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INCIDENCE OF COLORECTAL CANCER AND ITS HISTOPATHOLOGY GRADING IN YOUNG AGE

Original Research

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ABSTRACT

Background: Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related mortality. While traditionally considered a disease of older adults, recent evidence indicates a concerning rise in early-onset CRC (EOCRC), with nearly 30–40% of cases now diagnosed in individuals younger than 50 years. These patients often present with advanced-stage disease and aggressive histological features, highlighting the need for timely diagnosis and targeted preventive strategies.

Objective: To determine the incidence of colorectal cancer and describe its histopathological grading in young patients presenting to a tertiary care hospital in Karachi.

Methods: A prospective cross-sectional study was conducted at the Department of Pathology and Oncology, Jinnah Postgraduate Medical Centre (JPMC), Karachi, from March 2024 to March 2025. A total of 203 patients aged 18–49 years presenting with clinical suspicion of CRC, including rectal bleeding, altered bowel habits, abdominal pain, weight loss, anemia, or other gastrointestinal symptoms, were enrolled. Colonoscopy was performed for definitive diagnosis, and biopsy samples were obtained from abnormal lesions. Only histologically confirmed cases were considered true CRC. Data were recorded on a structured proforma and analyzed using SPSS version 25.0.

Results: The mean age of patients was 34.20 ± 8.67 years; 138 (68%) were male and 65 (32%) female. The overall incidence of CRC was 36.95% (75/203). The rectum was the most frequent tumor site, affecting 29 cases (38.67%), followed by the ascending colon (16%) and rectosigmoid region (14.67%). Histopathology revealed adenocarcinoma as the predominant subtype, with poorly differentiated tumors comprising 30.7%, moderately differentiated 25.3%, and well-differentiated 13.3%. Multivariate analysis showed age ≤30 years (AOR = 14.77, p = 0.0005) and 31–40 years (AOR = 18.11, p = 0.0005) as strong predictors, while family history (AOR = 2.33, p = 0.044), smoking (AOR = 5.18, p = 0.0005), red meat consumption (AOR = 3.33, p = 0.0004), and diabetes mellitus (AOR = 3.61, p = 0.045) were significant risk factors. Daily exercise conferred a protective effect (AOR = 0.27, p = 0.0009).

Conclusion: Colorectal cancer is increasingly affecting young adults, with a substantial proportion presenting with aggressive histopathological subtypes. Younger age, smoking, red meat consumption, family history, and diabetes mellitus significantly increase risk, whereas daily physical activity appears protective. These findings reinforce the urgent need for early screening, risk-based preventive strategies, and lifestyle interventions in younger populations.

Keywords: Adenocarcinoma, Colorectal Neoplasms, Colonoscopy, Early-Onset CRC, Exercise, Histopathology, Risk Factors.

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INTRODUCTION

Colorectal cancer (CRC) remains the third most common malignancy worldwide and the second leading cause of cancer-related mortality, presenting a substantial public health burden (1). Traditionally considered a disease of older individuals, CRC is now showing a concerning epidemiological shift with a rising incidence among younger adults. Recent data indicate that approximately 30% to 40% of CRC cases are now diagnosed in individuals under the age of 50 years, a group referred to as early-onset CRC (EOCRC) (1–3). In the United States, despite overall declines in CRC incidence due to effective screening initiatives, the rates among adults aged 20 to 49 years continue to rise steadily (4). This trend is not limited to high-income nations; similar patterns are emerging in low- and middle-income countries, where limited access to timely screening and diagnostic facilities often results in late-stage presentation (5). In addition to lifestyle and genetic predispositions, infectious diseases such as hepatitis C virus have also been linked with the development of certain malignancies, further emphasizing the complex interplay of factors in cancer epidemiology (6). This demographic transition has generated global concern and highlighted the need to investigate whether EOCRC represents a distinct clinical entity. Compared with older patients, younger individuals frequently experience delays in diagnosis due to atypical symptoms and the perceived low risk of malignancy in this age group, often leading to advanced disease at presentation and poor outcomes. Histopathological features of EOCRC also tend to differ, with a higher prevalence of poor differentiation, mucinous changes, and signet-ring cell components, all of which are associated with aggressive tumor biology and unfavorable prognosis (7).

