Left-Sided Dominance of Early-Onset Colorectal Cancers: A Rationale for Screening Flexible Sigmoidoscopy in the Young

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BACKGROUND: National databases show a recent significant increase in the incidence of colorectal cancer in people younger than 50. With current recommendations to begin average-risk screening at age 50, these patients do not have the opportunity to be screened. We hypothesized that most of the cancers among the young would be left sided, which would create an opportunity for screening the young by flexible sigmoidoscopy.

OBJECTIVE: This study aims to analyze the anatomic distribution of sporadic colorectal cancers in patients under the age of 50.

DESIGN: This is a retrospective review of a prospectively maintained database.

SETTING: This study was conducted at a single high-volume tertiary referral center.

PATIENTS: Patients under the age of 50 with colorectal cancer between the years 2000 and 2016 were included. Patients with IBD, familial adenomatous polyposis, Lynch syndrome, or hereditary nonpolyposis colorectal cancer were excluded.

MAIN OUTCOME MEASURES: The primary outcomes measured were tumor location and stage, demographics, and family history.

RESULTS: A total of 739 patients were included. Age range at diagnosis was 18 to 49 years; median age was 44 years. Five hundred thirty patients were between the ages of 40 and 49, 167 were between the ages of 30 and 39, 40 were between the ages of 20 and 29, and 2 were under 20. Two hundred thirty-one patients (32%) had a family history of colorectal cancer. The anatomic distribution of the cancers was: 485 rectum (65%), 107 sigmoid colon (15%), 19 descending colon (3%), and 128 right colon and transverse colon (17%). Therefore, 83% of the tumors were theoretically within the range of flexible sigmoidoscopy.

LIMITATIONS: Referral bias favors rectal cancer.

CONCLUSION: The combination of an increasing incidence of colorectal cancer in those under 50 years of age and the predominance of left-sided cancer suggests that screening by flexible sigmoidoscopy starting at age 40 in average-risk individuals may prevent cancer by finding asymptomatic lesions. See **Video Abstract** at http://links.lww.com/DCR/A579.

KEY WORDS: Colonoscopy; Colorectal cancer; Screening; Tumor location, Young patients.

In the United States, the overall incidence of colorectal cancer (CRC) continues to decline, but the situation with patients under the age of 50 is different. Recent population studies and national databases show a significant increase in the incidence of CRC in patients under the age of 50 occurring over the past 2 decades.[1–3] The national Surveillance, Epidemiology, and End Results (SEER) data reveal increased incidence of CRC in all 5-year age groups between 20 and 49 years, with the sharpest increase among the those aged 40 to 44 years (10.7 cases per 100,000 in 1988 and 17.9 per 100,000 in 2006).[4] A national cancer database study that includes 70% of all cancers annually in the United States has shown that

the age-adjusted incidence of CRC has declined among people over the age of 50 since 2001 (annual percentage change, –2.5%; 95% CI, –3% to –2%), whereas it has consistently increased for patients under 50 (annual percentage change, 2.1%; 95% CI, 1.1% to 3.1%).[5]

The overall decline in the incidence of CRC in this country is attributed largely to the increased use and effectiveness of CRC screening, which has been recommended for all adults older than 50 since 1996.[6] There have not been any convincing reasons proposed for the increase of CRC in the young, and, without an explanation for the phenomenon, it is hard to design a strategy to counter it: yet something needs to be done. We thought that a limited screening program might be offered to take advantage of differences in the biology of cancers found in the young.

Single-institution and population-based studies have suggested that early-onset CRC occurs more often within the left colon and the rectum than later-onset tumors.[7–11] A molecular explanation for this can be found in studies from our group that have shown that approximately 23% of all CRCs are associated with hypermethylation of the promoter region of tumor suppressor genes; so-called CIMP cancers (CpG Island Methylator Phenotype). These methylator cancers are almost always right sided, as is their precursor, the sessile serrated adenoma/polyp .[12,13] Because DNA methylation in colonocytes is an age-related phenomenon, we hypothesized that methylator cancers would be uncommon in young patients, and that therefore the anatomic distribution of CRCs and their precursor polyps in the young should be mostly left sided. Were this to be true, it would create an opportunity for screening the young by flexible sigmoidoscopy. The purpose of this study was to test our hypothesis by analyzing the anatomic distribution of sporadic CRCs in patients under the age of 50 in a large contemporary single-institution cohort. This would be the basis for suggestions regarding screening options, and, more specifically, what proportion of cancers will be detectable by flexible sigmoidoscopy.

