the same, Shaukat says that withdrawal time appears to be a "robust indicator" of interval cancer risk. She urges more research on the topic, and on related quality measures for colonoscopies. "We need to understand the quality indicators better, define thresholds, and be able to adjust them to the particular patient population and underlying risk. Until there are uniform methods for data collection, adjustment, and collection, the numbers don't mean much. We might be comparing apples to oranges." Shaukat says it's appropriate for patients to ask their gastroenterologists if they collect and review quality metrics for their colonoscopies. At the same time, though, she points out that most patients won't be in a position to properly make sense of the actual data. "The exact metrics and their cut-offs are debatable, but a commitment to quality needs to be there for every practice."

Aasma Shaukat, et al.. Longer Withdrawal Time Is Associated With a Reduced Incidence of Interval Cancer After Screening Colonoscopy*. Gastroenterology, *2015; DOI: 10.1053/j.gastro.2015.06.044

OTHER

12. Molecular Differences Found Between Tumours of Younger, Older CRC Patients (Sept.29/15)

Colorectal cancer (CRC) is on the rise among younger patients. Although some of the younger-onset cases can be explained by hereditary factors, the majority arise spontaneously. Researchers have now found that tumours in younger colorectal cancer patients may be molecularly distinct from those of older patients, and that these differences are related to the way genes are switched on and off (epigenetics) in the tumours of the younger patients. Such a discovery may lead to better treatment options tailored specifically to a younger age group, researchers say. Tumours from two groups of CRC patients were analyzed; the first included patients treated at Memorial Sloan Kettering, and the second patients from The Cancer Genome Atlas, a project aiming to catalogue cancer-causing genetic mutations, run by the US National Cancer Institute. Genomic sequencing techniques were used to look for gene mutations and other changes to DNA that affect the ways genes behave (processes known as gene expression and methylation). In the early onset group researchers found that 154 genes were under-methylated. Both under (hypo) and over (hyper) methylation of genes are found in cancer. They also found that an increase in methylation went hand in hand with an increase in age among the younger patients, and that this intensification was beyond that which would occur naturally in normal tissue. Finding such a distinctive molecular make-up in this group encourages researchers to believe that they may, in the future, be able to tailor treatments to them and attempt to prevent or slow down these processes in order to improve outcomes for them. Younger-onset CRC has increased at a continuous rate of 1.5% per year in men and 1.6% per year in women during the period 1992-2011, according to data from the Surveillance, Epidemiology, and End Result Registries (SEER), the agency that collects and collates cancer statistics on behalf of the US National Cancer Institute. Although CRC is the third most common cancer in the world, with nearly 1.4 million new cases diagnosed in 2012, younger patients tend to present and be diagnosed later, when their disease is more advanced and hence more difficult to treat. This is most likely to be due to a lack of awareness of symptoms in patients as well as doctors, in addition to the tendency to attribute those symptoms to other causes. Changes in bowel habits may be attributed to Crohn's disease, food allergies, or simply stress, for example, and doctors send younger patients for early CRC screening much less frequently than they do older ones. Raising awareness of the increasing frequency of younger-onset CRC among clinicians is very important. Younger CRC patients tend to be treated more aggressively, though currently there is no other difference in the therapies used. That is why the findings are important. Researchers hope to be able to continue research on the molecular and epigenetic characterization of tumours from younger-onset CRC patients in order to be able to develop better therapies for them, and improve their overall survival as well as their quality of life.

