Patterns of prescription medication use before diagnosis of early age-onset colorectal cancer: A population-based descriptive study

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Abstract

Background: Colorectal cancer (CRC) is estimated to be the fourth major cancer diagnosis in Canada (except for non-melanoma skin cancers) and the second and third leading cause of cancer-related death in males and females, respectively.

Objective: The rising incidence of early age-onset colorectal cancer (EAO-CRC; diagnosis at <50 years), calls for better understanding of patients' pathway to diagnosis. We evaluated patterns of prescription medication use before EAO-CRC diagnosis.

Methods: We used linked administrative health databases in British Columbia, Canada to identify cases diagnosed with EAO-CRC between 01/01/2010 to 12/31/2016, along with cancer-free controls (1:10), matched on age and sex. We identified all prescriptions dispensed from community pharmacies during the year prior to diagnosis and used the Anatomical Therapeutic Chemical (ATC) Classification system Level 3 to group prescriptions according to drug class. We conducted a parallel assessment for those diagnosed with average age-onset CRC (AAO-CRC; diagnosis at age ?50 year).

Results: We included 1,001 EAO-CRC cases (41.0 ± 6.1 years; 45% females), 12,989 prescriptions were filled in the year before diagnosis by 797 individuals (79.7%). Top filled drugs were antidepressants (1st; 13.1%). Drugs for peptic ulcer disease and gastroesophageal reflux disease (3rd; 6.1%) were more likely filled by EAO-CRC cases than controls (OR 1.4, 95% CI, 1.2 to 1.7) and with more frequent fills (OR 1.8, 95% CI, 1.7 to 1.9). We noted similar patterns for topical agents for hemorrhoids and anal fissures which were more likely filled by EAO-CRC cases than controls (OR 7.4, 95% CI, 5.8 to 9.4) and with more frequent fills (OR 15.6, 95% CI, 13.1 to 18.6).

Conclusions: We observed frequent prescription medication use in the year before diagnosis of EAO-CRC, including for drugs to treat commonly reported symptoms of EAO-CRC.

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ABSTRACT (287/450)

Background: Colorectal cancer (CRC) is estimated to be the fourth most common cancer diagnosis in Canada (except for non-melanoma skin cancers) and the second and third leading cause of cancer-related death in males and females, respectively.

Objective: The rising incidence of early age-onset colorectal cancer (EAO-CRC; diagnosis at <50 years), calls for better understanding of patients' pathway to diagnosis. Therefore, we evaluated patterns of prescription medication use before EAO-CRC diagnosis.

Methods: We used linked administrative health databases in British Columbia, Canada to identify cases diagnosed with EAO-CRC between 01/01/2010 to 12/31/2016, along with cancer-free controls (1:10), matched on age and sex. We identified all prescriptions dispensed from community pharmacies during the year prior to diagnosis and used the Anatomical Therapeutic Chemical (ATC) Classification system Level 3 to group prescriptions according to drug class. We conducted a parallel assessment for those diagnosed with average age-onset CRC (AAO-CRC; diagnosis at age ≥50 years).

Results: We included 1,001 EAO-CRC cases (41.0 ± 6.1 years; 45% females), 12,989 prescriptions were filled in the year before diagnosis by 797 individuals (79.7%). Top filled drugs were antidepressants (1st; 13.1%). Drugs for peptic ulcer disease and gastroesophageal reflux disease (3rd; 6.1%) were more likely filled by EAO-CRC cases than controls (OR 1.4, 95% CI, 1.2 to 1.7) and with more frequent fills (OR 1.8, 95% CI, 1.7 to 1.9). We noted similar patterns for topical agents for hemorrhoids and anal fissures which were more likely filled by EAO-

CRC cases than controls (OR 7.4, 95% CI, 5.8 to 9.4) and with more frequent fills (OR 15.6, 95% CI, 13.1 to 18.6).

Conclusion: We observed frequent prescription medication use in the year before diagnosis of EAO-CRC, including for drugs to treat commonly reported symptoms of EAO-CRC.

Keywords

Colorectal cancer; medications; medication patterns; cancer diagnosis; pre-diagnosis

INTRODUCTION

Colorectal cancer (CRC) is estimated to be the fourth most common cancer diagnosis in Canada (except for non-melanoma skin cancers) and the second and third leading cause of cancer-related death in males and females, respectively [1]. Given marked onset of CRC at 50 years old, it was historically considered a disease for older adults. However, recent evidence particularly over the past decade has revealed a rise in the incidence of early age-onset CRC (EAO-CRC), defined as diagnosis among those less than 50 years old [2]. For example, a 2020 Canadian study [3] showed that between 2008 to 2017, the 30-39 age group accounted for the most significant increase with age-specific average annual percent changes of 4.33 (2.79–5.91) for females and 4.53 (2.89–6.19) for males.