Several studies further indicate that EOCRC patients are more often diagnosed at advanced stages and harbor high-grade tumors compared with their older counterparts (8,9). Although younger patients generally have fewer comorbidities and better physiological reserves, these advantages do not necessarily translate into improved survival outcomes (10). This paradox emphasizes the critical prognostic role of histopathological grading, which remains a cornerstone in treatment decision-making. Tumor differentiation, ranging from well-differentiated to poorly differentiated lesions, is a powerful predictor of disease aggressiveness and survival, with poorly differentiated tumors carrying the worst outcomes (10,11). Given the global rise in EOCRC and the distinct biological and clinical challenges it presents, there is an urgent need to deepen understanding of its incidence and histopathological spectrum. This study is therefore designed to assess the incidence of colorectal cancer in young individuals and to describe its histopathological grading, with the ultimate aim of informing strategies for earlier diagnosis, optimized screening, and tailored treatment approaches.

METHODS

This prospective cross-sectional study was carried out in the Department of Pathology and Oncology, Jinnah Postgraduate Medical Centre (JPMC), Karachi, over a one-year period from March 2024 to March 2025. The study population comprised patients aged 18 to 49 years who presented to the Out-Patient Department with clinical suspicion of colorectal cancer (CRC). Clinical suspicion was based on common warning symptoms, including rectal bleeding, altered bowel habits, abdominal pain, unexplained weight loss, anemia, and other gastrointestinal complaints suggestive of malignancy. Ethical approval for the study was obtained from the Institutional Review Board (IRB) prior to initiation and written informed consent was secured from all participants before enrollment. Patients aged 50 years or above, those with inadequate or necrotic specimens, and those with a prior history of treatment for CRC were excluded from the study. Colonoscopy was employed as the diagnostic gold standard for visualization of the colon and rectum. In cases where abnormal lesions were identified, biopsy samples were obtained and subsequently processed for histopathological evaluation. The diagnosis of CRC was confirmed only in patients with the presence of malignant cells on histopathology. Histologically confirmed cases were therefore considered true CRC among symptomatic individuals. Patients were included in the final analysis only if their biopsy or resection specimens were adequate and provided sufficient tissue for tumor characterization.

Histopathological reports were reviewed to confirm diagnosis and determine tumor grading. Tumors were classified according to the World Health Organization (WHO) grading system: >95% gland formation as well-differentiated, 50–95% as moderately differentiated, and <50% as poorly differentiated. Data regarding demographic features (age, gender), tumor location, and histological subtype were extracted from hospital pathology records and entered into a predesigned proforma. The sample size was calculated based on the findings of a prior study, which reported a 5% prevalence of CRC in the relevant population (11). Using the formula $n = Z^2 \times P \times (1 - P)/d^2$, a

