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Risk of Colorectal Cancer Associated With Frequency of Colorectal Polyp Diagnosis in Relatives

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e1. Learning Objective: Upon completion of this CME activity, successful learners will be able to identify the association between the risk of colorectal cancer and the frequency of colorectal polyp diagnoses in relatives and apply this knowledge to more accurately personalize strategies for colorectal cancer screening.

BACKGROUND & AIMS: The aim of the study was to evaluate the association of frequency of polyp diagnosis in relatives with the risk of overall and early-onset colorectal cancer (CRC). **METHODS:** Data from nationwide Swedish family cancer datasets (1964–2018) were leveraged to calculate standardized incidence ratios for individuals with a family history of polyp by frequency of polyp diagnosis in family members. **RESULTS:** A total of 11,676,043 individuals were followed for up to 54 years. Compared with the risk in individuals without a family history of colorectal tumor (n = 142,234), the risk of overall CRC was 1.4-fold in those with 1 first-degree relative (FDR) with 1-time polyp diagnosis (95% CI, 1.3–1.4; n = 11,035; early-onset standardized incidence ratio [SIR], 1.4; 95% CI, 1.3–1.5; n = 742). The risk was significantly higher in individuals with 1 FDR with 2 or more (frequent) polyp diagnoses (overall CRC: SIR, 1.8; 95% CI, 1.8–1.9; early-onset CRC: SIR, 2.3; 95% CI, 2.0–2.6). A rather similar risk was observed for individuals with ≥2 FDRs with 1-time polyp diagnosis (overall CRC: SIR, 1.9; 95% CI, 1.7–2.1; early-onset CRC: SIR, 2.2; 95% CI, 1.5–2.9). Individuals with ≥2 FDRs with frequent polyp diagnoses had a 2.4-fold overall risk (95% CI, 2.2–2.7) and a 3.9-fold early-onset risk (95% CI, 2.8–5.3). Younger age at polyp diagnosis in FDRs was associated with an increased risk of CRC. A family history of polyp in second-degree relatives was important only when there were frequent diagnoses of polyp. **CONCLUSIONS:** A higher frequency of colorectal polyp diagnosis in relatives is associated with a greater risk of CRC, especially early-onset CRC. This risk is independent of number of affected relatives or youngest age at polyp diagnosis. These findings underscore the need for more personalized CRC screening strategies that are tailored to individuals with a family history of polyp.

Keywords: Colorectal Polyp; Family History; Colorectal Cancer; Cancer Screening; Colonoscopy; Cancer Prevention.

Colorectal cancer (CRC) is the third most common form of cancer and the second leading cause of cancer-related death worldwide.[1] The majority of CRCs originate from a colorectal polyp, with an estimated 10-year progression time from polyp to CRC.[2] Colonoscopy screening and subsequent polypectomy have been found to be effective in reducing both CRC incidence and mortality rates.[3] Some Western countries have implemented colonoscopy screening programs, typically starting at the age of 50 years, with a recent shift to 45 years in the United States.[4–6] However, there has been a notable increase in early-onset CRC (diagnosed before the age of 50 years), which accounts for 10%–12% of all new CRC cases.[7] These early-onset CRC cases are often diagnosed at an advanced stage and are associated with a poorer prognosis compared with late-onset CRC.[8] Given the increasing incidence of early-onset CRC, it is crucial to identify its risk factors and implement risk-adapted screening strategies.

Several known risk factors for CRC have been identified, including family history of CRC,[9] obesity,[10] and some lifestyle-related factors.[11] Multiple studies have reported an association between family history of colorectal polyp and increased CRC risk, with estimated odds ratios ranging from 1.35 to 1.78.[12–15] A recent study found an increased risk of early-onset CRC associated with number of first-degree relatives (FDRs) diagnosed with polyp and the age at diagnosis in relatives.[16] However, that study did not take into account the frequency of polyp diagnosis in relatives when they investigated the association between family history of polyp and risk of CRC.[16]

In the United States, the mean colorectal polyp detection rate during colonoscopy screening was reported to be 55%, whereas in Europe this rate is reported to be at least 41%.[17,18] More importantly, the prevalence of frequent

Abbreviations used in this paper: **CRC, colorectal cancer; FDR, first-degree relative; ICD, International Classification of Diseases; SDR, second-degree relative; SIR, standardized incidence ratio.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Family history of polyp is a well-established risk factor. The association of the frequency of polyp diagnosis in relatives with colorectal cancer risk, especially early-onset, has not been extensively investigated.