* ***Methyl is a naturally occurring combination of hydrocarbons (hydrogen + carbon).***

** ***Methylation, a process where methyl groups are added to DNA and modify its function, plays a role in many biological processes.***

2015 European Cancer Congress, Vienna:

Abstract no 2189. "Early onset colorectal cancer -- does the difference lie in epigenetics?." Gastrointestinal malignancies -- colorectal cancer poster session, 09.15-11.15 hrs (CEST), Sunday 27 September, Hall C.

http://www.sciencedaily.com/releases/2015/09/150927115522.htm

13. Scientists Find 4 Distinct Types of CRC (Oct. 10/15)

Bowel cancer can generally be classified as four distinct diseases - each of which has its own characteristics, new research has revealed. The discovery may lead to doctors treating each type of disease differently, and assist the development of more targeted drugs. Also known as colorectal cancer, bowel cancer affects the colon and rectum. The new conclusions were drawn after British scientists combined clinical and molecular data collected from 3,443 patients with bowel cancer around the world. Information on genetic mutations, gene activity, immune system activation, cell metabolism, cancer cell type and invasive ability was analyzed. The scientists found that 87 per cent of cancers fell into one of four distinct groups, or 'consensus molecular subtypes' (CMS). One set of patients, with the CMS4

subtype, were often diagnosed late. This meant the disease had often spread - and these people therefore had significantly worse survival rates. Another group, CMS2, had much better survival rates even after the cancer had relapsed. The study has identified four distinct types of bowel cancer, each with a definite set of genetic and biological characteristics, and some of which are more aggressive and more likely to be fatal than others. This could allow doctors to pick out those patients with more aggressive disease and treat them accordingly. Ultimately, it could lead to development of new tests to diagnose patients by their particular type of bowel cancer, and give them the most effective treatments for that type.

http://www.dailymail.co.uk/health/article-3269607/Bowel-cancer-breakthrough-scientists-FOUR-distinct-types-disease-paving-way-better-treatment.html

14. "Cancer Brain" not "Chemo Brain" Researchers Discover (Nov. 2/15)

In the largest study of its kind ever conducted, researchers have determined that almost half of all bowel cancer survivors suffer memory loss and have trouble multitasking and concentrating because of the disease. The University of Sydney researchers believe the results hold true for people with many cancers and has nothing to do with chemotherapy. It's often after they get back to work they notice it and in particular what they complain about is problems with multitasking. Researchers set out to find out just how many cancer patients were experiencing these cognitive lapses. They measured hundreds of colorectal, or bowel cancer, patients against healthy controls. What they found to their great surprise was that there was great high rates of cognitive impairment before people had received any chemotherapy whatsoever. "So what we found was that in those that had localised colorectal cancer, 43 per cent of those had cognitive impairment based on our definition, compared to only 15 per cent of the healthy controls." Even a year later, when there was no trace of bowel cancer in the patient's bodies, they were still three times more likely to have issues with things like memory and concentration than healthy people. The research team found patients who received chemotherapy were no worse off. "We were expecting the cancer patients who had received chemotherapy to have more cognitive impairment than those who did not go on to receive chemotherapy, but in fact there was very little difference between the two cancer groups with localised disease. So the nickname that's been given of 'chemo brain' is not very accurate and it's probably something more like a 'cancer brain'." Researchers focused on bowel cancer, but researchers believe the results would be similar for many cancers. The researchers did not find what caused the decline in cognitive ability. It's a little bit difficult for them to give solid advice about this, but on the basis of some of the work that's been done in other areas, and in particular in animals studies, which is probably that physical activity is something that can potentially help to preserve and protect cognitive function in cancer patients and cancer survivors. "And there's a possibility that some brain training exercises might help as well." This study shows cognitive impairment in bowel cancer patients last for at least two years after diagnosis. Whether the concentration and memory lapses continue beyond that will be the focus of follow up research.

http://www.abc.net.au/news/2015-11-03/researchers-discover-cancer-causes-memory-loss/6908076

