Colorectal Neoplasms in Young Vietnamese Individuals with First-degree Relatives Diagnosed with Colorectal Cancer

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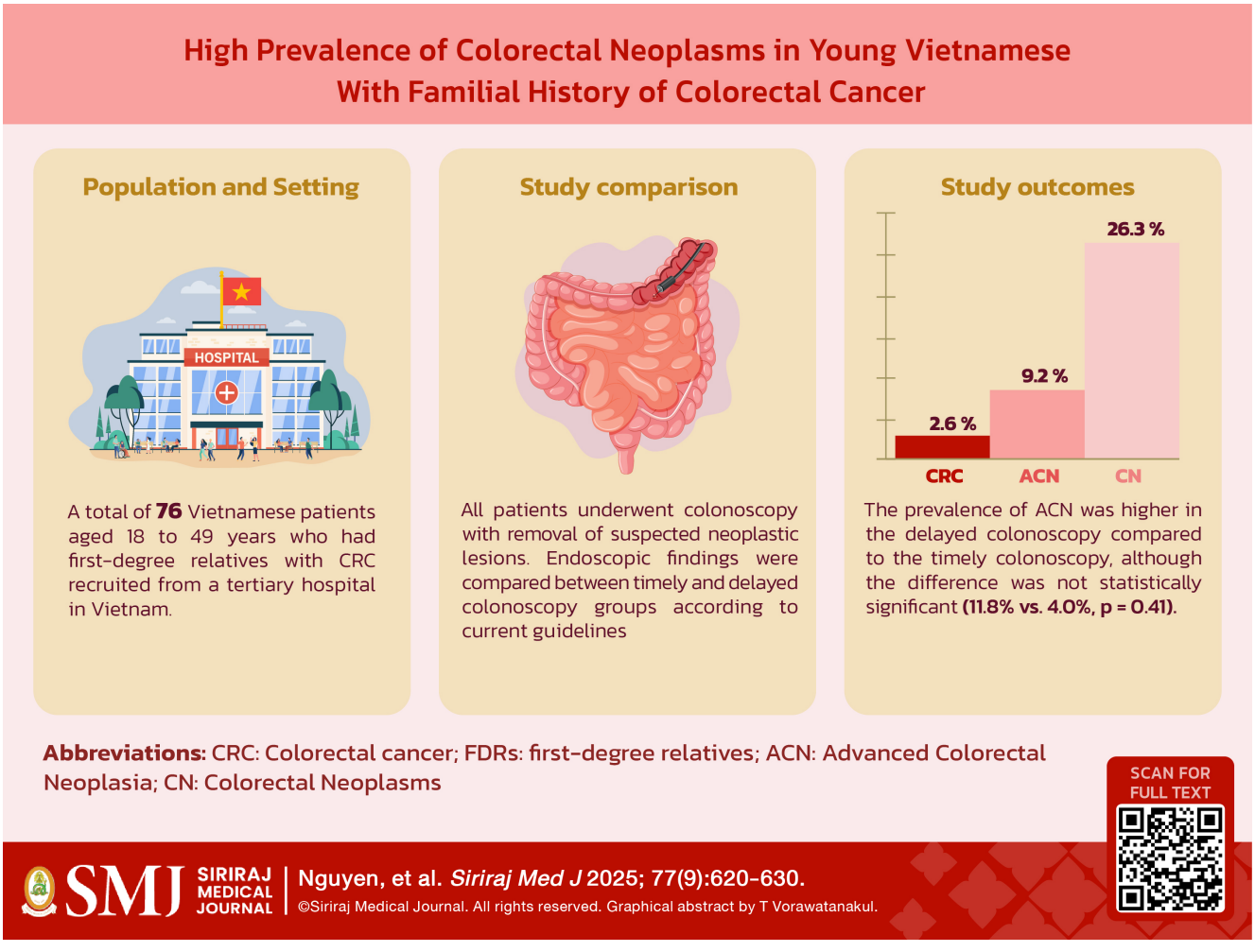

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ABSTRACT

Objective: Colorectal cancer (CRC) is increasingly prevalent, particularly among individuals with first-degree relatives (FDRs) diagnosed with CRC. Delayed colonoscopy beyond the recommended age increases the risk of advanced neoplasia and late-stage CRC. This study aims to characterize colorectal neoplasms in adults under 50 years of age with an FDR history of CRC.

