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Original Article

Prevalence of colorectal cancer in young patients with isolated bright red blood per rectum (BRBPR)

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Abstract: Purpose: Guidelines for evaluation of isolated bright red blood per rectum (BRBPR) in young patients vary widely and often cite only expert consensus. The rising incidence of CRC in young patients, along with the severity of the diagnosis often compel further evaluation, even though the exact incidence of CRC in this age group is not well known. We conducted a systematic review and pooled prevalence estimate of CRC in this population as an aid to clinical decision-making. Methods: We performed a systematic PubMed search using keywords including hematochezia, colonoscopy, young, and cancer. Articles were reviewed for topic relevance, subject age less than 50, isolated BRBPR, and report of CRC prevalence stratified by age. Study results were combined, pooled by age group, and analyzed for prevalence of CRC on colonoscopy or sigmoidoscopy, and, if reported, the location of the lesion. Results: Twelve studies were identified comprising 4,805 subjects. The prevalence of CRC in patients under 30, 30-39, and 40-49 was 0.72%, 1.45%, and 2.00%, respectively. Combining all age groups under 40 years, CRC prevalence was 1.29%. There were no significant differences in CRC prevalence or in lesion location between any pooled age groups. A non-significant trend of lower CRC prevalence in younger age groups was observed, as was a trend toward younger patients having more distal lesions. Conclusions: Current evidence supports a lower suspicion for CRC in younger patients with isolated BRBPR. The low absolute prevalence of CRC in patients <50 years of age should be considered when determining whether an endoscopic evaluation should be performed.

Keywords: Colorectal cancer, young patients, BRBPR

Introduction

Rectal bleeding in otherwise asymptomatic young patients is commonly encountered in clinical practice. A study of white adults living in a community in Minnesota found that 15% of adults age 20-64 years experienced rectal bleeding over the prior year, with a significantly higher prevalence in young compared to older adults [1]. A separate study of general practices in the UK estimated the consultation rate for rectal bleeding to be 1.5% per year in patients over 34 years old [2]. The differential diagnosis of isolated BRBPR is large and includes benign polyps, colorectal cancer (CRC), anal cancer, inflammatory bowel disease (IBD), hemorrhoids, angiodysplasia, diverticula, and anal fissure. A full history and clinical examination including digital rectal exam and anoscopy is warranted in all patients. However, the need for more extensive visualization of the large bowel to rule out CRC, a rare but serious diagnosis in young patients, remains unclear and controversial.

Clinical guidelines vary widely by specialty and are often heavily dependent on expert consensus [3-6]. Guidelines universally recommend a consideration of “alarm symptoms” suggestive of colorectal cancer, risk factors including family history, and a clinical evaluation for iron deficiency anemia, weight loss, other change in bowel habits, and abdominal pain or mass. Though the American Academy of Family Physicians (AAFP) has not published clinical guidelines specifically addressing this subject, the family medicine literature generally recommends considering the patient’s individual risk profile and results of any prior colonoscopies, with further visualization more strongly encouraged for patients over the age of 40 [6, 7].

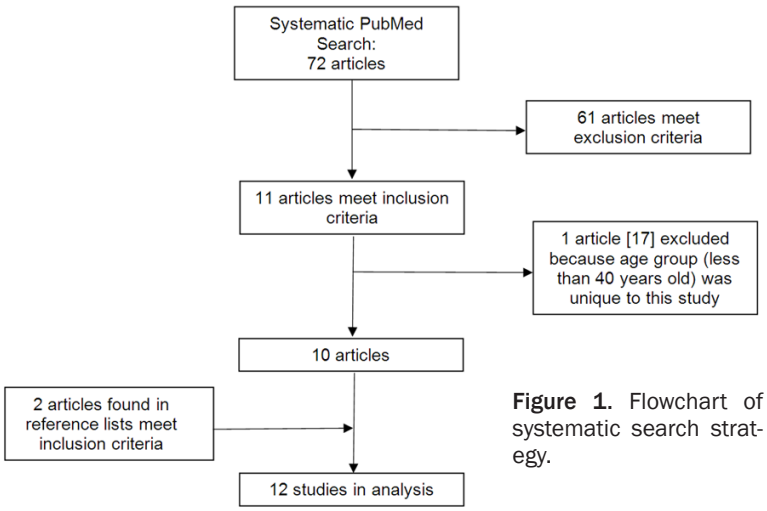

Figure 1. Flowchart of systematic search strategy.