The increasing incidence of EAO-CRC has called for research to better understand various aspects of the disease [2-4], including the path to diagnosis,

particularly patterns of healthcare utilization. Using administrative health databases in British Columbia, Canada, a 2022 case-control study found that in comparison to age- and sex-matched cancer-free controls, individuals diagnosed with EAO-CRC experienced a marked increase in outpatient physician visits during the year prior to diagnosis, with reason for visit most commonly documented as nausea, vomiting, and/or abdominal pain [5]. Therefore, delineating patterns of prescription medication use before diagnosis of EAO-CRC may provide further insight, particularly as certain pharmacologic treatments may suggest potential diagnostic opportunities for EAO-CRC. In 2017, Pottegard et al. used the Danish Cancer Registry to evaluate prescription drug use in the 24 months preceding a diagnosis of lung, breast, colon, and prostate cancer and found a stable pattern that markedly increased at 6 months before diagnosis [6]. Among a pre-specified list of drug classes that may likely be prescribed for symptoms of one of the cancers studied (e.g., drugs against overactive bladder/ prostate cancer; drugs against constipation or diarrhea/colon cancer), such as opioids, oral antidiabetics, and statins, authors found that for those with colon cancer, the increased prescription rates before diagnosis were for proton pump inhibitors and antibiotics [6]. It is important to assess whether a similar pattern is presenting in another jurisdiction with specific focus on CRC and considering age at diagnosis, particularly given the increasing incidence of EAO-CRC [2-4]. Thus, our primary aim was to assess patterns of prescription medication use among individual with EAO-CRC during the year preceding diagnosis. To contextualize our findings, we also assessed patterns of prescription medication use among age- and sex-matched cancer-free controls and individuals diagnosed with average-age onset CRC (AAO-CRC; ≥50 years). We aim to better

understand the pathway to diagnosis through evaluating patterns of prescription medication use in the year preceding EAO-CRC diagnosis.

METHODS

Data Sources

As with prior population-based research on the epidemiology of EAO-CRC [7], we linked administrative health databases capturing longitudinal and deidentified individual-level health services data for the province of British Columbia (BC), Canada [8-14]. Population Data BC facilitated data access to the Medical Services Plan database on outpatient visits [13], the Discharge Abstract Database on inpatient visits [14], the Consolidation File for demographics [11], Vital Statistics File for deaths [12], and PharmaNet database on all prescriptions dispensed in community pharmacies regardless of payer [15]. These databases were linked to the BC Cancer Registry, which includes data on cancer diagnosis (e.g., date, site) [9].

Study Design

We conducted a population-based descriptive observational study. First, we identified CRC cases as individuals diagnosed with CRC between January 1, 2010 to December 31, 2016 using International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes, specifically: C18.2 – C18.9 (colon); C19.9 (rectosigmoid); and C20, C21.8 (rectum). Our study period coincided with the beginning (in 2010) of population-based reporting of staging data, based on American Joint Committee on Cancer staging guidelines, with >85% capture in the BC Cancer Registry [16, 17]. We assigned the *index date* as the date of

definitive diagnosis from the BC Cancer Registry based on tissue diagnosis of CRC (endoscopist, surgeon or oncologist). Next, we further classified cases as those with EAO-CRC (diagnosed at less than 50 years of age) and AAO-CRC (diagnosed at 50 years of age or greater). We matched individuals with CRC to cancer-free controls (1: up to 10) on age and sex. Controls were also required to have a healthcare utilization (i.e., outpatient visit, hospitalization, or prescription fill) within the same year their matched case was diagnosed. Controls were assigned an index date, which corresponded to their match date (**Supplementary Figure 1** illustrates data sources and study sample).

Prescription Medication Use

We assessed use of prescription medications over the 1-year period preceding the index date using the PharmaNet database. We drew rationale for evaluating the 1-year period before diagnosis from Pottegard et. al's study showing marked prescription drug use 6 months before cancer diagnosis and from our own prior work with patterns of outpatient physician visits the year before cancer diagnosis [5]. By law, prescriptions dispensed from community pharmacies in British Columbia must be entered in PharmaNet, a province-wide network [15]. Thus, we were able to assess all prescriptions, regardless of payer, and extracted relevant information including prescription date, drug identification number, and Anatomical Therapeutic Chemical (ATC) Classification [18]. In particular, we used the third-level ATC code, allowing us to categorize drugs according to: first level – main anatomical or pharmacological group (e.g., **A** alimentary tract and metabolism); second level – pharmacological or therapeutic subgroup (e.g., A**10** drugs used in diabetes); **third**/fourth levels –

chemical, pharmacological or therapeutic subgroup (e.g., A10**B** blood glucose lowering drugs; A10B**A** biguanides) (**Supplementary Table 1**).

