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Article

Red-flag signs and symptoms for earlier diagnosis of early-onset colorectal cancer

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Abstract

Background: Prompt detection of colorectal cancer (CRC) among individuals younger than age 50 years (early-onset CRC) is a clinical priority because of its alarming rise.

Methods: We conducted a matched case-control study of 5075 incident early-onset CRC among US commercial insurance beneficiaries (113 million adults aged 18-64 years) with 2 or more years of continuous enrollment (2006-2015) to identify red-flag signs and symptoms between 3 months to 2 years before the index date among 17 prespecified signs and symptoms. We assessed diagnostic intervals according to the presence of these signs and symptoms before and within 3 months of diagnosis.

Results: Between 3 months and 2 years before the index date, 4 red-flag signs and symptoms (abdominal pain, rectal bleeding, diarrhea, and iron deficiency anemia) were associated with an increased risk of early-onset CRC, with odds ratios (ORs) ranging from 1.34 to 5.13. Having 1, 2, or at least 3 of these signs and symptoms were associated with a 1.94-fold (95% confidence interval [CI] = 1.76 to 2.14), 3.59-fold (95% CI = 2.89 to 4.44), and 6.52-fold (95% CI = 3.78 to 11.23) risk ($P_{trend} < .001$), respectively, with stronger associations for younger ages ($P_{interaction} < .001$) and rectal cancer ($P_{heterogenity} = .012$). The number of different signs and symptoms was predictive of early-onset CRC beginning 18 months before diagnosis. Approximately 19.3% of patients had their first sign or symptom occur between 3 months and 2 years before diagnosis (median diagnostic interval = 8.7 months), and approximately 49.3% had the first sign or symptom within 3 months of diagnosis (median diagnostic interval = 0.53 month).

Conclusions: Early recognition of red-flag signs and symptoms (abdominal pain, rectal bleeding, diarrhea, and iron-deficiency anemia) may improve early detection and timely diagnosis of early-onset CRC.

Early-onset colorectal cancer (CRC)—CRC diagnosed before age 50 years—is increasing in the United States and globally (1). In the United States, a 2% annual increase was documented between 2011 and 2016 (2,3), which is expected to more than double by 2030 (4). To address this trend, the American Cancer Society (5) and the US Preventive Services Task Force (6) lowered the recommended screening initiation age for average-risk individuals to 45 years. However, younger patients are more likely to be uninsured with lower adherence to screening, even if they have a family history of CRC (7,8). Moreover, half of the early-onset CRC patients are younger than age 45 years and thus will not be detected via screening (9). Therefore, most early-onset CRC patients will continue to be diagnosed after developing symptoms (10,11). To date, early-onset CRC patients, compared with older patients, are more likely to experience diagnostic delays (12-14), indicating a lack of awareness of red-flag signs and symptoms. Younger patients with CRC are more often diagnosed at advanced stages (27% distant disease vs 20% distant disease in older patients) (15-17). This has clinically significant implications as the 5-year survival decreases from 90% for early stage disease to only 14% for unresectable metastatic disease (18). Earlier detection of early-onset CRC could be critical to reducing the higher mortality associated with advanced disease (19). Additionally, earlier detection of early-onset CRC could

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reduce the need for aggressive treatment and improve survivor quality of life (18). Thus, identifying red-flag signs and symptoms to facilitate earlier detection is an unmet priority (20,21).

Signs and symptoms of early-onset CRC have been under investigation (22). Prior work has highlighted rectal bleeding, iron deficiency anemia, and rectal or abdominal pain (10,11,15,23-31). Yet, the majority of these studies have aggregated symptoms until the time of diagnosis, limiting information on early sign and symptom recognition to improve earlier detection. Although a study including average to late-onset CRC has demonstrated an increased risk of CRC with abdominal pain, rectal bleeding, and iron deficiency anemia as early as 6 months prior to diagnosis (32), similar studies are thus far lacking for early-onset CRC.

To address these critical knowledge gaps, we conducted a population-based case-control study, leveraging longitudinal claims data to identify red-flag signs and symptoms associated with early-onset CRC, with a primary focus on those that occurred between 3 months and 2 years before the index (diagnosis) date. We also reported the diagnostic delays associated with the identified red-flag signs and symptoms.

Methods

Study population

We conducted a case-control study of early-onset CRC using the IBM MarketScan Commercial Database. The MarketScan database provides longitudinal, de-identified, individual-level administrative claims data from approximately 113 million commercially insured adults aged 18-64 years in the United States (33). The database includes demographic information, outpatient and inpatient insurance reimbursable services, prescription data, employment status of the primary beneficiary, health plan type, number and type of office visits, and diagnostic testing. Compared with other national claims databases, the MarketScan enrollees have similar age and sex distributions (34) and contain a diverse geographic population (35).