MATERIALS AND METHODS

Patients with CRC under the age of 50 between the years 2000 and 2016 were identified from a single-institution (Cleveland Clinic, Cleveland, OH), institutional review board-approved, CRC surgery database. Patients routinely are asked to sign an informed consent for collection of their data and tumor tissues before enrollment in the database. The data extracted for this study included patient demographics, date of surgery, location of the tumor, family history of CRC, and personal history of IBD, and/or hereditary CRC syndromes such as familial adenomatous polyposis, Lynch syndrome, and hereditary nonpolyposis CRC. Family history is recorded in the electronic medical record and this was reviewed in each case. Lynch syndrome is defined by the presence of a deleterious mutation

in a DNA mismatch repair gene. Hereditary nonpolyposis CRC is defined as an Amsterdam compliant family history. Patient symptoms or reasons for referral were not an end point of the study.

Cancers were staged according to the TNM classification system used by the American Joint Committee on Cancer.[14] Patients with IBD, or any known hereditary CRC syndrome, were excluded from the analysis. For the purpose of this study, right colon was defined as from the splenic flexure to the cecum.

Statistics

We used the Pearson product-moment correlation test to assess the correlation between CRC incidence and age. The Pearson χ^2 test was used to compare patients with and without a family history of CRC.

RESULTS

A total of 2948 patients were diagnosed with a primary CRC between 2000 and 2016. This excludes patients with recurrent or metastatic cancer and carcinoma in situ. Among these patients were 837 with CRC diagnosed under the age of 50 (28.4%). We excluded 55 patients with IBD, 24 with familial adenomatous polyposis, and 24 with Lynch syndrome. Of the remaining 734 patients who make up the current study group, 330 (45%) were female. The age range at diagnosis was 18 to 49 years with a median age of 44, and mean age of 42. The incidence of CRC was significantly correlated with age ($R = 0.95$). Most patients were diagnosed between the ages of 40 and 49 (524, 71%); 162 patients were diagnosed between the ages of 30 and 39 (22%), 48 patients were diagnosed between the ages of 20 and 29 (7%), and 2 patients were diagnosed under 20 years old (Fig. 1). There was a family history of CRC in 230 patients (32%). The anatomic distribution of the cancers was as follows: 484 rectum (66%), 105 sigmoid colon (14%), 19 descending colon (3%), and 126 right and transverse colon (17%). Therefore, 80% of the tumors, or the polyps preceding them, were theoretically within the range of flexible sigmoidoscopy (rectum and sigmoid) with another 3% in the descending colon possibly reachable. A similar anatomic distribution was seen in all subgroups of age at diagnosis (Fig. 2) and in patients with or without a family history of CRC (Fig. 3) ($p = 0.27$).

According to pathology results and imaging, 166 (24%) of the cancers were stage 1, 142 (20%) were stage 2, 253 (36%) were stage 3, and 133 (20%) were stage 4. Hence, 56% of the cancers were advanced at the time of diagnosis.

DISCUSSION

Our findings confirm our hypothesis that the majority of CRC cases in young patients under the age of 50 are lo-

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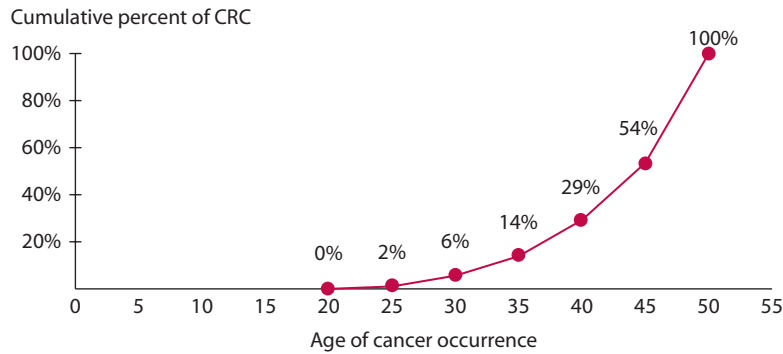
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Cumulative percent of CRC

FIGURE 1. Cumulative occurrence of colorectal cancer by age among study group showing that 71% of cases were diagnosed between the ages of 40 and 50 years. CRC = colorectal cancer.

cated on the left side of the large bowel. Specifically, 80% to 83% of those tumors were theoretically within the reach of a flexible sigmoidoscopy (rectum and sigmoid, +/− descending colon). As expected, the incidence of CRC rose with age, and 56% of the cases were diagnosed at an advanced stage (stage 3 or 4). This is consistent with either more aggressive biology in these patients, or a delay in diagnosis, or both.

