Trends in the incidence of young-onset colorectal cancer with a focus on years approaching screening age: A population-based longitudinal study

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ABSTRACT

Background: With recent evidence for the increasing risk of young-onset colorectal cancer (yCRC), our objective was to evaluate the incidence of yCRC in one-year age increments, particularly focusing around the screening age of 50 years.

Methods: We conducted a longitudinal study using linked administrative health databases in British Columbia, Canada including a provincial cancer registry, inpatient/outpatient visits, and vital statistics from January 1, 1986 to December 31, 2016. We calculated incidence rates per 100,000 at every age from 20 to 60 years and estimated annual percent change in incidence (APCi) of yCRC using joinpoint regression analysis.

Results: We identified 3,614 individuals with yCRC (49.9% women). The incidence of CRC steadily rose from 20 to 60 years, with a marked increase from 49 to 50 years (incidence rate ratio = 1.19; 95% confidence interval [CI] = 1.04 to 1.34). Furthermore, there was a trend of increased incidence of yCRC among women (APCi = 0.79%; 95% CI = 0.22% to 1.36%) and men (APCi = 2.17%; 95% CI = 1.59% to 2.76%). Analyses stratified by age yielded APCi’s of 2.49% (95% CI = 1.36% to 3.63%) and 0.12% (95% CI = -0.54% to 0.79%) for women aged 30-39 years and 40-49 years, respectively and 2.97% (95% CI = 1.65% to 4.31%) and 1.86% (95% CI = 1.19% to 2.53%) for men.

Conclusion: Our findings indicate a steady increase over one-year age increments in the risk of yCRC during the years approaching and beyond screening age. These findings highlight the need to raise awareness as well as continue discussions regarding considerations of lowering the screening age.
Colorectal cancer (CRC) is the third most commonly diagnosed cancer among both men and women in Canada and is traditionally considered a disease of older adults, with marked onset after the age of 50 years\textsuperscript{1,2}. However, research over the past decade indicate a rise in young-onset colorectal cancer (yCRC), that is, CRC diagnosed in individuals under 50 years of age. A systematic review and meta-analysis published in 2020 that included 39 articles on trends of yCRC incidence reported a pooled annual percent change in incidence (APCi) for yCRC of 1.33% (95% confidence interval [95%CI] = 0.97 to 1.68) internationally and 1.59% (95% CI = 1.24 to 1.93) when pooling was restricted to studies conducted in North America\textsuperscript{3}. The rising trend of yCRC incidence may be attributed to an increase in rectal cancer. A US population-based study by Bailey et al.\textsuperscript{4} showed a statistically significantly increased APCi for yCRC over the period of 1975 to 2010, with the most drastic changes observed for cases of rectosigmoid and rectal cancer in the 20- to 34-year age group, as APCi’s were 2.66%, 3.05%, 4.03% for distant, regional, and localized cancers, respectively.

Canadian guidelines introduced in 2001 recommend that screening for CRC begins for individuals 50 years of age or older\textsuperscript{5}. However, recent evidence on the increasing risk of yCRC has called for discussions to assess whether the guideline recommended initial screening age for CRC should be lowered\textsuperscript{6}. In 2018, the American Cancer Society made a qualified recommendation of lowering the recommended age for average-risk adults to initiate screening from 50 to 45 years\textsuperscript{7}. Recently in 2020, Abualkhair et al.\textsuperscript{8} used the US Surveillance, Epidemiology, and End Results (SEER) registries from 2000 to 2015 to analyze CRC incidence over one-year age increments. Study authors observed the most pronounced incidence increase (46.1%) in the 49- to 50-year age transition with an incidence rate ratio (IRR) of 1.46 (95% CI = 1.42 to 1.51)\textsuperscript{8}. These findings suggest that an excess of yCRC cases are going undetected and only becoming apparent when screening is implemented at 50 years of age\textsuperscript{8}. To evaluate whether such trends are also happening in Canada, a nation where average-risk screening begins at 50 years of age, but has universal medical and hospital
care, we used a population-level cancer registry from British Columbia to assess the incidence of CRC in one-year age increments.