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sample size of 203 was determined, with a 95% confidence interval and a 3% margin of error. Data entry and statistical analyses were performed using SPSS version 25.0. Continuous variables such as age were expressed as mean ± standard deviation, whereas categorical variables including gender, tumor site, histopathological type, and tumor grade were summarized as frequencies and percentages. Associations between categorical factors and CRC diagnosis were assessed using the Chi-square test or Fisher's exact test, as appropriate. Logistic regression analyses (both bi-level and multivariable) were conducted to identify significant predictors of CRC, with odds ratios (OR) and 95% confidence intervals (CI) presented. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 203 young patients with suspected colorectal cancer were evaluated, with a mean age of 34.20 ± 8.67 years. Among them, 138 (68%) were male and 65 (32%) were female. The most frequently reported symptoms included weight loss in 124 patients (61.08%) and abdominal pain in 120 patients (59.11%), followed by fever in 115 (56.65%), anemia in 73 (36.0%), bleeding per rectum in 61 (30.05%), black stool in 59 (29.06%), and altered bowel habits in 48 (23.60%). Fatigue was the least reported symptom, present in 19 patients (9.36%). A positive family history of colorectal cancer was documented in 56 cases (27.59%). Lifestyle characteristics revealed that 79 patients (38.92%) were smokers, 23 (11.33%) consumed alcohol, and 79 (38.92%) reported daily red meat intake. In contrast, 145 patients (71.43%) were physically sedentary, while only 58 (28.57%) reported daily exercise. Comorbidities included hypertension in 47 cases (23.15%) and diabetes mellitus in 34 cases (16.74%). The incidence of colorectal cancer among young patients was 36.95% (75 out of 203). The rectum was the most commonly affected site, accounting for 29 cases (38.67%), followed by the ascending colon in 12 (16%), rectosigmoid in 11 (14.67%), anorectum in 9 (12%), sigmoid colon in 6 (8%), descending colon in 4 (5.33%), and the transverse colon and caecum in one case each (1.33%). The anal canal was involved in two cases (1%). These findings indicated a predominance of tumors in the distal colon and rectal regions. Histopathological evaluation revealed that adenocarcinoma was the most prevalent type, with poorly differentiated adenocarcinoma identified in 23 cases (30.7%), moderately differentiated in 19 (25.3%), and well-differentiated in 10 (13.3%). Additional histological variants included squamous cell carcinoma, with six cases of moderately differentiated (8%) and two cases of well-differentiated (2.7%), as well as mucinous adenocarcinoma, observed across poorly differentiated (3; 4%), moderately differentiated (2; 2.7%), and well-differentiated (2; 2.7%) forms. Adenocarcinoma with signet-ring morphology was present in six cases (8%), and spindle cell tumors were documented in two cases (2.7%). Overall, poorly differentiated and aggressive subtypes predominated.

In univariate analysis, patients ≤30 years had 8.74 times higher odds ($p = 0.0005$) and those aged 31–40 years had 6.60 times higher odds ($p = 0.0005$) of developing CRC compared to the 41–50 year age group. Male gender was significantly associated with higher risk (OR = 2.05, $p = 0.029$). Education at matric and intermediate levels was significantly associated with CRC (OR = 12.95, $p = 0.018$ and OR = 17.0, $p = 0.009$, respectively) compared to graduates. Family history of CRC increased the odds nearly fourfold (OR = 3.99, $p = 0.0005$). Smoking and red meat consumption were both associated with threefold higher risk (OR = 3.13, $p = 0.0005$), while daily exercise was protective (OR = 0.34, $p = 0.002$). In the multivariable model, younger age remained a robust predictor. Patients ≤30 years had 14.77 times higher odds ($p = 0.0005$), and those aged 31–40 years had 18.11 times higher odds ($p = 0.0005$) compared to the reference group. Family history remained significant (AOR = 2.33, $p = 0.044$), smoking retained strong association (AOR = 5.18, $p = 0.0005$), and red meat consumption also remained significant (AOR = 3.33, $p = 0.0004$). Daily exercise continued to provide protection, reducing odds by nearly 73% (AOR = 0.27, $p = 0.0009$). Interestingly, diabetes mellitus, which was not significant in univariate analysis, became significant after adjustment, with diabetics showing 3.61 times higher odds ($p = 0.045$). Other variables, including gender, hypertension, alcohol consumption, and education, were excluded in the multivariate model, indicating a lack of independent association.

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Table 1: Demographic and clinical presentation of young patients (n=203)

Variables	Mean± SD / Number of patients	Range/ (%)
Age (Years)	34.20±8.67	17-50
Age Category		
≤ 30	83	40.89%
31-40	50	24.63%
>40	70	34.48%
Gender		
Male	138	68%
Female	65	32%
Education		
Illiterate	46	22.66%
Primary / Secondary	68	33.50%
Matric	41	20.20%
Inter	32	15.76%
Graduate	16	7.88%
Comorbid		
Hypertension	47	23.15%
Diabetic Mellitus	34	16.74%
Others	5	4.5%

Table 2: History and habit characteristics of young patients (n=203)

Variables	Number of patients	Percentage
Clinical Presentation		
Abdominal Pain	120	59.11%
Weight Loss	124	61.08%
Fever	115	56.65%
Bleeding PR	61	30.05%
Fatigue	19	9.36%
Black Stool	59	29.06
Altered bowel habits	48	23.60%
Anemia	73	36.0%
Family history of Colorectal Cancer		
Yes	56	27.59%
No	147	72.41%
Substance abuse		
Smoking Status	79	38.92%
Alcohol Used	23	11.33%
Red Meet Consumers		
Daily	79	38.92%
Seldom or No	124	61.08%
Exercise Daily		
Yes	58	28.57%
No	145	71.43%