Materials and Methods: A cross-sectional study was conducted on outpatients aged 18–49 years with an FDR history of CRC who presented with lower gastrointestinal symptoms and underwent colonoscopy at a tertiary hospital in Vietnam. All endoscopic lesions suspected of colorectal neoplasia were removed and subsequently reviewed for histopathological examination.

Results: Among 76 patients with FDRs diagnosed with CRC, the mean age was 40.2 ± 6.5 years, with a male-to-female ratio of 1:1.3. A total of 27 neoplastic lesions were identified in 20 patients, including 22 adenomas (81.5%), 3 sessile serrated lesions (11.1%), and 2 adenocarcinomas (7.4%). Overall, colorectal neoplasms were detected in 26.3% (20/76) of patients, with advanced colorectal neoplasia accounting for 9.2% (7/76), including 2.6% (2/76) adenocarcinomas. The incidence of advanced colorectal neoplasms was higher but not significantly different in the delayed colonoscopy group than in the screening group in terms of adherence to the guidelines (11.8% vs. 4%, p = 0.41).

Conclusion: The prevalence of colorectal neoplasms in young Vietnamese individuals with an FDR history of CRC is significantly high.

Keywords: Colorectal cancer; advanced colorectal neoplasms; first-degree relatives; delayed screening (Siriraj Med J 2025; 77: 620-630)

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers, ranking third in prevalence and second in mortality worldwide, with an increasing trend in younger populations.[1] A recent American Cancer Society study highlighted that the proportion of CRC diagnoses in individuals under 55 nearly doubled in the United States, rising from 11% in 1995 to 20% in 2019.[2] Similarly, in East Asia, the incidence of CRC among individuals under 50 has been increasing at an annual rate of approximately 1.5%.[3] In Vietnam, early-onset CRC (diagnosed under age 50) accounts for 28% of cases, with familial CRC history being more prevalent in early-onset cases than in late-onset cases.[4]

This growing burden of early-onset CRC may be partially explained by hereditary conditions such as Lynch syndrome, which accounts for 15–17% of cases,[5] while other cases involve familial risks without a clear genetic etiology.[6,7] These findings suggest that early-onset CRC may arise from complex genetic predispositions distinct from the somatic mutations commonly observed in older patients.[6,7] Evidently, a Korean study reported adjusted hazard ratios (HRs) of 1.46 and 1.61 for CRC in individuals with affected parents or siblings, rising to 2.34 when both were affected.[8] In a Hong Kong case–control study, asymptomatic siblings of CRC patients had a threefold higher prevalence of advanced neoplasms (7.5%) than did controls (2.9%).[9] A 16-country Asia–Pacific study reported significantly higher adjusted odds ratios (ORs) for CRC (2.02–7.89), advanced neoplasms (1.55–2.06), and adenomas (1.31–1.92) among those with FDRs diagnosed with CRC.[10]

Delayed colonoscopy screening in FDRs of CRC patients significantly increases the risk of advanced neoplasm and late-stage CRC, particularly in younger adults (<50 years), with studies showing up to a 1.90-fold higher risk and substantial reductions in life-years gained.[11] Studies have consistently shown that delays in CRC diagnosis are linked to an increased likelihood of advanced-stage (stage III or IV) disease, especially in adults under 50 years of age.[12-14] Given the increasing incidence and substantial familial risk associated with early-onset CRC, further research focusing on individuals with FDRs diagnosed with CRC is essential. This study aims to describe the clinical characteristics, endoscopic features, and histopathological findings of colorectal neoplasms in young adults under 50 with an FDR history of CRC.

MATERIALS AND METHODS

Study participants

A cross-sectional study was conducted from March 2022 to December 2023 at the University Medical Center in Ho Chi Minh City, Vietnam. The study included

outpatients aged 18–49 years who presented with lower gastrointestinal symptoms and had an FDR of CRC and underwent colonoscopy. The exclusion criteria included a history of colorectal surgery, inflammatory bowel disease (IBD), inherited cancer syndromes, coagulation disorders, inadequate bowel preparation (Boston Bowel Preparation Scale total score < 6 and/or any regional score < 2), incomplete colonoscopy, withdrawal time of less than 6 minutes, and unwillingness to participate.

