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RISK FACTORS ASSOCIATED WITH EARLY-ONSET COLORECTAL CANCER

[1]Dr Zara Nasir,[2]Dr Zaib Nasir,[3]Dr Adeel Ahmed
[1]MBBS.Ameer Ud Din Medical College,Lahore.
[2]MBBS,Punjab Medical College,Faisalabad.
[3]MBBS,Shalamar Medical and Dental College,Lahore.

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Abstract:
Introduction: *early-onset colorectal cancer appears to display an opposite trend with an overall prevalence in United States and European Union ranging from 3.0% and 8.6%. Colorectal cancer has a substantial proportion of familial cases. Colorectal cancer is the third most common cancer diagnosed worldwide. Although epidemiology data show a marked variability around the world, its overall incidence rate shows a slow but steady decrease, mainly in developed countries.* ***Aim:*** *Our aim was to compare the early- and late-onset groups to identify differences in sociodemographic factors and clinical risk factors, as well as tumor characteristics. Age-related medical conditions such as hypertension, hyperlipidemia, coronary artery disease, stroke, and diabetes were only compared between early-onset cases and controls.* ***Methods:*** *We conducted a retrospective chart review of patients who were seen at Kot Khawaja Teaching Hospital in Lahore. We identified all patients aged 18 and older with a diagnosis of CRC who received care at our institution.* ***Discussion:*** *the majority of early-onset CRC cases in our single-centre study were sporadic. Patients with early-onset CRC were more likely to be male and have a family history of CRC or personal history of IBD.*

Corresponding author:
Dr. Zara Nasir
MBBS.Ameer Ud Din Medical College,Lahore

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INTRODUCTION:

Colorectal cancer (CRC) is the third leading cause of cancer for women and men in the United States (US) (1). CRC incidence has declined overall, and this has been attributed to population-level reductions in modifiable risk factors as well as increased participation in screening over the past three decades (2). In contrast, CRC incidence among individuals younger than age 50 is on the rise, and at the current rate it is estimated to double by 2030 (3).

Almost 60% of cases occur in developed regions, particularly in the United States where colorectal is the third most common cancer site with approximately 142820 estimated cases(4), whereas in the European Union (EU) it is the second diagnosed cancer with approximately 330000 estimated cases (5). Furthermore, CRC is the fourth most common cause of death from cancer worldwide (608000 cases, 8% of overall cancer deaths, cumulative lifetime risk of 0.9%). There is less variability in mortality rates with the highest rates estimated in Central and Eastern Europe (20.3 per 100000 for male, 12.1 per 100000 for female), and the lowest in Middle Africa (3.5 and 2.7, respectively). Incidence and mortality rates are lower in women than in men (6).

Over the past two decades, in these more developed countries (United States, EU), incidence and death rates have decreased about 2% per year (7). This rapid decline has been largely attributed to the increase in screening programmes among individuals 50 years and older, allowing an early detection and treatment of CRC and precancerous lesions

For this reason, the evidence-based European Code Against Cancer and the American College of Gastroenterology in the United States, recommend that men and women from 50 years of age onwards should participate in colorectal screening (8).
The reasons for this trend are unclear, but they likely include a combination of no modifiable and modifiable risk factors. Current guidelines recommend screening at an earlier age for individuals with a family history of CRC and personal history of inflammatory bowel disease (IBD) (9), whereas specific recommendations for individuals with obesity or history of smoking do not exist. The American Cancer Society (ACS) recently advocated lowering the age of screening to 45 years for the general population (10). This approach has been shown to be cost-effective, but it would still add substantial cost to the healthcare system and there are concerns that it may divert resources away from older individuals who have a higher absolute risk of cancer (11).

Alternatively, identifying specific risk factors in patients with early-onset CRC may permit risk stratification and targeted screening. We performed a single-institution study in a large, diverse metropolitan centre to identify sociodemographic, medical, and histologic predictors of early-onset CRC.

MATERIALS AND METHODS:

We conducted a retrospective chart review of patients who were seen at Kot Khawaja Teaching Hospital in Lahore. The protocol was approved by MS of the hospital.

Patient selection

We identified all patients aged 18 and older with a diagnosis of CRC who received care at our institution. Based on recommendations from the US MultiSociety Task Force on Colorectal Cancer (USMSTF) and most other organizations to begin average-risk screening at 50 years, we defined early-onset CRC patients as those diagnosed between 18 and 49 years of age and created two comparison groups (12).

