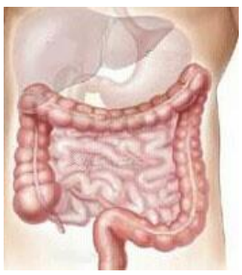
COLORECTAL CANCER RESEARCH UPDATES

Month Ending March 17th, 2017



The following colorectal cancer research update extends from February 17th to March 17th, 2017 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. An alternative theory on how aspirin may thwart cancer (Feb 8/17)

While aspirin is not a part of mainstream cancer treatment, it is recommended by the US Preventive Services Task Force for a subset of individuals to help prevent colorectal cancer (CRC). Many studies suggest that aspirin's chemopreventive effects may be attributed to the drug's anti-inflammatory properties. Its widespread regular use, however, has not been accepted due to the associated risk of gastrointestinal bleeding. Researchers from Veterans Affairs have a new theory which they have successfully tested in mice and cell cultures. They suggest that aspirin's effect on platelets, the blood cells that form clots to stop bleeding,

triggers its cancer preventive effects. Beyond clotting, platelets are important in forming new blood vessels – a process known as angiogenesis. When a blood clot forms after a wound, new blood vessels are necessary to redirect blood flow. Tumours rely on the same mechanism of angiogenesis to proliferate, and it is precisely this process that aspirin interferes with. Researchers' lab results demonstrate how aspirin was able to block the interaction between platelets and cancer cells by inhibiting the enzyme COX-1. Inhibition of COX-1 diminishes the number of circulating platelets and thus their level of activity. While some of the experiments used regular pharmacy-grade aspirin, another phase experimented with a special preparation of aspirin combined with phosphatidylcholine, a kind of fat molecule found in soy lecithin. The product is known as Aspirin-PC/PL2200, designed to reduce the gastrointestinal risk that is associated with everyday aspirin. Researchers found that the enhanced aspirin was even better at preventing cancer than its regular counterpart. Researchers plan to test the lipid-aspirin complex for safety and efficacy in individuals at high risk for CRC.

https://medicalxpress.com/news/2017-02-alternative-theory-aspirin-thwart-cancer.html

2. Human epithelial growth factor receptor type 2 as an emerging oncotarget for colorectal cancer treatment after failure of anti-epidermal growth factor receptor therapy (March 2017)

Increased expression of the human epithelial growth factor receptor type 2 (HER2) gene is an indicator of poor prognosis in colorectal cancer (CRC), and anti-HER2 targeting therapies provide clinical benefits among these patients. In anti-epidermal growth factor receptor (EGFR) antibody treatment of CRC, HER2 activation provides a bypass signalling pathway, thereby sustaining cancer cell growth. As such, HER2 has been identified as a "resistance molecule" for standard cetuximab (anti-EGFR antibody) therapy. Despite causing resistance to such molecular targeting agents, HER2 remains a promising target for oncotherapy. Future research aims to develop anti-HER2 drugs and introduce them into clinical practices in the treatment of patients with HER2-positive CRC.

http://www.clinical-colorectal-cancer.com/article/S1533-0028(16)30240-7/abstract

3. The role of aspirin as antitumoral agent for heavily pretreated patients with metastatic colorectal cancer receiving capecitabine monotherapy (March 2017)

Among patients with metastatic colorectal cancer (mCRC) who fail to respond to all available options, regorafenib and TAS-102 represent the only chance of treatment. While effective, these therapies carry a heavy economic cost and high toxicity. A recent study aimed to examine the use of aspirin in combination with capecitabine therapy as a salvage option prior to the introduction of regorafenib and TAS-102. Among the 66 participants, 20 patients were already taking aspirin for cardiovascular diseases. 12 partial responses (60%) were observed in patients receiving aspirin + capecitabine, compared to 3 partial responses (6%) in the non-aspirin group. 16 patients on aspirin (80%) obtained disease control compared to 14 (30%) patients who were not taking aspirin. The median progression-free survival (PFS) for patients receiving treatment with aspiring was 6.5 months compared to 3.3 months for patients not taking aspirin. Furthermore, a significantly improved overall survival was observed among aspirin users compared to non-users (14.7 months vs. 8.7 months). The study results demonstrate that aspirin may help to improve the clinical outcome of heavily pre-treated mCRC patients receiving chemotherapy. Further studies are necessary to deepen clinical understanding of this potential combined therapy.