Demographic, clinical, endoscopic, and pathologic data were collected and analyzed. Smoking status was categorized as "non-smoker" or "smoker." Overweight/Obesity was defined as a body mass index (BMI) of 23.0 kg/m² or higher for Asia.[15] Non-alcohol consumption was defined as either never drinking or consuming alcohol once a month or less.[16] A family history of CRC was defined as the presence of at least one FDR diagnosed with CRC. All eligible patients provided written informed consent before participation. The study protocol received approval from the Ethics Committee for Biomedical Research at the University of Medicine and Pharmacy in Ho Chi Minh City (Approval ID: 615/HDDD-DHYD, dated November 19, 2021).

Sample size consideration

For sample size calculations, we used the prevalence of colorectal neoplasms at 24%, as observed in a recent Vietnamese study involving the sibling group of individuals aged ≤50 years with early-onset advanced adenoma.[17] Using a 95% confidence level (Z = 1.96) and a margin of error (d) = 0.10, the minimum sample size was calculated according to the formula for estimating a proportion: $n = (Z^2 \times p \times (1 - p)) / d^2$, resulting in a sample size of approximately 70 participants.

Colonoscopy procedure

Bowel preparation was carried out using 3 liters of polyethylene glycol-based solution (Fortrans®, Beaufour Ipsen Industrie, France). The colonoscopies were performed by experienced endoscopists using the Olympus Evis Exera III High Definition CV-190 system (Olympus Co., Ltd., Tokyo, Japan). All endoscopists had an adenoma detection rate of over 30% and had completed at least 3,000 colonoscopic procedures within the past five years. All endoscopically detected lesion morphologies, locations, and sizes were prospectively recorded and analyzed. The polyp macroscopic type was divided into three categories according to the Paris classification: type 0-I: polypoid (0-Is: sessile, 0-Ip: pedunculated); type 0-II: nonpolypoid (0-IIa: slightly elevated, 0-IIb: flat, 0-IIc: slightly depressed); and type 0-III: excavated.[18] Morphologic classification of advanced colorectal cancers was based on the Japanese Classification of Colorectal Carcinoma (JCGA/JSCCR), in which gross tumor types are categorized as polypoid (Type 1), ulcerated with clear or infiltrative margins (Types 2 and 3), diffusely infiltrative (Type 4), or unclassified (Type 5).[19] The proximal colon included the cecum, ascending colon, hepatic flexure, and transverse colon, whereas the distal colon included the splenic flexure, descending colon, sigmoid colon, and rectum.

All the endoscopic lesions were categorized into four types according to JNET classification (1, 2A, 2B, and 3) based on vessel and surface patterns. Vessel patterns include invisible (type 1), regular caliber/regular distribution (type 2A), variable caliber/irregular distribution (type 2B), and loose vessel areas/interruption of thick vessels (type 3). Surface patterns progress from regular dark or white spots (type 1) to regular (tubular/branched/papillary) (type 2A), irregular (type 2B), and amorphous areas (type 3).[20] All lesions suspected of colorectal neoplasia were removed. The suspected invasive cancer lesions were biopsied, and the surgical decision was made based on the pathology results.

With respect to adhering to current guidelines for performing colonoscopy for patients who have FDRs diagnosed with CRC,[21,22] this study defined two concepts: "timely colonoscopy," including individuals who underwent colonoscopy by guidelines, initiating at or before age 40 or at least 10 years earlier than the youngest affected family member's age at diagnosis; and "delayed colonoscopy," comprising those who failed to meet these recommended timelines.

Histopathological analysis

Resected specimens were preserved in 10% buffered formalin, embedded in paraffin, and evaluated by an experienced gastrointestinal pathologist (H.M.L.). Adenomas were classified following the World Health Organization guidelines.[23] Advanced colorectal neoplasia (ACN) lesions were defined as either cancer or sessile serrated lesions with dysplasia or adenomas that were at least 10 mm in size, exhibited high-grade dysplasia, had villous or tubulovillous histology, or a combination of these features.

Statistical analysis

All the statistical analyses were conducted via SPSS software version 20 (SPSS Inc., Chicago, IL). The Kolmogorov–Smirnov test was applied to assess the normality of continuous variables. For variables with a nonnormal distribution, the median and interquartile range (upper and lower quartiles) were reported. Categorical variables are presented as frequencies and percentages.

RESULTS

Participant characteristics

82 patients aged 18–49 with lower gastrointestinal symptoms and an FDR history of CRC were referred for colonoscopy. Among these patients, six were excluded because of a history of colorectal surgery, IBD, or failure to provide informed consent. The analysis included 76 individuals with at least one FDR diagnosed with CRC (Fig 1). A total of 27 neoplastic lesions were detected in 20 individuals, comprising 22 adenomas (81.5%), three sessile serrated lesions (11.1%), and two adenocarcinomas (7.4%).