We restricted our primary analyses to adults aged 18-49 years with at least 2 years of continuous enrollment before the index date. For secondary analyses, we included adults aged 50-64 years. We excluded individuals with inflammatory bowel disease, any prior or concurrent cancer history, and genetic susceptibility to malignant neoplasm, as well as patients with any personal history of cancer except nonmelanoma skin cancer identified through the Healthcare Cost and Utilization Project's Clinical Classification Software (36) within 2 years prior to the index date. This study was considered exempt by the Washington University Human Research Protection Office.

Ascertainment of cases and controls

Participants with incident CRC diagnoses were identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes (153.0-153.4,153.6-153.9, 154.0, 154.1, and 154.8) on a pathology claim. We required pathologist coding for CRC and assigned the first date of confirmed CRC (adenocarcinoma) pathology as the index date. Automated pathology software assigns ICD-9-CM codes based on the pathologist's final diagnosis, which accurately reports pathology. Anatomic location for cases was identified using ICD-9-CM codes colon (153.0-153.4, 153.6-153.9) and rectal (154.0, 154.1, 154.8) tumors.

Controls were identified from individuals without CRC from insurance enrollment and were frequency matched to cases in a 4:1 ratio based on age (18-24 years and every 5 years thereafter), sex (female, male), geographical region (South, Northeast, North Central, West, unknown), duration of insurance enrollment before the index date (years), and prescription drug coverage for at least 2 years (yes, no). Controls were assigned random index dates and selected to ensure the distribution of control index dates matched the distribution of index dates among cases to account for changes over time.

Ascertainment of signs and symptoms

All signs and symptoms were prespecified based on literature review (10,11,24,37,38) and defined using ICD-9-CM diagnosis codes reported in Supplementary Table 1 (available online). Our primary analyses focused on identifying red-flag signs and symptoms between 3 months and 2 years prior to the index date, similar to a study that focused on CRC in an older population (32). We restricted the analyses to signs and symptoms with a frequency greater than 2% among cases to ensure adequate statistical power and appropriate interpretation. In secondary analyses, we examined the role of signs and symptoms within 3 months before the index date.

Assessment of covariates and other clinical information

Demographic information included age at the index date, sex, duration of insurance enrollment, prescription drug coverage for at least 2 years before the index date, US census geographical region, residence, full-time employment status of the primary beneficiary, and type of health plan. Information on potential confounders including Charlson Comorbidity Index (39), family history of gastrointestinal cancer (V16.0), obesity (278.00, 278.01, 649.1x, V85.3x, V85.4x, V85.54), and tobacco use (V15.82, 305.1) was obtained. Finally, health-care utilization was extracted, including the number of outpatient office visits from internal medicine, family practice, obstetrics and gynecology, gastroenterology, colorectal surgery, urgent care visit, emergency room visit, and hospital admission.

Statistical analysis

We evaluated the association of each prespecified sign or symptom occurring between 3 months and 2 years prior to the index date with the risk of early-onset CRC as the primary analysis. Because of frequency matching, multivariable unconditional logistic regression models were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs). We adjusted for matching factors, including age, sex, duration of insurance enrollment, prescription drug coverage, and geographical region. We further adjusted for residence (urban, rural, unknown), full-time employment status (yes, no), type of health plan (preferred provider organization, health maintenance organization, others), and the following factors between 3 months and 2 years prior to the index date: Charlson Comorbidity Index (continuous), family history of gastrointestinal cancer (yes, no), obesity (yes, no), tobacco use (yes, no), and health-care utilization (outpatient office visits [0, 1-3, ≥4 times], urgent care visit [yes, no], emergency room visit [yes, no], hospital admission [yes, no]). To evaluate potential differences for average-onset CRC, we also conducted the above analyses among cases diagnosed at age 50-64 years and their controls.

For early-onset CRC cases and controls, we evaluated the collective impact (0, 1, 2, ≥3, and per each additional associated sign or symptom). P_{trend} was calculated using the total number of signs and symptoms as a continuous variable. The area under the curve (AUC) was also calculated. We evaluated the associations according to age (18-34 vs 35-44 vs 45-49 years) and sex.