15. Colonic Diverticulosis Does Not Increase Risk For Colorectal Cancer (Sept.10/15)

Recent findings published suggested colonic diverticulosis did not increase the risk for colorectal or advanced adenomas, contrary to previous research. Colonic diverticula are associated with a spectrum of morbid and mortal disease, including diverticulitis, diverticular bleeding and free rupture. Now there are reports that diverticula are associated with an increased risk of missed colorectal cancers. Researchers found no association between diverticula and adenomas. Researchers analyzed data from a prospective study of 624 patients aged 30 years and older who underwent colonoscopy screening between 2013 and 2015 at the University of North Carolina Hospitals in Chapel Hill. During the screening, patients were examined for colorectal polyps and colonic diverticula. During the colonoscopy, the number and location of all colonic diverticula were documented. The researchers found 35% (n = 216) of patients had one or more colorectal adenomas. Colonic diverticulosis on colonoscopy did not increase the risk of adenomas or advanced adenomas. Colonic diverticulosis did not increase the risk of proximal or distal adenomas. Having 10 or more diverticula did not increase the risk of adenomas compared with having none. According to the researchers, the reported increased risk could be the result of detection bias, as patients with missed colorectal cancers have had more colonoscopies and greater opportunity for a diagnosis of diverticulosis vs. patients with sporadic colorectal cancers. "Any association between missed cancers and colonic diverticula is not due to greater risk for neoplasia in patients with diverticula," researchers maintain. "It's important to point out that because individuals with diverticulosis may have distorted colonic architecture, it might be easier for endoscopists to miss lesions so a careful exam is important."

Peery AF, et al. **Colonic Diverticula Are Not Associated With an Increased Risk of Colorectal Adenomas Am J Gastroenterol.** ***2015;doi:10.1038/ajg.2015.359.***

16. Mindfulness-based Stress Reduction Diminishes Chemo Brain (Dec.7/15)

Although cancer-related cognitive impairment, sometimes referred to as chemo brain or post-cancer cognitive fuzziness, is common among survivors -- disrupting social relationships, work ability, self-confidence, and quality of life -- clinicians have few treatment options to offer. Cognitive deficits have been seen to persist for more than a decade following cancer treatment for many survivors. In the study,

MBSR participants reported significantly greater improvement in the ability to pay attention, and also made fewer mistakes on difficult cognitive tasks than those in the control group, which received patient education materials and supportive counseling. Both groups attended eight weeks of two-hour classes led by skilled facilitators. Retention rates in the trial exceeded 95 percent, strongly suggesting that participants found the program to be worthwhile. Previous studies by the Regenstrief-IU research group have found MBSR to have a positive impact on post-cancer fatigue, depression and sleep disturbance. Mindfulness training is thought to improve cognitive functioning through mechanisms of focused attention and non-reactive coping with one's internal experiences, such as thoughts, feelings, and bodily sensations. Programs in MBSR include a variety of meditation and yoga practices and other elements. These programs typically range in cost between $200 and $800 for an eight-week program, and are widely available in communities and over the Internet. Those who participated in the MBSR arm of the Regenstrief-IU study reported significant engagement with high rates of self-reported home practice of mindfulness techniques during the study. The majority continued to practice mindfulness throughout the six-month period following conclusion of the program. "More people than ever are surviving cancer due to the development of targeted and effective treatments," said Shelley Johns, Psy.D., the clinical health psychologist and health services researcher who led the Regenstrief-IU study. "Yet many cancer survivors are living with difficult and persistent side effects of these treatments, which can be incapacitating. "Mindfulness meditation practices enable cancer survivors to better manage cancer-related cognitive impairment, reported by approximately 35 percent of cancer survivors who have completed treatment," said Dr. Johns, who is a Regenstrief Institute investigator and assistant professor of medicine in the IU School of Medicine. "MBSR provides a creative solution for survivors whose social and occupational functioning may have been negatively impacted by cognitive difficulties." While some oncologists provide patients with information on cancer-related cognitive impairment, the majority of clinicians do not address this symptom due to lack of evidence-based treatments for the condition according to Dr. Johns.

