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Dr. Raphael's clinical practice is entirely devoted to the care of patients with gastrointestinal malignancies, with a subspecialty focus on gastric, biliary tract, pancreatic and colorectal cancers. Dr. Raphael's research focus is on population-based cancer care. His research aims to identify ways to optimize the coordination and delivery of cancer care services, and to describe gaps in care, disparities in access to treatment, uptake of cancer therapies, and real-world toxicity and effectiveness.

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Early Age Onset Colorectal Cancer: A Canadian Perspective

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Background

In Canada, 92% of colorectal cancer cases occur in patients over 50 years of age.[1] Accordingly, most colorectal cancer research and early-detection efforts have traditionally focused on older Canadians. However, the epidemiology of colorectal cancer in Canada is changing. Over the past three decades there has been a substantial decrease in the incidence of colorectal cancer among patients over age 50 but an alarming increase in the incidence among patients under 50.[2] It is estimated that by 2040 colorectal cancer will be the leading cause of cancer-related death for individuals aged 20–49.[3] This paper will provide a broad overview of the unique characteristics and care needs affecting patients with early age onset colorectal cancer (EAOCRC) from a Canadian perspective. Unless otherwise specified, EAOCRC will refer to individuals diagnosed with colorectal cancer under age 50.

Epidemiology of Early Onset Colorectal Cancer

Colorectal cancer is the third most common cancer and the second leading cause of cancer-related deaths in Canada.[1] In positive news, colorectal cancer incidence is declining faster than that of any other cancer in Canada. Between 1984 and 2019, the age-standardized incidence rate of colorectal cancer decreased by 4.0% and 3.1% per year among males and females, respectively.[1] However, this overall decline is being driven by a decrease in the incidence of colorectal cancer among adults aged 50 and over and has been largely attributed to uptake of organized colorectal cancer screening programs that detect and remove pre-cancerous polyps.[4,5]

In contrast, the incidence of EAOCRC has risen dramatically in Canada. A recent analysis using national Canadian cancer registries found a mean annual percentage increase in the incidence of colorectal cancer of 3.47% and 4.45% among males and females under age 50, respectively.[2] This analysis also identified a strong birth cohort effect, with the

more recently born young adults having higher rates of EAOCRC compared to those born earlier. Canadian men and women born in 1986 have double the risk of EAOCRC compared to those born in 1936.

Importantly, the data shows there is an alarming increase in the incidence of EAOCRC among very young Canadians. Among patients under age 50, the largest annual increase in incidence for colon and rectal cancer was noted in patients aged 20–29 and 30–39, respectively.

Risk Factors for Early Age Onset Colorectal Cancer

The reason for a rise in the incidence of EAOCRC is not known. Most likely, the reason is multi-factorial and includes a complex interplay of lifestyle, environmental and genetic factors. While studies have sometimes reported conflicting results, the most consistently reported risk factors for EAOCRC include family history, sedentary lifestyle, obesity and Westernized diet.[6] Multiple pathobiological mechanisms have been proposed, including alterations to the gut microbiome,[7] fat-tissue associated dysregulation of insulin signalling, and inflammatory and hormonal response pathways.[8]

Family History – Lynch Syndrome is the most common cause of hereditary colorectal cancer, accounting for approximately 8% of EAOCRC.[9] Although patients with EAOCRC are more likely to have an underlying genetic condition compared to older adults, nearly 85% of EAOCRC is sporadic.[9] Accordingly, a negative family history is often falsely reassuring and should not materially alter a clinician's suspicion for a diagnosis of EAOCRC. In Canada, the rate of colorectal cancer is highest in Newfoundland;[1] this has been attributed to the fact that Newfoundland has one of the highest rates of familial colorectal cancer in the world.[10]

Lifestyle – A population-based, case-control study in Ontario investigated the association between medical, lifestyle and dietary factors and EAOCRC.[11] Compared to sex- and age-matched controls, patients aged 20–49 diagnosed with colorectal cancer self-reported having a more sedentary lifestyle (≥ 10 vs < 5 hours of exercise per day, OR, 1.93; 95% CI, 1.02–3.65); greater consumption of sugary drinks (≥ 7 vs < 1 drinks/week, OR, 2.99; 95% CI, 1.56–5.68); and a more Westernized diet (quartile 4 vs. 1, OR, 1.92; 95% CI, 1.01–3.66).