Statistical Analysis

We used descriptive statistics (e.g., mean, proportions) to characterize all individuals included in our study sample according to age, sex (females/males), socio-economic status (determined using neighborhood income per person equivalent adjusted for household size), type of residence (rural versus urban, determined using Census Metropolitan Area/Census Agglomeration from geographical census data). For individuals with CRC, we also determined cancer site using ICD-O-3 codes (e.g., rectum, left colon, right colon, transverse colon), and stage at diagnosis.

We assessed patterns of prescriptions among EAO-CRC cases overall and according to sex and stage age at diagnosis, reporting counts and proportions using both prescriptions and persons as units of analyses. Using logistic regression, we evaluated determinants of our outcome of having ≥1 prescription filled in the year before diagnosis among EAO-CRC cases. Potential determinants included age, sex, neighborhood income quintile, residence, cancer diagnosis site and stage. We used a backward stepwise approach and retained in the model variables based on statistical and/or clinical significance. We then compared patterns of prescription medications among EAO-CRC cases and controls, reporting counts, proportions, and odds ratios (OR) and corresponding 95% confidence intervals (CI), where relevant. We also compared patterns of prescription medications among EAO-CRC and AAO-CRC cases, reporting counts, proportions, ORs and corresponding 95% CIs, where relevant. We completed all

these analyses using SAS statistical software v. 9.4 (SAS Institute, Cary, North Carolina).

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

Our study included 1,001 cases with EAO-CRC (45% female, mean age 41.0 ± 6.1 years) and 10,010 matched cancer-free controls (45% female, mean age 41.0 ± 6.1 years). As shown in **Table 1**, EAO-CRC cases were most frequently diagnosed with cancer in the rectum (n = 418, 41.8%) and with Stage III (n = 351, 35.0%) and Stage IV (n = 270, 27.0%) disease. In our parallel analyses, we identified 12,331 cases with AAO-CRC (44.9% female, mean age 66.6 ± 9.2 years), who were most frequently diagnosed with cancer in the left colon (n = 5,210, 42.3%) and Stage III (n = 3,644, 29.6%) or Stage II (n = 2,996, 24.3%) disease.

There were 12,989 prescription events among 797 EAO-CRC cases (79.7%) and 174,806 prescription events among 7,796 matched cancer-free controls (77.9%). With respect to individuals, there is no significant difference in proportions of EAO-CRC cases and controls filling prescriptions (OR 1.11, 95% CI, 0.94 to 1.3). However, with respect to the number of prescriptions filled, among 797 EAO-CRC cases, there was a mean of 16.3 ± 73.7 prescriptions (median 5.0)

per case; whereas for 7,796 controls there was a mean of 22.4 ± 99.3 prescriptions (median 6.0) per control. **Table 2A** summarizes medication classes that represent ≥1% of all prescriptions in the year before diagnosis for EAO-CRC cases and controls. Assessing specific medications including ranking and frequency revealed patterns of use. For example, antidepressants (ATC3 N06A) were the top medications filled by both EAO-CRC cases (13.1% of prescriptions) and controls (9.9% of prescriptions) with EAO-CRC having more frequent fills (OR 1.4, 95% CI, 1.3 to 1.4) than cases. GI drugs (ATC3 N02A; for peptic ulcer disease and gastroesophageal reflux disease) were the third most filled prescriptions by EAO-CRC cases (6.1% of prescriptions) and fifth most filled by controls (3.5% of prescriptions) with EAO-CRC cases having higher odds of filling (OR 1.4, 95% CI, 1.2 to 1.7) and having more frequent fills (OR 1.8, 95% CI, 1.7 to 1.9). Relatedly, agents for treatment of hemorrhoids and anal fissures for topical use (ATC3 C05A) and drugs for constipation (ATC3 A06A) represent the 9th (2.1% of prescriptions) and 10th (1.9% of prescriptions) most filled prescriptions by EAO-CRC cases but were not among ≥1% of prescriptions for controls. EAO-CRC cases had higher odds of filling (OR 7.4, 95% CI, 5.8 to 9.4) and had more frequent fills (OR 15.6, 95% CI, 13.1 to 18.6) for topical agents for hemorrhoids and anal fissures. Among EAO-CRC cases, factors associated with having ≥1 prescription in the year before diagnosis were having inflammatory bowel disease (adjusted odds ratio [aOR], 3.43; 95% confidence interval [CI], 1.20 to 9.780) and depression (aOR, 4.20; 95% CI, 1.49 to 11.85). As well, number of outpatient visits was also a determinant with an aOR of 1.14 (95% CI, 1.09 to 1.18).