Among the 76 cases, the most common symptoms were abdominal pain (64.5%) and diarrhea (55.3%), followed by constipation (25.0%), while alarming symptoms like weight loss and hematochezia were less common (7.9% and 2.6%, respectively). The majority of participants (93.4%) had one FDR with CRC, most commonly siblings (56.6%), and a small number had both parents and siblings affected (3.9%). Of the relatives diagnosed with CRC, 27.1% were diagnosed before age 50, as presented in Table 1.

Table 2 summarizes the endoscopic and histological characteristics of colorectal neoplasia lesions. Sessile polyps (0-Is) were the most common lesion shape (70.4%), followed by pedunculated polyps (0-Ip) at 22.2% and flat elevated lesions (0-IIa) at 7.4%, with no depressed lesions (0-IIb) observed. Among the 27 lesions with histopathological results, adenomas were the most prevalent, comprising 81.5% (22/27). Of these, most were tubular adenomas (77.8%, 21/27), with only one case identified as a tubulovillous adenoma. Sessile serrated lesions were observed in 11.1% (3/27). Additionally, two cases (7.4%) were histologically diagnosed as adenocarcinomas. The characteristics of these two adenocarcinoma cases are presented in Table 4 and Fig 2.

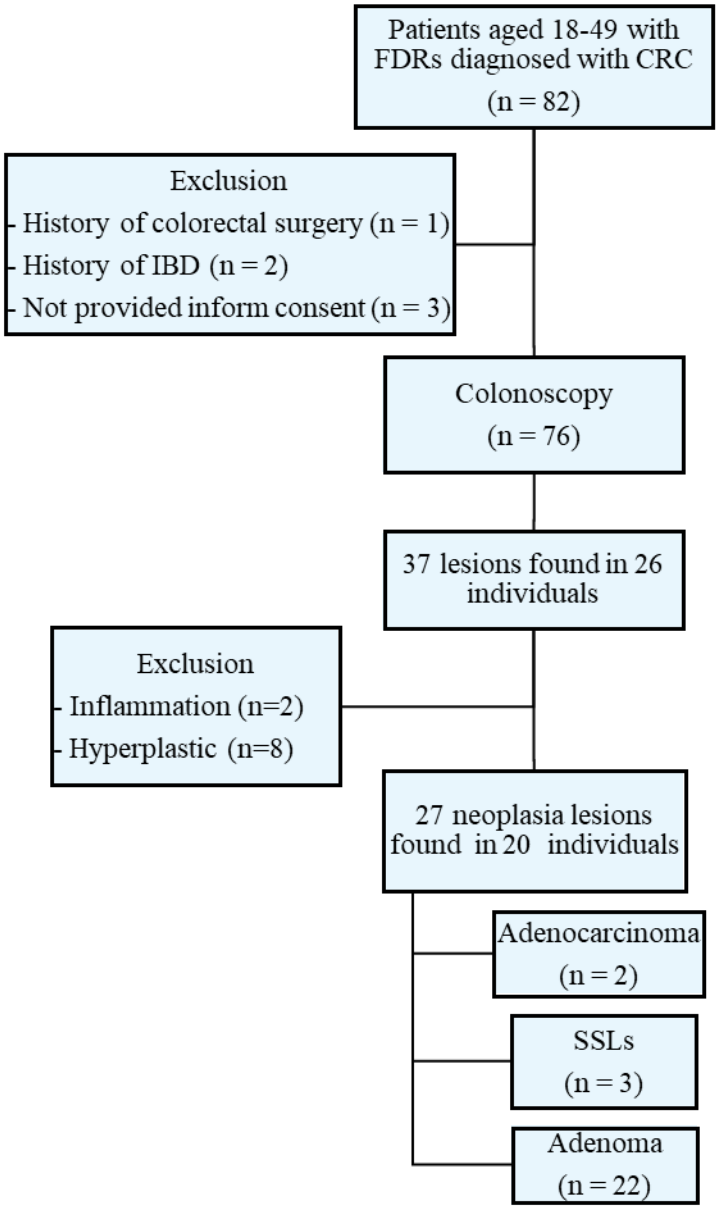

Fig 1. Flow chart of participant recruitment.
Abbreviations: IBD: Inflammatory bowel disease; SSLs: Sessile serrated lesions

TABLE 1. Demographic characteristics of the participants.

