BRIEF ARTICLE

Colorectal cancer in patients under 50 years of age: A retrospective analysis of two institutions' experience

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Abstract

AIM: To investigate the epidemiological characteristics of colorectal cancer (CRC) in patients under 50 years of age across two institutions.

METHODS: Records of patients under age 50 years of age who had CRC surgery over a 16 year period were assessed at two institutions. The following documents where reviewed: admission notes, operative notes, and discharge summaries. The main study variables included: age, presenting symptoms, family history, tumor location, operation, stage/differentiation of disease, and post operative complications. Stage of disease was classified according to the American Joint Committee on Cancer TNM staging system: tumor depth; node status; and metastases.

RESULTS: CRC was found in 180 patients under age 50 years (87 females, 93 males; mean age 41.4 ± 6.2 years). Young patients accounted for 11.2% of cases during a 6 year period for which the full data set was available. Eight percent had a 1st degree and 12% a 2nd degree family CRC history. Almost all patients (94%) were symptomatic at diagnosis; common symptoms included: bleeding (59%), obstruction (9%), and abdominal/rectal pain (35%). Evaluation was often delayed and bleeding frequently attributed to hemorrhoids. Advanced stage CRC (Stage 3 or 4) was noted in 53% of patients. Most tumors were distal to the splenic flexure (77%) and 39% involved the rectum. Most patients (95%) had segmental resections; 6 patients had subtotal/total colectomy. Poorly differentiated tumors were noted in 12% and mucinous lesions in 19% of patients of which most had Stage 3 or 4 disease. Twenty-two patients (13%) developed recurrence and/or progression of disease to date. Three patients (ages 42, 42 and 49 years) went on to develop metachronous primary colon cancers within 3 to 4 years of their initial resection.

CONCLUSION: CRC was common in young patients with no family history. Young patients with symptoms merit a timely evaluation to avoid presentation with late stage CRC.

Core tip: Colorectal cancer (CRC) is rising among patients under age 50 years. In our study, the majority of patients did not have a family history of CRC and presented with advanced disease stages. In America, many physicians wrongly believe that CRC in patients under age 50 years is uncommon and mostly found in patients with a 1st degree family history of CRC. This misconception delays time to diagnosis, contributing to a more advanced disease stage on presentation. The authors hope, after reading this article, doctors will recommend timely and complete colon evaluations for

patients under age 50 years who present with rectal bleeding.

INTRODUCTION

Colorectal cancer (CRC) remains a notable source of morbidity and mortality worldwide[1]. CRC is consistently the third most commonly diagnosed cancer in the United States. The American Cancer Society estimated that there would be 103170 new cases of colon and 40290 new cases of rectal cancer in 2012; in addition, 51690 deaths were predicted[2]. Although common, the overall incidence of CRC in the general population declined by 2.9% in men and 2.2% per year in women between 1998 and 2009[3]. An increase in the proportion of the population undergoing screening colonoscopy and the removal of benign precancerous polyps is thought to account for, at least, part of this decrease.

Patients with a first degree family history of CRC are advised to begin screening colonoscopy at age 40 or 10 years prior to the youngest age at which a family member with CRC was diagnosed. In addition, screening programs for CRC are now widely implemented for "average risk" patients, defined as those without a first degree family history of CRC or other risk factors, other than age. Universally, it is advised that screening begin at age 50 years for "average risk" patients. Asymptomatic patients under 50 years of age without a family history are excluded from almost all screening programs. Perhaps, in part, because of the age 50 years cut off many patients and doctors have a low index of suspicion for CRC in young patients without family history who present with bleeding or other symptoms. It is also the impression of many doctors and patients that the majority of young patients who develop CRC have a positive family history. Although less common than in older patients, sporadic CRC accounts for the majority of cases in patients under age 50 years.

The National Cancer Database Report on CRC noted that individuals under 50 years of age accounted for roughly 7% of all CRC in a 1990 study population of over 38000 patients[4]. As per the Surveillance Epidemiology and End Results (SEER) Program data from 1993 to 1997, patients younger than 55 accounted for roughly 12% of all CRC cases[5]. A recent study that examined data from the SEER Program cancer registries between 1992-2009 reported that the overall incidence of CRC per 100000 people (20-49 years age category) increased 1.6% and 1.7% per year in men and women, respectively, over this time period[3]. A review of SEER Program data from 2005-2009 provides more detailed information regarding CRC in younger patients; in patients under 20 years the incidence was about 0.1%, in those 20-34 years of age it was 1.1%, in the 35-44 years sub-group the incidence was 4.0% whereas in the 45-54 years group it was 13.4%[2]. The data suggests that the incidence in younger patients is increasing[3].