$P_{interaction}$ was calculated by a Wald test. We examined the performance of the total number of signs and symptoms according to the anatomic site of the tumor (colon vs rectal). Polytomous logistic regressions were used to calculate $P_{heterogeneity}$. As exploratory analyses, we created weighted scores based on statistically significant signs and symptoms and the corresponding coefficients. To evaluate the predictability of the total number of red-flag signs and symptoms according to time, we narrowed the time period by decreasing 3-month increments toward 2 years (eg, 3 months to 2 years, 6 months to 2 years before the index).

To elucidate potential diagnostic delays, diagnostic intervals (median, interquartile range [IQR]) were calculated according to the number and pattern of signs and symptoms for patients with their first sign or symptom occurring between 3 months to 2 years or within 3 months before diagnosis, respectively. For cases with 1 sign or symptom, the diagnostic interval accrued from the first date that the specific sign or symptom occurred to diagnosis. For patients who had 2 or more distinct signs and symptoms, the diagnostic interval accrued from when all signs and symptoms were present to diagnosis. All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA). Two-sided *P* values less than .05 were considered statistically significant.

Results

A total of 5075 early-onset CRC cases and 22 378 controls were included in the primary analyses. The average age was 43 years. Compared with controls, cases were more likely to have more comorbidities and a higher number of outpatient office visits and to be coded for obesity (Table 1). Most cases were diagnosed with colon cancer (63%). We also included 17 068 average-onset CRC cases and 71 222 matched controls in the secondary analyses (Supplementary Table 2, available online).

For early-onset CRC, 8 of the 17 prespecified signs and symptoms exhibited a frequency greater than 2.0% among cases between 3 months and 2 years prior to the index date, with abdominal pain (11.6%) and rectal bleeding (7.2%) being the most common symptoms. After accounting for matching factors and potential confounders, 4 red-flag signs and symptoms were associated with an increased risk of early-onset CRC, including abdominal pain, rectal bleeding, diarrhea, and iron deficiency anemia. Abdominal pain was associated with a 34% higher risk of early-onset CRC (prevalence in cases 11.6% vs controls 7.7%; OR = 1.34, 95% CI = 1.19 to 1.49). Although not as common as abdominal pain, rectal bleeding exhibited the highest odds ratio (cases 7.2% vs controls 1.3%; OR = 5.13, 95% CI = 4.36 to 6.04). Other predictive signs and symptoms included diarrhea (cases 2.8% vs controls 1.4%; OR = 1.43, 95% CI = 1.14 to 1.78) and iron deficiency anemia (cases 2.3% vs controls 0.9%; OR = 2.07, 95% CI = 1.61 to 2.66) (Table 2). Of the predictive signs and symptoms, no differential associations were observed by sex for each sign or symptom (all $P_{interactions} > .10$) (Supplementary Table 3, available online).

In contrast, for average-onset CRC (age 50-64 years), only 4 of the 17 prespecified signs and symptoms had a prevalence of more than 2.0% among cases. Among the 4, abdominal pain and rectal bleeding were associated with subsequent risk of average-onset CRC, and each exhibited a lower prevalence in cases and a lower odds ratio than for early-onset CRC (Table 2). For abdominal pain, the odds ratio was 1.07 (95% CI = 1.00 to 1.15). For rectal bleeding, the odds ratio was 2.49 (95% CI = 2.27 to 2.73).

Among early-onset CRC patients, 19.3% presented with 1 or more of the 4 clinically significant signs and symptoms (abdominal pain, rectal bleeding, diarrhea, and iron deficiency anemia) between 3 months and 2 years prior to the index date (15.6% with 1 sign or symptom, 3.7% presented with 2 or more). We also evaluated the collective impact of the 4 red-flag signs and symptoms. After multivariable adjustment, having 1, 2, or at least 3 distinct signs and symptoms were associated with a 1.94-fold (95% CI = 1.76 to 2.14), 3.59-fold (95% CI = 2.89 to 4.44), and 6.52-fold (95% CI = 3.78 to 11.23) risk of early-onset CRC, respectively (Table 3). For each additional red-flag sign or symptom, the risk of early-onset CRC increased by 91% (OR = 1.91, 95% CI = 1.78 to 2.05; $P_{trend} < .001$) (Table 3), and the AUC of this unweighted score was 0.579. Interestingly, the positive association was more pronounced for younger than for older age groups ($P_{interaction} < .001$). Each additional red-flag sign or symptom was associated with odds ratios of 2.46 (95% CI = 1.89 to 3.21), 2.19 (95% CI = 1.96 to 2.45), and 1.69 (95% CI = 1.53 to 1.87) for ages 18-34, 35-44, or 45-49 years, respectively (Table 3). We observed no differential associations according to sex ($P_{interaction} = .76$) or geographic region ($P_{interaction} = .09$) (Supplementary Table 4, available online). However, the association appeared more pronounced for rectal cancer compared with colon cancer ($P_{heterogenity} = .012$; Supplementary Table 5, available online). As exploratory analyses, we also derived a weighted score to capture the strengths of association for each sign and symptom. Each

