COLORECTAL CANCER RESEARCH UPDATES
Month Ending August 17th, 2018

The following colorectal cancer research updates extend from June 8th, 2018 to August 17th, 2018 inclusive and are intended for informational purposes only.

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**DRUGS / SYSTEMIC THERAPIES**

1. **Clinical trial: Study of BAY1834942 in Patients with Solid Tumours** (Jun 19/18)

This is an open-label (trial in which both the researchers and participants know which treatment is being administered), Phase 1, first-in-human, dose escalation and expansion study designed to assess the safety, tolerability, pharmacokinetics, pharmacodynamics and tumor response profile of the anti-carcinoembryonic-antigen-related-cell-adhesion-molecule-6 (CEACAM6) antibody BAY1834942 in patients with advanced solid tumors known to have a prevalence for CEACAM6 expression.

The study consists of dose escalation and tumor type-specific expansion in which BAY1834942 will be administered alone.

The primary objectives of the study are to evaluate and characterize the tolerability and safety profile of repeated doses of BAY1834942 and to characterize the pharmacokinetics of BAY1834942 after single dose.

Secondary objectives are to evaluate the tumor response profile, pharmacodynamics, pharmacokinetics after multiple doses, and immunogenicity of the drug.

The study consists of four treatment arms:

1. **Patients with solid tumours**, to receive escalating doses of BAY1834942 intravenously for 1 hour once every 21 days;
2. **Patients with gastric cancer and/or gastroesophageal adenocarcinoma**, to receive BAY1834942 intravenously for 1 hour every 21 days;
3. **Patients with colorectal cancer**, to receive BAY1834942 intravenously for 1 hour every 21 days;
4. **Patients with non-small-cell-lung cancer**, to receive BAY1834942 intravenously for 1 hour every 21 days.

Location: Princess Margaret Hospital-University Health Network, Toronto, Ontario, Canada, M5G 2M9. *Currently recruiting participants*

Actual study start date: June 19, 2018. Estimated Primary Completion Date: June 16, 2021

Estimated Study Completion Date: December 13, 2021. Eligibility criteria:

- 18 years or older, male or female. Does not accept healthy volunteers.

For further inclusion and exclusion criteria and detailed information regarding this trial please visit: [https://clinicaltrials.gov/ct2/show/NCT03596372](https://clinicaltrials.gov/ct2/show/NCT03596372) or contact Bayer by telephone: Bayer Clinical Trials (+) 1-888-84 22937

2. **Phase I Study of Cobimetinib with Bevacizumab and Atezolizumab for colorectal cancer** (Mar 30/18)

In this non-randomized phase I trial, the safety, tolerability and pharmacokinetics of cobimetinib in combination with atezolizumab and bevacizumab among patients with metastatic colorectal cancer will be evaluated. Cobimetinib is an oral MEK kinase inhibitor which targets cell signalling involved in cell division and growth. Atezolizumab is an anti-PD-L1 antibody which targets the PD-L1 and PD-1 receptor to prevent suppression of the immune system against cancer cells. Bevacizumab is an antibody which interferes with the process of new blood vessel formation (angiogenesis) in cancer cells. All patients will have received at least 1 previous therapy with fluoropyrimidine and oxaliplatin or irinotecan. Cobimetinib will be administered orally while atezolizumab and bevacizumab will be given intravenously in the first stage of the trial, patients will receive the drug combination until the disease progresses, unacceptable toxicity or withdrawal from the trial. In the second stage of the trial, the patients will be divided into two groups. The first group will receive the drug combination and undergo repeated tumour biopsy. The second group will receive atezolizumab and bevacizumab plus the cobimetinib dose that was given in stage I. For more information regarding the study, including inclusion and exclusion criteria, locations and contact information, visit: [https://clinicaltrials.gov/ct2/show/NCT02876224](https://clinicaltrials.gov/ct2/show/NCT02876224). The study is open and recruiting patients as of Oct 24, 2017 in the U.S., U.K., and Spain.


3. **Drug compound stops cancer cells from spreading in mice** (Jun 22/18)
For decades, a research team from Oregon Health & Science University has been focusing their research efforts on examining the movement of cancer cells through the body. In the vast majority of cancers such as breast, colon, lung or prostate, if detected early when the cancer has not yet become “mobile” and spread, the cancer will probably not cause death. On the contrary, if found once the cancer has spread throughout the body, the disease will likely be fatal. According to the researchers, the study of cancer cell movement or motility is key to understanding the disease and has therefore been the focus of the team’s work for several decades. In 2011, the team began to build a multi-disciplinary team to work together to discover a drug to inhibit the movement of cancer cells. A compound KBU2046 was found to inhibit cell motility in breast, prostate, colon and lung cancers. Their aim was to develop a compound that was able to minimize motility exclusively in tumour cells, with few side effects and low toxicity. They found that by developing a compound that bound to the heat shock proteins or “cleaners” of the cell, cell movement was inhibited without actually damaging those proteins. So far, the compound has not been tested in humans. The researchers hope that their work will help patients manage early stage disease before it has spread through the body and become the more incurable later-stage disease. So far, their drug has been highly effective in their laboratory tests against four cancer types (breast, colon, lung, and prostate). With more time and funding, the team hopes to move the drug forward as a therapy for humans.