http://www.clinical-colorectal-cancer.com/article/S1533-0028(16)30118-9/abstract

4. Scientists discover why some cancers may not respond to immunotherapy (Feb 7/17)

Pembrolizumab (Keytruda) is an antibody agent used in cancer immunotherapy. It inhibits a protective mechanism on cancer cells, allowing the immune system to search and destroy them. Scientists have recently discovered that patients with cancer containing JAK1 or JAK2 mutations will have little to no response from pembrolizumab. Mutations in JAK1 or JAK2 are known to stop tumours from receiving signals from the immune system to stop growing. These mutations are also understood to reduce the expression of a particular biomarker (PD-L1) expressed by tumour cells which pembrolizumab must recognize in order to initiate the cancer cell attack. Previous studies have analyzed patients' tumours before immunotherapy and after cancer relapse. It was found that the tumours lost a gene called B2M, leading to a change in how the immune system recognized the cancer. This change in cancer cell recognition then caused JAK1 and JAK2 genes to function improperly.

Pembrolizumab (Keytruda) was approved in 2014 in the treatment of advanced melanoma, and in 2016 in the treatment of non-small-cell lung cancer. Its use in the treatment of colorectal cancer is currently undergoing testing in clinical trials. Researchers are in the process of studying JAK1 and JAK2 mutations in animal models to uncover treatment alternatives for individuals who do not respond to pembrolizumab anti-PD-1 therapy.

Aurelien Marabelle et al. Mutations as Escape Mechanisms to Anti–PD-1 Therapy, Cancer Discovery (2017). DOI: 10.1158/2159-8290.CD-16-1439

https://medicalxpress.com/news/2017-02-scientists-cancers-immunotherapy.html

5. Treatment, diagnosis disparities among hospitals impacts survival of patients with colorectal cancer and peritoneal metastases (Feb 1/17)

A recent study examined the underutilization of hyperthermic intraperitoneal chemotherapy (HIPEC) due to lack of referral among patients with the same diagnosis. In the study, patients with the same diagnosis of colorectal cancer (CRC) with peritoneal metastases (PM) were offered different treatments leading to dramatically different outcomes based on the institution in which they received their diagnosis. Only patients diagnosed at a **HIPEC** center or an academic teaching hospital were likely to be offered **cytoreductive surgery (CRS) and HIPEC treatment**. 10 years of randomized controlled trials have demonstrated greater survival with the combined treatment compared to standard care of conventional surgery and systemic chemotherapy.

CRS/HIPEC therapy removes all visible tumours from the abdominal cavity, bathing it with chemotherapy that has been heated to 42 degrees Celsius to kill any remaining cancer cells. The localized delivery of chemotherapy allows for higher doses than are possible systemically (administered throughout the body). In the study, it was observed that 25-30% of patients with CRC and PM experienced significant clinical benefit from HIPEC. The disparity in the use of CRS/HIPEC treatment led to notable variations in patient outcomes, where overall survival (OS) was 14.1 months for patients diagnosed in a HIPEC center compared to OS of 9.6 months for patients diagnosed in a non-HIPEC center. Among academic/teaching hospitals, 17% of patients were referred for CRS/HIPEC compared to 11% in non-teaching hospitals. OS was 11.5 and 8.7 months for teaching hospitals and non-teaching hospitals, respectively. Thus, it was observed that although available in the Netherlands, CRS/HIPEC appears to be underused leading to suboptimal treatment of patients.

http://www.onclive.com/web-exclusives/treatment-diagnosis-disparities-among-hospitals-impacts-survival-of-patients-with-colorectal-cancer-and-peritoneal-metastases

Rovers K, Simkens G, Vissers P, et al. Survival of patients with colorectal peritoneal metastases is affected by treatment disparities among hospitals of diagnosis: a nationwide population-based study. Abstract presented at: 19th European Cancer Congress; January 27-30, 2017; Amsterdam, Netherlands.