NEW FINDINGS

A higher frequency of polyp diagnosis in relatives was associated with a greater risk of colorectal cancer, particularly early onset. This risk was independent of number of relatives with polyp and youngest age at polyp diagnosis.

LIMITATIONS

Information on specific polyp characteristics, including size, number, and histologic classification, was lacking. This limitation reflects real-world scenarios when family members often only know the number of colonoscopies with polyp removal among their relatives, rather than having detailed polyp information.

CLINICAL RESEARCH RELEVANCE

Frequency of colorectal polyp diagnosis in relatives should be considered as important as number of relatives with colorectal polyp when developing colorectal cancer screening strategies.

BASIC RESEARCH RELEVANCE

Understanding the mechanism (from both genetic and environmental perspectives) behind the association of frequent polyp diagnoses with increased familial risk of early-onset colorectal cancer may help reduce the incidence and mortality of early-onset colorectal cancer.

colorectal polyp was reported to be 1%–58% over a 5-year follow-up period.[19,20] As a result of the relatively high prevalence and frequency of colorectal polyp, it is important to investigate the risk of CRC in individuals with a family history of polyp and provide evidence-based screening recommendations for them. The current screening recommendations for individuals with a family history of polyp are inconsistent and based on low- or very-low-quality evidence.[21] Therefore, we aimed to elucidate the association between family history of benign colorectal polyp and risk of overall and early-onset CRC by frequency (1 time or 2 or more times) of polyp diagnosis in relatives, in addition to the number of FDRs and second-degree relatives (SDRs) with polyp and the youngest age at polyp diagnosis.

Materials and Methods

The study was approved by the Lund Regional Ethical Review Board (2012/795 and subsequent amendments). Written informed consent was not required, as only pseudonymized data were used and no personal information could be unmasked.

Datasets

This study leveraged the Swedish family cancer datasets, which are the most comprehensive of their kind in the world.[22] Records of the following 4 nationwide datasets were linked using an individually unique pseudonymized Swedish national identification number: The Multi-Generation Register, National Patient Register, Swedish Cancer Registry, and the Population Register. Children born in Sweden since 1932 are registered with their parents in the Multi-Generation Register database, which provides genealogic data of the whole population. Data on cancer in FDRs and SDRs could be extracted from this dataset using a record linkage with the cancer registry data. We could extract information on medical records related to colorectal polyp from the National Patient Register, which provides information on all clinical visits from all residents of Sweden (inpatient visits since 1964 and outpatient specialty visits from 2001 onwards). The Swedish Cancer Registry has recorded CRC patients since 1958 using the International Classification of Diseases, 7th Revision (ICD-7)[23] codes and later revisions (ie, ICD-8,[24] ICD-9,[25] and ICD-10[26]). The Population Register provides vital information about individuals' births, deaths, migration records, and socioeconomic measures for the entire study period. These datasets are updated periodically, and the last update in 2020, which was used for this study, includes more than 13 million individuals who were followed up to the end of 2018, with an overall completeness of cancer data estimated at $\geq$96%.[27]

Study Population and Follow-Up

Individuals who were born after 1931 (and their parents), ever lived in Sweden between January 1964 and December 2018, and had at least 1 known FDR in the database were included in our study. Individuals who were diagnosed with inflammatory bowel disease (n = 144,322) or hereditary non-polyposis CRC (n = 181) were excluded (Figure 1). We also excluded subjects with a family history of CRC or carcinoma in situ (n = 1,756,162). The follow-up started for each individual in our database from the beginning of 1964, the birth year, or the immigration year, whichever came last. The follow-up ended when the individual was diagnosed with CRC, emigrated, died, or at the end of 2018, whichever came first.