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Table 3: Histopathology grading in young age patients with CRC (n=75)

Variables	Frequency of patients with CRC n=75	Percentage
Site of cancer (n=75)		
Rectum	29	38.67%
Ascending colon	12	16.00%
Recto sigmoid	11	14.67%
Anorectum	9	12.00%
Sigmoid colon	6	8.00%
Descending colon	4	5.33%
Transverse colon	1	1.33%
Caecum	1	1.33%
Anal canal	2	1.00%
Histopathology (n=75)		
Adenocarcinoma-PD	23	30.7%
Adenocarcinoma-MD	19	25.3%
Adenocarcinoma-WD	10	13.3%
Squamous cell carcinoma-MD	6	8%
Squamous cell carcinoma-WD	2	2.7%
Mucinous Adenocarcinoma –PD	3	4%
Mucinous Adenocarcinoma –MD	2	2.7%
Mucinous Adenocarcinoma –WD	2	2.7%
Adenocarcinoma with signet ring morphology-PD	6	8%
Spindle cell tumour of colon-MD	2	2.7%
WD= Well Differentiated; MD = Moderately Differentiated, PD= Poorly Differentiated		

Table 4: Univariate and Multivariate analysis showing the Factors associated with colorectal cancer

Variables	N	Colorectal cancer (CRC)	Univariate		Multivariate	
			P-Value	UOR [95%CI]	p-Value	AOR [95%CI]
Age (Years)						
≤30	83	44(53%)	0.0005*	8.74[3.72-20.52]	0.0005	14.77[3.76-58.01]
31-40	50	23(46%)	0.0005*	6.60[2.62-16.61]	0.0005	18.11[4.53-72.42]
41-50	70	8(11.4%)		Ref		Ref
Gender						
Male	138	58(42%)	0.029*	2.05[1.07-3.91]		-
Female	65	17(26.2%)		Ref		
Education						
Illiterate	46	15(32.6%)	0.066	7.26[0.87-30.23]	0.985	1.03[0.07-13.82]
Primary / Secondary	68	23(33.8%)	0.056	7.67[0.95-61.71]	0.682	1.70[0.13-21.79]
Matric	41	19(46.3%)	0.018*	12.95[1.56-107.5]	0.252	4.67[0.33-65.65]
Inter	32	17(53.1%)	0.009*	17.0[2.0-144.49]	0.158	6.46[0.48-85.95]
Graduate	16	1(6.3%)		Ref		Ref
Hypertension						
Yes	47	15(31.9%)	0.415	0.75[0.37-1.50]		-
No	156	60(38.5%)		Ref		
Diabetic Mellitus						

Variables	N	Colorectal cancer (CRC)	Univariate		Multivariate	
			P-Value	UOR [95%CI]	p-Value	AOR [95%CI]
Yes	34	11(32.4%)	0.543	0.75[0.36-1.72]	0.045*	3.61[1.03-85.95]
No	169	64(37.9%)		Ref		Ref
Family History of CRC						
Yes	56	34(60.7%)	0.0005*	3.99[2.09-78.62]	0.044*	2.33[1.03-5.29]
No	147	41(27.9%)		Ref		Ref
Smoking Status						
Yes	79	42(53.2%)	0.0005*	3.13[1.73-5.67]	0.0005*	5.18[2.20-12.19]
No	124	33(26.6%)		Ref		Ref
Alcohol Used						
Yes	23	9(39.1%)	0.818	1.11[0.45-2.71]		-
No	180	66(36.7%)		Ref		
Red Meet Consumers						
Yes	79	42(53.2%)	0.0005*	3.13[1.73-5.67]	0.0004*	3.33[1.48-7.50]
No	124	33(26.6%)		Ref		Ref
Exercise Daily						
Yes	58	12(20.7%)	0.002*	0.34[0.17-.69]	0.0009*	0.27[0.10-0.72]
No	145	63(43.4%)		Ref		Ref
Gender, HTN, DM and alcohol used were excluded from the multivariate model Stepwise logistic regression used						