Table 1. Characteristics of early-onset colorectal cancer and controls, IBM MarketScan (2006-2015)

Characteristics	Cases No. (%) (n = 5075)	Controls No. (%) (n = 22 378)
Age at the index date, mean (SD), y	43.2 (5.6)	42.8 (5.9)
Sex		
Female	2442 (48.1)	10 781 (48.2)
Male	2633 (51.9)	11 597 (51.8)
Duration of insurance enrollment, mean (SD), y	4.0 (1.7)	3.9 (1.7)
≥2 years of prescription coverage	3956 (78.0)	17 297 (77.3)
Geographical region		
South	2220 (43.7)	9745 (43.5)
Northeast	776 (15.3)	3497 (15.6)
North Central	1193 (23.5)	5160 (23.1)
West	801 (15.8)	3617 (16.2)
Unknown	85 (1.7)	359 (1.6)
Residence		
Urban	4250 (83.7)	18 810 (84.1)
Rural	744 (14.7)	3218 (14.4)
Unknown	81 (1.6)	350 (1.6)
Full-time employment	2606 (51.3)	10 961 (49.0)
Health plan		
Preferred provider organization	3299 (65.0)	14 156 (63.3)
Health maintenance organization	646 (12.7)	3084 (13.8)
Other	1130 (22.3)	5138 (23.0)
Charlson Comorbidity Index, mean (SD)[a]	0.18 (0.64)	0.1 (0.44)
Family history of gastrointestinal cancer[a]	62 (1.2)	211 (0.9)
Obesity[a]	279 (5.5)	1069 (4.8)
Tobacco use[a]	194 (3.8)	929 (4.2)
No. of clinical visits, mean (SD)[a]		
Outpatient office visits[b]	3.5 (4.2)	3.1 (3.8)
Urgent care	0.09 (0.58)	0.07 (0.46)
Emergency room	0.29 (0.79)	0.25 (0.74)
Hospitalization	0.09 (0.35)	0.08 (0.36)
Tumor site		
Colon cancer	3201 (63.1)	—
Rectal cancer	1860 (36.7)	—

[a] Between 3 months and 2 years prior to the index date.
[b] Outpatient office visits from internal medicine, family practice, obstetrics and gynecology, gastroenterology, and colorectal surgery.

Table 2. Signs and symptoms (3 months to 2 years prior to the index date) and risk of colorectal cancer by age of onset

Signs and symptoms[a]	Cases No. (%)	Controls No. (%)	OR (95% CI)[b]	OR (95% CI)[c]
Early-onset, younger than 50 y				
Abdominal pain	588 (11.6)	1714 (7.7)	1.36 (1.22 to 1.52)	1.34 (1.19 to 1.49)
Rectal bleeding	363 (7.2)	287 (1.3)	5.25 (4.47 to 6.17)	5.13 (4.36 to 6.04)
Malaise and/or fatigue	324 (6.4)	1230 (5.5)	1.02 (0.89 to 1.16)	1.01 (0.88 to 1.15)
Nausea and vomiting	143 (2.8)	525 (2.3)	0.89 (0.72 to 1.09)	0.86 (0.70 to 1.06)
Diarrhea	140 (2.8)	308 (1.4)	1.47 (1.18 to 1.83)	1.43 (1.14 to 1.78)
Iron deficiency anemia	117 (2.3)	193 (0.9)	2.11 (1.65 to 2.71)	2.07 (1.61 to 2.66)
Constipation	106 (2.1)	244 (1.1)	1.28 (1.00 to 1.64)	1.27 (0.99 to 1.63)
Other deficiency anemias	102 (2.0)	314 (1.4)	1.16 (0.91 to 1.47)	1.16 (0.91 to 1.48)
Average-onset, 50-64 y				
Abdominal pain	1362 (8.0)	5036 (7.1)	1.07 (1.01 to 1.15)	1.07 (1.00 to 1.15)
Malaise and/or fatigue	869 (5.1)	3607 (5.1)	0.98 (0.90 to 1.05)	0.98 (0.90 to 1.06)
Rectal bleeding	772 (4.5)	1333 (1.9)	2.46 (2.25 to 2.70)	2.49 (2.27 to 2.73)
Nausea and vomiting	365 (2.1)	1338 (1.9)	1.07 (0.95 to 1.21)	1.01 (0.89 to 1.14)