SURGICAL THERAPIES

6. Living donor liver transplantation for unresectable colorectal cancer liver metastases (Dec 2016)

Approximately half of all colorectal cancer (CRC) patients develop metastases, commonly to the liver and lung. Surgical removal of liver metastases (LM) is the only treatment option, though only 20-40% of patients are candidates for surgical therapy. Surgical therapy adds a significant survival benefit, with a 5-year survival after liver resection for LM of 40-50%, compared to 10-20% 5-year survival for chemotherapy alone. Liver transplantation (LT) would remove all evident disease in cases where the colorectal metastases are isolated to the liver but considered unresectable. While CRC LM are considered a contraindication for LT at most cancer centers, a single center in Oslo, Norway demonstrated a 5-year survival of 56%. A clinical trial sponsored by the **University Health network in Toronto** will offer live donor liver transplantation (LDLT) to select patients with unresectable metastases limited to the liver and are non-progressing on standard chemotherapy. Patients will be screened for liver transplant suitability and must also have a healthy living donor come forward for evaluation. Patients who undergo LDLT will be followed for survival, disease-free survival and quality of life for 5 years and compared to a control group who discontinue the study before transplantation due to reasons other than cancer progression.

NB: the program is quite experimental and limited to highly restrictive patient population (young, liver only, primary must have been already removed and the donor must be made available for consideration).

https://clinicaltrials.gov/ct2/show/NCT02864485

RADIATION THERAPY

7. Preoperative chemoradiation with VMAT-SIB in rectal cancer: a phase II study (March 2017)

A recent study aimed to investigate the efficacy and toxicity of volumetric modulated arc therapy (VMAT)-simultaneous integrated boost (SIB) in preoperative treatment of locally advanced rectal cancer. VMAT is a novel radiation technique that is able to deliver even dose distributions of radiation with better coverage of target tissues while sparing healthy tissues. The SIB technique allows the simultaneous delivery of different doses of radiation per fraction in different target regions. In the study, a total of 18 patients with stage IV rectal cancer participated. Radiation therapy was performed with the VMAT-SIB technique followed by a chemotherapy regimen of capecitabine and oxaliplatin. 16 patients underwent surgical resection, all of whom achieved R0 resection (resection for cure or complete remission of the cancer). 2 patients did not undergo surgery due to early metastatic progression or death. Overall, 4 patients experienced a complete pathological response and 7 patients had only a microscopic residual of disease. 8 out of 18 patients experienced grade 3 toxicity, including cases of leukopenia, skin toxicity, genitourinary toxicity and gastrointestinal toxicities. One-, three- and five-year cumulative local control was 100%, 68.6% and 68.6%, respectively. One-, three- and five-year cumulative disease-free survival was 88.9%, 66.7% and 66.7%. One-, three- and five-year

cumulative overall survival was 85%, 63.8% and 63.8%, respectively. Study results demonstrate the effectiveness of the regimen among advanced rectal cancer patients. Despite the use of the VMAT technique, however, more than 30% of patients experienced severe acute toxicity.

http://www.clinical-colorectal-cancer.com/article/S1533-0028(16)30078-0/abstract

SCREENING

8. Editorial: Colon cancer awareness should start early for African-Americans (Mar 8/17)

While colorectal cancer (CRC) remains the third most commonly diagnosed cancer and the second leading cause of cancer deaths in men and women in the United States, CRC incidence and mortality is declining largely in part to greater awareness of the disease and increased screening. This decline, however, is less dramatic among the African-American population. Among all racial groups, African-Americans tend to have the highest mortality rate from the disease. CRC rates are 25% higher among the group compared to Caucasians, and mortality rate is 50% higher. African-Americans are also more likely to be diagnosed at more advanced stages of the disease. These health disparities may be linked to lower screening rates among this group, later state of disease at presentation and reduced access to healthcare. Furthermore, fear, distrust and anxiety regarding the test and the healthcare system may also limit screening participation. With screening and lifestyle adjustments, CRC incidence can be decreased significantly. Further efforts are necessary to increase awareness and uptake of CRC screening among underserved groups and diagnose CRC cases early while they are treatable.