https://www.sciencedaily.com/releases/2018/06/180622104731.htm

4. Soy lecithin NSAID combo drug protects against cancer with fewer side effects, UTHealth reports (May 29/18)

When a substance found in soybeans was combined with a non-steroidal anti-inflammatory drug (NSAID), it was found that the anticancer properties of the drug were improved with fewer side effects. The study was conducted at the University of Texas Health Science Center at Houston in a mouse model and in laboratory experiments. Soy lecithin, known in the scientific community as phosphatidylcholine, was combined with the NSAID indomethacin and compared head to head with three other NSAIDs, including aspirin. NSAIDs have been shown to be beneficial in the prevention of colorectal cancer, working by decreasing the production of substances that promote inflammation. Since many cancers are inflammation-based, NSAIDs may be important agents in cancer therapy and prevention. Their long-term use, however, is problematic due to side effects such as gastrointestinal bleeding. The combination of soy lecithin with indomethacin yielded superior colorectal cancer protection with less gastrointestinal bleeding. The study’s results shed light on the possibility of a new cancer prevention drug that could effectively protect against the disease while minimizing unwanted side effects.

Surgical Therapies

5. Hepatic Artery Infusion Pump (HAIP) Chemotherapy Program – Sunnybrook Odette Cancer Centre (Mar 20/18)

The HAIP program is a first-in-Canada for individuals where colon or rectal cancer (colorectal cancer) has spread to the liver and cannot be removed with surgery. The program involves a coordinated, multidisciplinary team approach to care, with close collaboration across surgical oncology, medical oncology (chemotherapy), interventional radiology, nuclear medicine, and oncology nursing. The Hepatic Artery Infusion Pump (HAIP) is a small, disc-shaped device that is surgically implanted just below the skin of the patient and is connected via a catheter to the hepatic (main) artery of the liver. About 95 percent of the chemotherapy that is directed through this pump stays in the liver, sparing the rest of the body from side effects. Patients receive HAIP-directed chemotherapy in addition to regular intravenous (IV) chemotherapy (systemic chemotherapy), to reduce the number and size of tumours. Drs. Paul Karanicolas and Yooj Ko are the program leads and happy to see patients eligible for the therapy.

Presently at Sunnybrook Odette Cancer Centre, HAIP is being used in patients with colorectal cancer that has spread to the liver that cannot be removed surgically and has not spread to anywhere else in the body. Patients who have few
(1-5) and very small tumors in the lungs may be considered if the lung disease is deemed treatable prior to HAIP. If you believe you may benefit from this therapy and/or would like to learn more about the clinical trial, your medical oncologist or surgeon may fax a referral to 416-480-6179. For more information on the HAIP clinical trial, please click on the link provided below.

http://sunnybrook.ca/content/?page=colorectal-colon-bowel-haip-chemotherapy

6. Visceral adhesion burden remains high with laparoscopic colorectal surgery (May 30/18)

Authors of a study published in *Annals of Surgery* aimed to determine whether there are differences in the frequency of abdominal adhesions between open and laparoscopic operations for colorectal surgery. Laparoscopic surgery is a minimally invasive procedure that requires smaller incisions and uses a tiny camera to facilitate the surgery. Abdominal adhesions are the formations of scar tissue between the intestine and the inner lining of the abdominal wall (peritoneal lining), or with other organs within the abdominal cavity (liver, gallbladder, uterus, ovaries, and urinary bladder). Adhesions form when inflammation occurs on the surface of the abdominal organs or the peritoneal lining, and is a common cause for complications after abdominal surgery. The study authors gathered information on the extent of adhesion formation at the time that a second surgery was performed on patients to resect colorectal liver metastases. Of the 151 patients in the study, 90 initially underwent open colorectal resection and 61 initially underwent laparoscopic resection.

At the time of the second surgery to remove the liver metastases, 71 patients (78.9%) with prior open surgery vs. 23 patients (37.7%) with prior laparoscopic surgery had adhesions at the previous incisions. 53 patients (58.9%) with prior open surgery and 27 patients (44.3%) with prior laparoscopic surgery had evidence of abdominal adhesions. It was expected that the laparoscopic surgery would result in fewer adhesions compared to open surgery due to the smaller incisions necessary for the procedure. The frequency of abdominal adhesions, however, between bowel organs was still relatively frequent among patients operated laparoscopically. These results provide important information about adhesion formation after laparoscopic surgery, and suggests that abdominal adhesions are still a significant concern and will remain a common problem even among the increasing number of patients undergoing laparoscopic surgery. Regimens to help prevent adhesion formation will still be useful following laparoscopic surgery of the abdomen.

![Abdominal adhesions surrounding the liver.](https://alignmentmonkey.nurturance.net/2016/abdominal-adhesions/)


7. Living donor liver transplantation for unresectable colorectal cancer liver metastases (Jun. 1/18)

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.