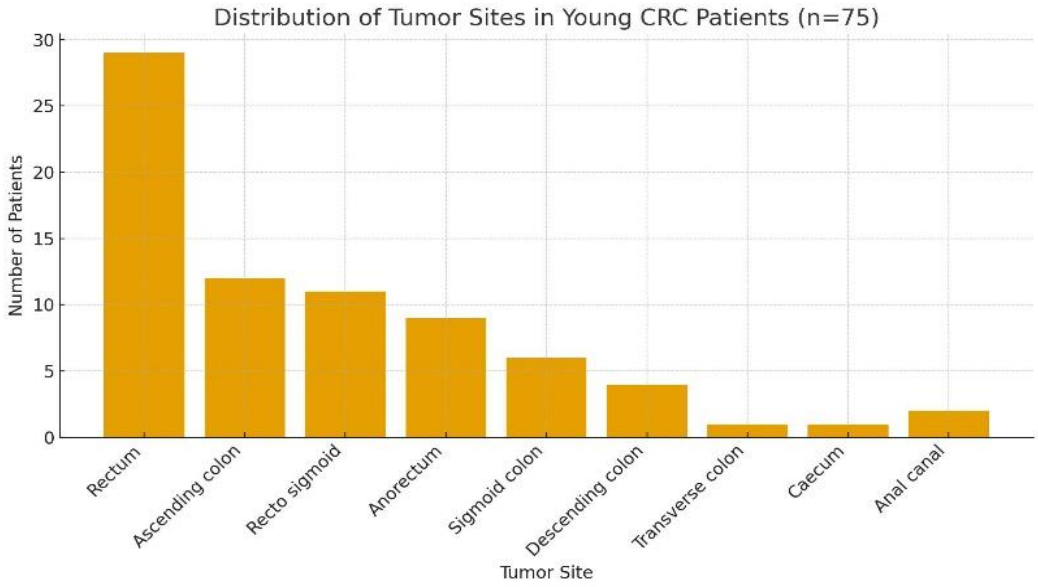

Figure 1 Distribution of Tumor Sites in Young CRC Patients (n=75)

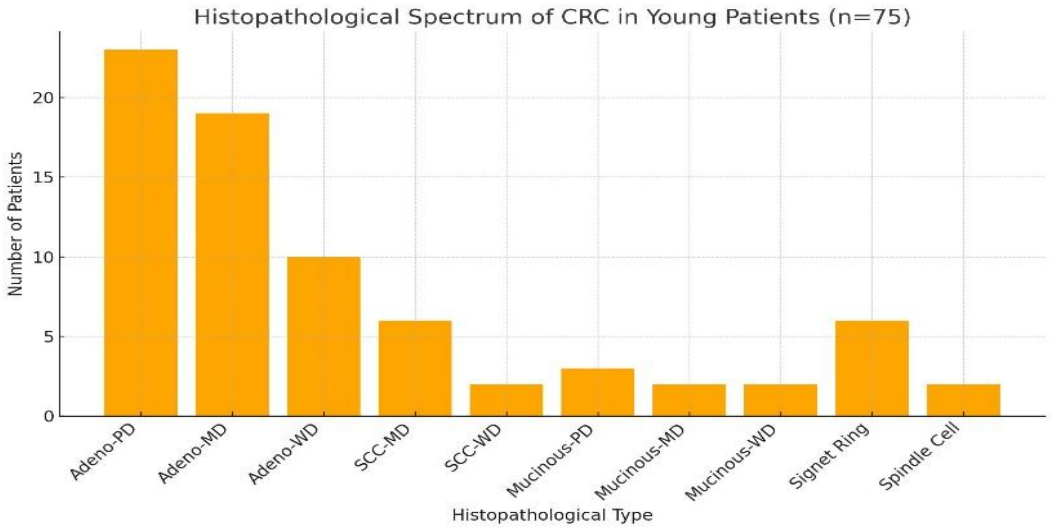

Figure 3 Histopathological Spectrum of CRC in Young Patients (n=75)