Shelley A. Johns, et al., . Randomized controlled pilot trial of mindfulness-based stress reduction for breast and colorectal cancer survivors: effects on cancer-related cognitive impairment. **Journal of Cancer Survivorship*, 2015; DOI: 10.1007/s11764-015-0494-3***

NUTRITION & HEALTHY LIFESTYLE

17. Increased Risk of CRC for Each 1cm Rise in Waist Circumference (Oct.26/15)

Experts speaking at the 23rd United European Gastroenterology Week (UEG Week 2015) in Barcelona, Spain revealed compelling evidence of the link between excess body weight and risk of colorectal cancer (CRC). Researchers in the UK presented data showing an overall increase of 18% in relative risk of CRC per 5 unit increase in BMI. In addition, in men, there is now evidence that increasing waist circumference in middle age is associated with increased bowel cancer risk. CRC risk was increased by nearly 60% in men who gained at least 10 cm in waist circumference over 10 years. This increased cancer risk may be due to persistent inflammation in people with obesity. Patients with Lynch Syndrome (LS) have a higher than normal risk of CRC because of an inherited defect in one of the genes responsible for repairing DNA. Researchers also presented new data showing that, in people with Lynch Syndrome, CRC risk increases with higher body weight and for those who are obese the risk of CRC is doubled. Quite surprisingly, the increase in CRC risk with higher body weight in people with Lynch Syndrome was about twice as great as that seen in the general population. Lead researcher said "There is now compelling evidence that improved lifestyle, particularly better dietary choices and being more physically active, can help to prevent obesity and this will lower bowel cancer risk." In addition, for those people who are already too heavy, losing weight may reduce their CRC risk but this is an area which requires further study. In his studies with Lynch Syndrome patients, lead researcher Prof. Mathers observed that aspirin lowered the excess CRC risk seen in patients with obesity, perhaps through its anti-inflammatory effects. "This is a very intriguing finding" said Prof Mathers "which suggests that dietary and other anti-inflammatory agents might be beneficial in reducing CRC risk in people with obesity." "Bowel cancer is strongly associated with age, obesity and diet -- and is driven by inflammation," explains Prof. Mathers. "We can now give the public clear advice on the benefits of staying physically active, eating a healthy diet and avoiding weight gain to lower CRC risk as we get older."

http://www.sciencedaily.com/releases/2015/10/151027074816.htm

18. In CRC, Low BMI Linked with Higher Risk of Progression, Death (Oct.27/15)

Low body mass index (BMI) may be associated with a higher risk of progression and death among patients with metastatic colorectal cancer (mcrc) enrolled in clinical trials, according to a meta-analysis published in the *Journal of Clinical Oncology.* Researchers looked at individual data from 21,149 patients who were enrolled in 25 first-line mCRC trials during 1997 to 2012. They assessed for prognostic and predictive effects of BMI on the overall and progression-free survival (PFS) of these patients while accounting for patient and tumor characteristics as well as therapy type. The researchers found that risk of progression and death was greatest among patients with low BMI, with a steadily decreasing risk as BMI increased up to 28 kg/m^2. Low BMI was also found to be associated with poorer survival in men than woman. Compared to obese patients, patients who had a BMI of 18.5 kg/m^2 were found to have a 27% increased risk of having a PFS event and a 50% increased risk of death. “Possible explanations include

negative effects related to cancer cachexia (fatigue/weight loss/loss of appetite) in patients with low BMI, increased drug delivery or selection bias in patients with high BMI, and potential for an interaction between BMI and molecular signaling pathways," the authors concluded.

Renfro LA, Loupakis F, Adams RA, et al. Body mass index Is prognostic in metastatic colorectal cancer: pooled analysis of patients from first-line clinical trials in the ARCAD database [published online ahead of print October 26, 2015]. J Clin. Oncol. doi: 10.1200/JCO.2015.61.6441.