Point of care risk stratification of individual patients depends on a variety of factors, including the prevalence of CRC in the patient's age group. Numerous smaller retrospective studies have evaluated the prevalence of CRC in young patients referred to colonoscopy for isolated BRBPR. However, clinical guidelines offer disparate recommendations, often with low quality supporting evidence [3-5]. We conducted a systematic literature review and pooled prevalence estimate of CRC in this population as an aid to clinical decision-making.

Methods

Search strategy

A systematic review was performed with the aim of identifying the prevalence of CRC as determined by direct colonic visualization in young patients with isolated BRBPR. We searched PubMed for original research using the following term: colonoscopy OR sigmoidoscopy AND [((blood rectum) OR hematochezia) AND cancer young]. This search yielded 72 articles (**Figure 1**). Reference lists of included studies were systemically searched, and cited studies were included if they met the inclusion criteria and had not otherwise been identified by the PubMed search.

Inclusion criteria

Articles were included if the research was original, study subjects were less than 50 years old, presenting symptoms were isolated rectal bleeding without other symptoms or red flags (i.e., anemia, weight loss, extensive family history of CRC), successful visualization of the colon either by colonoscopy or sigmoidoscopy, and report of CRC prevalence stratified by age group.

Exclusion criteria

Articles were excluded if the topic was not relevant (by evaluation of title, abstract, or manuscript body), the study represented results found in an included article, symptoms were present beyond rectal bleeding at presentation, prevalence estimates were not stratified by a comparable age group, and if the sample of patients who underwent colonoscopy/sigmoidoscopy was selected by factors other than the isolated presence of BRBPR. Articles not in English or Spanish were excluded. After exclusion, 12 studies were selected (**Table 1**; **Figure 1**). 10 of these studies were identified from the systematic PubMed search, and 2 were identified from included study reference lists.

Case definition

A case of colorectal cancer (CRC) was defined as: biopsy with pathology confirming colorectal cancer from a specimen obtained during initial colonic visualization after referral for colonoscopy. Patients with all other findings (including adenomas and polyps) were placed in the non-CRC category in the present analysis.

Data extraction

The following study-specific data were extracted: specified presenting symptoms required for inclusion/exclusion, age group, method of colon visualization, study population size, number with CRC confirmed on biopsy, number with no CRC, location of CRC (distal or proximal; proximal defined as proximal to the splenic flexure and distal defined as distal to the splenic flexure), study time period, and study location.

Statistical analysis

Study results were combined and pooled by age group (age groups were determined by the