Characteristics	FDR, n (%) N = 76
Age	
< 30	4 (5.3)
30 – 39	25 (32.9)
40 – 49	47 (61.8)
Sex (n, %)	
Male	33 (43.4)
Female	43 (56.5)
BMI	
Normal	36 (47.4)
Overweight/Obese	40 (52.6)
Hypertension (n, %)	8 (10.5)
Diabetes (n, %)	3 (3.9)
Smoking (n, %)	16 (21.1)
Alcohol (n, %)	15 (19.7)
Symptoms (n, %)	
Abdominal pain	49 (64.5)
Diarrhea	42 (55.3)
Constipation	19 (25.0)
Weight loss	2 (2.6)
Hematochezia	6 (7.9)
Alarming features	
Weight loss	2 (2.6)
Hematochezia	6 (7.9)
Number of FDRs with CRC diagnosis	
One member	71 (93.4)
Two members	5 (6.6)
Relationship	
Siblings	43 (56.6)
Parents	30 (39.5)
Parents and siblings	3 (3.9)
Age of diagnosis of CRC of FRD	
< 50	22 (27.1)
≥ 50	59 (72.9)

Abbreviations: BMI: Body mass index; CRC: Colorectal cancer; FDRs: First-degree relatives

TABLE 2. Endoscopic and histological characteristics of colorectal neoplasms.

Endoscopic characteristics	N= 27 (%)
Lesion numbers in individuals	20
1	16 (80.0)
2	2 (10.0)
3	1 (10.0)
4	1 (10.0)
Size	
≤ 5 mm	13 (48.1)
6 - 9 mm	4 (14.8)
10 – 19 mm	9 (33.3)
≥ 20 mm	1 (3.7)
JNET classification	
JNET 1	7 (26.0)
JNET 2A	18 (66.6)
JNET 2B	2 (7.4)
Shape (Paris classification)	
0-Is	18 (66.7)
0-Ip	5 (18.5)
0-IIa	2 (7.4)
0-IIb	0 (0.0)
Type 1 (Japanese Classification of CRC)	2 (7.4)
Location	
Proximal	14 (51.8)
Distal	13 (48.2)
Treatment methods	
Biopsy or CSP	11 (40.7)
HSP	12 (44.4)
EMR	2 (7.4)
ESD	0 (0.0)
Surgery	2 (7.4)
Histological characteristics	
Adenoma	22
Tubular adenoma with low-grade dysplasia	21 (77.8)
Tubular villous adenoma with low-grade dysplasia	1 (3.7)
Traditional serrated adenoma	0 (0.0)
Sessile serrated lesion	1 (3.7)
Sessile serrated lesion with dysplasia	2 (7.4)
Adenocarcinoma	2 (7.4)
Advanced colorectal neoplasia	8 (29.6)

Abbreviations: JNET: Japan NBI Expert Team, EMR: Endoscopic mucosal resection, ESD: Endoscopic submucosal resection, CSP: Cold Snare Polypectomy, HSP: Hot Snare Polypectomy

TABLE 3. Association between clinicopathologic characteristics and the occurrence of advanced colorectal neoplasia (ACN).

Characteristics	Non ACN (n = 69)	ACN (n = 7)	p value
Age ≥ 40 (%)	41 (59.4)	6 (85.7)	0.241
Number of FDRs with CRC ≥ 2 (%)	2 (2.9)	3 (42.9)	0.005
Youngest FDR diagnosed <50 (%)	15 (21.7)	3 (42.9)	0.346
Hematochezia (%)	4 (5.8)	2 (28.6)	0.092
Weight loss (%)	2 (2.9)	0 (0.0)	1
Delay colonoscopy	45 (65.2)	6 (85.7)	0.415

Abbreviations: FDRs: First-degree relatives; CRC: Colorectal cancer; ACN: Advanced colorectal neoplasia

TABLE 4. Demographic, endoscopic, and histological characteristics of two patients diagnosed with colorectal adenocarcinoma.