The first group comprised late-onset CRC patients diagnosed at age 50 or older. The second group comprised controls without cancer who were age-matched to early-onset cases in a 4:1 ratio. Controls were randomly selected from patients who received care at our institution during the study period between 2016 and 2019, without matching for sex. Our initial automatic query identified 297 early-onset CRC cases, 2864 late-onset CRC cases and 1188 age-matched controls. After manual review, we re-classified 11 late-onset cases as early-onset and excluded 8 controls due to an incorrect birth year, leaving a total of 4341 patients (308 early-onset cases, 2853 late-onset cases, and 1180 age-matched controls). We excluded cases with no personal history of CRC (incorrect ICD coding), a personal history of a hereditary CRC syndrome, and substantial missing data. A hereditary CRC syndrome was defined as documentation of Lynch syndrome, familial adenomatous polyposis or MUTYH-associated polyposis, or pathogenic germ line mutations in the mismatch repair or epithelial cellular adhesion molecule (EpCAM) genes. Controls with a prior history of cancer were also excluded. All patients received care at our institution, but some were diagnosed elsewhere.

Data collection

We collected data on demographics, clinical history, and CRC outcomes through a combination of automated extraction and manual chart review. Clinical variables of interest included personal history of known CRC risk factors such as IBD, obesity, smoking, and diabetes as well as a family history of CRC. These data were collected prior to

diagnosis for most cases and within six months of diagnosis when prior assessment was unavailable. Tumor data (location, stage, grade, and molecular testing) were available for a minority of cases (~17%) from our tumor registry and were supplemented by manual chart review. Missing data was excluded from frequency calculations. When data from the automated extraction conflicted with results of the manual chart review, the latter was considered more accurate and used for analysis.

Statistical analysis

For the univariable analysis, we used the chi-squared and Fisher's exact tests for categorical variables and Student's t-test and Mann-Whitney U test for continuous variables. A two-sided $P < 0.05$ was considered statistically significant. Variables with $P < 0.20$ were carried forward to the multivariable logistic regression model, where we obtained adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Some variables had either insufficient sample size or too much missing data to carry forward to multivariable analysis. Thus, they were left as univariable comparisons for the sake of hypothesis generation. Analysis was performed using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

RESULTS:

A total of 4193 individuals met the inclusion and exclusion criteria, of whom 47% were male and 65% were females. In addition, 0.9% had a personal history of IBD and 5% had a family history of CRC.

Sociodemographic and clinical risk factors of early-onset CRC

Compared to age-matched controls, patients with early-onset CRC were more likely to be male (OR 1.87, 95% CI 1.39-2.51) and have a family history of CRC (OR 8.61, 95% CI 4.83-15.75) or a personal history of IBD (Table 1). Of note, history of IBD was excluded from the multivariable logistic regression model because of the small sample size in the control group. Race as well as area-level mean household income and education level were not significantly different between these two groups. With respect to common age-related comorbidities, hyperlipidemia was more prevalent in the control group, and there was no difference in body mass index (BMI), smoking, coronary artery disease, hypertension, stroke, or diabetes between the two groups (Table 1).

Compared to patients with late-onset CRC, those with early-onset CRC were more likely to be male (OR 1.44, 95% CI 1.11-1.87), have a family history of CRC (OR 2.87, 95% CI 1.894.25), or have IBD (OR 2.97, 95% CI 1.16-6.63, Table 2). Mean household income and education level were similar between the two groups. The prevalence of common comorbidities such as obesity and diabetes were not compared because these comparisons in older versus younger CRC patients are intractably confounded by age.

Because patients with IBD or a family history of CRC are a high-risk population, we performed a sensitivity analysis that excluded early-onset CRC patients with any family history of CRC or personal history of IBD and compared them to both controls and late onset CRC cases (Supplementary Tables 1 and 2). The sensitivity analysis did not substantively alter our outcomes and therefore we have reported the main findings including these individuals.

Table 1: Comparison of individuals with early-onset CRC vs. young controls without cancer

	Variable, n (%)	Early-onset (n=269)	Controls (n=1122)	Univariable P*	Multivariable OR (95% CI)	Multivariable P
Medical	BMI, mean (SD)	27 (6)	28 (6)	.02	.98 (.95 - 1.00)	.06
	Family history of CRC	34 (13)	21 (2)	<.01	8.61 (4.83 - 15.75)	<.01
	Inflammatory bowel disease	7 (3)	5 (.4)	<.01		
	Crohns disease	4 (57)	4 (80)			
	Ulcerative colitis	3 (43)	1 (20)			
	Smoker	70 (27)	312 (29)	.53		
	Coronary artery disease	10 (4)	43 (4)	>.99		
	Hypertension	50 (19)	221 (20)	.85		
	Hyperlipidemia	41 (16)	259 (23)	.01	.57 (.38 - .83)	<.01
	Stroke	1 (.4)	8 (.7)	>.99		
	Diabetes	19 (7)	64 (6)	.48		