Our study represents the largest single-institution cohort to date of CRC under the age of 50. Our results stand in line with results from previous studies, confirming that left-sided dominance and diagnosis at a relatively advanced stage are typical of CRC among patients under the age of 50. Myers et al,[9] in a study from New York, analyzed 180 patients with CRC under the age of 50 and reported that 77% of the tumors were distal to the splenic flexure.

They also noted that 53% of the patients had stage 3 or 4 disease at diagnosis. A study from Germany by Schellerer et al[11] reported on 244 patients with CRC under the age of 50, finding that 75% of the tumors were potentially diagnosable by proctosigmoidoscopy. If the cancers are left sided, then their precursor polyps are left sided. The interval from polyp to cancer in young patients is not known, but may be accelerated compared with the interval in older patients. However, because screening endoscopy will detect both polyp and cancer, cancers could be prevented.

Our study has several limitations. We have not provided data on the race of the patients. This may be significant, because previous studies have shown that black patients are overrepresented in studies of young CRC.[15,16] There is also a suggestion that black individuals should have average-risk colonoscopy screening beginning at age 45 because evidence suggests an earlier onset of cancer in this group. We do not know if the distribution of the cancers differs by ethnicity, but our final recommendation would include both black and white populations. Second, this is a retrospective study, although the data were collected prospectively and represent consecutive patients with apparently sporadic cancer. Other than the exclusion criteria already stated, no patient was excluded from data collection. Third, we did not use a control group of patients with CRC over the age of 50, although we have published quite extensively on our overall cancer experience. Finally, our institution serves as a national referral center and possibly sees a biased pattern of cancers where rectal cancer predominates. This is reflected in the high proportion of young patients seen at the Cleveland Clinic compared with the proportion seen in the general population. To the extent that it is true, it will overestimate the number of cancers that are findable by flexible sigmoidoscopy. However, the close agreement between our study and those of others in terms of cancer distribution reinforces the legitimacy of our data. We have unpublished data that describe a significant decrease in the average age of patients presenting to us with rectal cancer over the years since 1983 (Church, unpublished data) but have not seen this phenomenon in patients with colon can-
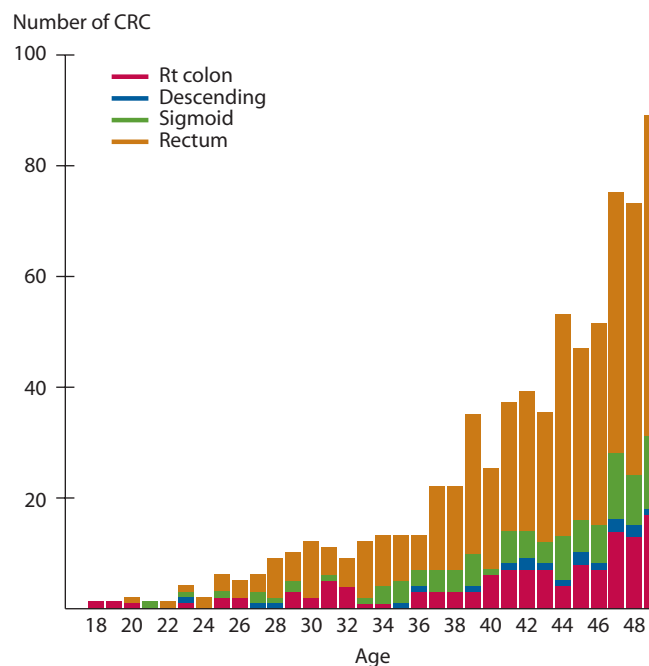
Number of CRC

