



Gravida and Birth Outcomes Prior to and after Diagnosis of Early Age-Onset Colorectal Cancer among Female Patients: Population-Based Epidemiologic Studies

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ABSTRACT

Background: Early age-onset colorectal cancer (EAO-CRC) strikes during the reproductive years, yet pregnancies before and after diagnosis have not been thoroughly studied. Our objective was to comprehensively examine: (i) the relationship between gravida and EAO-CRC and (ii) the relationship between EAO-CRC and births after cancer diagnosis.

Methods: We conducted a case-control and a cohort study using administrative health data from British Columbia, Canada, of females diagnosed with EAO-CRC from 2005 to 2017 and age- and sex-matched cancer-free controls. Multivariable logistic regression models were used to evaluate: (i) the association between gravida assessed over the 5-year prodrome period before cancer diagnosis and EAO-CRC and (ii) the association between EAO-CRC and births assessed over a 5-year period following cancer diagnosis.

Results: The study sample consisted of 865 females (age at EAO-CRC diagnosis 42.5 ± 6.1 years) with EAO-CRC and 8,291 controls (42.4 ± 6.3 years). Females with a gravida of ≥ 2 in the 5-year prodrome period had 1.82 times the odds of EAO-CRC compared with those with gravida of 0 (OR, 1.82; 95% confidence interval, 1.19–2.78). After cancer diagnosis, females with EAO-CRC had significantly lower odds of giving birth within five years (OR, 0.23; 95% confidence interval, 0.15–0.37). Older age, lower income, rural residence, and greater healthcare utilization were associated with lower odds of post-diagnosis births.

Conclusions: Our study highlights the complex relationship between reproductive health and EAO-CRC.

Impact: Findings indicate a need for comprehensive psychosocial support addressing family planning for female patients with EAO-CRC.

Introduction

Colorectal cancer is the fourth most diagnosed cancer among females in Canada, with approximately 10,500 new cases in 2023 (1). Although historically considered a disease among older adults, with average age at onset on or after 50 years, evidence in recent years shows an increasing risk of early age-onset colorectal cancer (EAO-CRC) among adults 50 years or older. An overview of colorectal cancer statistics in the United States found that the average annual overall incidence rate from 2015 to 2019 was 33% higher in men (41.5 per 100,000) than in women (31.2 per 100,000; ref. 2). The

same report highlighted increasing trends in EAO-CRC risk, reporting an average annual percent change of 1.9% among adults 20 to 49 years from 2015 to 2019 although sex-specific trends were not reported (2).

Because of the sex difference in the lifetime risk of colorectal cancer, female sex hormones have been explored as potential protective factors (3). Evidence indicates that oral contraceptives (i.e., exogenous hormones) significantly reduce colorectal cancer risk by 18% compared with never-users (4). Similar trends have been noted for postmenopausal hormone replacement therapy, with a 20% to 40% risk reduction of colorectal cancer (5, 6). The impact of endogenous female sex hormone exposure on colorectal cancer risk is uncertain as evidence is conflicting (3); gravida and parity are often used as proxies for such exposure given the substantial hormonal changes that occur during pregnancy. In a 2014 population-based case-control study which included 12,195 females with colorectal cancer (mean age 57 ± 10 years), Lu and colleagues (7) reported ORs for the association of parity and adenocarcinoma of the proximal colon as follows: for those with one or two children, 1.02 [95% confidence interval (CI), 0.93–1.13]; for those with three or four children, 1.18 (95% CI, 1.06–1.32); and those with ≥ 5 children, 1.30 (95% CI, 1.05–1.61). These findings were not replicated in the distal colon or rectum. In 2016, Bjørge and colleagues (8) conducted a population-based case-control study which included 22,185 female colorectal cancer cases (mean age 57 years, SD not reported) registered in Nordic birth registries and found no associations between parity and colorectal adenocarcinoma. A 2022 population-based case-control study by Amitay and colleagues (9) showed an inverse association (OR, 0.91; 95% CI, 0.86–0.97) between the number of pregnancies and colorectal cancer, with the

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mean age at diagnosis of 69.5 ± 11.6 years. It is important to note that these prior studies were conducted in older adults with colorectal cancer. Indeed, although colorectal cancer has long been considered a disease of older adults, recent evidence suggests a shift in its epidemiology, particularly with an increasing risk of EAO-CRC (2, 10–12). Given this changing epidemiology, there is a need to better understand the relationship between reproductive history and EAO-CRC, especially as diagnoses in younger adults often occur during their reproductive years.