A number of reports regarding young patients with CRC have been published over the last few decades (Table 1); however, these reviews typically span many years, often include patients with familial syndromes and/or ulcerative colitis, and do not adequately comment on the relevant family history of the study patients[6-15]. This focused review regarding two institutions' experiences with patients under 50 years of age with CRC that came to surgery over a 16 year interval was conducted to determine: the volume of CRC operations for young patients, the proportion with a family history of CRC, the stage at presentation, the specific cancer location, and the presenting symptoms, if any.

MATERIALS AND METHODS

Patient population

Hospital records of patients under the age of 50 years who underwent CRC operations between July 1996 and May 2012 at two institutions were reviewed (New York Presbyterian Hospital, Columbia University Campus and St. Luke's Roosevelt Hospital, NY, United States). Specifically , the following documents where reviewed; admission notes, operative notes, discharge summaries, endoscopy records, and pathology reports. A subset of this data was also obtained from an IRB approved prospective data base of patients undergoing colorectal resection maintained by the senior author from 2006 to June 30, 2009 at New York Presbyterian Hospital and from July 1, 2009 until May 2012 at St. Luke's Roosevelt Hospital. This prospective database also provided the information regarding CRC patients over 50 years of age (*n* = 392) used in this study. Additional information for this retrospective review was obtained from office charts and from telephone interviews.

Study endpoints

The main study variables included: demographics, presenting symptoms leading to diagnosis, family history of CRC, tumor location, type of surgical resection, stage and differentiation of disease, and post operative complications. Patients with inflammatory bowel disease or known polyposis syndromes such as familial adenomatous polyposis syndrome, Gardner's syndrome and the like were excluded from the study.

Disease stage was reported according to the TNM Classification System used by the American Joint Committee on Cancer[16,17]. "T" refers to the size or direct extent of invasion of the primary tumor; "N" refers to the degree of spread to regional lymph nodes, if any; and "M"

Table 1 Comparison of previously published reports of young patients with colorectal cancer

Ref.	Patients with CRC	Interval (yr)	Patient age (yr)	With family history of CRC (%)[1]
Recalde *et al*[6]	40	19	< 36	NR
Sanfelippo *et al*[7]	118	12	< 40	NR
Simstein *et al*[8]	41	15	< 40	4 (10)
Safford *et al*[9]	120[3]	33	< 41	6 (5)
Pitluk *et al*[10]	31	10	< 40	1 (3)
Behbehani *et al*[11]	47[3]	11	< 40	NR
Adloff *et al*[12]	32	7	< 40	NR
Domergue *et al*[13]	78[2]	18	< 41	NR
Palmer *et al*[14]	105[2]	12	< 40	NR
Fante *et al*[15]	90[2]	9	< 51	18 (20)
Present series	180	16	< 50	20 (12)[3]

[1]Degree of relation not otherwise specified; [2]Series includes patients with familial adenomatous polyposis and/or ulcerative colitis; [3]Patients with first degree relatives with colorectal cancer. NR: Not reported; CRC: Colorectal cancer.

Table 2 Patients' presenting signs and symptoms of colorectal cancer *n* (%)

Clinical presentation	Patients
Rectal bleeding	99 (57)
Anemia	19 (11)
Abdominal pain	54 (31)
Rectal pain	7 (4)
Change in bowel habits	37 (21)
Weight loss	20 (11)
Bowel obstruction	16 (9)
Perforation	5 (3)
Perforated diverticulitis	1 (0.6)
Screening	5 (3)
Unknown	7 (4)

refers to the presence of distant metastases.

Statistical analysis

Statistical methods for comparing stage and tumor distribution between the under age 50 years and the 50 and over years groups included a 2-proportion Z test.