[a] Signs and symptoms with at least 2% prevalence in cases between 3 months and 2 years prior to the index date. Other signs and symptoms (not shown) with less than 2% prevalence include abdominal mass, anal or rectal pain, anorexia, bowel habit change, bowel obstruction, gas or bloating, heartburn, incontinence of feces, and weight loss. CI = confidence interval; OR = odds ratio.
[b] Adjusted for matching factors: age (years), sex (female, male), duration of insurance enrollment (years), prescription coverage (yes, no), and geographical region (south, northeast, north central, west, unknown) before the index date.
[c] In addition to matching factors, the model was additionally adjusted for full-time employment (yes, no), residence (urban, rural, unknown), health insurance plan (preferred provider organization, health maintenance organization, others), and the following factors between 3 months and 2 years prior to the index date: Charlson Comorbidity Index (continuous), family history of gastrointestinal neoplasm (yes, no), obesity (yes, no), tobacco use (yes, no), outpatient office visits (0, 1-3, ≥4 times), urgent care visit (yes, no), emergency room visit (yes, no), hospital admission (yes, no).

standard deviation increment in the weighted score was associated with an 83% (OR = 1.83, 95% CI = 1.74 to 1.93; P_{trend} <.001) increased risk of early-onset CRC, with an AUC of 0.581 (Supplementary Table 6, available online). To evaluate the predictability of the total number of red-flag signs and symptoms according to time of symptom presentation before the index date, we narrowed the time period by decreasing 3-month increments toward 2 years and found that as early as 18 months before the index date, the total number of red-flag signs and symptoms was associated with an increased risk of early-onset CRC (OR = 1.18, 95% CI = 1.02 to 1.37; P_{trend} = .03; Figure 1; Supplementary Table 7, available online).

In addition to the 19.3% of cases with their first sign or symptom between 3 months and 2 years of diagnosis, 49.3% of cases presented with their first sign or symptom within 3 months of diagnosis (Supplementary Table 8, available online). Among patients who had their first red-flag sign or symptom within 3 months before diagnosis, the median diagnostic interval was short (<1 month) (Supplementary Table 8, available online). In contrast, the median diagnostic interval for cases with any identified red-flag signs and symptoms between 3 months and 2 years before diagnosis was 8.7 months (IQR = 4.8-15.9 months) (Figure 2; Supplementary Table 8, available online). Overall, the diagnostic intervals were longer for patients with a fewer number of signs and symptoms. Among cases with only 1 sign or symptom, abdominal pain appeared to have the longest diagnostic interval (median = 11.7 months), followed by diarrhea and iron deficiency anemia. Although patients with rectal bleeding experienced the shortest diagnostic interval, patients still encountered a median delay of 7 months from the first recorded occurrence to diagnosis. For patients who had 2 recorded symptoms, more than half of the diagnostic intervals were greater than 6 months. In addition, the interval was substantially longer (almost 9 months) if abdominal pain was experienced with either diarrhea or iron deficiency anemia. Even for cases with 3 or more distinct signs or symptoms, the median diagnostic intervals were approximately 5 months.

Discussion

In this case-control study utilizing longitudinal claims data with 5075 early-onset CRC cases, 4 red-flag signs and symptoms (abdominal pain, rectal bleeding, diarrhea, and iron deficiency anemia) between 3 months and 2 years prior to the index date were associated with increased risk of early-onset CRC, with the strongest association for rectal bleeding. Having 1, 2, or at least 3 of these red-flag signs and symptoms (between 3 months and 2 years of the index date) was associated with a 1.9-, 3.6-, and 6.5-fold increased risk. These associations were stronger for younger cases and rectal cancer. The total number of distinct red-flag signs was predictive of early-onset CRC beginning 18 months before diagnosis. For a red-flag sign or symptom first occurring between 3 months and 2 years before diagnosis, early-onset CRC patients had a median diagnostic interval of 8.7 months. The much weaker associations in average to later-onset CRC further support the specificity and utility of these signs and symptoms for earlier detection of early-onset CRC.