Table 1. Characteristics of studies meeting inclusion criteria

Study	Setting	Population	Intervention	Symptoms	Sample Size	Gender
Williamson et al 2015 [8]	Australia, tertiary care center	Women <30 yo	Colonoscopy	BRBPR, no anemia, no FH	1/48 (no location)	48 female
Khalid et al 2011 [9]	Pakistan, tertiary care center	<40 yo	Colonoscopy	BRBPR, asx, neg FH, no anemia	4/248 (4 distal)	257 male, 122 female
		40-50 yo			5/131 (5 distal)	
Nikpour and Asgari 2008 [10]	Iran, tertiary care center	<40 yo	Colonoscopy	BRBPR, asx, neg FN, no anemia	4/177 (4 distal)	Unknown
		<40 yo who declined colonoscopy	Flex sig		0/94	41 male, 53 female
Acosta et al 1994 [11]	USA, Naval Medical Center	<40 yo	Colonoscopy	Isolated BRBPR	1/280	Unknown
Helfand et al 1997 [12]	USA; VA health system	<50 yo	Rigid sig	BRBPR on ROS	0/58	Unknown
Spinzi et al 2007 [13]	Italy, 14 open-access endoscopy depts	30-40 yo	Colonoscopy	BRBPR, neg FH, no anemia, no weight loss	2/312 (2 distal)	198 male, 114 female
		40-50 yo			2/310 (1 distal, 1 prox)	192 male, 118 female
Eckardt et al 2002 [14]	Germany, community endoscopy referral dept	<40 yo	Colonoscopy	Scant BRBPR	3/89 (all distal)	Unknown
Manzotti et al 2013 [15]	Argentina, urban outpatient endoscopy unit	<50 yo	Colonoscopy	BRBPR, not high risk CRC	19/1203 (all distal)	614 male, 589 female
Liou et al 2007 [16]	Taiwan, University open-access colonoscopy referral dept	<30 yo	Colonoscopy	Rectal bleeding; neg FH	1/96 (1 distal)	333 male, 217 female
		30-39 yo			8/199 (1 prox)	
		40-49 yo			12/255 (1 prox)	
Carlo et al 2006 [17]*	Italy, University open-access endoscopy dept	<45 yo	Colonoscopy	Hematochezia, no blood mixed w/ stool, no FH	0/180	Unknown
Wong et al 2004 [18]	USA, tertiary care center and VA health system	<50 yo	Colonoscopy	BRBPR, no FH, weight loss, h/o CRC, colitis	4/223 (all distal)	Unknown
Mulcahy et al 2002 [19]	USA, tertiary care centers, military health center, VA health system	<40 yo	Colonoscopy	Hematochezia, no other abd sx	2/165 (2 distal)	Unknown
		40-49 yo			6/347 (3 distal, 3 isolated prox)	
Lewis et al 2001 [20]	USA, tertiary care center	<30 yo	Flex sig (59%) or colonoscopy (41%)	Hematochezia	0/133	261 male, 309 female
		30-39 yo			0/181	
		40-49 yo			1/256	

*Carlo et al 2006 [14] was not included in the pooled analysis because the age group <45 years old was unique to this study. All other studies in this table were included in the pooled analysis. Gender is included in this table when reported by the original study.

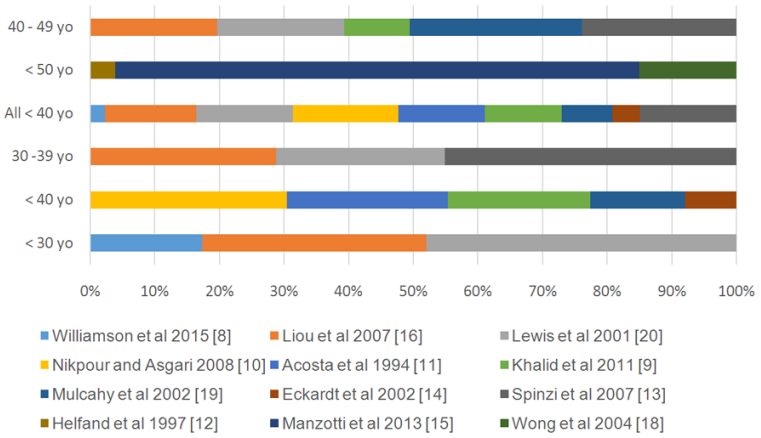

Figure 2. The proportion of subjects drawn from each study by pooled age groups.

Table 2. Prevalence of CRC in pooled age groups. 95% CI calculated by Wilson procedure with continuity correction

Age group	CRC prevalence (95% CI)	n (CRC)	Location	Number of studies
< 30 yo	0.72 (0.12-2.87)	277 (2)	1 distal 1 unknown	3
< 40 yo	1.33 (0.76-2.28)	1053 (14)	13 distal 1 unknown	5
30-39 yo	1.45 (0.74-2.74)	692 (10)	9 distal 1 proximal	3
All <40 yo	1.29 (0.86-1.91)	2022 (26)	23 distal 1 proximal 2 unknown	9
<50 yo	1.56 (1.01-2.36)	1484 (23)	23 distal	3
40-49 yo	2.00 (1.34-2.96)	1299 (26)	20 distal 5 proximal 1 unknown	5

presentation of the data in the original study; all studies presented pooled results with age group as a categorical variable rather than individual subject age as a discrete variable). The prevalence of CRC on colonoscopy or sigmoidoscopy, and, if reported, the location of the lesion, were reported by age group. 95% Confidence Intervals for prevalence were calculated by Wilson procedure with continuity correction. Chi-square and Fisher's Exact were used when appropriate. Alpha was set at 0.05.