RESULTS

Patient demographics

One hundred eighty patients under 50 years of age (87 females, 93 males; range 17-49 years; mean 41.4 ± 6.2 years) underwent a CRC operation between July 1996 and May 2012 at the two institutions. In regards to the total number of patients (regardless of age) that underwent a CRC operation, complete data is only available for the period between July 2006 and May 2012; during this time period 437 CRC operations on adults were carried out of which 49 (11.2%) involved patients less than 50 years of age. When the total population of 180 patients under age 50 is considered, the distribution of CRC within age categories is as follows: under age 30 years, 8 patients (4%); age 30-39 years, 46 patients (26%); age 40-49 years, 126 (70%). Of note, 30% of the patients were younger than

Table 3 Location of cancers *n* (%)

Anatomic location of cancer[2]	Cancers
Right colon[1]	31 (17.2)
Transverse colon	13 (7.2)
Descending colon	17 (9.4)
Descending and sigmoid colon junction	2 (1.1)
Sigmoid colon	29 (16.1)
Rectosigmoid colon	19 (10.6)
Rectum	71 (39.4)

[1]Right colon includes cecum, ascending, hepatic flexure; [2]Two patients had synchronous cancers.

40 years of age. One hundred and seventy patients (94%) reported symptoms upon presentation (Table 2).

Family history of CRC

Family history data was available for 167 patients; 13 patients (7.8%) did not know their family history. Regarding the 167 patients with family history data, 14 patients (8.4%) had a first degree family history of CRC, 20 patients (12.0%) had a second degree history, and 6 patients (3.6%) had both a first and second degree family history of CRC. Thus, a total of 12% of patients had, at least, a first degree family history of CRC. Seventy six percent were sporadic CRC cases. One patient (age 42 years) presented with synchronous primary cancers of the cecum and splenic flexure and had a family history notable for 3 first and 1 second degree relatives with CRC. The Amsterdam criteria for hereditary non-polyposis colorectal cancer (HNPCC) were met in this patient[14]. Unfortunately, none of the patients in this series were evaluated for gene mutations associated with HNPCC (*i.e.*, *hMLH1*, *hMSH2*, *etc*.)[18].

Distribution of tumor location and colorectal resection

The majority of tumors (77%) were located distal to the splenic flexure, with 39% involving the rectum (Table 3). Proximal (right and transverse colon) cancers were noted in only 24% of patients. In comparison, a cohort of 392 CRC patients 50 years of age and older who underwent an operation between 2006 and 2012 at the same institutions by the same surgeons, presented with more proximal tumors (age < 50 years, 24% *vs* age ≥ 50 years, 43%; $P < 0.0001$) and fewer rectal tumors (age < 50 years, 39% *vs* age ≥ 50 years, 27%; $P = 0.002$) using 2-proportion Z-test (Table 4).

A formal colorectal resection was done in the majority of patients (95%), a transanal excision of a rectal cancer in 1 patient, colocolonic bypass for unresectable Stage 4 disease in 1 patient, and proximal diversion in 6 patients with obstructing, locally invasive cancers (Table 5). Twenty three abdominoperineal resections and 3 low anterior resections with mucosectomy and subsequent coloanal anastomosis were performed. A Hartmann's procedure was done in 4 patients with sigmoid or rectal lesions. Two patients (ages 34 and 42 years) had synchronous primary colon cancers and underwent subtotal colectomy. Twenty-

Table 4 Colorectal cancer staging *n* (%)			
Present series	**Value**	**SEER²**	**Value**
Age < 50 yr			
Stage 1¹	37 (21)	Localized	30%
Stage 2	47 (26)	Regional	40%
Stage 3	70 (39)	Distant	27%
Stage 4	26 (14)	Unstaged	3%
Age ⩾ 50 yr			
Stage 1	88 (22)	Localized	38%
Stage 2	143 (36)	Regional	37%
Stage 3	135 (34)	Distant	19%
Stage 4	26 (7)	Unstaged	6%

¹Two patients had Stage 0 disease and one patient had Tis disease following polypectomy; ²Surveillance Epidemiology and End Results (SEER) 18, 2000-2009 stage distribution. Localized (confined to primary site), regional (spread to regional lymph nodes), distant (cancer has metastasized).

