

JULY 2021

# LIVING WITH CANCER



## COLORECTAL CANCER RESEARCH & PRACTICE UPDATES

Colorectal Cancer Canada curates monthly Research & Practice Updates to inform patients and their loved ones of new innovations in colorectal cancer care. The following updates extend from July 1<sup>st</sup> 2021 to July 30<sup>th</sup>, 2021 inclusive and are intended for informational purposes only

### JULY 2021 PREVIEW

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## SYSTEMIC THERAPIES, SURGERY & SCREENING

### Colon cancer data reinforce need to reduce unnecessary antibiotic use

July 2021

New findings from a study presented at the European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer 2021 (30 June – 3 July) suggest that excessive antibiotic use may increase the risk of colon cancer, particularly among people below the age of 50<sup>1</sup>. The study draws attention to the estimated 65% increase in global antibiotic consumption that was reported between 2000-2015<sup>2</sup> and the association with colon cancer development.

The Scottish study used a large database containing primary care health information to investigate the association between antibiotics use and risk of developing colon cancer. Among the 8000 people who were diagnosed with colon cancer, the investigators found that antibiotic use was linked to an increased risk of colon cancer across all ages, though the risk was increased by almost 50% in people under 50 compared to 9% in people over 50 years. Furthermore, among younger patients, antibiotic use was associated more strongly with cancers originating in the right colon. Cancer that begins in the right colon (ascending colon, hepatic flexure and transverse colon) tends to have poorer prognoses and clinical outcomes compared to cancer originating in the left colon (half of the transverse colon, splenic flexure, descending colon, and sigmoid colon)<sup>3</sup>. Quinolones, such as ciprofloxacin (Cipro) and sulfonamides/trimethoprim antibiotics, which are used to treat a range of infections, were associated with right-sided colon cancer.

The investigators note that the bacteria that inhabit the right colon may be very different from the bacteria that inhabit other sections of the colon. The totality of microorganisms that inhabit our digestive tract – the microbiome – is under close study to determine whether there is a link between antibiotic use and changes in the microorganism populations that can increase the risk of colon cancer.

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<sup>1</sup> Bowel cancer data reinforce need to reduce unnecessary antibiotic use. 2 Jul 2021. Retrieved from: <https://www.esmo.org/newsroom/press-office/bowel-cancer-data-reinforce-need-to-reduce-unnecessary-antibiotic-use>

<sup>2</sup> Klein EY et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci U S A* 2018 Apr 10; 115:E3463. (<https://doi.org/10.1073/pnas.1717295115>)

<sup>3</sup> Baran B et al. Difference between left-sided and right-sided colorectal cancer: a focused review of literature. *Gastroenterology Res.* 2018 Aug; 11(4): 264-273. Published online 2018 Feb 8. doi: [10.14740/gr1062w](https://doi.org/10.14740/gr1062w)

While it remains unknown whether excessive antibiotic use *directly* causes colon cancer, these findings show an association that highlights the importance of reducing unnecessary antibiotic use. The possibility that excessive antibiotic use may be exposing people to a higher risk of cancer cannot be ignored.

**Take away message:**

Findings from a recent study found that excessive antibiotic use is linked to an increased risk of colon cancer across all ages, with an alarming 50% increase in risk of colorectal cancer in people under 50.

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**Red meat consumption may promote DNA damage-associated mutations in patients with colorectal cancer**

July 2021

While many different risk factors for colorectal cancer (CRC) have been established, the underlying mechanisms are not well known. A recent study published in *Cancer Discovery* found that high red meat consumption was linked to higher levels of DNA damage in colon cells, driving CRC-specific mutations and greater cancer-related mortality in patients with CRC.

In 2015, the International Agency for Research on Cancer declared that processed meat was carcinogenic, and that red meat was probably carcinogenic to humans<sup>4</sup>. Preclinical studies have suggested that red meat consumption may promote the development of cancer-causing compounds in the colon, though a direct link to CRC development through specific mutations has not been shown.

**The Study**

The investigators sequenced DNA from normal and CRC tissues from 900 patients with CRC from large, prospective studies: the Nurses' Health Studies and the Health Professionals Follow-up Study. Information on patients' diet, lifestyle, and other factors were collected over the course of several years before their CRC diagnoses. Through DNA sequencing analysis, several mutational signatures or patterns were identified.

A strong association was found between levels of DNA alkylation and pre-CRC diagnosis intake of processed or unprocessed red meat. The study investigators also found that higher incidence of alkylating damage was found in the distal colon (descending and sigmoid colon) compared to the proximal colon (cecum, ascending and transverse colon).