We further assessed patterns of prescription medication use among EAO-

CRC cases stratified by sex and stage. **Table 2B** shows medication classes that represent ≥1% of all prescription events in the year before diagnosis for EAO-CRC according to sex. We observed a higher number of prescriptions (n = 7,295) representing 56.2% of all events among 420 (/551) male EAO-CRC cases (76.2%). In contrast, 377 (/450) female EAO-CRC cases (83.8%) had a lower number of prescriptions (n = 5,694) representing 43.8% of events. In terms of frequency of prescriptions by sex, we found higher fills for antidepressants (14.7% males; 10.9% females), antiepileptics (9.8% males; 7.4% females), GI drugs (8.0% males; 3.7% females), as well as pain-related medications such as opioids (5.8% males; 3.9% females) and other analgesics and antipyretics (1.1% males; <1% females) for males with EAO-CRC than females with EAO-CRC. When EAO-CRC cases were stratified by stage, we observed the following prescription events among individuals: Stage I (1,620 prescription events in 112 cases [78.3%]); Stage II (3,523 prescription events in 167 cases [81.5%]); Stage III (3,226 prescription events in 283 cases [80.6%]); and Stage IV (4,620 prescription events in 209 cases [77.4%]). As seen visually by the blue bars in **Figure 1**, drugs belonging to the nervous system class were the most represented across all four stages. Of note, when considering number of prescriptions, those among Stage IV EAO-CRC cases represented 35.6% of all prescription events, in contrast to those among Stage I EAO-CRC cases which represented 10.3% of all prescription events. Antidepressants were the most filled medications among individuals diagnosed at Stage II (14.2%) and IV (19.0%) (**Figure 1**). Of interest, GI drugs were the most used in Stage IV EAO-CRC cases (11.0%). Topical agents for treatment of hemorrhoids and anal fissures were mostly filled by Stage III EAO-CRC cases (4.0%). Drugs for

constipation were the highest used in Stage II EAO-CRC cases (2.6%) and lowest in Stage I EAO-CRC cases (1.4%).

For further context, when we analyzed 12,331 AAO-CRC cases, we observed a total of 317,271 prescription events among 10,979 individuals (89%) (**Supplementary Table 2**), mean of 28.9 ± 83.9 prescriptions (median 13.0) per AAO-CRC case. While antidepressants (13.1%) and antiepileptics (8.7%) were the top two most frequently filled medications among EAO-CRC cases, these drug classes were observed to be the third and seventh most used medications among AAO-CCRC cases (4.8% and 3.4% respectively). Instead, the AAO-CRC group showed lipid modifying agents (6.9%) and ACE inhibitors (5.1%) as the top two most used medication classes. Drugs that may be used to treat symptoms associated with potential CRC diagnosis were more frequently filled among EAO-CRC cases than AAO-CRC cases including: GI drugs (6.1% EAO-CRC; 4.7% AAO-CRC), non-steroidal anti-inflammatory and antirheumatic products (3.5% EAO-CRC; 1.1% AAO-CRC), topical agents for treatment of hemorrhoids and anal fissures (2.1% EAO-CRC; <1% AAO-CRC) and drugs for constipation (1.9% EAO-CRC; <1% AAO-CRC). EAO-CRC cases also revealed a higher use of opioids (5.0% EAO-CRC; 3.0% AAO-CRC).

DISCUSSION

Using population-based administrative data, we assessed patterns of prescription medications in the year before diagnosis among individuals with EAO-CRC to understand the role of medications in the pathway to diagnosis in a condition that has seen considerable increase in incidence [2-4]. Among 1,001 EAO-CRC cases, 12,989 prescriptions were filled in the year before diagnosis by

797 individuals (79.7%). With respect to medications, antidepressants were most commonly filled (13.1%), followed by antiepileptics (8.7%) and GI drugs (i.e., drugs for peptic ulcer disease and gastroesophageal reflux disease) (6.1%). Sex-based analyses revealed a higher number of prescriptions (56.2% of prescription events) among male EAO-CRC cases but at a lower proportion, 76.2% compared to a lower number of prescriptions (43.8% of prescription events) but at a higher proportion, 83.8%.