Table 5 Type of colon resection *n* (%)		
Operation	**Patients**	**Laparoscopic**
Right colectomy	34 (19.8)	17 (50)
Transverse colectomy	2 (1.2)	2 (100)
Left colectomy	20 (11.6)	10 (50)
Descending and sigmoid colectomy	1 (0.6)	1 (100)
Sigmoid colectomy	22 (12.8)	15 (7)
Rectosigmoidectomy	24 (13.9)	21 (88)
Low anterior resection	40 (23.2)	26 (65)
Abdominoperineal resection	23 (13.4)	11 (48)
Subtotal/total colectomy	6 (3.5)	4 (67)
Total resections	172 (95.0)	107 (62)

four distal resection patients were temporarily diverted (16% of all patients with anastomoses). Regarding the surgical methods used in the 172 patients who underwent bowel resection, the breakdown is as follows: laparoscopic-assisted, 78 patients (45.3%); hand-assisted or hybrid laparoscopic/open technique, 29 patients (16.9%); and open methods, 65 patients (37.8%).

Staging distribution
According to the TNM system for cancer staging by the American Joint Committee on Cancer[16,17], 37 patients (21%) had Stage 1 disease, 47 patients (26%) had Stage 2 disease, 70 patients (39%) had Stage 3 disease, and 26 patients (14%) had Stage 4 disease (Table 4). Three patients who underwent neoadjuvant chemoradiation for T3 rectal lesions based on preoperative endorectal ultrasound imaging had no residual disease on final pathology at the time of colorectal resection and were considered as Stage 2 lesions. Likewise, 3 patients who had sessile polyp cancers removed colonoscopically (invasion into submucosa noted on pathology) who underwent formal resection that revealed no residual cancer or involved lymph nodes on pathologic evaluation were classified as having Stage 1 cancers. Twenty patients with Stage 4 disease had known hepatic involvement and 3 patients had peritoneal carcinomatosis diagnosed at laparotomy.

Thirty-five patients (19%) underwent neoadjuvant chemoradiation, 3 patients (1.7%) underwent neoadjuvant chemotherapy alone, 10 patients (5.6%) underwent adjuvant chemoradiation, 56 patients (31%) underwent adjuvant chemotherapy, and 1 patient underwent adjuvant radiation alone for bony metastases. Of note, compared to the cohort of 392 CRC patients 50 years of age or older who underwent an operation between 2006 and 2012, patients under age 50 more often presented with Stages 3 and 4 disease (age < 50 years, 53% *vs* age ⩾ 50 years, 41%; $P = 0.003$ using 2-proportion *Z*-test) (Table 4).

Histopathological evaluation
Moderately or well differentiated cancers were noted in 124 patients (69%) whereas poorly differentiated cancers were found in 22 patients (12%). Of those with poorly differentiated histology, 67 percent presented with advanced Stage CRC (Stage 3 or 4). Thirty-four patients (19% of total) had mucinous adenocarcinomas of which 62% had advanced stage CRC.

Postoperative complications and short-term outcomes
Regarding postoperative complications, there was 1 anastomotic leak and 4 intra abdominal/pelvic abscesses (reoperation in 1 patient, percutaneous drainage in 3 patients). Other postoperative complications included: ileus, 6 patients; small bowel obstruction, 6 patients (all required reoperation); wound infection, 7 patients; wound dehiscence, 2 patients (reoperation × 2); urinary retention, 3 patients; portal vein thrombosis, 1 patient; *C. difficile* colitis, 1 patient (treated with antibiotics); and incisional hernia, 1 patient (surgically repaired). There were no deaths perioperatively. Twenty-two patients (13%) developed recurrence and/or progression of disease to date. Three patients (ages 42, 42, and 49 years) went on to develop metachronous primary colon cancers within 3-4 years of their initial resection.

DISCUSSION
It is well established that the incidence of CRC increases significantly beyond the 5th decade of life and continues to rise thereafter with increasing age. More recent reviews have shown that the percentage of CRC patients under 50 years of age has increased to approximately 12 percent[5]. Our data corroborates these findings as 11.2% of CRC patients in our study were younger than age 50 years.

Many people, lay and physician alike, falsely believe that the majority of patients under 50 years of age who develop CRC have a significant family history and are genetically predisposed to developing CRC. Interestingly, only 12% of patients in our study had a first degree relative with CRC and only 1 patient (age 42 years) met the Amsterdam criteria for HNPCC based on family history. A literature search revealed several reports regarding young patients with CRC that showed family history data[6-15] similar to that of our study findings. In the general population of CRC patients (all ages), an estimated 15%-20% of patients have a family history of colorectal

neoplasia[19]. Therefore, regardless of age at diagnosis, the vast majority of patients with CRC have sporadic disease and are "average risk" patients without a family or personal history of colorectal neoplasm, inflammatory bowel disease, polyposis syndromes, or other risk factors.