METHODS

Data Source and Study Population

We established a population-based CRC cohort for epidemiologic and health services research by linking administrative databases held in British Columbia (BC), Canada. Specifically, Population Data BC, contains longitudinal and deidentified individual-level health services data for the population of BC (approximately 4.86 million in 2016) since April 1985 including information on outpatient visits from the Medical Service Plan (MSP) database, inpatient visits from the Discharge Abstract Database (DAD), and vital statistics. PharmaNet captures information on all community dispensed prescriptions from 1996 onward. Finally, the BC Cancer Registry captures all new cancers diagnosed in BC residents since 1985 including information on diagnosis (e.g., date, tumour group, sites, stage) and treatment (e.g., dates, modality). Data are linked at the individual level across databases using provincial health numbers, which are replaced by data stewards with random depersonalized identifiers to maintain patient anonymity.

We established a source population from the period of January 1, 1986 to December 31, 2018, that included individuals with CRC identified in the BC Cancer Registry using the following International Classification of Diseases for Oncology, Third Edition codes: C18.2 – C18.9 (colon); C19.9 (rectosigmoid); and C20, C21.8 (rectum). The source population consisted of 54,971 individuals diagnosed with CRC. We classified age of CRC diagnosis using the age of diagnosis variable from the BC Cancer Registry and cases of yCRC were defined as individuals who received their diagnosis at less than 50 years of age (see Supplementary Figure 1 for data sources and source population).
For individuals included in the source population, the end of follow-up corresponded with the last recorded healthcare utilization visit, in MSP, DAD, or PharmaNet databases.

**Statistical Analysis**

For our primary analyses, we calculated the incidence rate (IR) of CRC per 100,000 population from January 1, 1986 to December 31, 2016 for each one-year age interval from 20 to 60, using the 2016 population distribution of BC as the standard to obtain age-adjusted estimates. We truncated the study period to account for 2-year lag in data reporting and submitting cycles. Descriptive statistics (e.g., age, sex) were determined for all incident CRC cases diagnosed between the ages of 20 to 60 years. We concentrated on incident cases of CRC among individuals receiving a diagnosis between 20 and 60 years of age as this permitted us to evaluate cumulative incidence trends encompassing the transition from 49 to 50 years of age, that is, the transition into the age for average-risk screening for Canadians. In addition, we calculated the percentage rate increase in incidence as well as IRR for each one-year age increment (e.g., IRR for 49 to 50 years). To reflect the introduction of CRC screening guidelines by the Canadian Task Force of Preventative Care in 2001, we additionally conducted stratified analyses by the calendar year period of 2001 to 2016. Analyses were also stratified according to sex and cancer site. We completed analyses using SAS statistical software v. 9.4 (SAS Institute, Cary, North Carolina).

As a secondary analysis, we evaluated temporal trends in the incidence of yCRC, focusing on 20 to 49 years of age, over the study period of 1986 through to 2016. We also calculated descriptive statistics for incident yCRC cases receiving a diagnosis between the ages of 20 to 49 years given our focus on individuals excluded from average-risk screening protocols. Exponentiated regression coefficients minus 1 estimate the annual percent change in incidence (APCi) of yCRC for a given segment, with potentially several segments over the study period. We conducted this overall as well
as according to sex, cancer site, and the following 10-year age groups: 30 to 39 years; and 40 to 49 years. The 20-29 age group was not examined due to few events. We completed analyses using the Joinpoint Regression Program (v. 4.7.0.0).

Study Conduct

This study was approved by the University of British Columbia (H17-03530). All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

RESULTS

Study Sample

A total of 12,770 incident cases (44.8% women; mean age = 51.6 [SD = 7.1] years) of CRC were diagnosed in individuals between the ages of 20 to 60 years over the period of 1986 to 2016. Of these, 3,614 cases (49.9 % women) were of incident yCRC (20 to 49 years), where the mean age at diagnosis was 42.3 years (SD = 5.8 years) (Table 1).