In addition to understanding the impact of reproductive history on EAO-CRC risk, it is also important to examine the impact of an EAO-CRC diagnosis on reproductive health outcomes—particularly because such diagnoses often occur during individuals' reproductive years. Only one study to date has evaluated reproductive health outcomes following EAO-CRC diagnosis. Specifically, in 2023, Cao and colleagues (13) conducted a matched case-control study of pregnancy (e.g., mode of delivery), maternal (e.g., gestational diabetes and preeclampsia), and neonatal outcomes in female patients with EAO-CRC. Authors reported higher odds of cesarean delivery (OR, 1.43; 95% CI, 1.00–2.06) and preeclampsia (OR, 2.52; 95% CI, 1.25–5.08). Although authors reported numbers of births among cases and controls, they did not report ORs. It is important to continue generating data on the impact of EAO-CRC on reproductive outcomes, considering treatment types and cancer sites, to better support patients and providers in making family-planning decisions.

Current literature has overlooked the assessment of pregnancies both before and after the diagnosis of EAO-CRC among females. As such, our objective was to gain comprehensive understanding of the associations between: (i) gravida, as a measure of endogenous hormone exposure in the prodrome period, and EAO-CRC diagnosis and (ii) EAO-CRC diagnosis and births after diagnosis.

Materials and Methods

Data source and source population

We conducted case-control and retrospective cohort analyses using Population Data British Columbia (BC) data, which capture longitudinal, deidentified individual-level data for all 5.4 million residents in BC, Canada, from 1985 forward. Holdings include the following databases: the Medical Services Plan (outpatient visits), Discharge Abstract Database (inpatient visits), Consolidation File (demographics), Vital Statistics File (deaths) since 1985, and PharmaNet (drug and dispensing information) since 1996. We linked Population Data BC data to the BC Cancer Registry (<https://www.popdata.bc.ca/data/health/bccancer>), which captures cancer diagnosis (date of diagnosis, tumor type, and site) and treatment (treatment type and dates) information since 1985. Lastly, we linked data to the BC Perinatal Data Registry (<http://www.perinatalservicesbc.ca/health-professionals/data-surveillance/perinatal-data-registry>), which captures information abstracted from obstetrical and neonatal medical records on nearly 100% of births in the province from more than 60 hospitals and at-home births attended by BC-registered midwives from 2000.

The source population for both analyses comprised of individuals diagnosed with colorectal cancer from January 1, 1985, to December 31, 2017, and identified in the BC Cancer Registry using International Classification of Diseases for Oncology, Third Edition codes C18-3, C18-0, and C18-2 (right colon); C18-6, C18-7, C18-5, and C19 (left colon); C18-4 (transverse colon); C20 and C21-8 (rectum); and C18-9, C18-1, and C18-8 (unspecified). For each individual with

colorectal cancer, the index date was defined as the diagnosis date using tissue samples from the BC Cancer Registry. Each individual with colorectal cancer was matched with 10 cancer-free controls on age, sex, and index date. The resulting study source included 54,634 individuals with colorectal cancer and 546,340 cancer-free controls (Fig. 1). To obtain the study sample, we identified females with EAO-CRC ($n = 865$), who were diagnosed <50 years of age, from April 2005 to December 2017 and their matched cancer-free controls ($n = 8,291$). We selected the study period of 2005 to 2017 to capture a more contemporary timeframe, during which increases in the incidence of EAO-CRC were beginning to emerge (10), while also ensuring sufficient prior data for the case-control analysis (e.g., six years before diagnosis) and adequate follow-up for the cohort analysis.

Outcomes

We ascertained gravida using the BC Perinatal Data Registry, defined as the total number of prior pregnancies measured at the time of delivery, including the current pregnancy, regardless of gestational age, type, timing, or method of termination or outcome. We also identified births, including both live births and stillbirths, using the same data source.

Covariates

We included covariates relevant to the respective case-control and cohort analyses, considering appropriate periods for their ascertainment (Fig. 2). Demographic factors included age, neighborhood income quintile (using quintile of adjusted income per person equivalent, an area-based socioeconomic measure of neighborhood income per person equivalent, adjusted for household size), and residence (urban versus rural as determined by using Census Metropolitan Area/Census Agglomeration from geographical census data; ref. 14). We also assessed comorbidities including inflammatory bowel disease (yes/no; ref. 15) as well as the Charlson-Romano comorbidity index (weighted score of comorbid conditions, considering their potential impact on patient outcomes; refs. 16, 17). We also considered history of oral contraceptive use and assessed health care utilization based on hospital visits (yes/no) and frequency of doctor visits (14). Finally, we also considered EAO-CRC characteristics including cancer site (left, transverse, unspecified, and right colon and rectum) and treatment (surgery, chemotherapy, and radiation).

Statistical analysis

Descriptive analysis

We utilized descriptive statistics (e.g., means, proportions, etc.), χ^2 tests, and t tests to characterize and compare demographic, clinical, and cancer-related variables available in study datasets. Although sex was accounted for by selecting females for our study sample, gender is not yet captured by administrative databases in BC.