Table 2: Comparison of individuals with early-onset CRC vs. late-onset CRC

	Variable, n (%)	Early-onset (n=269)	Controls (n=1122)	Univariable *P*[a]	Multivariable OR (95% CI)	Multivariable *P*
Medical	BMI, mean (SD)	27 (6)	28 (6)	.02	.98 (.95 - .99)	.04
	Family history of CRC	34 (13)	148 (5)	<.01	2.87 (1.89 - 4.25)	<.01
	Inflammatory bowel disease	7 (3)	27 (1)	.03	2.97 (1.16 - 6.63)	.01
	Crohns disease	4 (57)	21 (78)			
	Ulcerative colitis	3 (43)	6 (22)			
	Duration of IBD prior to CRC diagnosis, y, median (IQR)	22 (17-25)	13 (0-36)	.71		

Supplementary Table 1: Sensitivity analysis comparing individuals with early-onset CRC vs. young controls without cancer (excluding family history of CRC or personal history of IBD)

	Variable, n (%)	Early-onset (n=224)	Controls (n=1095)	Univariable *P*[a]	Multivariable OR (95% CI)	Multivariable *P*
	Age[b], mean (SD)	43 (6)	45 (6)			
Medical	BMI, mean (SD)	27 (6)	28 (6)	.07	.98 (.95-1.00)	.07
	Smoker	58 (27)	302 (29)	.62		
	Coronary artery disease	8 (4)	40 (4)	>.99		
	Hypertension	44 (20)	216 (20)	>.99		
	Hyperlipidemia	36 (16)	250 (23)	.03	.62 (.41-.92)	.02
	Stroke	0	7 (.6)	.61		
	Diabetes	17 (8)	64 (6)	.40		

Supplementary Table 2: Sensitivity analysis comparing individuals with early-onset CRC vs. late-onset CRC (excluding family history of CRC or personal history of IBD)

Variable, n (%)	Early-onset (n=224)	Late-onset (n=2644)	Univariable *P*[a]	Multivariable OR (95% CI)	Multivariable *P*
Age at CRC diagnosis, mean (SD)	43 (6)	71 (11)			
Income, mean (SD)	70785 (27176)	72270 (26207)	.43		
High school education, %, mean (SD)	84 (10)	86 (9)	.07	.53 (.11-2.61)	0.43
BMI, mean (SD)	27 (6)	28 (6)	.07	0.98 (.95-1.00)	.11

DISCUSSION:

In this large retrospective study of early-onset CRC, we identified male sex, family history of CRC, and personal history of IBD as predictors of early-onset CRC compared to both age-matched controls and late-onset CRC cases. Common age-related comorbidities were not more prevalent in early-onset cases than age-matched controls, and socioeconomic factors were not significant risk factors. These data show certain non-modifiable risk factors contribute to early-onset CRC.

After excluding all known cases of hereditary cancer syndromes, we found early-onset CRC patients were more than eight times as likely to have a family history of CRC compared to controls and nearly three times more likely than late-onset CRC patients.

CRC diagnosed before age 50 has been more strongly associated with family history of CRC or probable hereditary syndrome than CRC diagnosed later in life. Chen et al found an 8% higher absolute prevalence of family history in young-onset CRC cases compared to cases diagnosed at 50 years or older (25% vs. 17%, P=.03) (13). Although our study had a lower overall prevalence of positive family history due to the exclusion of hereditary syndromes, we also found an 8% absolute difference in prevalence of family history in the early-onset and late-onset CRC groups (13% vs. 5%, P<.01). The prevalence of hereditary syndromes is significantly higher in early-onset CRC cases than in healthy controls, but to our knowledge the association with family history of CRC in the absence of hereditary syndromes has not previously been reported. This could be attributed to weaker genetic risk factors for early-onset CRC including intermediate penetrant genes, low-risk genetic variations with additive effect, and genetic variants that modify the expression of known CRC susceptibility genes (14). Our results also confirm that IBD is a risk factor for early-onset CRC (15). The prevalence of IBD in early-onset CRC patients compared to controls has not been previously examined, but a recent Swedish study found that patients diagnosed with IBD as children were more likely to be diagnosed with early-onset CRC than individuals without IBD (16).