Of interest in our study were patterns of prescription medication use leading to diagnosis, particularly for individuals with EAO-CRC, given the increasing risk of this disease (4) and interest in understanding potential identification and/or diagnostic opportunities given reported diagnostic delays in prior studies [19, 20]. To our knowledge, our current study is the first to assess patterns of prescription use before diagnosis of EAO-CRC. In 2017, using Danish nationwide health registries on cancer and prescription drugs, Pottegard et al. assessed new use of prescription drugs among lung, breast, colon and prostate cancer patients 24 months preceding their cancer diagnosis [6]. Authors found similar patterns of drug use between cancer cases and population controls in the 24- to 12- month period before cancer diagnosis. Among colon cancer cases, authors showed increase in use of prespecified drug classes that were likely prescribed for symptoms relating to their cancer, namely, proton pump inhibitors, laxatives or drugs against diarrhea, and opioid analgesics. However, this study did not characterize participants and as such, it is not feasible to draw findings according to age as well as sex and stage, as with our current study. With respect to prescription medication use specifically among individuals with CRC, Engeland et al.’s 2021 cohort study using data from the Cancer Registry of

Norway primarily assessed prescription medications after diagnosis but also reported on use in the year before diagnosis [21]. Authors evaluated a pre-specified list of drugs according to five major categories and reported the top three most commonly used drug groups in the year before diagnosis such as those for cardiovascular diseases (use prevalence, 24.8%) endocrine, nutritional and metabolic diseases (use prevalence, 17.8%), and mental and behavioral disorders (use prevalence, 6.7%). Although the study included CRC patients aged 20 to 84 years, there was no reporting of drug use according to age groups. Furthermore, with 530 individuals in the 20- to 39- year age category comprising 2% of the study population, reported findings largely reflect drug use among older CRC patients.

Indeed, our study provides better understanding of patterns of prescription medication use specifically in EAO-CRC. In contrast to aforementioned studies [6, 21] which assessed pre-specified lists of drugs based on reimbursement, we were able to assess all prescriptions, regardless of payer, given comprehensive capture in the PharmaNet database. At the outset, we initially assumed that the most common prescriptions filled during the year of diagnosis were for GI and pain, based on previously reported symptoms of EAO-CRC [22]. Indeed, among the top ten classes of most frequently filled prescriptions by EAO-CRC cases were GI drugs for peptic ulcer disease and gastroesophageal reflux disease (3rd), opioids (4th), anti-inflammatory & antirheumatic drugs, non-steroids (6th), topical agents for hemorrhoids and anal fissures (9th), and drugs for constipation (10th). We believe the increased use of these drugs for EAO-CRC symptoms in the year prior to diagnosis may be early manifestations of red flag signs and symptoms of CRC. A 2023 population-based

case-control study by Fritz et. al identified four red flag signs and symptoms (rectal bleeding, abdominal pain, diarrhea and iron-deficiency anemia) that were associated with a heightened risk of EAO-CRC between 3 months to two years preceding diagnosis (ORs range between 1.34 to 5.13) [23]. These red flag symptoms align with the clinical indications of our results, where GI drugs, pain medications and rectal medications were among the top ten classes of most frequently filled prescriptions by EAO-CRC cases in the year prior to diagnosis. These results highlight the importance of ensuring individuals < 50 years old consistently presenting with these early warning signs and symptoms or medication use patterns are being given ample opportunities for further work-up and early detection of CRC at their healthcare interactions. Stratified analyses by sex and stage further reveal patterns such as higher use of pain-related medications and GI drugs by male EAO-CRC cases. Our findings also suggest sex differences in healthcare utilization in terms of more frequent prescriptions among a smaller number of male EAO-CRC cases compared to less frequent prescriptions among a greater number of female EAO-CRC cases. With respect to stage, GI drugs were most used in Stage IV EAO-CRC cases, topical agents for treatment of hemorrhoids and anal fissures were by Stage III EAO-CRC cases, and drugs for constipation were the highest used in Stage II EAO-CRC cases and lowest in Stage IV EAO-CRC cases. In contextualizing findings with those of controls, while opioids (4^{th}), GI drugs (5^{th}), and anti-inflammatory & antirheumatic drugs, non-steroids (7^{th}) were among the top ten classes of filled prescriptions by matched cancer-free controls, they were at lower frequency than EAO-CRC cases. Interestingly, topical agents for hemorrhoids and anal fissures and drugs for constipation, were not among ≥1% of prescription events

among controls.