Swedish Screening Guidelines and Diagnosis of Colorectal Cancer and Benign Colorectal Polyp

Sweden issued CRC screening guidelines in 2014, but it did not launch a nationwide screening program until September 2022.[28] Before this, there were some regional screening trials in Sweden, generally starting at age 60 years.[29–31] More details are presented in the Supplementary Materials and Methods. For individuals with FDRs who had early-onset CRC, Sweden recommended starting screening at age 55 years.[32] They did not mention any specific recommendation for family members of patients with colorectal polyp. Data on patients with CRC were extracted from the Swedish Cancer Registry dataset using the following ICD-7[23] codes: 153 and 154 (excluding code 154.1 for the anus). The diagnosis of colorectal polyp was extracted from the National Patient Register according to ICD-7, ICD-8,[24] ICD-9,[25] and ICD-10[26] coding systems (Supplementary Table 1).

Family History of Polyp

Family history of polyp was defined as the presence of a record of polyp diagnosis in either FDRs or SDRs. Using the Multi-Generation Register database, which provides comprehensive genealogical data for the entire population of Swedish residents born after 1931 and their parents, we identified FDRs

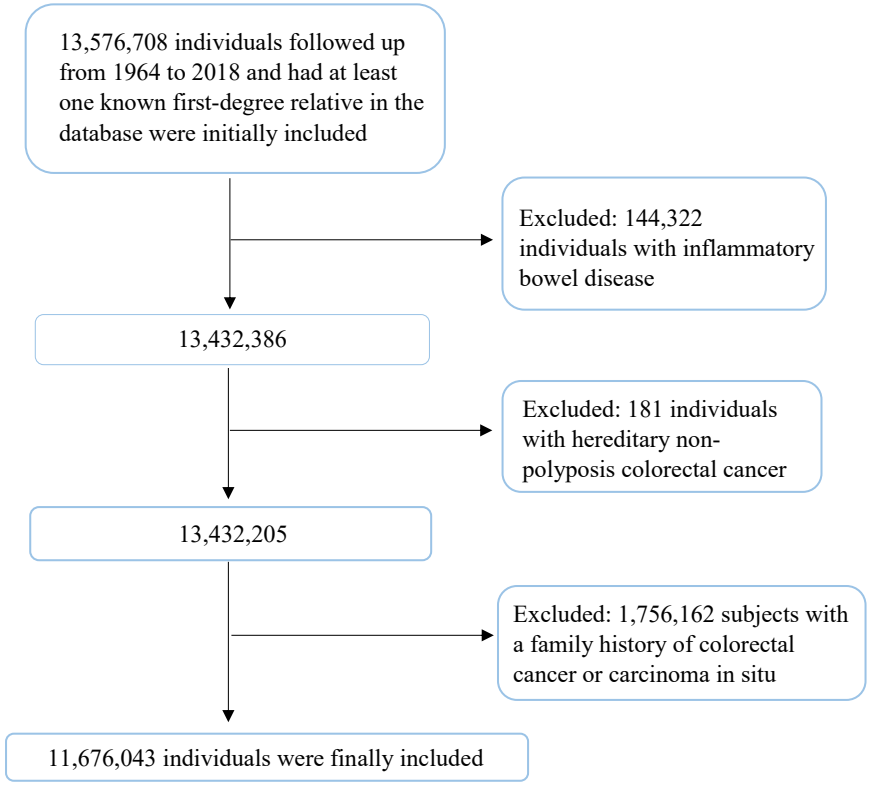

Figure 1. Flowchart of study population.

and SDRs of everyone in our study population. We also retrieved the history of polyp diagnosis for all individuals from the National Patient Register. The record linkage of these 2 datasets provided the history of polyp diagnosis in relatives of everyone. Relatives were also classified based on the frequency of their colorectal polyp diagnoses into the following 2 categories: those diagnosed once and those with frequent diagnoses. A frequent polyp diagnosis was defined as at least 2 separate diagnoses of colorectal polyp, with each diagnosis occurring at least 12 months apart. The youngest age at polyp diagnosis in relatives was also recorded and categorized into the following 3 age groups: younger than 50 years, 50–59 years, and 60 years and older. All genealogical and polyp diagnosis data were obtained from registry sources, ensuring that the information was not dependent on self-reported data.