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

**RADIATION THERAPIES/INTERVENTIONAL RADIOLOGY**

8. **Study Offered at the Odette Cancer Centre to Treat Recurrent Rectal Cancer (Jun 1/18)**

Magnetic resonance-guided focused ultrasound (MRg-FU) is a non-invasive, outpatient modality being investigated for the thermal treatment of cancer. In MRg-FU, a specially designed transducer is used to focus a beam of low intensity ultrasound energy into a small volume at a specific target site in the body. MR is used to identify and delineate the tumour, focus the ultrasound beam on the target and provide real-time thermal mapping to ensure accurate heating of the designated target with minimal effect to the adjacent healthy tissue. The focused ultrasound beam produces therapeutic hyperthermia (40-42°C) in the target field causing protein denaturation and cell damage. Currently, there is no prospective clinical data reported on the use of MRg-FU in the setting of recurrent rectal cancer. Recurrent rectal cancer is a vexing clinical problem. Current retreatment protocols have limited efficacy. The addition of hyperthermia to radiation and chemotherapy may enhance the therapeutic response. With recent advances in technology, the investigators hypothesize that MRg-FU is technically feasible and can be safely used in combination with concurrent re-irradiation and chemotherapy for the treatment of recurrent rectal cancer without increased side-effects. The study is being offered at the Odette Cancer Centre. Here is the link to the study protocol:

https://clinicaltrials.gov/ct2/show/NCT02528175?term=magnetic+resonance+guided+focused+ultrasound&recr=Open&rank=1

**SCREENING**

9. **Mailed FIT kits nearly double colon cancer screening rates (July 17/18)**

According to research from *Cancer Journal*, mailing fecal immunochemical tests directly to patients’ homes helped to improve colorectal cancer (CRC) screening rates. Despite the benefits of early detection of the disease, fewer than two-thirds of eligible patients actually undergo CRC screening. Low-income and other vulnerable populations tend to be screened at even lower rates. A research team from the Lineberger Comprehensive Cancer Center at the University
Currently, the options for CRC screening are annual fecal immunochemical test; annual high-risk adults at age 45, five years earlier than the previous recommendation. This change in recommendation is based on an increasing body of evidence demonstrating that more and more younger adults are being diagnosed with the disease. From 1994-2014, there has been a 55% increase in the incidence of CRC among adults younger than 55 years of age. From 2005 to 2015, there has been an 11% increase in CRC mortality among the same population. Among adults above the age of 55, CRC incidence has been on a steady decline for the past 20 years in part due to better screening programs and the timely removal of polyps. An adult born around 1990 has twice the risk of developing colon cancer and four times the risk of developing rectal cancer compared to the lowest-risk adults who are born around 1950.

Currently, the options for CRC screening are annual fecal immunochemical test; annual high-sensitivity guaiac-based fecal occult blood test; multi-target stool DNA test every 3 years; colonoscopy every 10 years; computed tomography colonography every 5 years; and flexible sigmoidoscopy every 5 years. All positive results on any screening method that

https://www.ingentaconnect.com/content/cid/1994-2014, there has been a 55% increase in the incidence of CRC among adults younger than 55 years of age. From 2005 to 2015, there has been an 11% increase in CRC mortality among the same population. Among adults above the age of 55, CRC incidence has been on a steady decline for the past 20 years in part due to better screening programs and the timely removal of polyps. An adult born around 1990 has twice the risk of developing colon cancer and four times the risk of developing rectal cancer compared to the lowest-risk adults who are born around 1950.

Currently, the options for CRC screening are annual fecal immunochemical test; annual high-sensitivity guaiac-based fecal occult blood test; multi-target stool DNA test every 3 years; colonoscopy every 10 years; computed tomography colonography every 5 years; and flexible sigmoidoscopy every 5 years. All positive results on any screening method that
is not colonoscopy should be followed up with a colonoscopy as soon as possible. Since the preferred screening method is so variable from adult to adult, facilitating conversations with a healthcare professional to decide the best screening option is an important step towards increasing screening rates across the population. The best CRC screening test is the one that gets done, and done well. The ACS therefore recommends that all adults at average risk of CRC undergo regular screening with any of the 6 options outlined above, beginning at age 45. Adults in good health should continue screening until age 75, beyond which the decision to continue screening should be individualized based on patient preferences, health status, life expectancy, and screening history. The ACS recommends that a patient who is initiating screening or previously has not complied with screening be offered a choice of tests based on the availability of high-quality options. As such, it is their hope that the widespread adoption of screening beginning at 45 years of age will have a positive impact on the incidence, suffering, and mortality caused by CRC.


PSYCHOSOCIAL

13. What is the best approach to managing “chemobrain”? (July 27/18)

About a decade ago, the term “chemobrain” was coined by patients with breast cancer to describe cognitive problems such as confusion or difficulty concentrating that were experienced after receiving chemotherapy. Today, the condition is known as cancer-related cognitive impairment or CRCI and remains poorly understood. It is believed to be caused by a number of factors, including chemotherapy, endocrine therapy, radiation therapy and cancer itself. Specialists have suggested that CRCI could be caused by a neurotoxic effect either from the cancer or the cancer treatment. Common medications that may contribute to CRCI include sedative hypnotics used for sleep and anxiety (antihistamines, benzodiazepines), anti-nausea agents, and pain medications. CRCI affects patients with various types of cancer and can happen at any point during the cancer journey. It can affect memory, attention, concentration, language skills, multitasking, organizational skills, daily functioning and quality of life of cancer survivors. Educating patients about CRCI ahead of time could help to validate their symptoms and discover helpful ways of coping with the condition.