Obesity - Obesity has consistently been identified as a risk factor for the development of EAOCRC,[12] particularly among women.[13] In the Nurses Health Study II, a prospective cohort study of U.S. female nurses aged 24–52 at study enrollment (1989), BMI at 18 years of age and weight gain since 18 years of age were associated with the development of EAOCRC. For every 5-unit increase in BMI, the relative risk of EAOCRC increased by 20%.[13]

Early Life Exposures – Given the noted birth cohort effect of accelerating incidence of EAOCRC among more recently born individuals, the most rapid rise in incidence affecting patients aged 20–39, and the typical long-latency period for development of colorectal cancer, it has been postulated that novel early life exposures may be important factors in the rising incidence of EAOCRC.[14] Multiple possible factors have been identified, including pre-natal (e.g. maternal stress[15]), peri-natal (e.g. cesarean delivery[16]) and early-life (e.g. antibiotic use[17], breastfeeding[18]), although no prospective studies have yet been able to establish causation.

Screening for Early Age Onset Colorectal Cancer

In Canada there are organized colorectal cancer screening programs in nine provinces and two territories, with Quebec and Nunavut being the outliers.[19] None of the organized screening programs include patients under age 50 and none recommend colonoscopy as the modality of choice for average-risk individuals. All screening programs recommend screening with a fecal immunochemical test (FIT) every 1–2 years.

In 2021, the United States Preventative Services Task Force updated their colorectal cancer screening guidelines and added a recommendation to start screening at age 45–49.[20] This recommendation was made after a modelling study showed screening for colorectal cancer with stool tests, endoscopic tests or CT colonography starting at age 45 years provides an efficient balance of "colonoscopy burden and life-years gained".[21]

In 2023, a microsimulation modelling study estimated the association of lowering the age of colorectal cancer screening using biennial FIT on colorectal cancer incidence, mortality and healthcare system costs in Canada.[22] This analysis found that screening initiation at age 45 resulted in 12,188 fewer colorectal cancer cases

and 5,261 fewer colorectal cancer deaths, and added 92,112 quality adjusted life years. Although the costs associated with screening at a younger age and the associated ensuing investigations increased, the overall healthcare system cost of managing colorectal cancer *decreased*.

In light of the rising incidence of EAOCRC, lowering the age for screening in Canada is passionately advocated for by patients, families and many clinicians.[23] Just recently, in December 2023, the Canadian Agency for Drugs and Technology in Health (CADTH) commissioned a health technology review of screening for colorectal cancer in individuals younger than age 50,[24] which many healthcare professionals anticipate may lead to a recommendation to lower the screening age.

Presentation and Diagnosis of Early Age Onset Colorectal Cancer

The diagnosis of EAOCRC is challenging because several more common conditions present with similar symptoms.[25] Therefore, a high index of suspicion is required and a diagnosis of colorectal cancer should be considered in any patient presenting with bright red blood per rectum or change in bowel habits, regardless of age, or the presence of hemorrhoids/fissures.

A population-based study from British Columbia of 1,992 patients with EAOCRC identified the most common presenting symptoms as: hematochezia (61%); abdominal pain (52%); change in bowel habits (27%); weight loss (20%); constipation (15%); anemia (14%); and diarrhea (12%).[26] The authors also found that EAOCRC patients had a significantly longer median time from symptom onset to diagnosis compared to older patients (median, 143 vs 95 days; P <0.0001).

A population-based study from Ontario evaluated time from healthcare contact, rather than symptom onset, for colorectal cancer-related signs or symptoms to diagnosis and treatment.[27] After healthcare contact, the median diagnostic interval (78 vs 85 days, P <0.001) and time to treatment interval (23 vs 27 days, P<001) were similar in early age onset vs older age onset. This study suggests that among patients who are ultimately diagnosed with colorectal cancer, once healthcare contact is made, the workup for younger and older patients occurs at a similar pace.