Characteristics	Patient 1	Patient 2
Age	43	45
Sex	Male	Male
Smoking	Yes	Yes
Overweight/Obese	Yes	Yes
Alarming signs	No	No
Number of FDRs of CRC	2	2
Relationship of FDR	Parent and sibling	Parent and sibling
Age of the youngest FDR diagnosed with colorectal cancer	54	49
Symptoms	Diarrhea	Abdominal pain
Alarming signs	No	No
Adhering to colorectal screening guidelines	Delayed colonoscopy (3 years)	Delayed colonoscopy (5 years)
Lesions		
Location	Rectum	Sigmoid colon
Size (mm)	15	25
Shape	Type 1	Type 1
Treatment modality	Low anterior resection	Left hemicolectomy
Pathology	Moderately differentiated carcinoma	Moderately differentiated carcinoma from tubular villous adenoma
Invasion	Muscularis propria	Submucosa
Diagnosis	pT2N0M0	pT1N0M0

Abbreviations: FDRs: First-degree relatives, CRC: Colorectal cancer

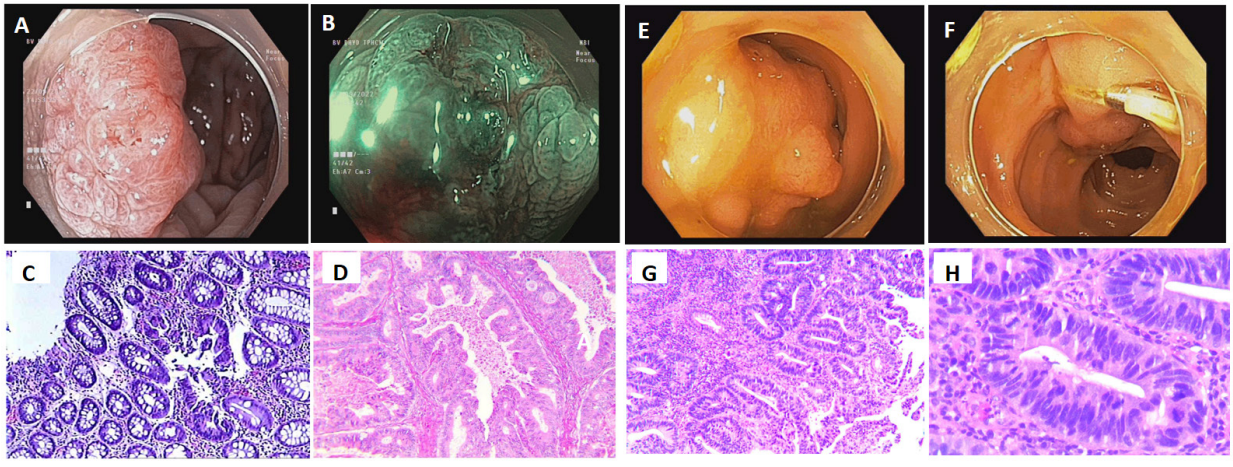

Fig 2. Endoscopic and histological findings of two adenocarcinoma lesions. Lesion 1: A type 1 lesion in the rectum was observed in white light endoscopy (A), and narrow-band imaging (B) showed JNET 2B. Histological images 10x (C) and (D) showed moderately differentiated adenocarcinoma with muscularis propria invasion; (C) from the biopsy specimen and (D) from the surgical resection. Lesion 2: A type 1 lesion in the sigmoid colon was observed in white light endoscopy (E), and another 0-Ip advanced adenoma was found in the sigmoid colon (F). Histological figures 10x (G) and 40x (H) confirmed that moderately differentiated adenocarcinoma arose in a tubular villous adenoma with deep submucosal invasion.

Table 3 shows the relationship between ACN and several clinicopathologic characteristics. Patients with two or more FDRs diagnosed with CRC had a significantly higher rate of ACN (42.9% vs. 2.9%, p = 0.005). Other factors, such as being aged 40 or older, having a youngest affected FDR aged under 50, the presence of hematochezia, and delayed colonoscopy, were more common among individuals with ACN. However, these differences were not statistically significant.

Overall, among the 76 participants, 26.3% (20/76) had colorectal neoplasms, 9.2% (7/76) had ACN lesions, and 2.6% (2/76) were diagnosed with adenocarcinoma. The occurrence of ACN lesions was higher in the delayed colonoscopy group than in the group that adhered to the guidelines, with rates of 11.8% and 4%, respectively (p value = 0.41), but the difference was not statistically significant.