Our findings on patterns of prescription medication use before diagnosis support a study rationale of exploring targets for raised awareness and education on the increasing risk of EAO-CRC to allied healthcare providers, particularly pharmacists. With patients reportedly seeing pharmacists 1.5 to 10 times more frequently than primary care physicians [24], these may represent windows of opportunity for education or identification of risks for diseases, including cancer. A survey of community pharmacists suggests that patients have long sought advice from pharmacists about possible cancer signs and symptoms [25]. With respect to CRC, pharmacists are gaining recognition for their roles in initiation of average age screening in various jurisdictions [26-28]. In the US, a two-phased study showed high satisfaction among individuals from socioeconomically disadvantaged populations with pharmacists speaking to them regarding CRC screening [27]. In Spain, evaluation of a population-based CRC screening program showed high adherence by participating pharmacies (82.4%) with respect to distributing fecal immunochemical test kits and high return rate by invitees (93.5%), demonstrating the important role that pharmacists play in the program [29]. There is indeed potential to expand on pharmacists' roles when it comes to educating individuals regarding CRC, including younger adults about EAO-CRC. To date, calls to action have largely focused on increasing awareness among primary care physicians on the increasing risk of EAO-CRC [30, 31]; however, it is also important to consider other health care providers, particularly pharmacists, given their accessibility and as prescriptions represent a frequent healthcare encounter prior to CRC diagnosis.

Aside from patterns of prescription medication use, a noteworthy finding from our study is that antidepressants represent the top prescribed drug class for EAO-CRC cases in the year before diagnosis, representing 13.1% of all prescription events. For context, antidepressants were also the top prescribed drug class for matched cancer-free controls but at a lower frequency, 9.9%. For further context, among AAO-CRC cases, antidepressants were the third most prescribed drug class (4.8%) after ACE inhibitors (5.1%), and lipid modifying agents (6.9%). A potential reason for this finding is a diagnostic delay of CRC that commonly occurs in the young patient population [20], which may lead to anxiety and depressive symptoms [32]. A systematic review that compared the delays and outcomes between younger and older CRC patients found that younger patients are at a higher risk of experiencing delays from symptom onset to presentation as they are not eligible for screening [20]. Consequently, a delay in cancer diagnosis in the younger population is associated with an increased risk of anxiety and depression [32]. A cross-sectional study in 2022 found that patient intervals (symptom onset to first seeing a general practitioner) of ≥1 month were associated with greater depression (aOR, 1.7; 95% CI: 1.1 to 2.5) compared to <1 month and having ≥3 pre-referral general practitioner consultations were associated with greater anxiety (aOR, 1.6; CI: 1.1 to 2.3) compared to 1-2 consultations. [32]. Main reasons that could contribute to the increased risk of emotional distress in the adolescents and young adult population prior to a diagnosis include patients' persistent symptoms being dismissed due to young age, unresolved symptoms, and the fear of a potential cancerous diagnosis [32, 33]. Furthermore, in a 2022 cohort study that used the same administrative databases as our current study, found

that compared to individuals without cancer, those with EAO-CRC did not have a higher onset of depression after diagnosis (adjusted hazard ratio [aHR], 1.00; 95% CI, 0.92 to 1.10) [34]. However, individuals with EAO-CRC had a 41% higher risk of onset of depression after diagnosis compared to individuals with AAO-CRC (aHR, 1.41; 95% CI, 1.25 to 1.60) [34]. Since we were not able to link indications to prescription events, we do not know whether antidepressants were prescribed for depression or for other reasons, such as pain. Nonetheless, findings in our current study suggest a substantial burden of depression even before EAO-CRC diagnosis, which further indicates the need for person-centered mental health services for individuals with EAO-CRC across the entire spectrum of care.

The strengths and limitations of our study warrant discussion. We drew EAO-CRC cases and controls from population-based administrative health databases, namely 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 (11). Nevertheless, this study is vulnerable to inherent limitations with administrative health data, which are not collected for research purposes. Although we have data on stage, it is important to note this information in the BC Cancer Registry is not acquired using a systematic approach with sources including death certificates, pathology reports, and death certificates. Finally, administrative databases in BC do not yet capture information on the social construct of gender and as such, we are not able to incorporate this into our analysis.