http://www.nbcnews.com/news/nbcblk/editorial-colon-cancer-awareness-should-start-early-african-americans-n730486

9. Newly discovered DNA enhancers help switch on colorectal cancer (Mar 7/17)

While genetic mutations can increase an individual's cancer risk, researchers suggest that other gene "enhancer" elements may also be responsible for disease progression. A recent study revealed that changes in specific regions of DNA outside of colorectal cancer genes can enhance gene expression in favour of tumour growth. These elements, referred to as enhancer elements, are short sequences of DNA which function to turn genes on and off. Researchers identified thousands of enhancer elements that were unexpectedly modified across colorectal cancer (CRC) samples. When these elements were manipulated by researchers, it was observed that colorectal cancer genes that were previously turned on, were turned off. Researchers believe that these enhancer elements work alongside genetic mutations to cause colorectal tumours. The ability to identify these sequences based on certain chemical markers on their DNA enables scientists to monitor a specific set of genes that are consistently activated during the process of cancer cell formation. These genes may be just as important to tumour growth as those that are most commonly mutated in CRC, and changes in enhancer elements could serve as potential treatment targets. Further studies are necessary to determine how to control the activity of the enhancer elements to eradicate tumour cells without affecting normal cells.

https://www.sciencedaily.com/releases/2017/03/170307112840.htm

10. Specific immune cells predict bowel cancer outcomes (Mar 6/17)

A study by the University of Otago suggests that among individuals with colorectal cancer (CRC), a certain kind of immune cell in their tumour may have improved their survival rate. Researchers found that people with more "effector T regulatory (Treg)" immune cells present in their colorectal tumours were more likely to remain disease-free for longer than people with fewer of these immune cells. In the study, 32 individuals with stage II CRC were followed up for a minimum of 5 years. 13 individuals experienced cancer recurrence during this time. Using a tool to measure basic immune cell filtration in tumours, Immunoscore, the researchers examined which types of immune responses were linked to patient survival. Immunoscore proved better at estimating patient survival compared to current staging, and the presence of "effector Treg" immune cells made the prediction even better.

About 25% of patients considered low-risk for the disease by current staging methods will eventually develop the disease again. Such low-risk patients often do not receive chemotherapy or radiotherapy as the costs and risks are believed to outweigh the benefits. The study findings highlight the potential for measuring immune responses with tools such as Immunoscore in CRC patients to determine which patients are likely to have cancer recurrence and thus be given further treatment options. Such information could be used to better personalize therapies and treat patients more effectively.

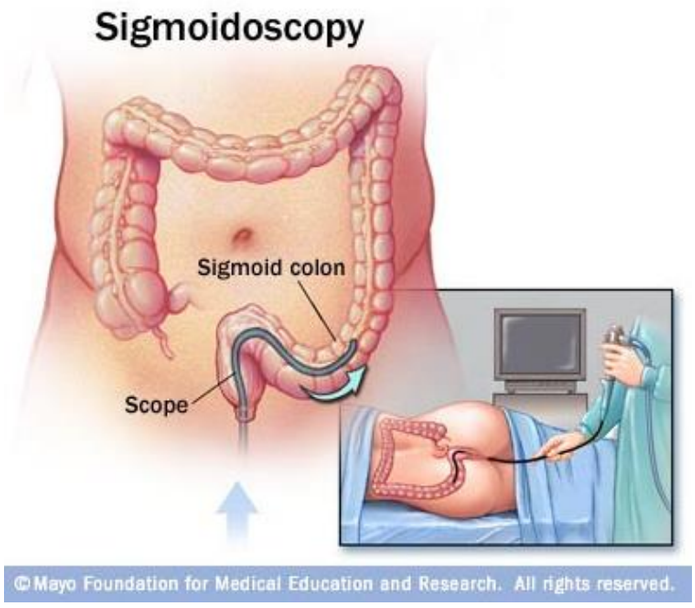
https://medicalxpress.com/news/2017-03-specific-immune-cells-bowel-cancer.html