Case-control analysis of gravida and EAO-CRC diagnosis

In the case-control analysis, we evaluated the association between gravida (exposure) assessed during the prodrome period, i.e., within 5 years preceding the index date, and EAO-CRC diagnosis (outcome; Fig. 2). We computed multivariable conditional logistic regression models with EAO-CRC diagnosis as the outcome and gravida as the exposure. First, we considered gravida overall (ever pregnant vs. never pregnant) and then according to the following categories: gravida, 0, 1, and ≥ 2 . Models were adjusted for age, neighborhood income quintile (quintiles 1, 2, 3, and 4 vs. quintile 5),

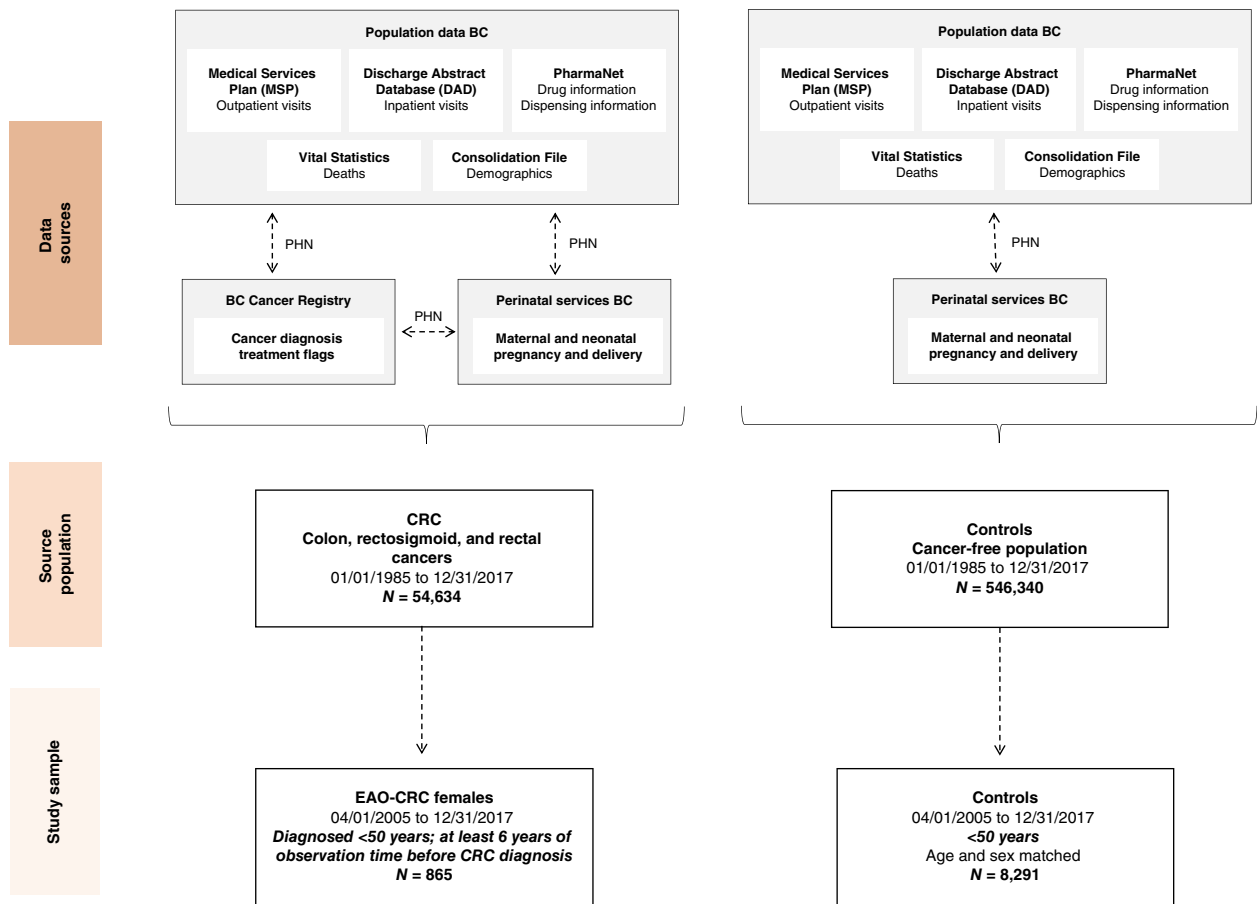


Figure 1. Flow of data sources and linkages, source populations, and study sample (dashed arrows show linkages between databases using personal health numbers which are then de-identified). CRC, colorectal cancer; PHN, personal health number.

residence (rural vs. urban), the Charlson–Romano comorbidity index, history of contraceptive use (yes vs. no), healthcare utilization through hospital visits (yes vs. no), and number of doctor visits.