Are CRC's in the under 50 population different from tumors that occur in older patients? In the absence of detailed genetic analyses of the tumors we must use clinical and basic pathologic data to address this question. The stage breakdown data may be helpful in this regard, although it is influenced by factors other than the tumors' biologic aggressiveness (*i.e.*, the timeliness of diagnosis). Similarly, the differentiation profile of the tumors in the younger and older CRC populations permits comparison of the 2 groups.

SEER stage distribution data from 2000-2009 for individuals with CRC under 50 years of age noted that 30% had localized disease (confined to primary site), 40% had regional disease (spread to mesenteric lymph nodes), and 27% had distant disease (metastatic) at the time of diagnosis; thus, 67% had Stage 3 or 4 disease. In contrast, in the over 50 age group, 39% of patients had localized disease, 37% had regional disease and 19% had distant disease at diagnosis; thus, 56% had Stage 3 or 4 disease[2]. Our study results, as well as other investigators[8,10,11,13], support the notion that advanced Stage (Stage 3 or 4) at presentation is more common among young patients compared to older patients (50 years and older). Taken together, the available data suggests that younger patients with CRC more often present with advanced disease when compared to the general population[8,10,11,13].

Regarding tumor differentiation, previous studies report a greater percentage of poorly differentiated (19%-49% of total) and mucinous tumors (9%-49%) in younger CRC populations[3,8,20,21], whereas, in the current study, only 12% of patients had poorly differentiated adenocarcinomas and 20% had mucinous histology. Data concerning the general CRC population from two previously published studies suggests that about 15% of colorectal adenocarcinomas are poorly differentiated and 17% demonstrate mucinous histology[22,23]. The relatively low percentage of poor prognosis histologies in our study may be related, in part, to the small number of HNPCC patients in the study population since HNPCC is associated with a higher incidence of poorly differentiated and mucin producing tumors. Regardless, the histology data does not provide an explanation for the high incidence of advanced stage tumors seen in the current study population. As mentioned earlier, there may be factors other than unfavorable histology and aggressive tumor biology contributing to the high rate of advanced stage tumors seen in younger CRC patients.

It has been suggested that delays in diagnosis may account, in part, for the advanced Stage at presentation noted in many CRC patients under 50 years of age[14,24]. Young symptomatic patients may delay presentation to a physician out of ignorance, fear, or denial. Furthermore, when confronted with young, average risk patients, clini-

cians may attribute their symptoms to any number of common benign anorectal disorders. The already mentioned fixation on 50 years as the age after which CRC occurs likely figures into the practioner's thinking as well. Consequently, a full colorectal evaluation may not be carried out for months to years following the onset of symptoms. For example, in the current study multiple patients reported a history of intermittent rectal bleeding and were treated for "hemorrhoids" for a year or longer before referral for diagnostic endoscopy. In one patient with an 18 mo history of diarrhea and occasional bleeding with mucus, a corresponding note from a gastroenterologist stated that the change in bowel habits likely represented irritable bowel syndrome with hemorrhoids. This patient ultimately underwent a colonoscopy and was found to have a sigmoid cancer. Another patient who reported postpartum rectal bleeding was told by her family practitioner that the cause was most likely hemorrhoids. This patient was eventually referred for a colonoscopy two years later after developing abdominal pain at which time she had a palpable rectal mass; she proved to have a Stage 3 lesion.

The ramifications of delayed diagnosis, specifically presentation with a more advanced CRC stage with its attendant increased mortality, justify, in the authors' opinion, prompt and complete large bowel evaluation in all patients under 50 years of age who present with suspicious colorectal symptoms in order to "rule out" an occult neoplasm. Signs and symptoms that may prompt such an evaluation include: bleeding, heme-positive stool, anemia, changes in stool caliber or bowel habits, and abdominal pain or persistent distension of unclear etiology.

Current screening and surveillance guidelines
There are currently no screening guidelines in place by the American Society of Colon and Rectal Surgeons (AS-CRS) or the American Cancer Society (ACS) pertaining specifically to young patients who present with symptoms that could signify an underlying neoplasm. The ASCRS[25] does recommend, in general, that anyone "with symptoms or signs that suggest the presence of CRC or polyps who fall outside the domain of screening should be offered an appropriate diagnostic evaluation." However, it appears that in the United States too few practitioners are following this recommendation when confronted with young patients who report bleeding or other symptoms.