Results

Characteristics of included studies

Thirteen relevant studies with appropriately reported data were identified, comprising a total of 4,985 subjects (**Table 1**). An Italian study [17] with 180 subjects was excluded as the sole age category was <45 years old, a category found in no other study (0 of 180 subjects had CRC in this study). Therefore, 4,805 subjects from 12 studies were similarly age categorized to facilitate comparison and were thus included in the pooled analyses (**Figure 1**).

The studies all analyzed outcomes of colonoscopies completed for initial evaluation of isolated BRBPR. Though studies had various long-term follow-up, the present analysis concerns only the outcome of the immediate work-up following initial identification of isolated BRBPR. Most endoscopy units were described as "open-access", indicating that colonoscopies were performed after referral from primary care clinicians without additional pre-screening.

The largest study [15], conducted in Argentina, had 1,203 subjects, 25% of the pooled total. The largest 4 studies had a combined 2,887 subjects, 60% of the total [13, 15, 16, 19]. Though these large studies comprised the majority of the pooled subjects, no age group aside from the <50 years old age group, where 81% of subjects were from the large Argentina study [15], was dominated by a single study (**Figure 2**). The large study conducted in Argentina was accessible only as an abstract, though it was included in the analysis as the abstract contained the data necessary for the pooled prevalence estimates. The selected studies were all retrospective reviews of consecutive colonoscopies, and consequently the clinical decision to refer for colonoscopy was not standardized. Rather, the studies collected data from medical records or standard questionnaires completed at the time of the colonoscopy or sigmoidoscopy.

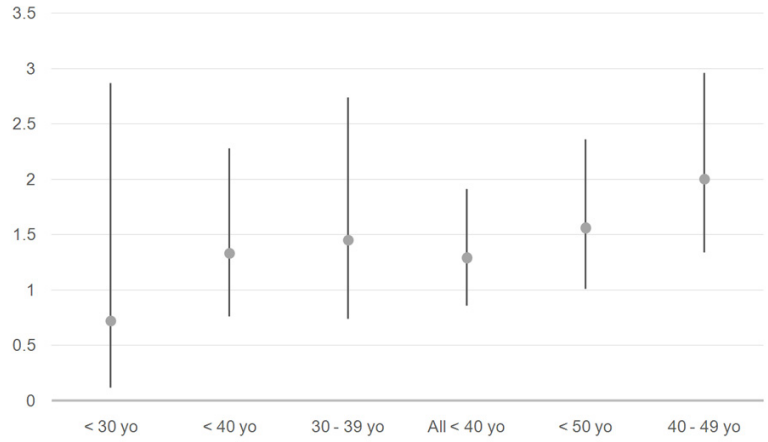

Figure 3. Forest plot of pooled prevalence estimates with 95% Confidence Intervals calculated by Wilson procedure with continuity correction.

Demographics of the pooled study subjects

Because the included studies variably reported demographic data, and individual level data was not available, demographic variable availability was limited beyond age group designation. For the 72% of pooled subjects whose study reported gender (6 of 12 studies reported gender), 45% were female and 55% were male.

34% (1,643/4,805) of subjects were in studies conducted in the USA, 15% (711/4,805) of subjects were in studies in European countries, and 14% of subjects (650/4,805) were enrolled in studies conducted in Iran or Pakistan. One study [12] was conducted in the Veterans Health Administration and included 58 subjects, 3% of the USA total.

Of the pooled study subjects, 95.2% (4,575/4,805) underwent colonoscopy, 3.6% flexible sigmoidoscopy (172/4,805; two studies reported flexible sigmoidoscopy if the patient deferred colonoscopy), and 1.2% rigid sigmoidoscopy (58/4,805; one study reported only rigid sigmoidoscopy).

Each study reported results by age groups (**Table 2**). As individual level data was not available, results were pooled only when age group definitions were identical. Therefore, age categories were determined by the source studies. The following unique age categories were therefore utilized, based on how they were reported in the individual studies: <30 yo, 30-39 yo, <40 yo, 40-49 yo, and <50 yo (**Table 2**). A composite age group for all <40 yo (comprising all subjects in previously mentioned <30 yo, 30-39 yo, and <40 yo categories) was also used.