When it comes to diagnosis of CRCI, guidelines such as those from the National Comprehensive Cancer Network provide assessment, evaluation, and management recommendations for cognitive dysfunction in cancer survivors. According to Lori Bernstein, a neuropsychologist in the Department of Supportive Care, Cancer Rehabilitation and Survivorship Program at Princess Margaret Cancer Centre and University of Toronto, a brain scan may take place. If patients with metastatic cancer experience sudden or severe cognitive impairment, then brain imaging can help rule out the possibility that the cancer has spread to the brain. Furthermore, blood tests can sometimes reveal reversible causes of cognitive symptoms such as abnormal thyroid or anemia. In older individuals, even small-scale infections such as a urinary tract infection can sometimes be associated with cognitive impairment. These cases should be ruled out if cognitive symptoms are sudden, since the underlying cause is treatable and is not a true case of CRCI. The standard neuropsychological tools that are currently available were not designed for the cognitive changes that cancer survivors experience. These tools were designed for patients suffering from head injuries, stroke, Parkinson’s, or Alzheimer’s. More specific tools for assessing cancer-specific cognitive dysfunction are currently being developed. When treating CRCI, there is currently no pharmacologic treatment. Many guidelines recommend non-pharmacologic interventions such as instruction in coping strategies, and management of distress, pain, sleep disturbances and fatigue. Pharmacologic interventions are normally left as a last line of therapy in survivors for whom other interventions have been unhelpful. It is important to note that there is no medical cure for chemobrain, though there are things that can be done to help to reduce the symptoms and the impact those symptoms have on a person’s quality of life. Possible treatments are still under investigation, but various options including cognitive behavioural training or exercise-based regimens look promising for the future.


14. Candirect research study: Learn more about a study for patients who have completed their cancer treatments and are experiencing low mood (Apr 1/18)

15% of cancer survivors are estimated to experience mood problems even one year post-treatment. The CanDirect research study aims to support cancer survivors with mood problems by providing study participants with a self-care toolkit designed to help users better manage their mood and anxiety as well as phone coaching for a maximum duration of 6 months. Participation is open to eligible adult survivors residing in Quebec and Ontario who have completed cancer treatment for a non-metastatic cancer and who are experiencing depressive symptoms. For additional information, please click on the following link:

https://clinicaltrials.gov/show/NCT02890615

15. New target protein for colon cancer identified (July 17/18)
Researchers from the Boston University School of Medicine have found a new protein (c-Cbl) which they believe may help to better understand the mechanisms of colon cancer. It was observed that colon cancer patients with high levels of c-Cbl lived longer than those with low c-Cbl. This is the first time this protein has been studied in the context of colon cancer, despite having been studied in other cancers. The researchers aimed to determine the effect of switching off this protein’s expression in the cell. Two types of colon cancer cells were used and were separated into three groups. One group contained colon cancer cells as they were naturally found, the second group contained increased expression of normal c-Cbl, and the last group had increased expression of the “off” version of c-Cbl. The “off” c-Cbl lacked the ability to carry out a fundamental c-Cbl function known as ubiquitin ligase activity. It was observed that cells that were given the “off” version of c-Cbl grew more tumours than those that were given the normal functioning version.

Since blood vessel development and growth (angiogenesis) is essential for tumours to grow and metastasize, the researchers wanted to discover whether c-Cbl affected such growth. Three experimental models were used; one group was normal, one group was given the c-Cbl protein and the third group was given the “off” version of the protein. The model with the “off” c-Cbl demonstrated greater blood vessel growth. This led researchers to conclude that the ubiquitin ligase activity of c-Cbl may help to prevent tumours from growing by affecting its ability to grow necessary blood vessels. This study could help cancer researchers develop new treatment targets that boost the lacking ubiquitin ligase activity in patients with lower levels of c-Cbl.


16. A study points to new therapeutic targets for tumours associated with chronic inflammation (July 11/18)

Each year, more than one million people are diagnosed with colon cancer across the globe. While many cases of the disease are spontaneous, chronic inflammation in the body remains one of the main causes that underlies the development of this disease. IGF-1 is a hormone that is structurally similar to insulin. It is a primary mediator of the effects of growth hormone in the body, which induces growth-promoting effects on nearly every type of cell. IGF-1 has emerged as a potential therapeutic target in intestinal diseases linked to inflammation. A study conducted by the Institute for Research in Biomedicine in Barcelona demonstrated that the genetic or drug-induced inhibition of IGF-1 suppresses the recruitment of inflammatory cells and reduces the burden of colon cancer tumours that are associated with inflammation. Based on their findings, researchers conclude that IGF-1 levels in biopsies from patients with inflammatory intestinal diseases or colitis-associated cancer should be considered when making decisions regarding therapy for inflammatory-related colon conditions.


17. Stem-cell niche for 10 billion colon cells a day (Jun 6/18)

The lining of the human intestine is constantly renewing itself. Just in the colon, which makes up the last 1.5 meters of the digestive tract, about 10 billion epithelial cells are renewed each day. The epithelium is the layer of cells that lines the small and large intestine and is responsible for absorbing nutrients from our food. The regeneration of this layer is driven by stem cells that are found in the crevices of the folds of the epithelium, also known as crypts, where they make contact with other cells that activate the cellular renewal process. Researchers from the University of Zurich in Switzerland have discovered the cells responsible for providing the signal to the intestinal stem cells that tells them to regenerate. These Gli1-positive cells are found around the intestinal folds and form what scientists refer to as the “stem-cell niche”. When Gli-1-positive cells are eliminated or destroyed, the activation of the stem-cell regeneration pathway is lost. As a result, the stem cells will die, the epithelium of the colon will not be renewed, and eventually the organism will die due to a lack of nutrient absorption. When the activation signal is driven in the other direction, stimulating intestinal stem cells to divide excessively, polyps and cancers develop. It is clear that a well-regulated stem-cell niche is key to a healthy intestine and organism. The researchers conducted further tests to examine how the cells of the stem-cell niche behave in response to inflammation of the colon. In this case, many more epithelial cells are lost compared to healthy animals. The need for cell renewal is greater, since the tissue needs to be maintained and repaired more frequently. The researchers discovered that the amount of Gli-1-positive cells increased significantly in response to an inflamed colon. The discovery of the colon’s stem-cell niche has relevance for a vast array of intestinal diseases from inflammatory conditions to cancer. A deeper understanding of this special microenvironment could help shed light on specific pathways involved in colon cancer and inflammatory conditions and new potential therapeutic targets.
Crypts of the large intestine make up the stem-cell niche microenvironment.