Annual incidence rates of CRC (20 to 60 years)

Findings from our primary analyses evaluating the IR of CRC per 100,000 population for each one-year age interval from 20 to 60 are illustrated in Figure 1. Overall, CRC IRs presented according to 1-year age increments and spanning our 30-year study period show a steady rise in incidence over the 49- to 50-year age transition (see Table 2 for IRs and IRRs of surrounding age transitions). The 49- to 50-year age transition is specifically characterized by a CRC rate increase of 18.5%, rising slightly from an IR of 26.2 (95% CI = 23.9 to 28.7) per 100,000 population at 49 years of age to an IR of 31.1 (95% CI = 28.5 to 33.8) per 100,000 population at 50 years of age, with a
corresponding IRR of 1.19 (95% CI = 1.04 to 1.34). This analysis was repeated for the period of 2001 to 2016 to reflect when guidelines for CRC screening were introduced by the Canadian Task Force on Preventive Health Care, and findings similarly suggest an IR increase of 19.7% over the 49 to 50 years of age transition (27.5 (95% CI = 24.5 to 30.7) per 100,000 population to 32.9 (95% CI = 29.6 to 36.4) per 100,000 population) (Table 2 and Supplementary Figure 2). This increase from 49 to 50 years of age corresponds to an IRR of 1.20 (95% CI = 1.02 to 1.40), which is similar to the IRR for the consecutive age transition of 50 to 51 years of age (IRR 1.17, 95% CI = 1.02 to 1.35).

IRs according to cancer site over the period of 1986 to 2016 are presented in Figure 2. The corresponding IRRs for the 49- to 50-year age transition are as follows: colon – 1.08 (95% CI = 0.90 to 1.30); rectosigmoid – 1.17 (95% CI = 0.80 to 1.73); and rectum – 1.33 (95% CI = 1.09 to 1.62). A marked increase in the incidence of rectosigmoid cancer was observed over the 54- to 55-year age transition with an IRR of 1.63 (95% CI = 1.21 to 2.20). The 1-year IRs of CRC according to cancer site for the contemporary cohort (2001 to 2016) are shown in Supplementary Figure 3.

**Trends in the incidence of yCRC (<50 years)**

Trends in the annual incidence of yCRC over the study period are reported in Table 3. Results show an increase in the overall rate of yCRC from 1986 to 2016 by an APCi of 1.48% (95% CI = 1.02%, 1.93%). Stratified analyses suggest the increasing rate of yCRC is largely driven by rectal cancer (APCi = 2.35%; 95% CI = 1.58% to 3.14%) and by yCRC among men, as evidenced by an APCi of 2.17% (95% CI = 1.59% to 2.76%) compared to an APCi of 0.79% (95% CI = 0.22% to 1.36%) for women. When evaluating the rate of yCRC incidence according to 10-year age groupings, the largest APCi is observed in the 30-39-year age group, with an APCi of 2.82% (95% CI = 1.87% to 3.78%) for women and men combined. Stratification by age and gender yielded APCi’s of 2.49%
(95% CI = 1.36% to 3.63%) for women and 2.97% (95% CI = 1.65% to 4.31%) for men in the 30-30 age group. For the 40-49 age group, the APCi was 0.12% (95% CI = -0.54% to 0.79%) for women and 1.86% (95% CI = 1.19% to 2.53%) for men. The 20-29 age group was omitted in the stratified analysis as this age group had several years with zero yCRC cases.

DISCUSSION

Our population-based evaluation using administrative health data from 1986 to 2016 that included 12,770 individuals diagnosed with CRC between the ages of 20 to 60 years showed a steady increase in the incidence of CRC particularly over the 49 to 50-year age transition when incidence was presented in one-year age increments. These findings persisted when assessment was restricted to the more contemporary time period of 2001 to 2016 with the intent of encompassing when CRC screening guidelines were introduced in Canada. Specifically, the 49- to 50-year age transition was characterized by an IRR of 1.20 (95% CI = 1.02 to 1.40), as compared to an IRR of 1.19 (95% CI = 1.04 to 1.34) when evaluating data for all study years (1986 to 2016). When considered collectively with results of our secondary analysis that shows an increasing trend of yCRC incidence from 1986 to 2016 (APCi = 1.48%; 95% CI = 1.02% to 1.93%), our study highlights the changing epidemiology of CRC among younger adults and the need for widespread awareness among patients and healthcare providers.