Altogether, using generalizable, population-based data, including

complete capture of all prescriptions, we delineated patterns of medication use before diagnosis of EAO-CRC. Our findings suggest a high frequency of prescription fills in the year before diagnosis of EAO-CRC, including for drugs to treat commonly reported symptoms of EAO-CRC. As efforts continue to raise awareness on the increasing risk of EAO-CRC, our findings provide support for also considering the role of other health care providers, particularly pharmacists. Altogether, prescription medications represent a common and potentially, frequent, point-of-contact with the healthcare system and thus, may lend to better understanding of trajectories for individuals with EAO-CRC.

DECLARATIONS

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- **Author contributions:**
  - VC 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.
  - VC and RG contributed to conceptualization, investigation,

visualization, data interpretation, and writing original draft.

- MDV contributed to funding acquisition, conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, visualization, data interpretation, and writing original draft.
- All study authors reviewed and edited the manuscript.

- **Institutional review board statement:** This study was approved by the University of British Columbia's Behavioural Research Ethics Board (H17-03530) and was performed in accordance with relevant guidelines and regulations.
- **Informed consent statement:** Consent to participate was waived by the University of British Columbia's Behavioural Research Ethics Board as this research involves secondary use of data.
- **Data availability statement:** The data that support the findings of this study are available from Population Data BC [https://www.popdata.bc.ca/] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from Population Data BC through a data access request [dataaccess@popdata.bc.ca].
- **Conflicts of interest:** The authors declare that they have no conflicts of interests.

Multimedia Appendix 1: Table 1. Characteristics of individuals with early age-onset colorectal cancer (EAO-CRC; <50 years), average age-onset colorectal cancer (AAO-CRC; ≥50 years), and their respective controls.

Multimedia Appendix 2: Table 2A. Frequency of prescriptions in the year before diagnosis for EAO-CRC cases and cancer-free controls according to Anatomical Therapeutic Chemical Level 3 (ATC 3) Classification.

Multimedia Appendix 3: Table 2B. Frequency of prescriptions according to Anatomical Therapeutic Chemical Level 3 (ATC 3) Classification in the year before diagnosis among male, and female EAO-CRC cases.

Multimedia Appendix 4: Supplementary Table 1. ATC Level 1 Groups.

Multimedia Appendix 5: Supplementary Table 2. Frequency of prescriptions in the year before diagnosis for EAO-CRC and AAO-CRC cases according to Anatomical Therapeutic Chemical Level 3 (ATC3) Classification.

Multimedia Appendix 6: Supplementary Figure 1. Overview of data sources and study sample (dashed arrow indicates linkages between databases using personal health numbers which are then de-identified/ scrambled).