FIGURE 2. Anatomic distribution of CRC according to age at diagnosis, showing no significant difference between age groups in the proportion of left-sided cancers ($p = 0.44$). CRC = colorectal cancer; rt = right.
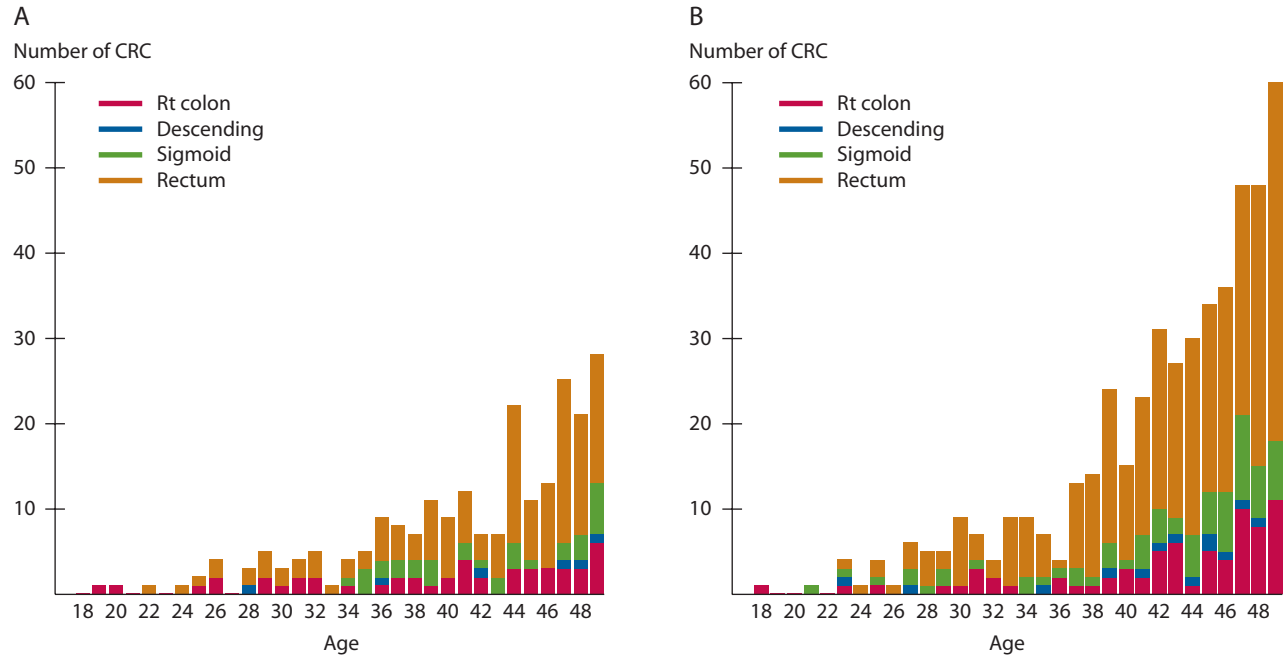
FIGURE 3. Anatomic distribution of CRC according to age in patients with a family history of CRC (A) and patients without family history of CRC (B), showing no significant difference in the proportion of left-sided cancers between the 2 groups ($p = 0.272$). CRC = colorectal cancer; rt = right.

cer. However, we have referred to national databases as a complementary tool for assessing the actual prevalence of CRC in patients under the age of 50.[1,2,4]

Current CRC screening guidelines for average-risk individuals in the United States call for screening to begin at the age of 50 years. These include the latest versions of recommendations by the US Multi Society Task Force on Colorectal Cancer (USMSTF), the US Preventive Services Task Force, and the American College of Gastroenterology.[17–19] The recommendation is based on studies showing that 90% of sporadic CRCs are diagnosed in people aged 50 or older. The USMSTF has addressed the increasing incidence of CRC in people under the age 50 by a call for "thorough diagnostic evaluation" in cases with "suspected rectal bleeding." We feel this is an insufficient response to the challenge. Certainly rectal bleeding or other unusual and significant symptoms (abdominal pain, change in bowel habit) in young people are indications for colonoscopy without delay, but, in view of the dramatic rise in incidence of CRC in patients under the age of 50, and the tendency toward advanced stage of disease in the young, we believe there is a case to consider for revising the current screening guidelines. Some of the Society guidelines already mentioned call for earlier colonoscopy screening when the patient is an average-risk black individual (age 45),[17,18] or when there is a family history of advanced colorectal neoplasia (advanced adenoma or cancer) in a relative under the age of 60. In this case, both the American College of Gastroenterology and USMSTF recommend screening of relatives with colonoscopy starting 10 years before the age at which the youngest affected relative

was diagnosed, or age 40, whichever is younger. In fact, USMSTF recommends screening at age 40 even for those with a first-degree relative affected above age 60.[18] The US Preventive Services Task Force examines the effect of starting average-risk screening for all at age 45, with models showing a modest benefit in life years gained, at the cost of an increased number of lifetime colonoscopies.

Family history is obviously a key risk factor in determining age to start screening. In a previous smaller study, we showed that about 40% of patients with CRC diagnosed under age 50 have some sort of explanation for the young age of onset.[20] In this study, we excluded 103 patients with IBD (55/837 (6.6%)), familial adenomatous polyposis coli or Lynch syndrome (48/837 (5.7%)). However, of the remaining 734 patients, 230 (32%) had a positive family history. This is a high percentage and indicates family history as a significant risk factor in young patients. We do not have details of the family history in these patients, but our data agree with the recommendations of the USMSTF that any positive family history of CRC (especially with a first-degree relative) should be an indication for starting screening by the age of 40.