DISCUSSION

This study highlighted the clinical, endoscopic, and histopathological findings of colorectal neoplasms in individuals under 50 with an FDR history of CRC. Currently, limited data exists on colorectal neoplasia lesions in this population across Asian countries, particularly in Vietnam. Our study revealed that 26.3% (20/76), 9.2% (7/76), and 2.6% (2/76) of the patients had neoplasia lesions, ACN lesions, and adenocarcinoma, respectively. When these findings were compared with those of a screening program in 1,404 individuals in Thailand, which included 117 patients of all ages with FDRs diagnosed with CRC, the detection rates were 11.1% for neoplasia lesions, 3.4% for ACN lesions, and 3.4% for CRC.[24] Similarly, in a prospective cross-sectional study in Hong Kong, ACN lesions and CRC were detected in siblings of patients with CRC at rates of 7.5% (28/374) and 1.6% (6/374), respectively, which were relatively higher than those in controls in the average group.[9] The rates of ACN lesions and CRC in studies from Thailand and Hong Kong are lower than our findings. Nevertheless, our study focused on those under 50 years of age, suggesting a higher detection rate in our younger population. The rate of early-onset CRC in Vietnam was 28%, with a significantly greater prevalence of familial CRC in the early-onset group than in the late-onset group (21.4% vs. 7.6%, p < 0.001).[4] Similarly, in this series of cases, we observed a nearly identical rate of CRC diagnoses in relatives before age 50, at 27.1% (22/81), which is consistent with earlier findings.

In a screening program in Australia, the data for 485 patients under 50 showed that the detection rates were 16.5% for neoplastic lesions, 4.3% for ACN lesions, and 1% for adenocarcinomas.[25] Similarly, a study from Korea reported detection rates of 19.5% for neoplasia lesions, 1.9% for ACN lesions, and 0.8% for CRC among 570 individuals under 50.[26] Although these two studies did not focus on individuals with FDRs diagnosed with CRC, and thus cannot be directly compared. However, the rates of advanced lesions and CRC in our study (9,2%) were higher than those reported in these studies, emphasizing the increased risk among those with a

family history of CRC. Our study is the first to evaluate the prevalence of colorectal neoplasms in this specific population. While comparisons with other studies are indirect, these findings offer insight into the influence of having FDRs on the occurrence of colorectal lesions in individuals under 50.

Regarding delayed screening in our study, the incidence of ACN lesions was higher in the "delayed colonoscopy" group than in the "timely colonoscopy" group at 11.8% versus 4%, respectively. Given the limited number of ACN cases and the small overall sample size, this subgroup analysis was underpowered to detect statistically significant differences and should be considered exploratory. Further research with a larger cohort is needed to better clarify these relationships. This is particularly important, as previous studies have demonstrated a high rate of early-onset CRC in Vietnam, especially among individuals with an FDR history of CRC, who should adhere strictly to recommended screening timelines.[4] A large multicenter cross-sectional study by Quintero et al. assessed the risk of advanced neoplasia in FDRs of patients with CRC. This study revealed that delayed screening in FDRs in individuals with two FDRs diagnosed with CRC was associated with a 1.90-fold increased risk, with an OR of 1.90 (95% CI: 1.36–2.66), of developing advanced neoplasia compared with the average risk group.[11] Several studies have reported that delays in the diagnosis of CRC are associated with increased odds of being diagnosed at an advanced stage (stage III or IV), particularly in younger adults (<50 years).[12-14] A systematic review of 39 studies, which included 185,710 younger and 1,422,062 older CRC patients, evaluated clinical delays and outcomes between these age groups. Sixteen studies examining prediagnostic intervals consistently reported longer delays for younger adults, who also had significantly higher odds of presenting with advanced-stage CRC, with a pooled OR of 1.76 (95% CI: 1.52–2.03).[13] A simulation study by Rutter et al. found that a 5-year delay in screening initiation increased the incidence of CRC by 21.7% and that of late-stage CRC by 26.8%, with a 12.4% reduction in life-years gained.[14] Delayed colonoscopy in high-risk individuals may not only increase the likelihood of detecting CRC at a more advanced stage but also affect postoperative recovery and quality of life. A recent study conducted in Thailand highlighted the influence of psychosocial and socioeconomic factors, such as financial strain, limited familial support, and heightened anxiety, on the postoperative well-being of CRC patients. These findings emphasize the critical importance of timely screening and comprehensive, patient-centered care, particularly among younger individuals with a significant familial predisposition.[27] Timely colonoscopic evaluation may have facilitated earlier detection and enabled the endoscopic removal of precancerous or early-stage lesions. This aligns with findings from Mongkhonsupphawan et al., who reported a 5-year overall survival rate of 70.9% among stage I–III CRC patients undergoing curative resection in Thailand. Furthermore, rectal cancer was associated with less favorable prognoses compared to colon cancer, with distant recurrence observed in up to 28.6% of rectal cancer cases.[28] Therefore, early sigmoidoscopic screening also holds promise in detecting neoplastic lesions in the rectum at an earlier, more treatable stage.