Questions regarding cancer surveillance and screening for patients and their families commonly arise when caring for young CRC patients. The following guidelines from the ASCRS and the ACS have evolved over the last 3 decades; although there are some minor differences they are quite similar. People with a first-degree relative (parent, sibling, or child) who has had CRC or adenomatous polyp(s) are advised to have screening colonoscopy starting at age 40 or ten years younger than the age, at diagnosis, of the youngest family member with CRC (whichever comes first) with repeated evaluation every

5 years. Individuals with two second degree relatives (grandparent, aunt, or uncle) with CRC or polyps are advised to be screened as average risk patients (see below), but beginning at age 40 years. Individuals with a single second or third degree relative (cousin, great-grandparent) with CRC or polyp(s) are advised to follow average risk screening guidelines. Individuals in HNPCC kindreds are advised to begin colonoscopic evaluation starting at 20-25 years of age or 10 years before the age of diagnosis in the youngest CRC patient in the immediate family, whichever comes first[25].

In average risk patients the ASCRS[25] recommends that routine screening commence at age 50 years. As per the ASCRS, acceptable screening strategies for average risk patients include: (1) flexible sigmoidoscopy every 5 years; (2) a double contrast barium enema every 5-10 years; or (3) a colonoscopy every 10 years. The ACS recommendations are almost identical to those of the ASCRS except that they include virtual colonoscopy every 5 years as an acceptable screening option. In regards to average risk patients under age 50 years without family history, the ASCRS[25] advises that they commence annual digital rectal examination and fecal occult blood testing at age 40 years; the ACS makes no recommendations for this group.

Future directions

Is endoscopic screening indicated for asymptomatic patients under 50 years of age? The rising incidence of CRC in this group and the tendency towards advanced Stage at presentation would argue in favor of such programs. Yet, the cost of screening colonoscopy programs would be very high and given the current economic climate and the fact that the incidence of CRC is still considerably lower in this group (*vs* the over age 50 population) the initiation of such programs is highly unlikely. However, perhaps a case can be made for a single screening sigmoidoscopy at age 40. In the present series a screening sigmoidoscopy would most likely have revealed a significant number of the neoplasms. As per the ACS, sigmoidoscopy identifies 70%-80% of individuals with advanced lesions and is associated with a 60%-80% reduction in CRC mortality for the area of the colon within its reach. Furthermore, in a recent multi-center randomized trial a single screening sigmoidoscopy carried out between the ages of 55 and 64 reduced CRC incidence by 33% and mortality by 43%[26]. Sigmoidoscopy, although invasive, is a safe procedure with a very low rate of perforation that is well tolerated without sedation. Although the chances for successful initiation of a flexible sigmoidoscopy screening program for young patients are small, the authors believe that our current dismal record with young CRC patients justifies the effort.

Study limitations

The lack of genetic testing for HNPCC in this study population is a clear weakness of this study. Similarly, the lack of long term cancer recurrence and survival results is also a major shortcoming. Ideally, genetic categorization of the tumors *via* microarray would be done which would permit a detailed analysis and comparisons.

In conclusion, this review corroborates recent national data regarding the rising incidence of CRC in the under age 50 population and the fact that a greater percentage of younger patients present with Stages 3 and 4 disease when compared to the entire CRC population. The vast majority of the young patients in this study had sporadic CRC; only 12% had a first degree family history of CRC and only 1 patient met the clinical criteria for HNPCC. The histologic breakdown of the tumors was similar to that reported in the general population of CRC patients.

Although it is impossible to confirm, it is the impression of the authors that in many patients there was a delay, either by the patient, physician, or both, in carrying out the appropriate diagnostic evaluation. The widely held belief that CRC occurs in patients age 50 and older likely contributes to this mind set. Clearly, at the very least, young symptomatic patients with rectal bleeding, a change in bowel habits, or abdominal pain should be promptly evaluated, preferably with a full colonoscopy. Finally, the medical and surgical community need to consider the concept of some type of screening program for young patients, perhaps flexible sigmoidoscopy, beginning at age 40 years. The goal is to diagnose CRC in this population at an earlier stage so that the recurrence rates and mortality can be reduced. The medical community and the public must be made aware of the fact that CRC occurs in patients under age 50 years with regularity and that thorough evaluation is indicated for symptomatic patients regardless of their age.