Bahar Degirmenci, Tomas Valenta, Slavica Dimitrieva, George Hausmann, Konrad Basler. GLI1-expressing mesenchymal cells form the essential Wnt-secreting niche for colon stem cells. Nature, 2018; DOI: 10.1038/s41586-018-0190-3

https://www.sciencedaily.com/releases/2018/06/180606132737.htm

18. Young adult colorectal cancer clinic available at Sunnybrook (Mar 18/18)

A recent study led by University of Toronto doctors has observed a rise in colorectal cancer rates in patients under the age of 50. The study mirrors findings from the U.S., Australia and Europe. The growing colorectal cancer rates in young people come after decades of declining rates in people over 50, which have occurred most likely due to increased use of colorectal cancer screening (through population-based screening programs) which can identify and remove precancerous polyps. Patients diagnosed under the age of 50 have a unique set of needs, challenges and worries. They are unlike those diagnosed over the age of 50. Dr. Shady Ashamalla (colorectal cancer surgical oncologist), and his team at the Sunnybrook Health Sciences Centre understand the needs of this patient population.

Dr. Ashamalla belongs to a multidisciplinary team of experts in the Young Adult Colorectal Cancer Clinic who will work with young colorectal cancer patients, regardless of disease stage, to create an individualized treatment plan to support each patient through their cancer journey. Their needs and concerns will be addressed as they relate to:

- Fertility concerns and issues
- Young children at home
- Dating/intimacy issues
- Challenges at work
- Concerns about hereditary cancer
- Relationships with family and friends
- Psychological stress due to any or all of the above

The team of experts consist of:

- Oncologists (medical, surgical, radiation)
- Social workers
- Psychologists
- Geneticists
- Nurse navigator

Should a patient wish to be referred to Sunnybrook, they may have their primary care physician or their specialist refer them to Sunnybrook via the e-referral form which can be accessed through the link appearing below. Once the referral is received, the Young Adult Colorectal Cancer Clinic will be notified if the patient is under the age of 50. An
appointment will then be issued wherein the patient will meet with various members of the team to address their specific set of concerns.

http://sunnybrook.ca/content/?page=young-adult-colorectal-cancer-clinic

### NUTRITION/ HEALTHY LIFESTYLE

19. Summary of Specific foods that help prevent colorectal cancer: From CCC’s Foods That Fight Cancer Program (June 2018)

<table>
<thead>
<tr>
<th>Category</th>
<th>Family</th>
<th>Examples</th>
<th>Info</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetables</td>
<td>Cruciferous vegetables</td>
<td>Cabbage, cauliflower, Brussel sprouts, kale, broccoli, radishes, turnips, cress, arugula</td>
<td>Helps the body to eliminate carcinogenic substances, thus reducing their ability to cause DNA mutations that would encourage the appearance of cancer cells. High consumption of cruciferous vegetables is associated with a 20% decrease of colorectal cancer risk.</td>
<td>Ann Oncol 2013; 24:1079-87.</td>
</tr>
<tr>
<td></td>
<td>Garlic Family</td>
<td>Garlic, onions, shallots, chives, asparagus</td>
<td>They have a protective action against damage caused by carcinogenic substances. Molecules responsible for this anticancer effect are released by the chewing process.</td>
<td>Am J Clin Nutr. 2007; 86: 1754-64.</td>
</tr>
<tr>
<td></td>
<td>Legumes</td>
<td>Beans, peas, lentils</td>
<td>High consumption of fibre is associated with a 20% decrease of colorectal cancer risk.</td>
<td>Am J Clin Nutr. 2014; 100: 394S-8S.</td>
</tr>
<tr>
<td></td>
<td>Good fats</td>
<td>Virgin or extra-virgin olive oil, macadamian nuts, avocado, pecans, hazelnuts</td>
<td>Antioxidant and anti-inflammatory phenolic compounds in olive oil play a role in helping to reduce the risk of colorectal cancer.</td>
<td>Beliveau, R, Gingras, D. Foods that Fight Cancer, Firefly Books. 2016.</td>
</tr>
<tr>
<td></td>
<td>Omega-3</td>
<td>Fatty fish (salmon, trout), chia seeds, canola oil, walnuts</td>
<td>High consumption of fatty fish is associated with a 37% decreased risk of colorectal cancer.</td>
<td>Cancer Epidemiol Biomarkers Prev. 2008; 17:1136-43.</td>
</tr>
<tr>
<td></td>
<td>Seasonings</td>
<td>Turmeric, pepper, ginger, cumin, chili pepper</td>
<td>Turmeric and its main component, curcumin, have many anticancer properties that could contribute to the major differences in the incidence of cancers seen in North America compared to India.</td>
<td>Beliveau, R, Gingras, D. Foods that Fight Cancer, Firefly Books. 2016.</td>
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<td></td>
<td></td>
<td>*Pepper added to turmeric dishes increases significantly the amount of curcumin absorbed by the body.</td>
<td></td>
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<tr>
<td></td>
<td>Fresh herbs</td>
<td>Parsley, thyme, oregano, rosemary</td>
<td>Contain anti-inflammatory molecules that help hinder cancer development.</td>
<td>Beliveau, R, Gingras, D. Foods that Fight Cancer,</td>
</tr>
<tr>
<td>Other</td>
<td>Milk and dairy products</td>
<td>According to the World Cancer Research Fund, there is good evidence that dairy products may play a positive role in the prevention of colorectal cancer.</td>
<td><a href="https://www.wcrf.org/dietandcancer/colorectal-cancer">https://www.wcrf.org/dietandcancer/colorectal-cancer</a></td>
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<tr>
<td>Green tea</td>
<td>Japanese green tea (like Sencha) are the best options</td>
<td>Contains large amounts of catechins, molecules with a host of anticancer properties. Regular consumption of green tea reduces the risk of colorectal cancer by 57%.</td>
<td>Cancer Epidemiol Biomarkers Prev 2007 ; 16 : 1219-23</td>
<td></td>
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"Regular absorption of anticancer phytochemical molecules is necessary to keep precancerous cells off balance and help prevent them from growing." Richard Béliveau, Ph.D, author of Foods that Fight Cancer – Preventing Cancer through Diet.