11. Flexible sigmoidoscopy test performed just once, greatly reduces life-time risk of bowel cancer (Mar 3/17)

Evidence from a UK trial conducted in New Zealand supports the use of flexible sigmoidoscopy screening for bowel cancer instead of the currently planned screening approach of fecal occult blood test (FOBT). Flexible sigmoidoscopy is a procedure that allows the rectum and lower (sigmoid) colon to be examined for pre-

cancerous growths. Results from the trial suggest that a flexible sigmoidoscopy screening test just once between the age of 55-64 reduces the lifelong risk of bowel cancer by 35% and mortality by 41%. The study confirmed that the reduced bowel cancer incidence and mortality persists for at least 17 years post-screening. The screening test only needs to be offered once for the benefits to be seen, requiring far fewer referrals for colonoscopy than other screening programmes such as FOBT. Furthermore, the test requires only 15 minutes to complete and does not carry a high risk of false-positives or false-negatives. In a country that does not currently have a government-funded nationwide colorectal cancer screening programme, widespread use of the flexible sigmoidoscopy test in New Zealand may be a promising next step.

https://medicalxpress.com/news/2017-03-flexible-sigmoidoscopy-greatly-life-time-bowel.html



12. New generation high-definition colonoscopies increase adenoma detection when screening a moderate-risk population for colorectal cancer (March 2017)

Adenoma detection rate (ADR) is the most important quality indicator for screening colonoscopy. An observational study among moderate risk patients undergoing a screening colonoscopy aimed to compare the ADR and mean adenoma per procedure (MAP) of either standard-definition colonoscopes or high-definition (HD) colonoscopes. 395 patients (60.5% male with a mean age of 66.8 years) underwent screening colonoscopy with 45% performed using HD colonoscopes. ADR with standard-definition was 63.13% compared to 75.71% with HD. MAP in the HD group was 2.1, compared to 1.6 in the standard-definition group. The study concluded that the 12% improvement in ADR among the HD colonoscope group might lead to an increase in the protection provided by colonoscopy among moderate risk individuals. Further studies are necessary to examine the cost-effectiveness of the new technology on a wider population level.

http://www.clinical-colorectal-cancer.com/article/S1533-0028(16)30107-4/abstract

NUTRITION/ HEALTHY LIFESTYLE

13. Lifestyle choices condition colon and rectal cancer risk more than genetics (Mar 7/17)

Researchers from the colorectal cancer research group of Bellvitge Biomedical Research Institute have published the first predictive risk model of colon and rectal cancer based on data from Spain that incorporates genetic and lifestyle information. The researchers suggest the use of the predictive risk model to divide the population into different CRC risk groups, streamlining current screening methods. The risk model is a mathematical tool that allows researchers to determine who is most likely to suffer from CRC. Data was gathered from over 10,000 participants included in the MCC-Spain Spanish multicentre study. All participants were analyzed for known risk factors (diet, physical exercise, body mass index, alcohol, family history of cancer, etc) and among the subgroup of 1,336 cases of CRC and 2,744 controls, a blood test was performed in order to detect the genetic predisposition to the disease. Using this information, the researchers concluded that lifestyle factors influence cancer risk more than genetic predisposition. It was calculated that if one risky lifestyle choice is changed, such as achieving a healthy weight, it can compensate for 4 genetic risk predisposition points. This information is important, given our ability to modify lifestyle factors far more than our genetics. CRC screening among individuals with no family history is based purely on the person's age. By including information about lifestyle and genetics, the population could be classified into groups of greater or lesser risk, allowing for a more tailored approach to follow-up. Researchers are currently developing a new study, COLSCREEN, to determine the social perception about genetic screening. Currently, no studies exist that discuss patients' perceptions of genetic tests, or whether they want to be informed of their risks of developing certain diseases.