Cohort analysis of EAO-CRC diagnosis and births after diagnosis

In the cohort analysis, we evaluated the association between EAO-CRC diagnosis (exposure) and births after diagnosis, i.e., 5 years following the index date (Fig. 2). We computed multivariable logistic regression models adjusted for age, neighborhood income quintile (quintiles 1, 2, 3, and 4 vs. quintile 5), residence (rural vs. urban), the Charlson–Romano comorbidity index, inflammatory bowel disease (yes vs. no), healthcare utilization through hospital visits (yes vs. no), and number of doctor visits. We also considered births in the five years prior to index date (yes vs. no). Finally, we conducted sensitivity analyses among individuals with EAO-CRC to evaluate associations between cancer characteristics, namely site (left, transverse, and unspecified and rectum vs. right colon) and treatment (surgery: yes vs. no; chemotherapy: yes vs. no; and radiation: yes vs. no), and births after diagnosis. As systematic collection of staging information in the BC Cancer Registry only began in 2010, consideration of this variable would be limited to cases diagnosed from that year onward. Nonetheless, we conducted additional sensitivity analyses limited to this subset of the study sample,

i.e., EAO-CRC diagnosed from 2010 to 2017, using reduced models only, as the limited sample size could lead to issues with model convergence. All analyses were completed on SAS statistical software v9.4 (https://www.sas.com/en_ca/home.html).

Ethics approval

This study was approved by the University of British Columbia (H17-03530), which is guided by the Canadian Tri-Council Policy Statement (TCPS2 2014).

Data availability

Access to data provided by the Data Stewards is subject to approval but can be requested for research projects through the Data Stewards or their designated service providers (https://www.popdata.bc.ca/index.php/data_access/process). All datasets listed above were used in this study. Further information on these datasets can be found by visiting the PopData project webpage at https://my.popdata.bc.ca/project_listings/18-088/.

Results

The study sample used for respective case–control and cohort analyses included 865 females with EAO-CRC and 8,291 matched

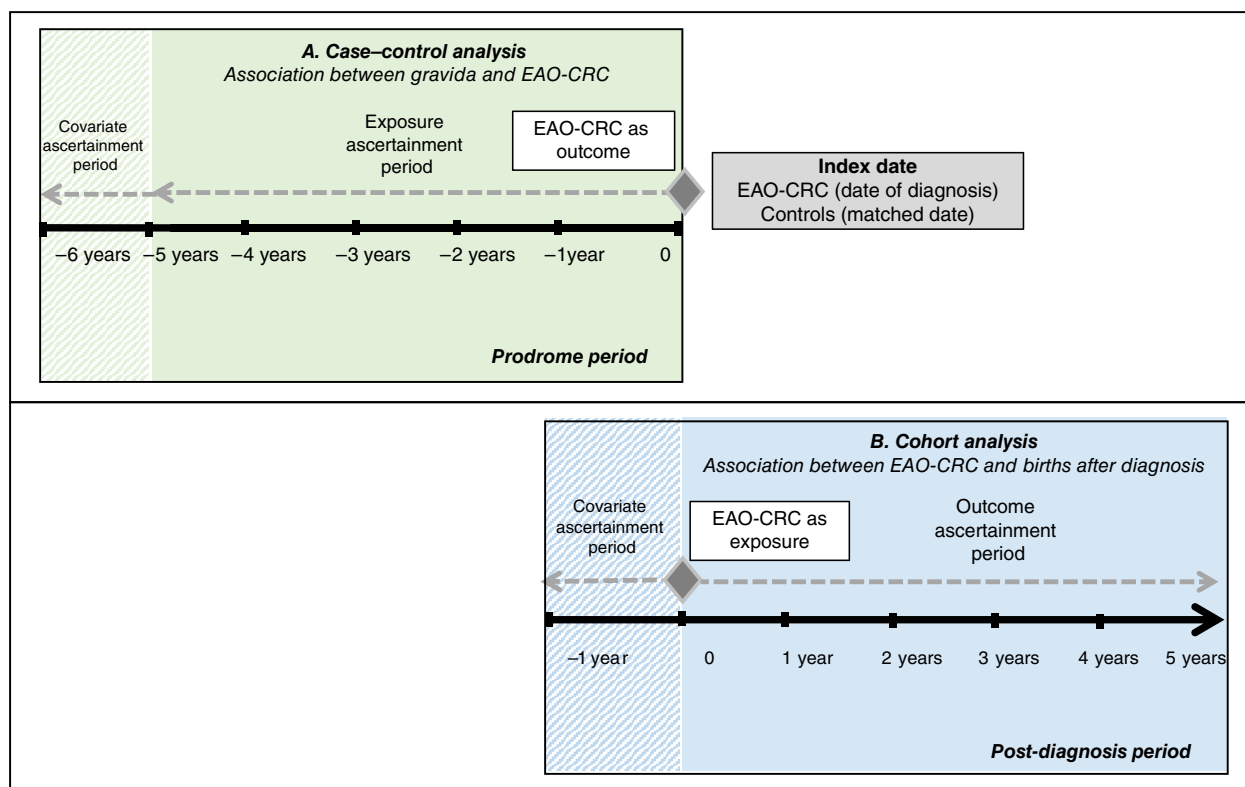


Figure 2.