"No food contains by itself all the anticancer molecules that can act on the different processes involved in the development of cancer – hence the importance of incorporating a wide variety of foods into eating habits." Richard Béliveau, Ph.D, author of Foods that Fight Cancer – Preventing Cancer through Diet.

"We have to increase our consumption of plants if we hope to help reduce the incidence of colorectal cancer in our society." Richard Béliveau, Ph.D, author of Foods that Fight Cancer – Preventing Cancer through Diet.

24. Dietary insulin load and risk of disease recurrence in stage III colon cancer (June 28/18)

Research from the Dana-Farber Cancer Institute has suggested that among patients treated for non-metastatic stage III colon cancer, the risk of the disease coming back may be drastically reduced by following a diet low in foods that raise insulin levels. The researchers found that patients with stage III disease who had the highest dietary insulin load, or level of insulin produced by the body in response to diet, had double the risk of disease recurrence or death from the disease compared to patients with the lowest load. This correlation was found to be true independent of physical activity and was particularly pronounced among obese patients. While a large body of evidence supports the adoption of a healthy lifestyle by colon cancer survivors, this study suggests that the better prognosis among these individuals may be due in part to the lower levels of insulin that accompany these healthy behaviours.

The study included 1,023 colon cancer patients who had undergone surgery and were participating in a clinical trial for follow-up chemotherapy. Halfway through chemotherapy treatment and 6 months after completing therapy, patients were asked to fill out a questionnaire about their dietary intake in order to calculate dietary insulin load. Researchers found that patients who followed Western diets rich in simple carbohydrates tended to produce the highest insulin levels. Patients who followed Mediterranean-style diets rich in vegetables, fruits, legumes, healthy fats and proteins were associated with lower insulin levels. The link between dietary insulin load and an increased risk of colon cancer recurrence and death stresses the importance of diet as a powerful factor in determining disease outcomes. As one of the most important “environmental” factors in the development and outcomes of cancer, patients and their doctors should incorporate diet and nutrition as indispensable tools in the healing and prevention of the disease.

http://www.ascopost.com/News/59006

25. Blood vitamin D levels linked to colorectal cancer risk (Jun 14/18)

A new study with data from over 20 medical centers and organizations across the United States has found that higher levels of circulating vitamin D in the blood are significantly associated with lower colorectal cancer (CRC) risk. This study strengthens existing data supporting a protective relationship that has thus far been considered inconclusive. Vitamin D is known for its important role in maintaining bone health, and is believed to lower CRC risk via various pathways linked to cell growth and regulation. While a few clinical trials of vitamin D supplementation and CRC have shown an effect, study size, supplementation duration and patient compliance have rendered their results inconclusive. In the new study, data was collected before CRC diagnosis from 17 different patient groups using standardized criteria. A single, widely accepted assay and laboratory was used for vitamin D measurements and calibration of existing vitamin D measurements. Data from past vitamin D studies has been difficult to integrate as the ways in which vitamin D levels were measured and administered to patients varied tremendously. The new study’s
standardized approach enabled the researchers to systematically explore the effects of a broad range of vitamin D concentration seen internationally.

When compared to participants with circulating vitamin D concentrations considered sufficient for good bone health, patients with deficient vitamin D concentrations had a 31% higher risk of CRC during the follow-up period of the study, which averaged 5.5 years. Concentrations above what is required for bone health were associated with a 22% lower risk of CRC. The protective effect was noticeably stronger in women than in men at concentrations above bone health needs. Currently, health agencies do not recommend vitamin D for the prevention of CRC. This study provides evidence to suggest that concentrations of vitamin D recommended for bone health may be lower than what would be optimal for CRC prevention. Vitamin D can be synthesized by the body through sun exposure, and can be obtained through diet from fortified foods and supplements.