In three studies, patients were evaluated in a group that was less than 30 years of age, which comprised 5.8% (277/4,805) of the subjects. In three studies, patients were evaluated in a group that was 30-39 years old, and this comprised 14.4% (692/4,805) of the subjects. In five studies, subjects were evaluated as a group that was less than 40 years of age, which comprised 22.0% (1053/4,805) of the subjects. All studies that evaluated subjects aged less than 40 years old were pooled in a combined group known as “all <40 years old”. This combined group comprising 42.1% of the subjects (2022/4,805). In five studies, patients were evaluated in a group that was 40-49 years old, which comprised 27.0% (1,299/4,805) of the subjects. In three studies, patients were evaluated in a group that was less than 50 years of age, which comprised 30.9% (1,484/4,805) of the subjects.

Pooled prevalence estimates

There were no significant differences in CRC prevalence between any pooled age groups (**Table 2**). There was a moderate trend of higher CRC prevalence in older age groups (**Figure 3**). Patients under 30 years old had 0.72% prevalence of CRC (2/277). Patients age 30-39 had 1.45% prevalence of CRC (10/692). For combined all age groups under 40 years old, CRC prevalence was 1.29% (2/2,022). Patients with an age between 40-49 years had CRC prevalence 2.00% (26/1,299).

Location of lesions

There was no significant difference in CRC lesion location between any pooled age groups, though there was a trend toward more proximal lesions in older age groups (**Table 2**). In the combined “all subjects under 40 years old” group there were 26 total CRC lesions: 23 distal, 1 proximal, and 2 of unreported location.

This increased in the 40-49 year old age group: 20 distal lesions, 5 proximal lesions, and 1 lesion of unreported location.

Discussion

This pooled analysis did not reveal any significant difference in CRC prevalence by age group in patients under 50 years old presenting with isolated BRBPR. Moreover, no differences were noted by location of lesions within the colon. A slight and non-significant trend of lower CRC prevalence in younger age groups was observed, as was a trend toward younger patients having more distal lesions. Though the width of the Confidence Intervals may elicit concern that this analysis is underpowered, we deferred a post-hoc power analysis given concerns of accuracy and utility [21]. The low absolute prevalence of CRC in younger patients presenting with isolated BRBPR (close to 1%) may encourage clinicians to initially manage this clinical situation more conservatively, especially if lesions suspicious for bleeding are found on rectal exam or anoscopy.

The main limitation in the present study, aside from heterogeneity of source study methods and case definitions, is the likely sampling bias introduced by the clinical decision to refer to colonoscopy, which was a non-uniform inclusion criteria. However, this likely biases our study toward a higher prevalence of CRC given that clinicians are more likely to refer to colonoscopy and encourage patients to follow through if they are more concerned for cancer due to informal or formal risk stratification during the clinical encounter. Finally, about 4% of subjects in the study were visualized by rigid or flexible sigmoidoscopy. In those patients, CRC prevalence was likely underestimated due to the possibility of missed proximal lesions. Generalizability may be affected by the international composition of the studies included. Differing standards of care and healthcare capacity between countries may bias the subset of the population eligible for colonoscopy services and therefore for study inclusion. Also, we were not able to determine how many of these young patients who were diagnosed with colorectal cancer had a sporadic vs. hereditary form.

It is important to remember that this study addresses CRC prevalence and does not reflect morbidity or mortality avoided due to colonic visualization. These results also do not take into account the work-up of the wide range of etiologies of BRBPR. It is also not known whether other colon conditions, such as the presence of benign polyps, colitis, inflammatory bowel disease or diverticular disease, were identified at the time of colonoscopy and may have impacted patient care beyond the identification of CRC.

Our study demonstrates that in patients younger than 50 years of age with isolated BRBPR, the incidence of finding CRC is low (1.29% in all patients under 40 years of age, 2% in patients between the ages of 40-49). While our findings do not suggest a need for routine colonoscopy in all young patients presenting with isolated BRBPR, the risk of CRC does remain and should not be ignored, particularly if other risk factors or symptoms exist. A proper history and physical exam, including a digital rectal exam and anoscopy must be performed. The results of this study should aid in the shared decision-making that occurs between providers and young patients with isolated BRBPR, on whether to proceed with an endoscopic evaluation for CRC.

Disclosure of conflict of interest

None.

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