Incidence of colorectal cancer (CRC) of young patients n=203

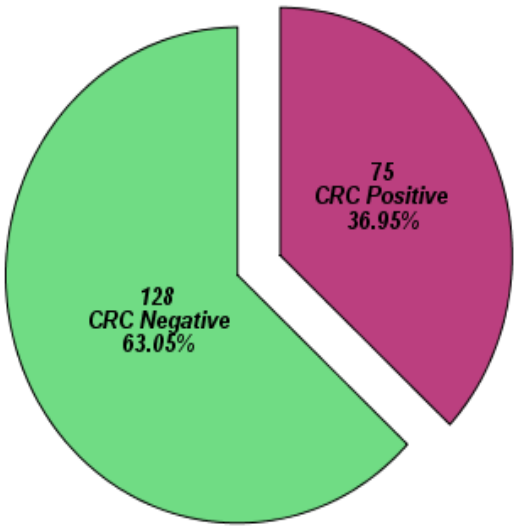

Figure 2 Incidence of Colorectal Cancer (CRC) of Young Patients n=203

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DISCUSSION

The present study explored the incidence and histopathological spectrum of colorectal cancer in young individuals under the age of 50 and demonstrated a striking incidence rate of 36.95% among symptomatic patients with a mean age of 34.2 ± 8.67 years. This finding reinforces the alarming shift in the epidemiology of colorectal cancer from older to younger populations and supports the growing body of evidence indicating a true rise in early-onset colorectal cancer globally (12–14). Both univariate and multivariate analyses confirmed younger age as an independent risk factor, with individuals aged ≤40 years showing 14–18 times higher odds of developing the disease compared to those aged 41–50 years. These findings are consistent with earlier national and international studies that have emphasized the importance of initiating screening protocols at younger ages, particularly in high-risk groups (15,16). This strengthens the argument for re-evaluating existing screening guidelines, most of which recommend initiation between ages 45 and 50, despite mounting evidence of substantial disease burden in younger adults (17). Gender differences were also evident, with males demonstrating a higher incidence of colorectal cancer compared to females. However, after adjustment for confounders, gender did not emerge as an independent predictor, suggesting that lifestyle-related exposures or biological differences, rather than gender alone, may account for these disparities. This observation mirrors earlier reports that described comparable incidence rates in early adult years, with divergence beginning in the late 30s and early 40s (18-20). Family history of colorectal cancer was another significant predictor, associated with more than twice the risk of developing the disease. This is in line with published literature suggesting that 10–30% of new colorectal cancer diagnoses occur in individuals with a family history, particularly when a first-degree relative is diagnosed at an early age (19,20). The finding underscores the importance of family-centered approaches, including genetic counseling and targeted screening for high-risk individuals. Lifestyle factors also played a central role, as smoking and red meat consumption emerged as strong independent predictors of colorectal cancer, each associated with more than threefold higher risk. These associations support earlier evidence linking tobacco use and diets rich in red or processed meats to colorectal carcinogenesis through mechanisms such as altered bile acid metabolism, intestinal dysbiosis, and exposure to carcinogenic nitrosamines (16,21). Conversely, alcohol consumption did not show a significant association in this study, although several population-based studies and meta-analyses have demonstrated a dose-dependent risk with habitual use (22).

One of the most notable protective factors identified in this study was daily exercise, which reduced the risk of colorectal cancer by nearly three-quarters. This aligns with global evidence demonstrating that physical activity improves insulin sensitivity, reduces chronic inflammation, and enhances immune function, thereby reducing the risk of both colon and rectal cancers (18,20). The findings reaffirm the role of lifestyle modification as a cornerstone of primary prevention in younger populations at risk. Anatomical distribution revealed a predominance of rectal tumors, followed by ascending colon and rectosigmoid involvement, with distal colorectal regions being disproportionately affected. This pattern corresponds with earlier studies which consistently reported left-sided predominance and particularly high involvement of the rectum in younger patients (23,24). The biological basis for this distribution remains unclear but may relate to differences in embryological origin, gut microbiome distribution, and environmental exposures. From a histopathological perspective, poorly differentiated adenocarcinoma was the most common subtype, followed by moderately and well-differentiated tumors, alongside aggressive variants such as mucinous adenocarcinoma and signet-ring morphology. These findings emphasize the biologically aggressive nature of early-onset colorectal cancer and are consistent with earlier studies reporting a predominance of poorly differentiated and mucinous subtypes in younger cohorts (14,25). Such aggressive histological features highlight the urgency of early diagnosis and the tailoring of treatment approaches.