Marjorie McCullough, et al., Circulating Vitamin D and Colorectal Cancer Risk: An International Pooling Project of 17 Cohorts. JNCI: Journal of the National Cancer Institute, 2018; DOI: 10.1093/jnci/djy087

https://www.sciencedaily.com/releases/2018/06/180614101241.htm

26. Meat Free Week Challenge: 24th-30th September 2018

Meat Free Week challenges you to give up meat for 7 days and raise funds for a good cause. Each participant is challenged to cut out meat from their diet, adopt a physically active lifestyle and consume a healthy diet with an emphasis on plant-based foods.

By not eating meat for one week, it will create an opportunity to think about how much meat you eat and the impact that eating too much meat can have.

The World Health Organization has classified red meat - including beef, veal, pork, lamb, mutton, horse and goat – as “probably carcinogenic to humans”. An even stronger link between colon cancer and processed meats such as bacon, hot dogs and cold cuts was found.

Studies by the World Cancer Research Fund found that colon cancer risk increases by 17% per 100g of red meat consumed per day and 18% per 50g of processed meat consumed per day.

For many recipes and tips on eating meat free and how to get involved in the challenge, please visit: https://www.meatfreeweek.org/. If you’re already a vegetarian, there are many ways to get involved, like supporting others to participate in the challenge and sharing nutritious plant-based recipes.

27. A Phase III study on the impact of a physical activity program on disease-free survival in patients with high risk stage II or stage III colon cancer: a randomized controlled trial (CHALLENGE) (Mar 15/18)
The purpose of this study is to compare the disease-free survival of patients involved in a physical activity program (designed to increase physical activity participation) who also receive general health education materials (about diet and physical activity) to patients who receive the general health education materials only. This study is being done because, as of yet, there is no conclusive evidence that physical activity will decrease the likelihood of colon cancer recurrence. This study will also obtain important information about the impact of physical activity on patients’ physical functioning, body composition, quality of life, fatigue, mood, cytokines and the insulin pathway, and their influence on prognosis, as well as cost-effectiveness.

Eligibility: Medically fit colon cancer patients (high risk stage II and stage III) who have completed adjuvant chemotherapy within the past 60-180 days. Current physical activity levels must not meet the recommended guidelines (≥150 minutes of moderate-to-vigorous or ≥75 minutes of vigorous exercise/week). Following registration, and prior to randomization, patients must successfully complete at least two stages of a submaximal exercise test to ensure they are able to safely exercise at a moderate to vigorous intensity.

Participation: Limited to invited centres. For more information, visit the link below: https://scooby.ctg.queensu.ca/tum_bank/tum.php?g_cmd=trial_info&g_trial_cd=CO21

28. High dose Vitamin D supplementation in Stage 4 Colorectal Cancer Patients (Mar 18/18)

A large body of evidence suggests that high blood levels of Vitamin D decreases the risk of developing cancer, especially colorectal cancer. 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) colorectal cancer patients. Who is eligible to participate? Anyone who has a stage four colorectal cancer 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. What is involved? This 40-month study involves regular lab tests and follow up phone calls. Participation is fully voluntary, and participants may withdraw at any time. Participants will be randomized into either a high-dose vitamin D treatment group or a control group. Participants in both groups may continue all other cancer treatments including chemotherapy. Treatment group: Participants in the treatment group receive daily oral high dose Vitamin D supplementation provided free of charge through the clinical study. They also receive daily calcium supplementation 1000mg daily as per guidelines, provided free through the clinical study. Participants have monthly blood and urine tests for monitoring purposes. All laboratory tests are free of charge. Participants also need to be available for a 15-minute phone consultation with a study coordinator every 2 months. Control group: Participants in the control group will continue their usual amount of Vitamin D and/or calcium if they wish to do so. No supplements will be provided through the study. Participants will be asked to provide a small blood and urine sample at the beginning of the study, every 8 months and at the end of the study. These blood and urine tests will be free of charge. Contact person: If you have any further questions regarding this study or you are interested in participating in this study, please contact us: 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

29. World Cancer Research Fund recommendations to help prevent cancer (graphic)
30. Obesity increases infection risks after colorectal surgery (Jul 31/18)

A retrospective study has found that Body Mass Index (BMI) serves as an independent risk factor for many adverse outcomes that arise within 30 days of colorectal surgery for patients who are obese. The study was conducted in response to the growing problem of obesity in the United States, where about 30% of the population is classified as overweight or obese. Studies have clearly shown that obesity is linked to morbidity and mortality and often causes a great deal of complications particularly among colorectal patients. The study aimed to better understand how obesity was associated with colorectal disease outcomes. The researchers hypothesized that an increase in BMI or an increase in obesity classification was associated with an increase in surgical site infection rates and outcomes. Using the data from the American College of Surgeons National Surgical Quality Improvement Program, the researchers assessed patients who underwent elective colorectal surgery between 2011 and 2013. Thirty-day post-surgical site infection was used as the primary endpoint of the study. Less than 5% of patients were overweight, while 29% of patients were listed as normal weight and 33% were overweight. Underweight patients had the lowest risk of surgical site infection. The adjusted risk of developing a surgical site infection significantly increased as BMI class increased from overweight (BMI 25-29.9 kg/m²) to obesity class III (BMI 40kg/m²). A clear proportional relationship was observed between BMI and rate of worse post-surgical outcomes. The researchers hope that future work will focus on obesity as a modifiable risk factor for interventions that may improve patients to a more normal weight physiology and hopefully decrease their risk for having poor surgical outcomes.

https://www.healio.com/gastroenterology/practice-management/news/online/%7b7b2c1f40a-58c0-41ef-a5fc-c58929e9c9d7d%7d/obesity-increases-infection-risks-after-colorectal-surgery?page=2

31. Modifiable risk factors for colon cancer (May 2/18)

Dr. David Johnson, professor of medicine and chief of gastroenterology at Eastern Virginia Medical School in Norfolk, Virginia, shares his thoughts on modifiable risk factors important in colon cancer.