It is important to contextualize our findings with those reported by Abualkhair et al.8 who used population-based US data from 2000 to 2015 to evaluate the incidence of CRC in one-year age increments among individuals 30 to 60 years of age with the rationale that a drastic increase of CRC cases as individuals shift from 49- to 50-years of age, when average-risk screening begins, would suggest an abundance of preclinical undetected yCRC cases and thereby support a lower age for guideline-based screening. Authors found that this age transition captured the largest increase of
CRC incidence, characterized by a 46.1% increase and an IRR of 1.46 (95% CI = 1.42 to 1.51)\(^8\). In contrast, our replication of this analysis in a Canadian cohort displayed a steady increase of CRC incidence through the same age transition and represented a 19.7% increase (IRR = 1.20; 95% CI = 1.02 to 1.40) in the contemporary cohort. This discrepancy between our study and that of Abualkhair et al.\(^8\) could be a result of differing health care systems as well as the timing of guideline implementation. First, fewer CRC cases clustered at 50 years of age in our study may be explained by Canadians experiencing less barriers to early CRC symptom workup as a result of publicly funded health care, leading to CRC case detection being more distributed over each year of age. In addition, although Canadian guidelines were published in 2001\(^5\), the BC Colon Screening Program, which screens asymptomatic individuals between the ages of 50 to 74 every two years, was not piloted until 2009 and was fully implemented in 2013\(^17,18\). The recentness of BC’s screening program is reflected in results from the nationally administered Canadian Community Health Survey in 2012 that indicate that only 49.6% of eligible BC residents received up to date CRC screening\(^19\). Given that our study captured the early implementation phase of CRC screening, we would expect to observe a rise in CRC incidence for all ages above 50 years, rather than an isolated increase. Indeed, the constant rise in CRC incidence from 49 to 50 years (IRR = 1.20; 95% CI = 1.02 to 1.40) and from 50 to 51 years (IRR = 1.17; 95% CI = 1.02 to 1.35) lends support to this explanation.

Differences in CRC screening modalities used in Canada compared to the US may also explain the steady increase. In BC, for the majority of the study period, FOBT was the first screening test performed and only if this test was positive would patients be referred for colonoscopy. In contrast, in the US there is a larger use of colonoscopy, which is considered a gold standard when evaluating assay sensitivity. Although newer FIT tests have reduced some of the disparity in sensitivity\(^20\), these practice differences may explain the larger increase in CRC incidence reported by Abualkhair et al.\(^8\). The influence of screening practices also extends to our
understanding of the large increase in rectosigmoid cancer incidence noted at age 55 and periodic increases for rectal cancer occurring every 2 years. The 5-year interval increase may be explained by individuals who had a low risk adenoma detected at age 50 and subsequently had a follow up colonoscopy at age 55 as per current screening guidelines in BC. While periodic increases of rectal cancer at 2-year age intervals could reflect the average-risk screening pathway that includes FIT testing every 2 years.