The study carried several strengths. It specifically targeted a younger demographic, a group increasingly affected by colorectal cancer yet often overlooked in traditional research focused on older adults. The detailed assessment of histopathological subtypes, combined with rigorous statistical modeling, provided meaningful insights into the clinicopathological profile of colorectal cancer in this age group. Additionally, the inclusion of multiple lifestyle and dietary variables allowed for a holistic assessment of both environmental and hereditary risk factors. Nevertheless, some limitations should be noted. The cross-sectional design prevented causal inference, limiting the ability to determine temporality between exposures and outcomes. The study was conducted at a single tertiary care center, which may restrict the generalizability of findings to other populations, especially rural or socioeconomically diverse groups. Reliance on self-reported lifestyle behaviors introduced the possibility of recall bias or underreporting, particularly for socially sensitive exposures such as smoking and alcohol. Importantly, the absence of genetic testing limited the assessment of hereditary syndromes like Lynch syndrome, which account for a substantial proportion of early-onset colorectal cancers. The lack of tumor staging and follow-up data further restricted conclusions regarding disease progression, treatment outcomes, and survival. Despite these limitations, the study provides critical evidence of the rising incidence and aggressive pathological features of colorectal cancer in younger populations. Future research should incorporate multicenter prospective cohorts with genetic profiling and longitudinal follow-up to clarify causal pathways,

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determine stage-specific prognostic implications, and assess treatment outcomes. Expanding screening programs to incorporate younger age groups, particularly those with family history or lifestyle-related risk factors, appears essential. The findings collectively underscore the pressing need to adapt public health strategies and clinical guidelines to address the rising burden of early-onset colorectal cancer.

CONCLUSION

This study highlights the growing burden of colorectal cancer among younger individuals, revealing a predominance of aggressive histopathological subtypes and underscoring the role of both lifestyle factors and genetic predisposition in shaping disease risk. The findings emphasize the urgent need for early screening strategies in high-risk populations, as well as the promotion of preventive measures through education and lifestyle modification. By drawing attention to this shifting epidemiological trend, the study contributes valuable evidence that supports re-evaluation of existing screening guidelines and the strengthening of targeted public health interventions aimed at reducing the impact of early-onset colorectal cancer in younger populations.

AUTHOR CONTRIBUTION

Author	Contribution
Asghar Ali*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Zahid Mehmood	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Mariyah Anwar	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Syed Muhammad Raza	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Shahzeb	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Salma Khatoon	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33.
2. Sung H, Siegel RL, Laversanne M, Jiang C, Morgan E, Zahwe M, et al. Colorectal cancer incidence trends in younger versus older adults: an analysis of population-based cancer registry data. Lancet Oncol. 2025;26(1):51-63.
3. Osama M, Moosa H, Rangwala HS, Rangwala BS, Farrukh A, Fayaz S, et al. Analysis of demographic associations and survival outcomes in patients with colorectal cancer at a tertiary care hospital in Pakistan: a retrospective cross-sectional study. Cancer Control. 2025;32:10732748251351423.
4. Bhutto S, Hashmat S, Haider G, Rehman A, Zahoor S, Qazi SA, et al. The changing trends amongst patients with colorectal carcinoma presenting at Medical Oncology Department, JPMC. 2024;6(4).
5. Klimeck L, Heisser T, Hoffmeister M, Brenner H. Colorectal cancer: a health and economic problem. Best Pract Res Clin Gastroenterol. 2023;66:101839.
6. Muhammad SK, Chandio MA, Soomro MA, Shaikh BA. Hepatitis C virus infection in non-Hodgkin's lymphoma: a case-control study. Hepatitis Monthly. 2012; 12(142): 16-22.
7. Shaukat A, Kahi CJ, Burke CA, Rabeneck L, Sauer BG, Rex DK. ACG clinical guidelines: colorectal cancer screening 2021. Am J Gastroenterol. 2021;116(3):458-79.