In part related to delays to diagnosis,[28] but also related to a lack of organized screening programs and a more aggressive tumor biology, patients diagnosed with EAOCRC present with more advanced tumors at the time of diagnosis.[29] A population-based study from Ontario of 6,775 patients identified that patients with EAOCRC are more likely to have left-sided tumors (50% vs 44%, P <0.001), lympho-vascular invasion (35% vs 27%, P=0.005), T3/T4 tumors (88% vs 79%, P=0.005), and lymph node positive disease (58% vs 41%; P <0.001).[30] Another population-based study from Ontario identified that one in five patients with EAOCRC present with metastatic disease.[27] Similarly, an analysis of 8,748 patients with colorectal cancer in Alberta identified that early-onset patients were more likely to be diagnosed with tumors in the distal colon and rectum, and have Stage 3 or 4 disease at diagnosis.[31]

Treatment of Early Age Onset Colorectal Cancer

Colon Cancer, Localized Disease - The standard upfront treatment for localized colon cancer is an oncological resection and sampling of at least 12 lymph nodes.

For most patients with Stage 2 colon cancer, adjuvant chemotherapy is not routinely recommended given the modest survival benefits.[32] Chemotherapy is selectively recommended to those with the highest-risk features, such as those patients with mismatch-repair (MMR) proficient tumors that are T4 or with less than 12 lymph nodes sampled.[32,33] A population-based study from Alberta identified that patients <40 years old were more likely to be treated with chemotherapy for Stage II colon cancer (OR, 3.41, 95%CI, 1.75-6.47), but this did not translate into better survival than for older patients.[31]

For patients with Stage 3 colon cancer, adjuvant chemotherapy is recommended in most cases. Three months of CAPOX chemotherapy is now the recommended standard of care for most patients.[34] The IDEA collaboration showed that 6 vs 3 months of oxaliplatin-based chemotherapy improved survival by 0.4% but was associated with a tripled risk of Grade 2 or higher neurotoxicity (15% vs 46%).[34]

Young age is a negative prognostic factor in Stage 3 colorectal cancer. In a retrospective analysis of the IDEA collaboration, early-onset patients had lower three-year relapse-free survival (54% vs 65%, HR 1.33; 95% CI, 1.14–1.55) and a higher five-year cancer-specific mortality rate

(24% vs 20%, HR 1.21; 95% CI, 1.00–1.47).[35] These poorer outcomes occurred despite the fact that early-onset patients had better performance status and were more likely to complete the planned treatment duration (76% completion of six months of CAPOX vs 65% in an older population, P<0.001). In an exploratory analysis of 3 vs 6 months of adjuvant therapy by age of cancer onset, EAOCRC patients with "low-risk" Stage 3 disease had lower three-year disease-free survival (DFS) with 3 months of treatment (81 vs 87%; HR, 1.49; 95% CI, 1.00–2.20). In the high-risk Stage 3 subset, there was no difference in DFS with 3 vs 6 months of treatment (57% vs 56%, HR 0.97; 95% CI, 0.73–1.29).[35]

There is no uniformly agreed upon duration of adjuvant therapy for EAOCRC with resected Stage 3 disease. Given the poorer cancer outcomes seen in EAOCRC patients, and concerns of the non-inferiority of 3 vs 6 months of adjuvant therapy particularly for low-risk Stage 3 disease in the IDEA collaboration, some experts advocate that three months of chemotherapy should not be the standard in this cohort of patients.[35] One option for early-onset patients that balances the risks of neurotoxicity and potential benefits of longer therapy is to provide three months of oxaliplatin and six months of a fluoropyrimidine. A combined review of the ACCENT/IDEA databases showed among patients planned for six months of adjuvant therapy, early discontinuation of all treatment (fluoropyrimidine and oxaliplatin) was associated with poorer oncological outcomes; however, discontinuation of the oxaliplatin component alone after the first three months was not.[36] Specifically among patients with EAOCRC (n=1312), early discontinuation of all treatment was associated with worse three-year DFS (64% vs 77%; HR, 1.89; 95% CI, 1.45–2.46) but early discontinuation of oxaliplatin was not (73% vs 78%; HR, 1.23; 95% CI, 0.87-0.74).