Our study also reinforces the notion that incidence of yCRC is increasing. In 2019 Brenner et al.21 assessed CRC incidence in Canada according to sex and age (< 50 year, ≥50 years) from 1969 to 2015 and found that yCRC incidence increased for both women (APCi = 4.45%) and men (APCi = 3.47%) beginning in 2010 and 2006, respectively. An evaluation of yCRC incidence trends worldwide by Siegel et al.22 further emphasizes this phenomenon, with incidence particularly increased in high-income countries and in the form of rectal cancer among Canadians, a finding corroborated in our study. Our analysis illustrates that yCRC incidence is specifically accelerating for both women and men between 30 to 39 years of age (APCi = 2.49% – women; 2.97% – men) and yCRC incidence remains increased for men between 40 to 49 years of age (APCi = 1.86%). A concentrated increase in the incidence of yCRC among 30 to 39-year old’s has also been reported in a Canada-wide cohort study by Patel et al.23 (1996 to 2010 APCi = 2.4% – overall; 2.3% – women; 2.5% – men) as well as a 2017 US study by Siegel et al.24 that reported steeper increases in rectal cancers (1980 to 2013 APCi = 3.2%) over colon cancers (1988 to 2013 APCi = 1.0%) for the 30 to 39 year age group. Low case counts prohibited our analysis of yCRC incidence in individuals under 30 years of age, however, North American studies have also noted a rising trend in the risk of yCRC for this age group, with APCi’s ranging from 2.4% to 6.3% and 3.2% to 7.0%, for colon and rectal cancers, respectively23,24. The rising incidence of yCRC calls for greater recognition of symptoms by both patients and physicians and provides support for discussion and consideration of lowering the
recommended age for initiating screening, especially given that patients with yCRC often present with more advanced-stage disease\textsuperscript{25}.

The strengths and limitations of our study must also be addressed. Our CRC study sample that spans a 30-year period was drawn from a population-based cohort, created by linking data from Population Data BC and the BC Cancer Registry, which captures data on approximately 95\% of all cancer cases in the province. The BC Cancer Registry is reviewed annually for quality, completeness, and accuracy by the North American Association of Central Cancer Registries\textsuperscript{26}. Importantly, data in the BC Cancer Registry is collected for the purpose of generating cancer statistics and conducting surveillance on the burden of cancer in BC\textsuperscript{26}. However, administrative health data is not without its limitations. The BC Cancer Registry lacks sufficient data on CRC disease stage, which was collected beginning in 2010 and is not acquired using a systematic approach as information on stage relies on a variety of data sources such as death certificates and pathology reports. Access to disease stage would have permitted a more comprehensive assessment of CRC incidence among young adults. However, the absence of this data does not influence results as our study did not involve any analyses on impacts of stage on patient outcomes.

Altogether, in evaluating trends in the incidence of yCRC at the population level, we observed a steady increase in the annual rate of yCRC over the age span from 20 to 60 years, which was characterized by a marked rise around the screening age from 49 to 50\-years. Combined with the observed rising incidence of yCRC in the population of BC, with a notable increase for individuals between 30 to 39 years of age, our study demonstrates the need to increase education and awareness on the changing epidemiology of CRC, particularly the increased risk among younger adults. Consideration on whether to lower the age for average-risk screening in BC to ensure that guidelines recognize the growing risk of yCRC and minimize the occurrence of delayed diagnoses necessitates ongoing discussion and evaluation as the screening program becomes well-established.
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Author contributions: MDV contributed to conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, visualization, data interpretation, and writing original draft.

AH contributed to conceptualization, formal analysis, investigation, methodology, project administration, visualization, data interpretation, and writing original draft.

ECS contributed to data curation, formal analysis, investigation, methodology, software, validation, and visualization.

JML, SG, CJB, MJR, and AF contributed to conceptualization, methodology, and data interpretation.

MDV, JML, SG, and CJB contributed to funding acquisition.

All study authors reviewed and edited the manuscript.

DATA AVAILABILITY

Data used for this study are protected by a strict data sharing agreement between the researchers and data stewards.
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Table 1. Characteristics of individuals with young-onset colorectal cancer diagnosed between the ages of 20 to 49 years (n = 3,614)