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ABBREVIATIONS

AAO-CRC: Average age-onset colorectal cancer

aHR: Adjusted hazard ratio

aOR: Adjusted odds ratio

ATC: Anatomical Therapeutic Chemical Classification

BC: British Columbia

CI: Confidence interval

CRC: Colorectal cancer

EAO-CRC: Early age-onset colorectal cancer

GI: Gastrointestinal

GI Drugs: Drugs for peptic ulcer and gastro-oesophageal reflux disease

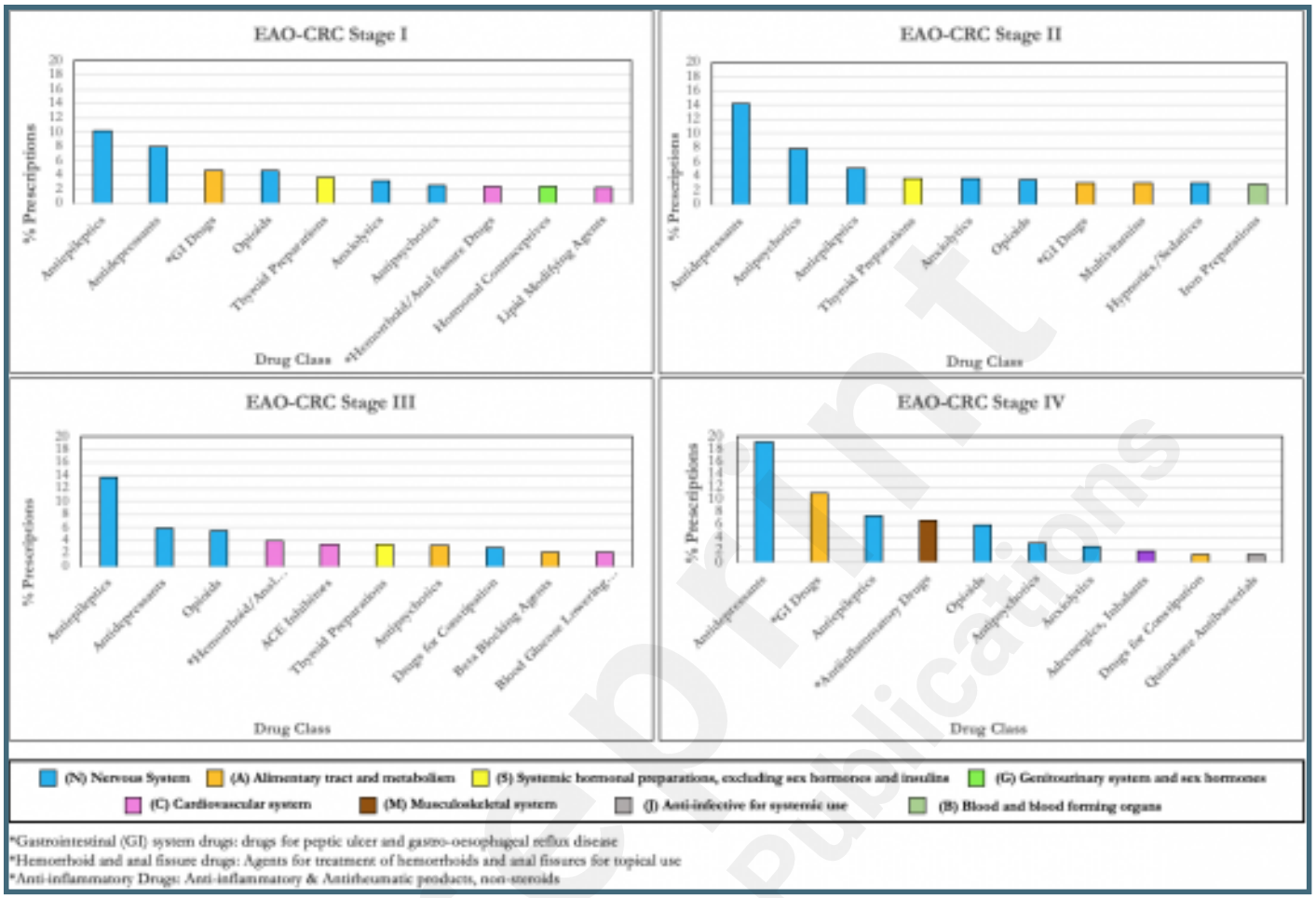
ICD-O-3: International Classification of Diseases for Oncology, Third Edition

OR: Odds ratio

Supplementary Files

Figures

Bar charts showing % of prescriptions for the top 10 drug classes by ATC Level 3 code according to stage for EAO-CRC cases.



*Gastrointestinal (GI) system drugs: drugs for peptic ulcer and gastro-oesophageal reflux disease
*Hemorrhoid and anal fissure drugs: Agents for treatment of hemorrhoids and anal fissures for topical use
*Anti-inflammatory Drugs: Anti-inflammatory & Antirheumatic products, non-steroids

Multimedia Appendixes

Table 1. Characteristics of individuals with early age-onset colorectal cancer (EAO-CRC;
URL: http://asset.jmir.pub/assets/1c951173b83905655202b902c648ae6f.docx

Table 2A. Frequency of prescriptions in the year before diagnosis for EAO-CRC cases and cancer-free controls according to Anatomical Therapeutic Chemical Level 3 (ATC 3) Classification.
URL: http://asset.jmir.pub/assets/aeade6dd9d200ae661764e5b266fd44d.docx

Table 2B. Frequency of prescriptions according to Anatomical Therapeutic Chemical Level 3 (ATC 3) Classification in the year before diagnosis among male, and female EAO-CRC cases.
URL: http://asset.jmir.pub/assets/9aedfd97475796d7be1c0a65a7b820df.docx

Supplementary Table 1. ATC Level 1 Groups.
URL: http://asset.jmir.pub/assets/2a4f6285ea3bac16d52ffa9e486529c4.docx

Supplementary Table 2. Frequency of prescriptions in the year before diagnosis for EAO-CRC and AAO-CRC cases according to Anatomical Therapeutic Chemical Level 3 (ATC3) Classification.
URL: http://asset.jmir.pub/assets/a10bab73aa07f786b59985aa28d7b9dc.docx

Supplementary Figure 1. Overview of data sources and study sample (dashed arrow indicates linkages between databases using personal health numbers which are then de-identified/scrambled).
URL: http://asset.jmir.pub/assets/6af30b34235d3ebe52db6e62c972238b.png

CONSORT (or other) checklists

STROBE Checklist.
URL: http://asset.jmir.pub/assets/c40aac31408812f3b4fc9c5c3e050f75.pdf