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<sup>4</sup> IARC Monographs evaluate consumption of red meat and processed meat  
[https://www.iarc.who.int/wp-content/uploads/2018/07/pr240\\_E.pdf](https://www.iarc.who.int/wp-content/uploads/2018/07/pr240_E.pdf)

The researchers used predictive models to identify which CRC-related genes were potential targets of mutation by alkylation. Both KRAS and PIK3CA, two mutations commonly mutated in CRC, were more likely to show evidence of alkylation compared to tumours without these mutations. Furthermore, the presence of higher levels of alkylating damage was linked to greater risk of CRC-specific death (47% increase) compared to patients with lower levels of alkylating damage.

### Conclusions & Future Directions

The study is the first to show how a specific mutational pattern (alkylation) in the DNA of colon cells is linked to red meat consumption and the mutations that drive CRC. The findings suggest that red meat consumption may cause alkylating damage, resulting in cancer-causing mutations in KRAS and PIK3CA, therefore promoting CRC development.

The study investigators note that the alkylating mutational signature could potentially be used as a biomarker in the future to better identify patients who are at greater risk of developing CRC or to help detect the presence of CRC at an earlier age. Since the alkylating signature is also linked to patient survival, it may also have potential as prognostic biomarker.

### Take away message:

Study findings show that high red meat consumption was linked to higher levels of DNA damage in colon cells, driving mutations that are specific to the development of colorectal cancer. High red meat consumption was also linked to greater mortality among patients with CRC. Levels of DNA damage increased with increased consumption of red and processed meat.

[READ THE ARTICLE](#)

### Is daily preoperative dietary fiber intake associated with risk of complications after surgery for colorectal cancer?

July 2021

Dietary fiber is an important nutrient which nourishes intestinal cells, protects the intestinal barrier, and maintains a healthy immune response. A recent study suggests that patients with colorectal cancer (CRC) who consume higher levels of dietary fiber may be at a lower risk of developing complications after surgery.

### The study

A Dutch research team used data from the Colorectal Longitudinal, Observational Study on Nutritional and Lifestyle Factors (COLON) study, which recruited adult patients with CRC at any stage from 11 hospitals in the Netherlands between August 2010 and December 2017. With the hypothesis that a healthier intestine might tolerate and recover from an invasive procedure like CRC surgery better, investigators evaluated the association between daily dietary fiber intake and risk of complications after surgery. The study included 1399 patients with stage 1 to 4 CRC who underwent abdominal surgery (average age 66 years; 64% men). Daily dietary fiber intake was

assessed using a 204-item food frequency questionnaire in the 30 days prior to CRC diagnosis, and ‘any complications’, ‘surgical complications’, and ‘anastomotic leakage’ (leak of intestinal contents at a surgical site) were recorded. The average daily intake among study participants was 29.6 grams/day.

‘Any complications’ occurred in 28% of the patients, whereas 17% manifested ‘surgical complications’ and 5% experienced ‘anastomotic leakage’. Each additional 10 grams of fiber/day was associated with a significantly lower risk of ‘any complications’ and ‘surgical complications’, although no association with ‘anastomotic leakage’ was found. In particular, fiber intake from vegetables was associated with a significantly lower risk of any complications and of surgical complications. When the investigators examined the effects in men and women separately, higher daily fiber intake was significantly associated with a lower risk of any complications among women but not among men.

### **Study limitations**

Since there were few events that occurred overall, particularly for surgical complications, this may have limited the statistical power of the study analysis. Furthermore, observing fiber intake over only 30 days before diagnosis does not reflect longer-term dietary patterns which play an important role in intestinal health.

### **Conclusions**

While fiber did have a protective effect, the protection was small – the difference in fiber intake between participants who had complications and those who did not was very minimal – a 2 grams/day of fiber difference. While fiber does contribute to a healthy gut microbiome, it is also possible that participants who consumed more fiber also had healthier lifestyles in other ways compared to people who do not consume as much fiber. Future randomized studies should be done to gain a deeper understanding of the effects of a high-fiber diet on surgical outcomes after CRC surgery, though it is still prudent for patients to increase daily fiber intake

### **Take home message:**

According to this study, higher habitual dietary fiber intake before surgery was related to a lower risk of postoperative complications among patients with CRC. The results suggest that improving preoperative dietary fiber intake may be considered in future prehabilitation programs for patients undergoing surgery for CRC.

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## **Patients with KRAS wild-type metastatic colorectal cancer may experience better responses to hepatic arterial infusion therapy**

July 2021

The KRAS gene is responsible for coding a protein which is involved in cell signaling pathways, controlling cell growth, cell maturation and cell death. Mutated forms of this gene (KRAS positive) have been found in some kinds of cancer, such as colorectal cancer. Knowing whether a patient's tumor has a wild-type KRAS or mutated KRAS may help to plan specific treatments.

### **The study**

Compared to KRAS-positive patients, wild-type patients exhibited better responses to hepatic arterial infusion pump chemotherapy, as demonstrated by a retrospective cohort study<sup>5</sup>. According to Hordur M. Kolbeinsson, MD, a resident physician at Spectrum Health, College of Human Medicine, Michigan State University, KRAS-positive patients had objective response rates of 64%, compared to 100% displayed by wild-type patients. The overall median magnitude of response for wild-type patients was 70% vs 58% for KRAS-positive, and the rate of conversion to resectability was 62% for wild-type, whereas this rate was 18% for KRAS-positive. These findings were reported at the Society of Surgical Oncology (SSO) 2021 International Conference on Surgical Cancer Care.