Rectal Cancer, Localized Disease – In 2024, there are a number of accepted standard of care treatment options for localized rectal cancer. These include: neoadjuvant chemoradiation or short course radiation followed by surgery with or without adjuvant chemotherapy; neoadjuvant chemotherapy alone followed by surgery; upfront surgery followed by adjuvant chemotherapy; and total neoadjuvant chemotherapy with or without surgery.[37] There is also increasing evidence for neoadjuvant immunotherapy for MSI-H rectal cancer.[38-40] There is often no evidence-based way to choose between these multiple treatment options as most have never been compared directly and the individual aspects of each patient's case and their values and preferences need to determine the treatment approach.

Colorectal Cancer, Metastatic - The mainstay of treatment for metastatic colorectal cancer is sequential use of systemic therapy, and at present the age of patient does not influence the treatment approach. A pooled analysis of 6,284 patients from nine first-line Phase 3 clinical trials for advanced colorectal cancer showed that the relative benefits of chemotherapy were similar regardless of age. Age was minimally prognostic for progression-free survival (<50 vs >50, median 6.0 vs 7.5 months, HR 1.10; P=0.02), and not at all for response rate (RR) (<50 vs >50, 42% vs 43%, OR, 1.02; P=0.84) or overall survival (<50 vs >50, 15.8 v 16.6 months; HR, 1.03).[41]

Considerations In Early-Age Onset Colorectal Cancer Patients

There are several considerations particularly relevant to the care of EAOCRC patients. Importantly, the treatment, including the time invested to undergo treatment, and side effects, may have particularly pronounced effects on the financial, physical and emotional well-being of EAOCRC patients. (**Figure 1**.)[23]

Fertility Preservation - All chemotherapy poses some risk of infertility in both male and female patients. Thus, early referral for fertility counselling and preservation measures is essential for all patients diagnosed with EAOCRC. Fluoropyrimidines are the backbone of most therapies for colorectal cancer. While fluoropyrimidines have been shown to be gonadotoxic, pre-clinical studies suggest they are unlikely to cause permanent infertility.[42] The impact of oxaliplatin on gonadal function was assessed in a small clinical study of 11 female patients under the age of 43 and eight male patients under the age of 45 who were treated with six months of folinic acid, fluorouracil and oxaliplatin (FOLFOX) chemotherapy.[43] All female patients continued menstruation through treatment or resumed post-treatment. All male patients demonstrated laboratory evidence of reduced spermatogenesis; however, they retained intact function of Leydig cells. Similarly, a small clinical study from five hospitals in Nordic countries of 20 males aged <55 and 16 females aged <40 who received FOLFOX chemotherapy showed no male patients developed hypogonadism post-treatment