COMMENTS

Background
While the incidence of colorectal cancer (CRC) is declining in the overall population, it is on the rise among individuals under 50 years of age. Many patients and practioners, alike, believe most cases of early-age onset CRC are attributed to a family history of CRC; however, a growing number of small studies now show that the majority of these young patients have no family history.

Research frontiers
A growing number of small studies are being published that examine the rising incidence of CRC among patients under age 50 years. It is becoming increasingly evident that the majority of these patients do not have a family history of CRC; however, it is unclear what predisposition these patients have to develop CRC at an earlier age. The research hotspot may be to perform genetic categorization of these tumors *via* microarray analysis to determine how they differ from sporadic CRC in older patients.

Innovations and breakthroughs
Previous studies in the literature that have examined the incidence of early-age onset CRC often include patients with hereditary, familial, and sporadic CRC's (see below). In the study, the authors excluded patients with a known genetic CRC predisposition or history of inflammatory bowel disease. The vast majority of patients under age 50 years in the study had no reported family history of CRC and did not meet criteria by family history for hereditary nonpolyposis colorecal cancer (HNPCC). Therefore, the authors believe the majority of patients in the study had early-age onset "sporadic" CRC similar to the general population.

Applications
The study corroborates the findings of several other studies evaluating early-age onset CRC in that the majority of patients have no family history of CRC and most tumors were found in the distal colon and rectum. This contradicts the

believe of many practioners that early-age onset CRC's are more often located in the proximal colon and are attributable to inherited predispositions (*i.e.*, hereditary non-polyposis colorectal cancer). The next logical step is to investigate what triggers the development of a "sporadic" CRC at a younger age of onset among some individuals.

Terminology

Familial CRC is defined as CRC that presents 10-20 years earlier than the general population with no clear inheritance pattern. It is presumed that lower-penetrance susceptibility genes may play a role. Hereditary CRC accounts for approximately 5%-10% of patients diagnosed with CRC. Examples include familial adenomatous polyposis syndrome and HNPCC (Lynch Syndrome), which show autosomal dominant inherited germline mutations. Tumors are often located in the proximal colon and can be synchronous or metachronous in nature. Sporadic CRC occurs in patients without identifiable genetic predispositions or a reported family history of CRC.

Peer review

This is a descriptive study in which the authors investigate the incidence of early-age onset CRC among two institutions. The results corroborate a growing body of literature that now suggests that most CRC's, regardless of age of onset, occur without a particular genetic or familial predisposition.