Schematic of the (A) case-control analysis on the association between gravida and EAO-CRC, and (B) EAO-CRC and births after diagnosis. The index date represents the diagnosis date for individuals with EAO-CRC (and matched date for controls), dividing the timeline into prodrome and post-diagnostic periods.

cancer-free controls. Of note, the incidence rate for EAO-CRC in the study sample was 5.5 per 100,000, with mean age at diagnosis of 42.5 ± 6.2 years. Study samples were characterized at appropriate time periods for each of the case-control and cohort analysis and summarized in **Tables 1** and **2**, respectively. With respect to the study sample for the cohort analysis, mean age at EAO-CRC diagnosis was 42.5 years, with the most frequent site at left colon (45.3%), followed by rectum (36.7%) and right colon (11.2%).

Gravida and EAO-CRC

Table 3 summarizes conditional logistic regression models for the case-control analysis of the association between gravida and EAO-CRC diagnosis. Although there was no significant association when gravida was assessed as a binary variable (OR, 1.08; 95% CI, 0.85–1.37), when assessed according to specific categories, we found that females with a gravida of ≥ 2 during the 5-year prodrome period had 1.82 times the odds of EAO-CRC compared with those with a gravida of 0 during the same period (OR, 1.82; 95% CI, 1.19–2.78).

EAO-CRC and births after diagnosis

Table 4 summarizes univariate and multivariable logistic regression models for the cohort analysis of the association between EAO-CRC and births after diagnosis. The univariate model showed that females with EAO-CRC had 0.28 times odds of birth during the 5-year post-diagnosis period compared with females without EAO-CRC (OR, 0.28; 95% CI, 0.19–0.41). This significant association was

also evident in the multivariable model with females with EAO-CRC having 0.23 times the odds of birth during the 5-year post-diagnosis period (OR, 0.23; 95% CI, 0.15–0.37). In terms of demographic factors, older age (OR, 0.79; 95% CI, 0.78–0.80) and residence in a rural location (OR, 0.71; 95% CI, 0.52–0.98) were associated with lower odds of having a birth during the 5-year post-diagnosis period. We also observed a positive association between reproductive history before EAO-CRC diagnosis and births after diagnosis (OR, 2.62; 95% CI, 2.17–3.16).

We also conducted sensitivity analysis evaluating the association between cancer characteristics and births after diagnosis among individuals with EAO-CRC. We found an inverse association with age in that every 1-year increase in age among females with EAO-CRC was associated with 25% lower odds of births after diagnosis. Point estimates suggest negative associations between respective treatments and births after diagnosis – radiation (OR, 0.71; 95% CI, 0.10–5.28), surgery (OR, 0.58; 95% CI, 0.19–1.73), and chemotherapy (OR, 0.28; 95% CI, 0.08–0.98) although statistical significance was only observed for chemotherapy (Supplementary Table S1). To enable assessment of cancer stage, a separate sensitivity analysis was conducted among females diagnosed with EAO-CRC between 2010 and 2017. In this reduced logistic regression model, increasing age was associated with lower odds of post-diagnosis births (OR, 0.76; 95% CI, 0.67–0.85). Compared with stage 1 disease, the odds of post-diagnosis births were also lower for stage 4 (OR, 0.07; 95% CI, 0.006–0.76) and stage 3 (OR, 0.16; 95% CI, 0.03–0.84), suggesting that higher cancer stage was associated with decreased likelihood of

Table 1. Characteristics of female patients with EAO-CRC (<50 years) and respective controls for case-control analysis^a.

Characteristic	EAO-CRC (n = 865)	Controls (n = 8,291)	P value ^b
Demographic factors			
Age, years [mean (SD)]	37.5 (6.1)	37.4 (6.3)	0.5047
Neighborhood income, n (%)			
Quintile 1	168 (19.4)	1,817 (21.9)	0.0194
Quintile 2	156 (18.0)	1,786 (21.5)	
Quintile 3	194 (22.4)	1,679 (20.3)	
Quintile 4	184 (21.3)	1,587 (19.1)	
Quintile 5	163 (18.8)	1,422 (17.2)	
Residence, n (%)			
Urban	768 (88.8)	7,404 (89.3)	0.6413
Rural	97 (11.2)	887 (10.7)	
Health care utilization			
Doctor visits, mean (SD)	7.2 (9.3)	7.8 (9.7)	0.0762
Hospital visits, n (%)	119 (13.8)	994 (12.0)	0.1299
Comorbidities			
Charlson-Romano comorbidity index, mean (SD)	0.01 (0.1)	0.01 (0.2)	0.9352
Obstetric history			
Gravida during the prodrome period			
0	762 (88.1)	7,361 (88.8)	0.0167
1	74 (8.6)	770 (9.3)	
2+	29 (3.4)	160 (1.9)	
Medication use			
Contraception, n (%)	132 (15.3)	1,215 (14.7)	0.6323

^aCovariates assessed -6 to -5 years from the index date.