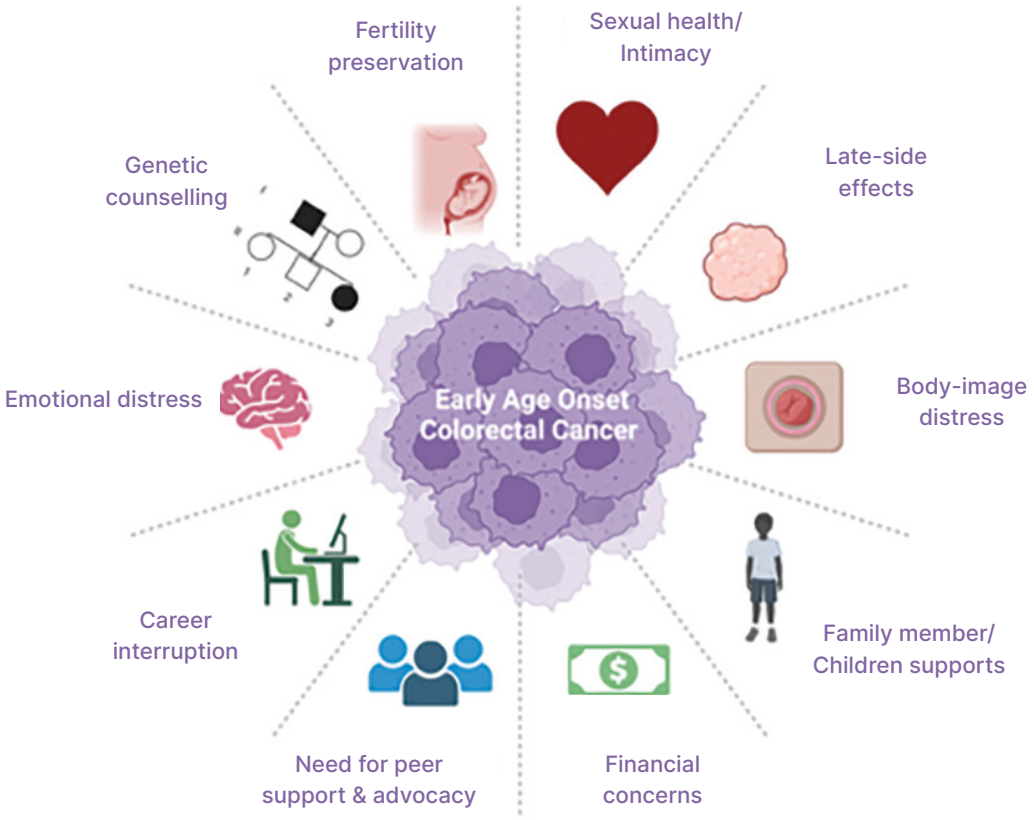

Figure 1. Important considerations in the care and survivorship of EAOCRC; *created with BioRender.com.*

and no female patient experienced alterations in sex hormones or treatment-induced menopause.[44]

Temporary ovarian suppression through use of gonadotrophin-releasing hormone agonists (GnRHa) to prevent chemotherapy-induced premature ovarian insufficiency has shown conflicting results in clinical studies.[45] The majority of the evidence for the use of this therapy comes from studies evaluating patients with breast cancer. A systematic review and meta-analysis of 12 randomized clinical trials (RCTs) including 1,231 breast cancer patients found that temporary ovarian suppression during chemotherapy reduced the rate of chemotherapy-induced premature ovarian insufficiency and increased the subsequent pregnancy rate.[46]

Radiation for rectal cancer may cause infertility and premature ovarian insufficiency. Ovarian tissue is known to be very sensitive to the effects of radiation, with 2 Gray being the estimated dose that will destroy 50% of the oocyte population.[47] If the decision is made that including radiation is part of the best treatment plan for a young female patient, for those considering future childbearing, options to consider include surgical transposition of the ovaries out of the radiation field and cryopreservation (embryo, oocyte or ovarian).[48] For young male patients, sperm cryopreservation is recommended. For female patients requiring radiation, even if fertility preservation measures are taken, it is important to recognize that the effect of radiation on the uterus can make future successful pregnancy challenging.[49]

Secondary Malignancies - A modelling study evaluated patients treated with radiation for rectal cancer and estimated that the overall lifetime attributable risk of a secondary cancer was approximately 2% for a patient aged 69, but up to 10% for a patient aged 30 years at treatment onset; secondary cancer risk increased exponentially with decreasing age at exposure to radiation.[50]

Career Interruption – In addition to the time needed to receive treatment and recover, long-lasting symptoms may impair the ability to return to work in the prior capacity. Following sphincter-sparing rectal surgery, almost all patients[51] will suffer from some symptoms of Low Anterior Resection Syndrome (LARS), which may include some or all of fecal incontinence, urgency, frequency, soiling, and difficulty with compete evacuation. A systemic review and meta-analysis of 50 studies identified the incidence of major LARS to be 44% (95% CI, 40%-48%).[52] Long-term follow-up studies have shown that bowel changes may be permanent and over 50% of patients report ongoing symptoms at 10 years.[53] LARS can be particularly problematic for younger adults, who are more likely to still be working. A study from Montreal of 154 survivors of rectal cancer found that among patients experiencing major LARS, 53% reported financial stress; 71% of those who were working pre-operatively reported that their bowel function impaired their ability to work, delayed their return to work, resulting in them needing to change work schedules and roles; and 15% reported needing long-term disability.[54]

Body-Image Distress – The need for an ostomy following rectal cancer surgery can be associated with body-image distress, intimacy concerns and financial toxicity. For some patients, avoidance of a stoma has been rated as a higher priority than prolongation of DFS. In a survey study of 98 patients with locally advanced rectal cancer, avoiding surgery with a permanent stoma was rated as the most important goal, with a relative importance (RI) of 24.4 (95% CI, 21.88-26.87) and prolongation of DFS was related as least important (RI, 5.6; 95% CI, 4.9-6.2).[55] A pan-Canadian cross-sectional survey of 467 patients living with an ostomy identified that ostomies can impose a significant financial burden.[56] Approximately 75% of respondents reported having to choose between purchasing ostomy supplies or other items such as food, medications or travel; 76% reported spending more than $1,000 dollars per year on supplies.