The current options for screening average-risk patients are: occult blood testing (hemoccult sense, fecal immunochemical testing), fecal DNA testing, colonoscopy, flexible sigmoidoscopy, and virtual colonoscopy. Although fecal testing is noninvasive, relatively cheap, reasonably sensitive for cancer, and capable of preventing cancer-related deaths, it is not effective in absolutely preventing cancer by discovering premalignant polyps. A possible exception is fecal DNA testing which has a sensitivity of 69%

for adenomas with high-grade dysplasia and 42% for sessile serrated adenoma/polyp.[21] Future possibilities include enhanced fecal DNA testing and liquid biopsy techniques that would diagnose malignant or premalignant lesions with high sensitivity and would allow colonoscopy to be more efficiently targeted. Such tests would make endoscopic screening obsolete, but they are not yet available. Right now, endoscopy can routinely diagnose polyps and cancers and is the only test that can also remove the premalignant lesion.

There is extensive literature to support flexible sigmoidoscopy screening for CRC,[22–25] showing that flexible sigmoidoscopy reduces deaths from left-sided cancers. The reason that it is unpopular for general CRC screening is that it fails to prevent deaths from right-sided CRCs,[26] a reason that we have shown is much less compelling in the young (<50 years old). Performing any sort of colorectal endoscopy for colon cancer screening in the United States is a daunting prospect, because the vast numbers of patients and the limited resources make this logistically and financially problematic. However, these issues have not stopped screening colonoscopy from being performed in millions of patients across the country. Adding flexible sigmoidoscopy screening for people over 40 could make an impact on the "young" CRCs, with a much lower cost than that of colonoscopy. Of course, it would be better to understand the reason for the increasing incidence of CRC in the young and to target interventions based on this understanding, but as yet there is no such ability. The best that can be done is to insist that symptoms suggestive of CRC, such as rectal bleeding, a permanent change in bowel habits, and unexplained abdominal pain, be investigated aggressively. This is, however, akin to closing the stable door after the horse has left the barn.

Colonoscopy is not the right screening tool for the young, because it is relatively expensive, requires prolonged bowel preparation, and poses some risk. In addition, there are neither the resources nor the logistical ability to screen the millions of patients that expanded age guidelines would mean. However, flexible sigmoidoscopy, a safe procedure well tolerated by patients without prolonged bowel preparation or sedation, has the potential to diagnose the majority of colorectal neoplasms among patients under the age of 50. Therefore, we propose that people turning 40 be offered a flexible sigmoidoscopy, with 2 sodium phosphate enemas as a preparation. There are many primary care physicians who are already trained to perform such an examination, and there is the possibility that other allied health professionals can also be used. Flexible sigmoidoscopy can be done at relatively low cost and with little discomfort in most patients. Arguments against the test include its discomfort and lack of ability to traverse the sigmoid colon. However, both of these problems are related to the increasing effects of diverticulosis and sigmoid sensitivity found with advancing age or pelvic adhesions. Flexible sigmoidoscopy in young patients is likely to be easier and more comfortable than series published from other cohorts that include all age groups. Potential adverse effects from flexible sigmoidoscopy include perforation and bleeding, but a recent review by the US Preventive Services Task Force shows these risks to be extremely low (1 perforation (95% CI, 0.4–14) and 2 major bleeds (95% CI, 1–4) per 10,000 examinations).[27] A finding of adenomas would prompt colonoscopy. Isolated hyperplastic polyps could be biopsied and ignored, but multiple (>5) hyperplastic polyps should also prompt colonoscopy.

CONCLUSIONS

We propose that, based on the predominant left-sided distribution of CRC in people under the age 50, the significant increase in the incidence of cancer in this age group, and the proportion of patients with "young" age-of-onset cancers that are diagnosed between ages 40 and 49, that everyone should be offered a flexible sigmoidoscopy when they turn 40. If this is negative then another examination is offered at age 45. At age 50, screening colonoscopy is recommended. Rectal bleeding is always an indication for colonoscopy, and any family history of CRC is an absolute indication for flexible sigmoidoscopy between ages 40 and 45. If at least 1 relative is first degree (parent, sibling, child), a full colonoscopy is offered when the screening is 10 years younger than the youngest affected relative, or age 40 (whichever is younger). We suggest that prospective studies be planned to assess the yield of such a screening program.

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