### **Liver metastases**

Among the patients with colorectal cancer who develop metastases, the liver is by far the most common organ affected by it, as noted by Dr. Kolbeinsson. Although limited to a few specialized centers, the hepatic arterial infusion chemotherapy (HAI) is gaining momentum as a treatment modality for colorectal liver metastases, compared to systemic chemotherapy alone, improving the survival of patients.

### **Suitable for both KRAS wild-type and KRAS-positive patients**

Overall, KRAS-positive patients with liver metastases had a worse objective response rate, overall magnitude of response, and lower rates of conversion to resectable disease when compared with wild-type patients, Dr. Kolbeinsson acknowledged. The physician also stated that these results were unexpected, considering the prior knowledge on KRAS mutations outcomes in colorectal cancer.

However, the objective response of KRAS-positive patients was 64%, which was still a favorable response, considering that this was third-line treatment for 36% of the patients in that group. In select patients, the response and conversion rates are still better than in second- and third-line

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<sup>5</sup> Preihs R, Bengel A, Assifi M, et al: KRAS mutation predicts magnitude of response and outcomes in hepatic arterial infusion pump therapy of unresectable colorectal liver metastases. SSO 2021 International Conference on Surgical Care. Abstract 39. Presented March 18, 2021.

systemic chemotherapy alone. This means that the KRAS mutational status alone should not guide the selection of HAI treatment.

**Take home message:**

KRAS wild-type metastatic colorectal cancer patients may experience better response to hepatic arterial infusion chemotherapy (HAI) than KRAS-positive patients. However, KRAS-positive patients may also benefit from this treatment, which is currently limited to a few specialized centers. Study limitations include size and lack of survival data, therefore larger studies are required to acquire meaningful survival data.

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**Young adult colorectal cancer survivors and treatment-induced infertility: are we discussing it enough?**

July 2021

When a patient is evaluating their treatment options, a key aspect of informed decision making includes full disclosure of the possible risks of treatment options including the impact of therapies on a person's fertility. While clinical guidelines do suggest that oncologists openly discuss the risks of infertility associated with colorectal cancer (CRC) treatments among all patients of reproductive age, findings from a recent study found that the prevalence of fertility discussions among young patients with CRC was low. The findings were presented at the ASCO 2021 Annual Meeting and published in the Journal of Clinical Oncology<sup>6</sup>.

**The study**

The study included an online cross-sectional survey administered in collaboration with a national patient advocacy organization for young adult CRC survivors (currently under age 50). The participants were asked if their doctors had ever discussed the potential of treatment-induced infertility with them, and if they were informed about their options to bank eggs or sperm prior to their cancer therapy. In addition, those who did not preserve fertility were asked to explain why (not sure; I chose not to; I did not know this was an option; I wanted to but could not afford it).

A total of 234 CRC survivors (61.9% male; 77.9% white; most with stage 2 CRC) were included in the study. Over half of male and female survivors informed that their doctor did not discuss treatment-induced infertility with them, and 75% reported not banking eggs or sperm prior to their cancer therapy. Within these 75%, 20% said that 'I wanted to, but could not afford it' and over 20% said that 'I did not know this was an option'.

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<sup>6</sup> Stal J, Yi S, Cohen-Cutler S, et al: Prevalence of fertility discussions between young adult colorectal cancer survivors and their providers. Journal of Clinical Oncology 39(15). DOI: 10.1200/JCO.2021.39.15\_suppl.3518. May 20 2021 3518-3518.

Cost was identified as a significant barrier to preservation of sperm or eggs – given that high cancer treatment costs may already create financial burden on the individual, fertility preservation may become an added burden. Furthermore, the researchers point out that there is often little time to make important fertility preservation decisions before the start of cancer treatment, which can make financial decision making more complicated for patients.

The investigators underline the importance of maintaining patient quality of life during and post-treatment – factors that are equally as important as the cancer treatment itself. Increased dialogue between the patient and their healthcare team to facilitate a mutual understanding of all the patient’s treatment options and their potential effects is a crucial element in cancer survivorship.

**Take home message:**

Findings from a recent study demonstrated that most CRC survivors had never discussed treatment-induced infertility with their doctors, and one fifth (20%) of survivors were not aware of preservation options. This could mean a lack of guideline-concordant cancer care and healthcare and/or provider-level barriers to appropriate fertility counseling. The cost of fertility preservation may also be another obstacle to proper delivery of care. Therefore, despite the fact that providers must ensure that patients receive timely fertility discussions, CRC patients should also request treatment-induced infertility information from their providers.

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