Sexual dysfunction and Intimacy Concerns – Treatment for EAOCRC may result in emotional, hormonal or physical changes that affect sexual function. A prospective, longitudinal survey was conducted among patients with rectal cancer at four high-volume academic centres in Ontario.[57] Among 45 patients who completed the survey, sexual dysfunction was reported in both male and female patients that continued to increase from baseline up to one year post-surgery. In qualitative interviews, patients noted that sexual function was an important topic to discuss and felt it was the responsibility of the care team to initiate these conversations. In the multinational Never Too Young Survey among patients with EAOCRC, 48% of patients reported sexual dysfunction that put a strain on their relationship; 47% worried "they are not enough for their intimate partner"; and 33% reported not feeling as a "complete person due to sexual dysfunction".[58]

Conclusion

"Children are not just small adults" is a common adage learned in medical school to highlight the unique pathophysiology and care needs of the pediatric population. Similarly, it is increasingly apparent that patients with EAOCRC have a unique epidemiology, disease biology, treatment and survivorship experience compared to older adults with colorectal cancer. Accordingly, Canada needs to appropriately invest in early detection, research and more comprehensive supportive care resources for patients and families affected by EAOCRC. For further details on the diagnosis, management and supportive care measures for patients and families affected by EAOCRC, International Management Guidelines have recently been released.[59]

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Financial Disclosures

None declared.