| Characteristic               | No. (%)  |
|------------------------------|----------|
| Age, mean (SD)               | 42.3 (5.8) |
| Women                        | 1804 (49.9) |
| Cancer site                  |          |
| Colon                        | 1816 (50.3) |
| Rectum                       | 1440 (39.9) |
| Rectosigmoid                 | 358 (9.9)  |
| Neighbourhood income quintile|          |
| Quintile 1                   | 678 (18.8) |
| Quintile 2                   | 696 (19.3) |
| Quintile 3                   | 855 (23.7) |
| Quintile 4                   | 710 (19.7) |
| Quintile 5                   | 675 (18.7) |
| Residence                    |          |
| Urban                        | 3161 (87.5) |
| Rural                        | 453 (12.5)  |
Table 2. Incidence rates and incidence rate ratios describing the incremental one-year age transitions surrounding the initial age (50 years) for average-risk screening of colorectal cancer

| Age transition | Study period   | 1985 to 2016 | 2001 to 2016 |
|----------------|----------------|--------------|--------------|
|                | Incidence rate (95% CI) per 100,000 | Incidence rate ratio (95%CI) | Incidence rate (95% CI) per 100,000 | Incidence rate ratio (95%CI) |
| 51 to 52 years | 36.7 (33.9, 39.7) to 42.3 (39.3, 45.6) | 1.15 (1.03, 1.29) | 38.5 (34.9, 42.4) to 43.1 (39.3, 47.2) | 1.12 (0.98, 1.28) |
| 50 to 51 years | 31.1 (28.5, 33.8) to 36.7 (33.9, 39.7) | 1.18 (1.05, 1.33) | 32.9 (29.6, 36.4) to 38.5 (34.9, 42.4) | 1.17 (1.02, 1.35) |
| 49 to 50 years | 26.2 (23.9, 28.7) to 31.1 (28.5, 33.8) | 1.19 (1.04, 1.34) | 27.5 (24.5, 30.7) to 32.9 (29.6, 36.4) | 1.20 (1.02, 1.40) |
| 48 to 49 years | 25.1 (22.8, 27.5) to 26.2 (23.9, 28.7) | 1.05 (0.92, 1.20) | 25.1 (22.2, 28.2) to 27.5 (24.5, 30.7) | 1.09 (0.93, 1.29) |
| 47 to 48 years | 20.7 (18.7, 22.9) to 25.1 (22.8, 27.5) | 1.21 (1.05, 1.39) | 21.5 (18.9, 24.4) to 25.1 (22.2, 28.2) | 1.17 (0.98, 1.39) |

*CI = confidence interval
Table 3. Average annual percent change in incidence (APCi) of young-onset colorectal cancer from 1986 to 2016

| Overall and subgroups | APCi, % (95% CI) |
|-----------------------|------------------|
|                       | Overall | Women | Men |
| All yCRC (20-49 years)| 1.48 (1.02, 1.93) | 0.79 (0.22, 1.36) | 2.17 (1.59, 2.76) |
| 10-year age grouping  |         |       |     |
| 30-39 years           | 2.82 (1.87, 3.78) | 2.49 (1.36, 3.63) | 2.97 (1.65, 4.31) |
| 40-49 years           | 1.02 (0.54, 1.50) | 0.12 (-0.54, 0.79) | 1.86 (1.19, 2.53) |
| Cancer site           |         |       |     |
| Colon                 | 1.33 (0.77, 1.90) | 0.83 (-0.05, 1.72) | 1.80 (1.07, 2.55) |
| Rectosigmoid          | -1.38 (-2.68, -0.06) | -1.83 (-3.36, -0.27) | -1.34 (-3.19, 0.55) |
| Rectum                | 2.35 (1.58, 3.14) | 1.45 (0.60, 2.31) | 3.21 (2.12, 4.31) |

*CI = confidence interval; yCRC = young-onset colorectal cancer
FIGURE TITLES AND LEGENDS

Figure 1. Incidence rates of colorectal cancer (per 100,000 population) in 1-year age increments (1986-2016). Incidence rates are shown for A) overall population, B) women, and C) men.

Figure 2. Incidence rates of colorectal cancer (per 100,000 population) in 1-year age increments according to cancer site (1986-2016). Incidence rates are shown according the following sites A) colon, B) rectosigmoid, and C) rectum.
Figure 2--FINAL
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