A 1973-2009 SEER analysis found that the proportion of CRC patients who were diagnosed under age 50 was 1.8-fold higher in Asians/Pacific Islanders than in non-Hispanic whites, however overall CRC incidence in Asians was lower (17). It has been hypothesized that the rising incidence of

CRC in Asians may be attributed to the adoption of the Western diet (18). Asians who are born in the US and exposed to a lifetime Western diet may carry a higher risk for early-onset and overall CRC. On the other hand, the majority of Asians in the US are immigrants who may have less exposure to the Western diet. Thus, lifestyle differences between Asians born in the US and those who immigrated may explain the discrepancy between overall and early-onset CRC risk. With respect to black patients, a study of rectal and recto sigmoid cancers in individuals under age 40 years found a higher absolute incidence in blacks compared to whites (0.67 per 100,000, 95% CI, 0.60-0.74 vs. 0.51 per 100,000, 95% CI, 0.48-0.53) (19).

In contrast to a large prospective cohort study that found higher risk for early-onset CRC in obese women (20), we did not observe an association between obesity and early onset CRC. A large retrospective study comparing young CRC cases and controls found specific dietary components, but not obesity or diabetes, to be risk factors for early-onset CRC (21). Therefore, the relationship between metabolic conditions such as obesity or diabetes and early-onset CRC may be confounded by unmeasured dietary or environmental factors. Additional prospective studies with dietary and environmental exposure data are needed to further investigate this relationship.

Socioeconomic disparities in CRC incidence are well-documented and have been attributed to a higher burden of predisposing comorbidities and lower rates of screening in groups with lower socioeconomic status (22). That socioeconomic status was not a risk factor for early-onset CRC in our study may be explained by our patient demographics. The relative affluence of our population and abundant local resources for CRC screening may have reduced our ability to detect disparities related to healthcare access. Moreover, it is not clear that socioeconomic disparities observed for CRC overall are applicable for early-onset disease, since biological mechanisms may be distinct and access to screening may be less relevant for early-onset cases.

The finding that early-onset CRC presents at a more advanced stage than late-onset disease is consistent with the literature (23). Ample evidence suggests the existence of biological differences in early- vs. late-onset CRC. First, the rising incidence of early-onset CRC is predominantly due to left-sided disease, in contrast to a higher proportion of right-sided tumors in late-onset CRC (24). Second, early-onset CRC exhibits a higher prevalence of mucinous or signet-ring histology with poor differentiation than that of older adults. Lastly, as our study demonstrated, late onset CRC also has a higher prevalence of microsatellite instability (MSI), which is associated with early-stage and right-sided disease (25). Prior studies have shown that approximately 12-17% of all CRC is positive for MSI, and the majority of these are sporadic (26).

Forty percent of the average-risk early-onset cases in our population were diagnosed between 46-49 years, which may support the ACS recommendation to start screening at age 45. However, it is unclear what proportion of these cases would have been prevented or detected at an earlier stage. Additionally, as a recent Markov model analysis demonstrated, targeted screening in high-risk individuals may be a more cost-effective approach (27). Consequently, simple risk scores that can identify individuals at highest risk for early-onset CRC are needed. Our data highlight that efforts to construct these scores should include non-modifiable risk factors.

The strengths of our study include its large sample size, the availability of sociodemographic, medical, and tumor data, as well as a hospital-based control group that is representative of the local population. However, several limitations should be noted.

First, certain established risk factors—such as dietary history, physical activity, and aspirin use—were not included in the analysis because they were either unavailable or could not be easily extracted from the medical record.

Second, because data was collected retrospectively, it is possible that certain medical data (e.g., BMI) for cases may have been influenced by cancer itself. We tried to minimize this bias by including medical data obtained before or within 6 months of CRC diagnosis for cases diagnosed at our institution.

Third, although we conducted a manual chart review to identify and exclude patients with hereditary syndromes, it is possible that some genetic testing was missing and a small number of patients with hereditary syndromes were included in the analysis.

Fourth, because not all patients underwent surgery and some received resection outside of our institution, only a minority of patients had tumor data available. Therefore, the tumor analysis should be considered exploratory and the results interpreted with caution.

Finally, there may be selection bias in that the hospital based control cohort may not reflect a truly healthy population.

In summary, the majority of early-onset CRC cases in our single-centre study were sporadic. Patients with early-onset CRC were more likely to be male and have a family history of CRC or personal history of IBD. We did not observe associations with well-established modifiable risk factors such as obesity, smoking, and diabetes.

These data suggest non-modifiable factors should be included in risk prediction models to facilitate targeted screening in individuals under age 50. Such efforts can be refined as more granular predictors of early-onset CRC, especially early-life exposures that are measurable and readily available in the clinical setting, are identified from future prospective studies.

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