References

1. Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society: Canadian Cancer Statistics 2023. Toronto, ON, 2023
2. Brenner DR, Heer E, Sutherland RL et al. National trends in colorectal cancer incidence among older and younger adults in Canada. JAMA Network Open 2:e198090-e198090. 2019.
3. Rahib L, Smith BD, Aizenberg R etl. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Research. 2014; 74:2913-2921.
4. Zauber AG, Winawer SJ, O'Brien MJ et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med. 2012;366:687-696.
5. Murphy CC, Sandler RS, Sanoff HK. Decrease in incidence of colorectal cancer among individuals 50 years or older after recommendations for population-based screening. CGH. 2017;15:903-909. e6.
6. Patel SG, Karlitz JJ, Yen T et al. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. Lancet Gastroenterol Hepatol. 2022;7:262-274.
7. Yang Y, Du L, Shi D et al. Dysbiosis of human gut microbiome in young-onset colorectal cancer. Nature Communications. 2021;12:6757.
8. Murphy N, Jenab M, Gunter MJ. Adiposity and gastrointestinal cancers: epidemiology, mechanisms and future directions. Nat Rev Gastroenterol Heptaol. 2018;15:659-670.
9. Pearlman R, Frankel WL, Swanson B et al. Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. JAMA Oncology. 2017;3:464-471.
10. Green R, Green J, Buehler S et al. Very high incidence of familial colorectal cancer in Newfoundland: a comparison with Ontario and 13 other population-based studies. Familial Cancer. 2007;6:53-62.
11. Chang VC, Cotterchio M, De P.Risk factors for early-onset colorectal cancer: a population-based case–control study in Ontario, Canada. Cancer Causes & Control. 2021;32:1063-1083.
12. O'Sullivan DE, Sutherland RL, Town S et al. Risk factors for early-onset colorectal cancer: a systematic review and meta-analysis. Clin Gastro Hepatol. 2022;20:1229-1240. e5.
13. Liu P-H, Wu K, Ng K. Association of obesity with risk of early-onset colorectal cancer among women. JAMA Oncology. 2019;5:37-44.
14. Murphy CC, Singal AG, Baron JA. Decrease in incidence of young-onset colorectal cancer before recent increase. J Gastroenterol. 2018;155:1716-1719. e4.
15. Zhang Q, Berger FG, Love B et al. Maternal stress and early-onset colorectal cancer. Medical Hypotheses. 2018;121:152-159.
16. Cao Y, Nguyen LH, Tica S et al. Evaluation of birth by cesarean delivery and development of early-onset colorectal cancer. JAMA Network Open. 2023;6:e2310316-e2310316.
17. McDowell R, Perrott S, Murchie P et al. Oral antibiotic use and early-onset colorectal cancer: findings from a case-control study using a national clinical database. Br J Cancer. 2022;126:957-967.
18. Yuan C, Wang Q-L, Kim H et al. Being breastfed in infancy and risk of colorectal cancer and precursor sesions. Clin Gastroenterol Hepatol. 2023 Sep 6:S1542-3565(23)00673-0.
19. Cancer CPA: Colorectal cancer screening in Canada 2021/2022, 2022.
20. Davidson KW, Barry MJ, Mangione CM et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2021;325:1965-1977.
21. Knudsen AB, Rutter CM, Peterse EF et al. Colorectal cancer screening: an updated modeling study for the US Preventive Services Task Force. JAMA. 2021;325:1998-2011.
22. Kalyta A, Ruan Y, Telford JJ et al. Association of reducing the recommended colorectal cancer screening age with cancer incidence, mortality, and costs in Canada using OncoSim. JAMA Oncology. 2023;9:1432-1436.
23. Raphael MJ, Wildgoose P, Servidio-Italiano F. Breaking down barriers to detection and care in early-age-onset colorectal cancer in Canada. MDPI, 2023.
24. Khangura SD, Spry C. Screening for colorectal cancer in individuals younger than 50 years. Canadian Journal of Health Technologies. 2023;3.
25. Hawks MK, Svarverud JE. Acute lower gastrointestinal bleeding: evaluation and management. AFP. 2020; 101:206-212.
26. Baronas V, Arif AA, Bhang E et al. Symptom burden and time from symptom onset to cancer diagnosis in patients with early-onset colorectal cancer: a multicenter retrospective analysis. 2023.
27. Castelo M, Paszat L, Hansen BE et al. Comparing time to diagnosis and treatment between younger and older adults with colorectal cancer: A population-based study. J Gastroenterol. 2023;164:1152-1164.
28. Chen FW, Sundaram V, Chew TA et al. Advanced-stage colorectal cancer in persons younger than 50 years not associated with longer duration of symptoms or time to diagnosis. Clin Gastroenterol Hepatol. 2017;15:728-737. e3.
29. Willauer AN, Liu Y, Pereira AA et al. Clinical and molecular characterization of early-onset colorectal cancer. Cancer. 2019;125:2002-2010.
30. Rodriguez L, Brennan K, Karim S et al. Disease characteristics, clinical management, and outcomes of young patients with colon cancer: a population-based study. Clin Colorectal Cancer. 2018; 17:e651-e661.
31. O'Sullivan DE, Cheung WY, Boyne DJ et al. Treatment patterns and survival outcomes of early-onset colorectal cancer patients in Alberta, Canada: A population-based study. CTARC. 2022; 32:100585.
32. Baxter NN, Kennedy EB, Bergsland E et al. Adjuvant therapy for stage II colon cancer: ASCO guideline update. J Clin Oncol. 2022;40:892-910.
33. Group QC: Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. The Lancet. 2007;370:2020-2029.