^bA *t* test was used for numerical variables and χ^2 test for categorical variables; *P* < 0.05 for significance.

giving birth after diagnosis. We did not observe a significant association with stage 2 (OR, 0.37; 95% CI, 0.05-2.51).

Discussion

Using linked population-based administrative health data including cancer and perinatal registries, we conducted a comprehensive evaluation that spanned the relationship between gravida in the prodrome period and EAO-CRC diagnosis and the relationship between EAO-CRC and births after diagnosis. Using a case-control analysis, we found that females with ≥ 2 gravida during the 5-year prodrome period had 82% higher odds of an EAO-CRC diagnosis compared with females who did not have pregnancies during the same period. Using cohort analysis, we found that females with EAO-CRC had 77% lower odds of births during the 5-year post-diagnosis period compared with females without EAO-CRC. We also found associations between demographic factors and pre-EAO-CRC obstetric history and births after diagnosis. Taken together, these epidemiologic studies highlight an intricate relationship between reproductive history and EAO-CRC.

Our case-control analysis of the association between gravida and EAO-CRC builds on previous studies that have specifically evaluated colorectal cancer as the outcome and with samples with older females (7-9). For example, in Lu and colleagues (7) case-control study which reported associations with higher parity (e.g., 3 or 4 children and ≥ 5 children) and colorectal cancer, the mean age for cases was 57 years; in Bjorge and colleagues (8) case-control study which showed no association, the median age for cases was also 57 years;

Table 2. Characteristics of female patients with EAO-CRC (<50 years) and respective controls for cohort analysis^a.

Characteristic	EAO-CRC (n = 865)	Controls (n = 8,291)	P value ^b
Demographic factors			
Age, years [mean (SD)]	42.5 (6.1)	42.4 (6.3)	0.5047
Neighborhood income, n (%)			0.0168
Quintile 1	174 (20.1)	1,738 (21.0)	
Quintile 2	148 (17.1)	1,771 (21.4)	
Quintile 3	179 (20.7)	1,609 (19.4)	
Quintile 4	182 (21.0)	1,688 (20.4)	
Quintile 5	182 (21.0)	1,485 (17.9)	
Residence, n (%)			0.9828
Urban	776 (89.7)	7,436 (89.7)	
Rural	89 (10.3)	855 (10.3)	
Health care utilization			
Doctor visits, mean (SD)	12.1 (10.0)	10.3 (11.8)	<0.0001
Hospital visits, n (%)	371 (42.9)	1,193 (14.4)	<0.0001
Comorbidities			
Charlson-Romano comorbidity index, mean (SD)	0.59 (1.8)	0.02 (0.3)	<0.0001
Inflammatory bowel disease, n (%)	50 (5.8)	70 (0.84)	<0.0001
Obstetric history			
Births 5 years before diagnosis ^c , n (%)	103 (11.9)	934 (11.3)	0.5706
CRC characteristics			
Cancer site, n (%)			
Left colon	392 (45.3)		
Rectum	317 (36.7)		
Right colon	97 (11.2)		
Transverse colon	38 (4.4)		
Unspecified	21 (2.4)		
Treatment			
Surgery, n (%)	537 (62.1)		
Chemotherapy, n (%)	564 (65.2)		
Radiation, n (%)	264 (30.5)		

Abbreviation: CRC, colorectal cancer.

^aNon-cancer-related covariates were assessed -1 to 0 years from the index date; cancer-related covariates assessed at the index date.

^bA *t* test was used for numerical variables and χ^2 test for categorical variables; *P* < 0.05 for significance.

^cAssessed -5 to 0 years from the index date.

and in Amitay and colleagues (9) case-control study which showed an inverse association with the number of pregnancies and colorectal cancer, the mean age for cases was 69.5 years. Our finding of an association between multigravida (≥ 2 pregnancies) and EAO-CRC aligns most closely with the Lu and colleagues study. However, given previous conflicting findings, further research is warranted, especially as mechanisms underlying the relationship between reproductive history and colorectal cancer also remain unclear. A 2018 review by Troisi (3) showed conflicting associations between reproductive history/endogenous hormone exposure and cancers in females, including colorectal cancer, with some studies such as the European Prospective Investigation into Cancer and Nutrition Study showing little association (18) and other studies such as the US NIH-AARP Diet and Health Study showing positive associations between age at menopause and at first childbirth with colorectal cancer diagnosis (19) and negative associations with parity and age at menarche. Troisi and colleagues (3) also reported that prospective studies observing circulating estrogens and colorectal cancer

Table 3. ORs and 95% CIs from logistic regression models for case-control analysis of the association between gravida and EAO-CRC.