https://medicalxpress.com/news/2017-03-lifestyle-choices-condition-colon-rectal.html

Gemma Ibáñez-Sanz et al, Risk Model for Colorectal Cancer in Spanish Population Using Environmental and Genetic Factors: Results from the MCC-Spain study, Scientific Reports (2017). DOI: 10.1038/srep43263

Image courtesy of: http://health.sunnybrook.ca/cancer/prevent-colon-cancer/

OTHER

14. Colon and rectal cancer rising in young people (Feb 28/17)

While colon and rectal cancer incidence among older adults has been on the decline in recent years, there has been a sharp increase in the incidence of colorectal cancers among young adults. Despite this new trend, the majority of diagnoses of the disease still occur among older individuals - 90% of all colorectal cancer diagnoses occur among people over the age of 50. A recent study by the American Cancer Society observed that cancer incidence has dropped steadily for people born between 1890 and 1950 but has been increasing for every generation born since 1950. Considering that many colorectal cancers are considered a disease of aging, the increase in incidence among young people remains poorly understood. Cancer of the rectum in particular has been on the rise, a rate that has been increasing faster than cancers in other parts of the large intestine. Since doctors generally do not consider colorectal cancer diagnosis a real threat among young individuals, the disease risks being diagnosed at a later stage when the cancer becomes less treatable. While widespread screening tests like colonoscopies which detect precancerous cells have aided in the decline of overall colorectal cancer rates, these screening tests have not been considered practical for widespread use in a younger population. Researchers believe that increased rates among young individuals may be tied to rising obesity rates and sedentary lifestyles, along with increased heavy alcohol use and chronic conditions such as inflammatory bowel disease and type II diabetes. Individuals with colorectal cancer may experience some warning signs and symptoms, though these typically remain vague, including general digestive complaints like diarrhea or constipation, cramping and abdominal pain. As the causes of the disease among younger individuals become better understood, more effective screening methods must be developed to allow for earlier detection and treatment among this newly at risk age group.

https://www.nytimes.com/2017/02/28/well/live/colon-and-rectal-cancers-rising-in-young-people.html?smid=tw-nytimeswell&smtyp=cur&_r=0

15. Scientists identify mechanisms driving gut bacterial imbalance and inflammation (Feb 8/17)

Recent research has identified key molecular pathways involved in the disruption of the gut bacterial balance in inflammatory disease. Understanding these pathways may help scientists develop better prevention and treatment options for conditions such as inflammatory bowel disease (IBD), for which there is no current cure or means of prevention, as well as other gastrointestinal infections and colorectal cancers. Findings from the study describe an important mechanism that is linked to changes in the intestine in an inflammatory state. Scientists discovered that gut inflammation correlates with a change in the nutrients available to the bacteria. In a healthy state, the human gut is full of microbes, where bacterial cells outnumber human cells 10 to 1. The beneficial bacteria or flora aid digestion, protect against infections and play an important role in the development of a healthy immune system. During cases of intestinal inflammation, a process that occurs during IBD, gastrointestinal infections and cancers, the makeup of the bacterial communities becomes radically disturbed. Beneficial bacteria colonies decline as less beneficial and even harmful bacteria flourish. Scientists believe that the bacterial imbalance augments the inflammatory response. In a healthy state, the gut is an anaerobic environment, or oxygen-free. Good bacteria are adapted to this environment, whereas harmful bacteria such as *E. coli* are better adapted to aerobic or oxygen-rich environments. In a state of inflammation, the anaerobic environment changes and becomes more conducive to the growth of harmful bacteria waiting for their opportunity to thrive. A better understanding of these shifts in the gut bacterial composition will enable scientists to have greater insights into treatments tailored to the individual as well as diagnostic resources. For example, future drugs could inhibit the metabolic functioning of harmful bacteria such as *E. coli*.

https://medicalxpress.com/news/2017-02-scientists-mechanisms-gut-bacterial-imbalance.html