Our study is among the first to characterize red-flag signs and symptoms 3 months prior to early-onset CRC diagnosis. Prior studies have included symptoms up to the diagnosis date (10,11,15,23-31). For instance, analyses in the Veterans Health Administration reported positive associations between rectal bleeding (hazard ratio [HR] = 10.7) and iron deficiency anemia (HR = 10.8) with risk of early-onset CRC up to diagnosis (257 and 556 cases, respectively) (31). Our much larger-scale analyses not only in part validate these but also expand these findings by showing that rectal bleeding (OR = 5.13) and iron deficiency anemia (OR = 2.07) were still associated with increased risk of early-onset CRC even after restricting to 3 months before diagnosis. Our findings underscore the importance of prioritizing prompt diagnostic work-up for patients aged younger than 50 years who are presented with rectal bleeding and/or iron deficiency anemia. Although validation in large-scale and diverse electronic health records is needed, improved recognition of early signs and symptoms would result in earlier diagnosis, thereby mitigating the need for aggressive treatments associated with advanced-stage

Table 3. Number of red-flag signs and symptoms (3 months to 2 years prior to the index date) and risk of early-onset colorectal cancer overall and according to age groups

No. of red-flag signs and symptoms[a]	Cases No. (%)	Controls No. (%)	OR (95% CI)[b]	OR (95% CI)[c]
All participants				
0	4092 (80.7)	20 140 (90.0)	1 (Referent)	1 (Referent)
1	792 (15.6)	1998 (8.9)	1.97 (1.80 to 2.15)	1.94 (1.76 to 2.14)
2	159 (3.1)	217 (1.0)	3.66 (2.97 to 4.51)	3.59 (2.89 to 4.44)
≥3	32 (0.6)	23 (0.1)	6.96 (4.07 to 11.91)	6.52 (3.78 to 11.23)
Per each additional sign and symptom	–	–	1.94 (1.81 to 2.07)	1.91 (1.78 to 2.05)
P_{trend}	–	–	<.001	<.001
Age groups				
18-34 y				
0	326 (78.4)	1770 (90.5)	1 (Referent)	1 (Referent)
1	72 (17.3)	169 (8.7)	2.33 (1.72 to 3.16)	2.45 (1.75 to 3.42)
≥2	18 (4.3)	16 (0.8)	6.02 (3.03 to 11.96)	6.67 (3.19 to 13.96)
Per each additional sign and symptom	–	–	2.34 (1.86 to 2.95)	2.46 (1.89 to 3.21)
P_{trend}	–	–	<.001	<.001
35-44 y				
0	1581 (78.9)	8031 (90.6)	1 (Referent)	1 (Referent)
1	336 (16.8)	746 (8.4)	2.33 (2.02 to 2.68)	2.36 (2.03 to 2.74)
≥2	86 (4.3)	89 (1.0)	5.08 (3.76 to 6.88)	4.99 (3.64 to 6.84)
Per each additional sign and symptom	–	–	2.20 (1.98 to 2.44)	2.19 (1.96 to 2.45)
P_{trend}	–	–	<.001	<.001
45-49 y				
0	2185 (82.2)	10 339 (89.4)	1 (Referent)	1 (Referent)
1	384 (14.5)	1083 (9.4)	1.71 (1.51 to 1.94)	1.66 (1.45 to 1.90)
≥2	87 (3.3)	135 (1.2)	3.11 (2.36 to 4.10)	3.00 (2.26 to 3.98)
Per each additional sign and symptom	–	–	1.72 (1.57 to 1.89)	1.69 (1.53 to 1.87)
P_{trend}	–	–	<.001	<.001
$P_{interaction}$[d]	–	–	<.001	<.001

[a] The total number of red-flag signs and symptoms included the 4 red-flag signs and symptoms (abdominal pain, rectal bleeding, diarrhea, and iron deficiency anemia) statistically significantly associated with increased risk of early-onset colorectal cancer between 3 months and 2 years prior to the index date. CI = confidence interval; OR = odds ratio.
[b] Adjusted for the same set of variables as in Table 2, model b.
[c] Adjusted for the same set of variables as in Table 2, model c.
[d] $P_{interaction}$ was calculated for age at the index date (years) and the number of red-flag signs and symptom (continuous) using Wald test.