REFERENCES

1   **Greenlee RT**, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. *CA Cancer J Clin* 2000; **50**: 7-33 [PMID: 10735013]
2   **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; **62**: 10-29 [PMID: 22237781 DOI: 10.3322/caac.20138]
3   **Howlader N**, Noone AM, Krapcho M, Neyman N, Aminou R, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA. SEER Cancer Statistics Review, 1975-2009, National Cancer Institute. Bethesda, MD, 2012. Available from: URL: http://seer.cancer.gov/csr/1975_2010/
4   **Steele GD**. The National Cancer Data Base report on colorectal cancer. *Cancer* 1994; **74**: 1979-1989 [PMID: 8082105]
5   **Ries LAG**, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg LX, Edwards BK. SEER Cancer Statistics Review. 1973-1997, National Cancer Institute. NIH Pub. No. 00-2789. Bethesda, MD, 2000. Available from: URL: http://seer.cancer.gov/csr/1973_1997/
6   **Recalde M**, Holyoke ED, Elias EG. Carcinoma of the colon, rectum, and anal canal in young patients. *Surg Gynecol Obstet* 1974; **139**: 909-913 [PMID: 4421378]
7   **Sanfelippo PM**, Beahrs OH. Carcinoma of the colon in patients under forty years of age. *Surg Gynecol Obstet* 1974; **138**: 169-170 [PMID: 4810853]
8   **Simstein NL**, Kovalcik PJ, Cross GH. Colorectal carcinoma in patients less than 40 years old. *Dis Colon Rectum* 1978; **21**: 169-171 [PMID: 206417]
9   **Safford KL**, Spebar MJ, Rosenthal D. Review of colorectal cancer in patients under age 40 years. *Am J Surg* 1981; **142**: 767-769 [PMID: 6895579]
10   **Pitluk H**, Poticha SM. Carcinoma of the colon and rectum in patients less than 40 years of age. *Surg Gynecol Obstet* 1983; **157**: 335-337 [PMID: 6623323]
11   **Behbehani A**, Sakwa M, Ehrlichman R, Maguire P, Friedman S, Steele GD, Wilson RE. Colorectal carcinoma in patients under age 40. *Ann Surg* 1985; **202**: 610-614 [PMID: 4051610]
12   **Adloff M**, Arnaud JP, Schloegel M, Thibaud D, Bergamaschi R. Colorectal cancer in patients under 40 years of age. *Dis Colon Rectum* 1986; **29**: 322-325 [PMID: 3009108]
13   **Domergue J**, Ismail M, Astre C, Saint-Aubert B, Joyeux H, Solassol C, Pujol H. Colorectal carcinoma in patients younger than 40 years of age. Montpellier Cancer Institute experience with 78 patients. *Cancer* 1988; **61**: 835-840 [PMID: 3338041]
14   **Palmer ML**, Herrera L, Petrelli NJ. Colorectal adenocarcinoma in patients less than 40 years of age. *Dis Colon Rectum* 1991; **34**: 343-346 [PMID: 1706654]
15   **Fante R**, Benatti P, di Gregorio C, De Pietri S, Pedroni M, Tamassia MG, Percesepe A, Rossi G, Losi L, Roncucci L, Ponz de Leon M. Colorectal carcinoma in different age groups: a population-based investigation. *Am J Gastroenterol* 1997; **92**: 1505-1509 [PMID: 9317073]
16   **Sobin LH**, Gospodarowicz MK, Wittekind CH, editors. TNM classification of malignant tumors. 7th ed. Oxford: Wiley-Blackwell, 2009: 100-109
17   **Edge S**, Byrd D, Compton C, Fritz A, Frederick G, Trotti A, editors. AJCC Cancer Staging Manual. 7th ed. New York: Springer, 2009
18   **Peltomäki P**, Vasen HF. Mutations predisposing to hereditary nonpolyposis colorectal cancer: database and results of a collaborative study. The International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer. *Gastroenterology* 1997; **113**: 1146-1158 [PMID: 9322509]
19   **Winawer SJ**, Fletcher RH, Miller L, Godlee F, Stolar MH, Mulrow CD, Woolf SH, Glick SN, Ganiats TG, Bond JH, Rosen L, Zapka JG, Olsen SJ, Giardiello FM, Sisk JE, Van Antwerp R, Brown-Davis C, Marciniak DA, Mayer RJ. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology* 1997; **112**: 594-642 [PMID: 9024315]
20   **Chan KK**, Dassanayake B, Deen R, Wickramarachchi RE, Kumarage SK, Samita S, Deen KI. Young patients with colorectal cancer have poor survival in the first twenty months after operation and predictable survival in the medium and long-term: analysis of survival and prognostic markers. *World J Surg Oncol* 2010; **8**: 82 [PMID: 20840793 DOI: 10.1186/1477-7819-8-82]
21   **Parry BR**, Tan BK, Parry S, Goh HS. Colorectal cancer in the young adult. *Singapore Med J* 1995; **36**: 306-308 [PMID: 8553099]
22   **Minsky BD**. Clinicopathologic impact of colloid in colorectal carcinoma. *Dis Colon Rectum* 1990; **33**: 714-719 [PMID: 2165455]
23   **Qizilbash AH**. Pathologic studies in colorectal cancer. A guide to the surgical pathology examination of colorectal specimens and review of features of prognostic significance. *Pathol Annu* 1982; **17** (Pt 1): 1-46 [PMID: 6289231]
24   **Corman ML**. Colon & Rectal Surgery. 4th ed. Philadelphia: Lippincott-Raven Publishers, 1998: 702
25   **Winawer S**, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, Ganiats T, Levin T, Woolf S, Johnson D, Kirk L, Litin S, Simmang C. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. *Gastroenterology* 2003; **124**: 544-560 [PMID: 12557158 DOI: 10.1016/S0140-6736(10)60551-X]
26   **Atkin WS**, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, Parkin DM, Wardle J, Duffy SW, Cuzick J. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* 2010; **375**: 1624-1633 [PMID: 20430429 DOI: 10.1016/S0140-6736(10)60551-X]