34. André T, Meyerhardt J, Iveson T et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials. Lancet Oncol. 2020;21:1620-1629.
35. Fontana E, Meyers J, Sobrero A et al. Early-onset colorectal adenocarcinoma in the IDEA database: treatment adherence, toxicities, and outcomes with 3 and 6 months of adjuvant fluoropyrimidine and oxaliplatin. J Clin Oncol. 2021;39:4009-4019.
36. Gallois C, Shi Q, Meyers JP et al. Prognostic impact of early treatment discontinuation and early oxaliplatin discontinuation in patients treated with 6 months of oxaliplatin-based adjuvant chemotherapy for stage III colon cancer: an ACCENT/IDEA pooled analysis of 11 trials. J Clin Oncol. 2023 Feb 1;41(4):803-815.
37. Dossa F, Baxter NN. Changing the treatment paradigm for locally advanced rectal cancer. N Engl J Med. 2023 July;389(4):375-377.
38. Cercek A, Lumish M, Sinopoli J. PD-1 blockade in mismatch repair–deficient, locally advanced rectal cancer. N Engl J Med. 2022;386:2363-2376.
39. Chalabi M, Fanchi LF, Dijkstra KK et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. Nature Medicine. 2020;26:566-576.
40. Chalabi M, Verschoor Y, Van den Berg J et al.LBA7 Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: The NICHE-2 study. Annals of Oncology. 2022;33:S1389.
41. Blanke CD, Bot BM, Thomas DM et al. Impact of young age on treatment efficacy and safety in advanced colorectal cancer: a pooled analysis of patients from nine first-line phase III chemotherapy trials. J Clin Oncol. 2011;29:2781.
42. Stringer JM, Swindells EO, Zerafa N et al. Multidose 5-fluorouracil is highly toxic to growing ovarian follicles in mice. Toxicol Sci. 2018;166:97-107.
43. Levi M, Shalgi R, Brenner B et al. The impact of oxaliplatin on the gonads: from bedside to the bench. MHR: Basic Science of Reproductive Medicine. 2015;21:885-893.
44. Falk P, Severin M, Berglund Å et al. Sex hormones and sperm parameters after adjuvant oxaliplatin-based treatment for colorectal cancer. CTARC. 2022;31:100517.
45. Oktay K, Harvey BE, Partridge AH et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36:1994-2001.
46. Lambertini M, Ceppi M, Poggio F et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. Ann Oncol. 2015;26:2408-2419.
47. Wallace W, Thomson A, Kelsey T. The radiosensitivity of the human oocyte. Hum Reprod. 2003;18:117-121.
48. Lee SJ, Schover LR, Partridge AH et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006;24:2917-2931.
49. Mariani S, Chiloiro G, Villa P et al. Fertility preservation in chemo-radiotherapy for rectal cancer: A combined approach. Clinical and Translational Radiation Oncology. 2019;19:77-79.
50. Zwahlen DR, Bischoff LI, Gruber G et al. Estimation of second cancer risk after radiotherapy for rectal cancer: comparison of 3D conformal radiotherapy and volumetric modulated arc therapy using different high dose fractionation schemes. Radiat Oncol J. 2016;11:1-9.
51. Bryant CL, Lunniss PJ, Knowles CH et al. Anterior resection syndrome. Lancet Oncol. 2012;13:e403-e408.
52. Sun R, Dai Z, Zhang Y et al. The incidence and risk factors of low anterior resection syndrome (LARS) after sphincter-preserving surgery of rectal cancer: a systematic review and meta-analysis. Support Care Cancer. 2021;29:7249-7258.
53. Nguyen TH, Chokshi RV. Low anterior resection syndrome. Curr Gastroenterol Rep. 2020;22:1-8.
54. Garfinkle R, Ky A, Singh A et al. Financial and occupational impact of low anterior resection syndrome in rectal cancer survivors. Colorectal Dis. 2021; 23:1777-1784.
55. van der Valk MJ, van der Sande ME, Toebes RE et al. Importance of patient reported and clinical outcomes for patients with locally advanced rectal cancer and their treating physicians. Do clinicians know what patients want? EJSO. 2020;46:1634-1641.
56. LeBlanc K, Heerschap C, Martins L et al. The financial impact of living in Canada with an ostomy: a cross-sectional survey. JWOCN. 2019;46:505-512.
57. Leon-Carlyle M, Schmocker S, Victor JC et al. Prevalence of physiologic sexual dysfunction is high following treatment for rectal cancer: but is it the only thing that matters? Dis Colon Rectum. 2015;58:736-742.
58. Colorectal Cancer Alliance CC: Never Too Young Survery, 2022. Available at: https://www.ccalliance.org/about/never-too-young/survey
59. Cavestro GM, Mannucci A, Balaguer F, Hampel H, Kupfer SS, Repici A, Sartore-Bianchi A, Seppälä TT, Valentini V, Boland CR, Brand RE. Delphi initiative for early-onset colorectal cancer (DIRECt) international management guidelines. Clinical Gastroenterology and Hepatology. 2023 Mar 1;21(3):581-603.