Smoking

This adds a strong risk for the primary development of colon cancer and advanced abnormal growths. Cigarette smoking nearly doubles one’s risk of developing colon polyps, and in particular, sessile serrated polyps which are more difficult to detect during screening. In 2009, the American College of Gastroenterology suggested that patients who smoke might warrant screening at an earlier age, such as 45 years instead of 50. Importantly, the risk associated with smoking extends beyond quitting. Stopping smoking shows risk reduction, but the risk actually extends 20-30 years after quitting. Smoking is a very significant risk factor in colon cancer, though most recently the research emphasis has been placed on the association of serrated polyps in the right colon (a characteristic that often leads to a worse prognosis) and smoking.

COX-2 Inhibitors and aspirin

COX-2 inhibitors are a type of non-steroidal anti-inflammatory drug (NSAID) that directly target inflammation pathways in the body. Two COX-2 inhibitors, celecoxib and rofecoxib, were studied for the prevention of recurrent polyps. The drugs demonstrated a risk reduction of nearly 3-4 times during the 3- and 5-year analyses for these studies. An increase in cardiovascular disease development, however, nullified these studies. Celecoxib remains on the market while rofecoxib was removed.

With respect to aspirin, colon cancer risk reduction has been clearly demonstrated, though it takes anywhere from 5-10 years of NSAID use for this risk reduction to become significant. According to the US Preventative Services Task Force (USPSTF), among patients 50-59 years with a greater than 10% 10-year risk for cardiovascular disease, daily aspirin can help to reduce risk while simultaneously reducing risk for colon cancer. Use of aspirin should be discussed with a physician, ensuring that the individual does not have high risks for intracranial hemorrhage or gastrointestinal bleeding which are side effects of long-term aspirin use.

Among patients aged 60-69 with a >10% 10-year risk for cardiovascular disease, aspirin should be considered on an individual basis. For patients above 70 years, there is not enough evidence to support aspirin use for risk reduction, since it takes 5-10 years to begin to see a benefit. There is also not enough evidence to support the recommendation of aspirin for primary prevention among patients below the age of 50. The recommended, daily, preventative dose of aspirin is 81mg. The risk of complications with long-term NSAID use increases with dosage, so it follows that a lower dose for regular use can help to decrease risk of cancer while minimizing adverse effects.

Diet: Red Meat

High consumption of red meat is not healthy for many reasons, especially when it comes to cooking at high temperatures. Cooking red meat by frying, grilling or broiling at high temperatures may be associated with the
development of mutagenic, heterocyclic amines, which are thought to interact with our body's amino acids and lead to abnormal growths in the colorectum.

**Diet: Calcium and vitamin D**

It has been suggested that calcium reduces the risk of colorectal cancer by binding to toxic bile acids and increasing the insoluble salts. The Nurses' Health Study and the Health Professionals Follow-Up Study found that calcium reduced risk of cancer in the distal colon but not the proximal colon. Calcium intake was between 700-800mg/day, beyond which, supplemental calcium does not seem to increase risk reduction. All in all, the data on calcium and cancer risk reduction are not very strong.

Vitamin D levels in the blood need to be in the range of higher than 30 ng/ml. Dr. Johnson recommends a dose of 2000 IU/day to patients including those with inflammatory bowel disease and diverticular disease.

**Vitamins**

While vitamins, especially B vitamins, have been studied extensively to determine any possible link to cancer reduction, none have shown any strong association with minimizing risk of the disease. The antioxidants, vitamin A, C and E have also been extensively studied for the prevention of colon cancer and the take-home message is that none have been proven to have a significant impact on cancer risk reduction.

**Alcohol intake and obesity**

Regular and heavy alcohol use have been associated with an increased risk for colon cancer and advanced colon neoplasia polyps. While many studies have focused on alcohol consumption and the development of serrated polyps in particular, it makes sense no matter what to decrease regular alcohol consumption for various health reasons.

Obesity is definitely associated with an increased risk for colon cancer and advanced colon neoplastic lesions. What kind of obesity is important, as it has been observed that abdominal obesity has a greater impact on risk than central, truncal obesity. Abdominal obesity seems to be more metabolically active, stimulating the upregulation of cytokines important in cancer-promoting pathways. Weight reduction in patients, especially in those with abdominal obesity or body mass index 30 or above, is a good health-promoting recommendation.

**Take-home messages**

Stop smoking. The evidence is highly in favour of smoking cessation and risk reduction for adenomas, serrated lesions and colon cancer. For NSAID use, follow the USPSTF guidelines for low-dose aspirin and primary prevention according to age and cardiovascular risk. Vitamin D supplementation is probably reasonable to recommend. Reduce red meat consumption especially that which is cooked at high temperatures. Losing weight is important for reducing risk of cancer and improving overall health, as is decreasing alcohol consumption. With respect to calcium and vitamin supplements including A, C and E, there simply is not enough data to support a significant cancer risk reduction.