8. Gupta S, Bharti B, Ahnen DJ. Potential impact of family history-based screening guidelines on the detection of early-onset colorectal cancer. Cancer. 2020;126(13):3013-20.
9. Veettil SK, Wong TY, Loo YS. Role of diet in colorectal cancer incidence: umbrella review of meta-analyses of prospective observational studies. JAMA Netw Open. 2021;4(2):e2037341.
10. Chang VC, Cotterchio M, De P, Tinmouth J. Risk factors for early-onset colorectal cancer: a population-based case-control study in Ontario, Canada. Cancer Causes Control. 2021;32:495-506.
11. Gausman V, Dornblaser D, Anand S. Risk factors associated with early-onset colorectal cancer. Clin Gastroenterol Hepatol. 2020;18(12):2752-2759.e2.
12. Rumgay H, Shield K, Charvat H. Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study. Lancet Oncol. 2021;22(8):1071-80.
13. McNabb S, Harrison TA, Albanes D. Meta-analysis of 16 studies of the association of alcohol with colorectal cancer. Int J Cancer. 2020;146(3):861-73.
14. Breau G, Ellis U. Risk factors associated with young-onset colorectal adenomas and cancer: a systematic review and meta-analysis of observational research. Cancer Control. 2020;27(1):1073274820976670.
15. Archambault AN, Lin Y, Jeon J, et al. Nongenetic determinants of risk for early-onset colorectal cancer. JNCI Cancer Spectr. 2021;5(3):pkab029.
16. Archambault AN, Su YR, Jeon J, et al. Cumulative burden of colorectal cancer-associated genetic variants is more strongly associated with early-onset vs late-onset cancer. Gastroenterology. 2020;158(5):1274-1286.e12.
17. Cercek A, Chatila WK, Yaeger R. A comprehensive comparison of early-onset and average-onset colorectal cancers. J Natl Cancer Inst. 2021;113(10):1227-36.
18. Griffiths CD, McKechnie T, Lee Y. Presentation and survival among patients with colorectal cancer before the age of screening: a systematic review and meta-analysis. Can J Surg. 2021;64(1):E91-100.
19. Cao Y, Nguyen LH, Tica S, Otegbeye E, Zong X, Roelstraete B, et al. Evaluation of Birth by Cesarean Delivery and Development of Early-Onset Colorectal Cancer. JAMA Netw Open. 2023;6(4):e2310316.
20. Savu E, Șurlin V, Vasile L, Petrescu IO, Singer CE, Pirici ND, et al. Early-Onset Colorectal Cancer-A Retrospective Study from a Tertiary Referral Hospital in Romania. Diagnostics (Basel). 2024;14(10).
21. Lingas EC. Early-Onset Colon Cancer: A Narrative Review of Its Pathogenesis, Clinical Presentation, Treatment, and Prognosis. Cureus. 2023;15(9):e45404.
22. Everhov Å H, Erichsen R, Järås J, Pedersen L, Halfvarson J, Askling J, et al. Colorectal cancer in elderly-onset inflammatory bowel disease: a 1969-2017 Scandinavian register-based cohort study. Aliment Pharmacol Ther. 2022;56(7):1168-82.
23. Watson MM, Watson DC, Maddern GJ, Wichmann MW. Colorectal adenomatous and serrated polyps in rural South Australia: who, why, what and where? ANZ J Surg. 2023;93(12):2939-45.
24. Borowsky J, Haruki K, Lau MC, Dias Costa A, Väyrynen JP, Ugai T, et al. Association of Fusobacterium nucleatum with Specific T-cell Subsets in the Colorectal Carcinoma Microenvironment. Clin Cancer Res. 2021;27(10):2816-26.
25. Nguyen LH, Cao Y, Batyrbekova N, Roelstraete B, Ma W, Khalili H, et al. Antibiotic Therapy and Risk of Early-Onset Colorectal Cancer: A National Case-Control Study. Clin Transl Gastroenterol. 2022;13(1):e00437.