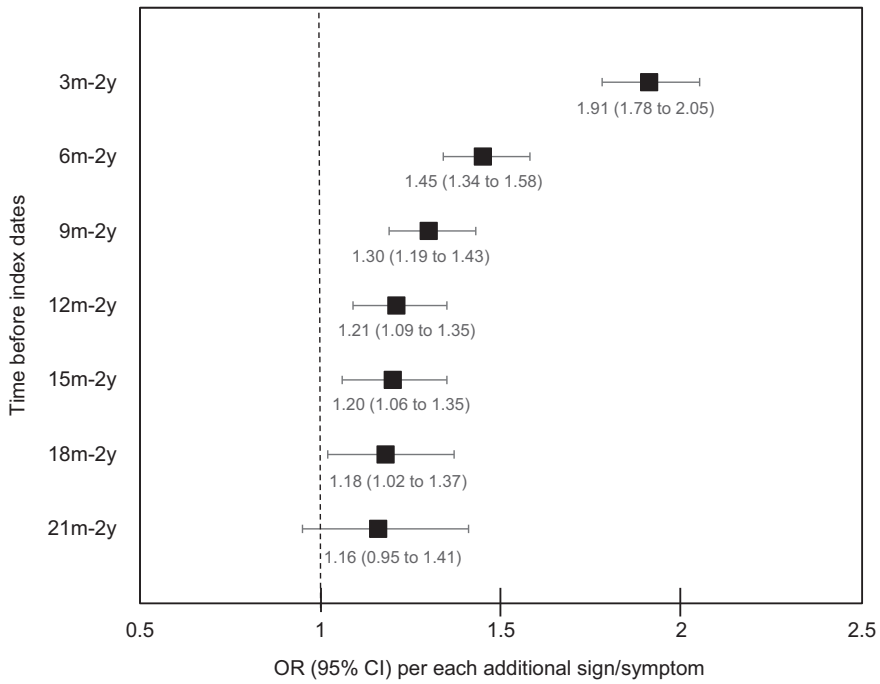

Figure 1. Number of red-flag signs and symptoms and risk of early-onset colorectal cancer according to 3-month time intervals prior to the index date. The total number of signs and symptoms were derived from the 4 red-flag signs and symptoms identified to be associated with an increased risk of early-onset colorectal cancer (abdominal pain, rectal bleeding, diarrhea, and iron deficiency anemia) between 3 months and 2 years prior to the index date. The multivariable models were adjusted for the same set of variables as in Table 2, model c. CI = confidence interval; OR = odds ratio.