Exposure definition 1		Exposure definition 2	
	OR (95% CI)		OR (95% CI)
Univariate model		Univariate model	
Gravida during prodrome period (ever vs. never)	1.08 (0.85-1.38)	Gravida during the prodrome period (≥ 2 vs. 0)	1.82 (1.19-2.78)
Multivariable model		Multivariable model	
Gravida during prodrome period (ever vs never)	1.08 (0.85-1.37)	Gravida during the prodrome period (≥ 2 vs. 0)	1.82 (1.19-2.78)
Covariates ^a		Covariates ^a	
Age ^b	1.02 (0.86-1.22)	Age ^b	1.02 (0.86-1.22)
Neighborhood income		Neighborhood income	
Quintile 1 vs. 5	0.82 (0.65-1.02)	Quintile 1 vs. 5	0.82 (0.65-1.02)
Quintile 2 vs. 5	0.77 (0.61-0.97)	Quintile 2 vs. 5	0.77 (0.61-0.97)
Quintile 3 vs. 5	1.04 (0.83-1.30)	Quintile 3 vs. 5	1.04 (0.83-1.30)
Quintile 4 vs. 5	0.99 (0.79-1.24)	Quintile 4 vs. 5	0.99 (0.79-1.24)
Rural (vs. urban)	1.04 (0.83-1.30)	Rural (vs. urban)	1.04 (0.83-1.30)
Hospital visits (yes vs. no)	1.36 (1.08-1.71)	Hospital visits (yes vs. no)	1.36 (1.08-1.71)
Number of doctor visits ^b	0.99 (0.98-1.00)	Number of doctor visits ^b	0.99 (0.98-1.00)
Charlson-Romano comorbidity index ^b	0.97 (0.69-1.38)	Charlson-Romano comorbidity index ^b	0.97 (0.69-1.38)
Contraceptive status (yes vs. no)	1.07 (0.87-1.32)	Contraceptive status (yes vs. no)	1.07 (0.87-1.32)

^aAssessed -6 to -5 years from the index date.

^bAssessed as a continuous variable.

diagnosis are inconclusive. Authors synthesized that inconsistencies may be because of difficulty of quantifying lifetime hormone exposure, changes in reproductive behaviors, and dynamic usage of exogenous hormones over time (3). In our study, we used gravida as a measure of endogenous hormone exposure; however, this outcome is measured at the time of delivery. Therefore, the database does not capture gravida history of those who do not experience a delivery (still or live birth). Furthermore, there are many other

Table 4. ORs and 95% CIs from logistic regression models for cohort analysis of the association between EAO-CRC and births after diagnosis.

	OR (95% CI)
Univariate model	
EAO-CRC (yes vs. no)	0.28 (0.19-0.41)
Multivariable model ^a	
EAO-CRC (yes vs. no)	0.23 (0.15-0.37)
Age ^b	0.79 (0.78-0.80)
Neighborhood income	
Quintile 1 vs. 5	0.55 (0.42-0.74)
Quintile 2 vs. 5	0.94 (0.72-1.23)
Quintile 3 vs. 5	0.84 (0.63-1.12)
Quintile 4 vs. 5	0.93 (0.71-1.23)
Rural (vs. urban)	0.71 (0.52-0.98)
Hospital visits (yes vs. no)	0.74 (0.58-0.95)
Number of doctor visits ^b	1.01 (1.00-1.02)
Charlson-Romano comorbidity index ^b	0.74 (0.52-1.05)
Inflammatory bowel disease (yes vs. no)	0.79 (0.35-1.78)
Births 5 years prior to diagnosis (yes vs. no) ^c	2.62 (2.17-3.16)

^aCovariates assessed -1 to 0 years from the index date.

^bAssessed as continuous variables.

^cAssessed -5 to 0 years from the index date.

reproductive health factors that need to be accounted - age at menarche and miscarriages - which are not routinely available in administrative health data, including the one we utilized.

Female patients with EAO-CRC increasingly face disruptions to their fertility and family planning due to cancer diagnosis and treatment through both social and medical facets (20, 21). Our study uniquely explores reproductive health both before and after an EAO-CRC diagnosis, with the latter being especially relevant given the limited prior research. In 2023, Cao and colleagues (13) conducted a matched case-control study examining reproductive health outcomes following EAO-CRC diagnosis. Although birth counts for cases and controls were reported, ORs were not reported. Our cohort analysis shows that females with EAO-CRC had 77% lower odds of giving birth in the 5 years after diagnosis compared with those without EAO-CRC, contributing to the literature on reproductive health outcomes after diagnosis. Beyond EAO-CRC, a 2023 systematic review and meta-analysis by our team found an increased risk of poor maternal reproductive health outcomes (preeclampsia, gestational age, cesarean delivery, and fertility treatment) in patients with early age-onset cancer (22). At the intersection of affected number of births and riskier pregnancies lies a need for increased fertility and family planning counseling. A 2022 multi-method study exploring reproductive health after female EAO-CRC diagnosis found that 43.6% of participants did not have discussions about reproductive health with their healthcare providers (23) despite evidence highlighting the need for these discussions by patients with early age-onset cancer (20, 21, 24). A 2021 interview study exploring improvements to fertility care with adolescent and young adult female patients with cancer found that a combination of online information should be provided, with in-person follow-up visits and referrals as required (25). Although the need for tailored care is established, persistent barriers such as lack of appropriate healthcare provider training and resources, stigma and misconceptions, and cost prevent support realization (21, 26).