19. High Intensity Exercise May Benefit Colorectal Cancer Survivors (Nov.2/15)

High-intensity exercise training appears to be safe, feasible, and efficacious to improve cardiorespiratory fitness and body composition for colorectal cancer survivors. Because reductions in cardiorespiratory fitness and body composition lead to significant increases in morbidity and mortality among patients with colorectal cancer who have received anticancer therapy, researchers sought to evaluate the impact of 4 weeks of high-intensity exercise compared with moderate-intensity exercise training on peak oxygen consumption and body composition in survivors of colorectal cancer. For the study, researchers enrolled 47 post-treatment colorectal cancer survivors and randomly assigned them to undergo high-intensity or moderate-intensity exercise in accordance with current physical activity guidelines. Participants completed 12 exercise training sessions over a period of 4 weeks. Results showed that high-intensity exercise was superior to moderate-intensity exercise in improving peak oxygen consumption. Researchers also found that high-intensity training led to significant increases in lean mass and reductions in fat mass and fat percentage. No changes in lean mass, fat mass, or fat percentage were observed in the moderate-intensity exercise group. In regard to safety, researchers observed no severe adverse events in either treatment arm. "[High-intensity exercise] appears to offer superior improvements in cardiorespiratory fitness and body composition in comparison to current physical activity recommendations for colorectal cancer survivors and therefore may be an effective clinical utility following treatment," the authors conclude.

Devin JL, et al. The influence of high-intensity compared with moderate-intensity exercise training on cardiorespiratory fitness and body composition in colorectal cancer survivors: a randomised controlled trial [published online ahead of print October 19, 2015]. J Cancer Surviv. doi:10.1007/s11764-015-0490-7.

20. Research: Vitamin A Effectively Reverses Potential Relapse of Colon Cancer (Dec.28/15)

A biological mechanism to counteract colon cancer relapse (recurrence) was identified by a team of Swiss researchers. The approach uses vitamin A to activate a protein that was lost in persisting cancer cells. Most colon cancer cells die off with treatments such as chemotherapy. However, the genetic mutations that caused the cancer can survive in some stem cells within the colon. After cancer treatment ends, the surviving stem cells can produce new colon cells, along with any cancer-causing mutations, and result in a relapse of disease. The laboratory of Joerg Huelsken, PhD, at École Polytechnique Fédérale de Lausanne (EPFL) in Switzerland, studied how differentiated colon cells are developed from stem cells in the gut. Using several techniques, the team looked at cells, mouse models, and samples from human patients. This study focused on the **HOXA5 protein**, which belongs to a family of proteins that regulate the fetal development. These proteins are made during early development and work together to ensure that every tissue is correctly identified and that the fetus' body and limbs are patterned properly. In the adult body, proteins such as HOXA5 regulate the body's stem cells to maintain both the identity and function of different tissues. Huelsken's team found that in the gut, HOXA5 plays a major role in restricting the number of stem cells, as well as the cells that make them. As with all proteins, HOXA5 originates from a specific gene. The researchers found the cancerous stem cells of the colon use a biological mechanism that blocks it. The mechanism, called a *signaling pathway,* involves a domino of molecules, each activating the next one down the line. The purpose of a signaling pathway is to transmit biological information from one part of the cell to another, eg, from the outer membrane to the nucleus. By blocking the HOXA5 gene, the cancerous stem cells of the colon can grow uncontrollably and spread, resulting in relapses and metastasis. The researchers looked for ways to reverse the HOXA5 blockage. Their answer was found in vitamin A. This small chemical structure, called a *retinoid*, is known to induce differentiation of stem cells in the skin. The EPFL scientists found that retinoids can re-activate HOXA5. In mice with colon cancer, the retinoid treatment blocked tumor progression and normalized the tissue by turning the gene for HOXA5 back on. The treatment eliminated cancer stem cells and prevented metastasis in the live animals. Similar results were achieved with samples from actual patients. The new study suggests that the expression pattern of the HOXA5 gene can identify those patients who may benefit from this well-tolerated treatment. Retinoid differentiation therapy could be significantly effective against colon cancer, not only as treatment of existing disease but also as preventive in patients at high-risk for the disease.

http://www.oncologynurseadvisor.com/colorectal-cancer/vitamin-a-effectively-reverses-potential-relapse-of-colon-cancer/article/461718/
Cancer Cell (doi:10.1016/j.ccell.2015.11.001