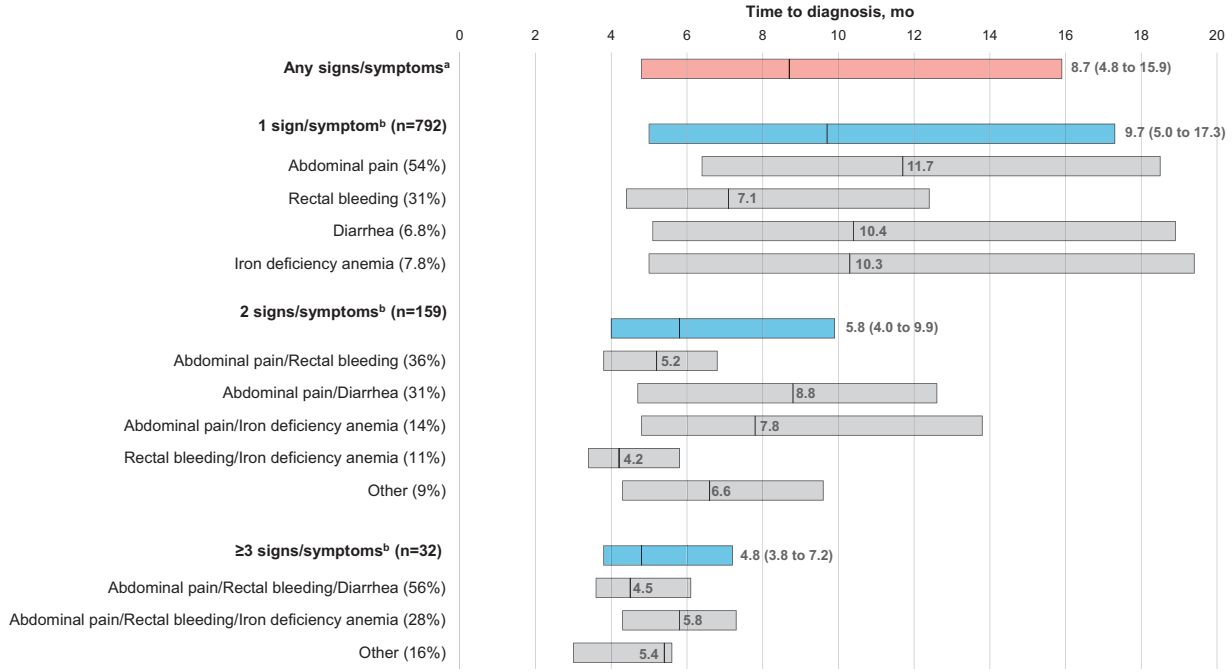

Figure 2. Diagnostic intervals of early-onset colorectal cancer with the first red-flag sign and symptom between 3 months and 2 years before diagnosis. [a]A total of 983 cases have had 1 or more of the 4 red-flag signs and symptoms associated with increased risk of early-onset colorectal cancer (abdominal pain, rectal bleeding, diarrhea, and iron deficiency anemia) between 3 months and 2 years prior to diagnosis. [b]For cases with 1 sign or symptom between 3 months and 2 years prior to diagnosis, the diagnostic interval accrued from the date of first sign or symptom claim to date of diagnosis. For patients who had 2 or more red-flag signs and symptoms between 3 months and 2 years prior to diagnosis, the diagnostic interval accrued from the time point when all the red-flag signs and symptoms have been presented to the date of diagnosis. IQR = interquartile range (P25 to P75).

disease and improving quality of life (40). Ultimately, such early detection could help stem the rising mortality rates in younger patients (17) at the population level. We also highlighted 2 additional signs and symptoms that may facilitate early detection, including abdominal pain and diarrhea.

We also reported the collective impact of these signs and symptoms in early detection. Intriguingly, we observed stronger associations among younger (aged 18-34 and 35-44 years) than older (aged 45-49 years) adults. A meta-analysis showed that rectal bleeding reported in the primary care setting was more predictive for younger patients than older patients (41), likely explained by fewer comorbid competing diagnoses that accompany increasing age. Although validations are warranted, our findings lend initial support to the clinical utility of the 4 red-flag signs and symptoms in the early detection of early-onset CRC, especially for younger adults (aged younger than 45 years) who are not covered by updated screening guidelines (5,6).

Studies on diagnostic intervals for early-onset CRCs are limited. We reported that 19% of early-onset CRC had their red-flag sign or symptom first occurring 3 months before diagnosis, with a prolonged diagnostic interval. Importantly, we also reported that the diagnostic intervals varied according to the combination of signs and symptoms, with shorter intervals for patients presenting with rectal bleeding and considerably longer intervals for iron deficiency anemia. Although further studies are needed to evaluate subsequent diagnostic evaluations, especially among patients with delayed diagnosis to identify avenues for improvement, our findings call for heightened awareness from providers and patients of the associated red-flag signs and symptoms, especially when experienced in combination. Although diagnostic strategies may not be required for every event of abdominal pain or diarrhea, close clinical follow-up to assess symptom resolution or fecal immunochemical testing for endoscopic triage could decrease diagnostic delays for younger patients (22).

Our major strength is that we leveraged one of the largest real-world claims databases to address the set of questions of immediate clinical priority. To address the issue of underreporting (eg, signs and symptoms, family history) in claims data, cases and controls were matched, and a list of variables related to health-care utilization was adjusted to ensure interval validity. Of note, our findings on rectal bleeding and iron deficiency anemia are generally in line with a report using electronic health record–based data from the Veterans Health Administration, further lending confidence to these findings. Another major strength is that we evaluated individual signs and symptoms and their collective impact before 3 months of diagnosis with an overarching goal to facilitate early detection. The stronger associations among younger adults further support the opportunities for earlier detection among individuals aged younger than 45 years. Because of the lack of data, we were unable to assess weight loss as a predictive sign (23). Furthermore, staging information was not available, limiting our understanding on the impact of diagnostic delays. Finally, race and ethnicity are not routinely collected by major health plans. Future analyses within diverse populations are needed.

In conclusion, this large case-control study involving 5075 early-onset CRC patients identified 4 red-flag signs and symptoms (abdominal pain, rectal bleeding, diarrhea, and iron deficiency anemia) occurring at least 3 months before diagnosis that were associated with subsequent risk. Although validations are warranted, these findings indicate the potential utility of

leveraging red-flag signs and symptoms to improve the early detection of early-onset CRC.

Data availability

Marketscan data were obtained with a data use agreement through a third-party license from IBM. Therefore, the authors are unable to make the data publicly available. Researchers interested in accessing the data can purchase a license through IBM and use the inclusion criteria outlined in the methods section. More information on how to access IBM databases can be found here: https://marketscan.truvenhealth.com/marketscanportal/.

Author contributions

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Conflicts of interest

The authors declared no competing interests.

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Drs. Fritz, Otegbeye, and Cao had full access to all study data and take responsibility for the integrity and accuracy of the data analysis.

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