Increased training and development of person-centered programming can reduce burdens from this growing patient population (21, 26).

Although our cohort analysis found a relationship only between chemotherapy and post-diagnosis births, Shandley and colleague's 2019 systematic review on fertility preservation and counseling for reproductive-aged women with colorectal cancer indicates premature menopause in greater than 90% of rectal cancer cases treated with a dose of 45 to 50 Gy radiation (27, 28). Furthermore, the fertility impacts of chemotherapy vary and depend largely on age at the time of treatment, treatment protocol, and baseline fertility (27).

Strengths and limitations of this study warrant discussion. The dataset used for this study is a comprehensive provincial linkage using Population Data BC, containing demographics and clinical information, and the BC Cancer Registry, containing cancer characteristics. The BC Cancer Registry is reviewed annually for quality, comprehensiveness, and accuracy, and the BC Perinatal Data Registry undergoes rigorous data quality checks. Nevertheless, administrative health databases inherently have quality issues due to heterogeneity in data entry and monitoring. With respect to the administrative health databases used in our studies, several key factors were unavailable that have implications for both associations evaluated, including race/ethnicity, body mass index, smoking status, and alcohol consumption. Furthermore, they only capture information on sex and do not contain information on gender, gender diversity, or sexual orientation, which may affect healthcare access and outcomes evaluated across both analyses. We were also unable to account for certain factors in each analysis because of their absence in the administrative health data. With respect to the case-control analysis of the EAO-CRC outcome, one factor we could not account for due to data unavailability was family history of colorectal cancer. With respect to the cohort analysis of births after EAO-CRC diagnosis, we did not have data on religion, relationship status (e.g., married or single), and fertility preservation procedures. We also lacked more nuanced information on individuals' reproductive decisions—for example, the impact of financial constraints resulting from cancer on these factors—which are more likely to be captured through qualitative research. Another limitation of the administrative health databases used in this study, particularly the cancer registry, is that systematic collection of staging information only began in 2010. As a result, our ability to examine cancer stage was restricted to a subset of the study population—individuals diagnosed with EAO-CRC between 2010 and 2017. A sensitivity analysis within this subgroup suggested that higher cancer stage was associated with lower odds of post-diagnosis births. However, these findings were derived from reduced models because of limited sample size, and larger studies are needed to confirm these associations and allow for adjustment for additional covariates. Indeed, larger, prospective studies should rigorously measure lifetime hormone exposure and its impact on female EAO-CRC diagnosis and further exploration of site, stage, and treatment impacts of cancer on the number of births after diagnosis.

Altogether, through case-control and cohort analyses of population-based administrative data, our study highlights the complex relationship between reproductive history and EAO-CRC. Altogether, given the increasing risks of EAO-CRC, there are pressing needs for comprehensive patient psychosocial support addressing fertility preservation and family planning and critical quality of life components for female patients with EAO-CRC. Additionally, given the potential association between gravida and EAO-CRC, pregnancy can be used as an opportunity to educate on risks and prevention of EAO-CRC. By addressing these factors, we can better support the growing population of patients with EAO-CRC in their reproductive health and overall well-being, ultimately improving quality of life and long-term outcomes.

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Authors' Contributions

N. Oveisi: Conceptualization, formal analysis, methodology, writing—original draft, writing—review and editing. **E.C. Sayre:** Formal analysis, methodology, writing—review and editing. **S. Gill:** Conceptualization, methodology, writing—review and editing. **V. Cheng:** Conceptualization, validation, methodology, writing—review and editing. **V. Cheng:** Validation, methodology, writing—review and editing. **L.A. Brotto:** Conceptualization, methodology, writing—review and editing. **S. Peacock:** Conceptualization, methodology, writing—review and editing. **H. McTaggart-Cowan:** Conceptualization, methodology, writing—review and editing. **G.E. Hanley:** Conceptualization, methodology, writing—review and editing. **A. Srikanthan:** Conceptualization, methodology, writing—review and editing. **M.A. De Vera:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, methodology, writing—original draft, writing—review and editing.

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Note

Supplementary data for this article are available at *Cancer Epidemiology, Biomarkers & Prevention Online* (<http://cebp.aacrjournals.org/>).

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