Our study identified two cases of adenocarcinoma in patients who underwent colonoscopy later than the recommended age; both had exceeded the indications for endoscopic intervention. If these two lesions had been screened earlier, they could have been completely removed via endoscopic resection. These two cases share the common characteristic of early-onset CRC, with the prevalent anatomic site in the distal colon (50%-80% of cases).[7] Among the 143 immigrant Asian CRC patients included in the retrospective review, Lynch syndrome was identified in 4.19% of them. In the Lynch group, two-thirds of the tumors were located on the left side of the colon, similar to the distribution observed in the sporadic CRC group.[29] CRC associated with Lynch syndrome in Asian individuals is predominantly observed in the distal colon, a distribution pattern that aligns with findings in sporadic CRC patients. Therefore, if individuals with an FDR of CRC are not prepared for colonoscopy, sigmoidoscopy could be considered an alternative screening option to detect early lesions and encourage them to proceed with a complete colonoscopy. Since their young age at diagnosis (43 and 45 years) and the presence of CRC in both a parent and a sibling, these two patients may fulfill clinical criteria for hereditary colorectal cancer syndromes such as Lynch syndrome. According to international guidelines—including the National Comprehensive Cancer Network (NCCN)[30] and the European Society for Medical Oncology (ESMO)[31] recommend that patients diagnosed with CRC before age 50, particularly those with two or more FDRs affected (regardless of age), be referred for genetic counseling and germline testing, ideally using multigene panels. In our study, neither patient underwent molecular or genetic testing, which highlights a significant gap in how hereditary cancer risk is currently assessed in our healthcare setting. Although access to genetic testing in Vietnam is still limited, expanding its availability and improving awareness of guideline-based evaluations for Lynch syndrome and other inherited CRC syndromes

should be a key priority. This is an important step forward in improving patient care and preventing cancer in high-risk families.

This study has several limitations. First, it was conducted at a single tertiary center with a relatively small sample size, which may limit the generalizability of the findings. Second, we did not include a comparison group of individuals without a family history of CRC, which restricts our ability to assess relative risk. Third, although two young patients with multiple affected relatives met criteria for genetic evaluation, germline testing was not performed, reflecting the limited availability of such services in our setting.

In conclusion, our study identified neoplasia lesions in 26.3% of patients, advanced colorectal neoplasia in 9.2%, and colorectal cancer in 2.6% of young Vietnamese individuals with FDRs diagnosed with CRC. Two cases of CRC in this series were delayed-screened according to the guidelines' recommendations, which have been proven to be associated with increased odds of being diagnosed at an advanced stage.

Data Availability Statement

All the data generated or analyzed during this study are included in this published article. Further inquiries can be directed to the corresponding author.

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DECLARATIONS

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This study was not supported by any sponsor or funder.

Conflict of Interest

The authors declare no conflicts of interest. All the authors involved in this article reviewed and approved the final version of the manuscript.

Registration Number of Clinical Trial

Trial registration: Not applicable. This study is an observational study and does not require trial registration.

Author Contributions

Conceptualization and methodology, D.T.Q.; Investigation, D.T.N.N., N.T.H.V., M.N.L., Q.D.L., T.L.T.T., V.L.T.T.; Histological analysis, H.M.L.; Supervision and critical revision, D.T.Q.; Writing – original draft, D.T.N.N.; Writing – review and editing, D.T.Q. All authors have read and approved the final version of the manuscript.

Use of Artificial Intelligence

Artificial intelligence tools (ChatGPT by OpenAI) were used to improve the manuscript's language, structure, and clarity. All authors reviewed and approved the final content.

Statement of Ethics

The study protocol complies with the ethical principles outlined in the 1975 Helsinki Declaration. The study received approval from the Ethics Committee in Biomedical Research at the University of Medicine and Pharmacy in Ho Chi Minh City, Vietnam (Approval ID: 615/HDDD-DHYD, dated November 19, 2021). Written informed consent was obtained from all participants and/or their legal guardians.

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