Statistical Analysis

We calculated the standardized incidence ratios (SIRs) to assess the familial risk of CRC, including both overall and early-onset CRC as the primary outcomes, for individuals with varying family history patterns of polyp. These calculations were adjusted based on 5-year age groups, sex, calendar year (ranging from 1964 to 2018 in intervals of 5 years), region (including large cities, small cities in southern Sweden, and small cities in northern Sweden), diabetes mellitus, as well as socioeconomic status (categorized as blue-collar worker, white-collar worker, farmer, self-employed, professional, or other/unspecified). We also performed the sensitivity analyses by additional adjustment for history of hospitalization due to obesity, alcoholism, and chronic obstructive pulmonary disease (as a proxy for heavy smoking). We also conducted sensitivity analyses excluding individuals with relatives diagnosed with 1-time polyp only from 1 colonoscopy. The expected cases were calculated from strata-specific person-years in individuals with a certain family history of colorectal polyp multiplied by strata-specific incidence rates in those without any family history. We calculated the 95% CIs of SIRs by assuming a Poisson distribution.

We calculated the SIRs for individuals who had a family history of only benign colorectal polyp, stratified by frequency of polyp diagnosis (1-time polyp diagnosis and $\geq$2 times polyp diagnoses), number of relatives with polyp (1 FDR + 0 SDR, $\geq$2 FDRs + 0 SDR, 0 FDR + 1 SDR, and 0 FDR + $\geq$2 SDRs), and youngest age at polyp diagnosis (younger than 50 years, 50–59 years, 60 years and older). All analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC).

Results

A total of 11,676,043 individuals with at least 1 known FDR were included in this study (Table 1). Of these, 51% (n = 5,934,544) were men, median follow-up was 31 years, and 162,927 patients were diagnosed with CRC. In our study sample, a total of 850,198 individuals underwent at least 1 colonoscopy and the median age at their first colonoscopy was 63 years (interquartile range, 49–74 years). Among relatives diagnosed with colorectal polyp (n = 196,910), 162,769 had only 1-time polyp diagnosis (70.7% of them underwent only 1 colonoscopy) and 34,141 had frequent ($\geq$2 times) polyp diagnoses. Approximately 11% (n = 1,326,117) of the individuals in our database exclusively had a family history of benign colorectal polyp without family history of CRC or in situ carcinoma.

Table 1. Characteristics of Included Individuals

Characteristic	Data
Total, n	11,676,043
Sex, male, n (%)	5,934,544 (50.8)
Age, *y*, median (25th and 75th percentile)	49 (24–71)
CRC diagnosis, n	162,927
Individuals with at least 1 colonoscopy, n	850,198
Age, *y*, at first colonoscopy, median (25th and 75th percentile)	63 (49–74)
Relatives with 1-time polyp diagnosis, n	162,769
Underwent only 1 colonoscopy, n (%)	115,090 (70.7)
Underwent more than 1 colonoscopy, n (%)	47,679 (29.3)
Relatives with frequent polyp diagnoses, n	34,141
Underwent only 2 colonoscopies, n (%)	14,694 (43.0)
Underwent more than 2 colonoscopies, n (%)	19,447 (57.0)

Overall Risk of Colorectal Cancer in Relatives of Patients With Polyp Diagnosis

In individuals with a family history of polyp, the risk of CRC increased with the number of FDRs with polyp and the frequency of polyp diagnosis in relatives (Table 2). Compared with those without any family history, individuals with 1 FDR with a history of 1-time polyp diagnosis had a 1.35-fold increased risk of CRC (95% CI, 1.32–1.38). The risk was significantly increased in individuals with 1 FDR with frequent polyp diagnoses (SIR, 1.82; 95% CI, 1.76–1.88), close to individuals with ≥2 FDRs with 1-time polyp diagnosis (SIR, 1.89; 95% CI, 1.73–2.06). Individuals with ≥2 FDRs with frequent polyp diagnoses had a 2.44-fold risk of CRC (95% CI, 2.20–2.69).

We did not find a significant association between CRC risk and having any number of SDRs with a 1-time polyp diagnosis. However, there was a 1.21-fold increased risk of CRC associated with having 1 SDR with frequent polyp diagnoses (95% CI, 1.10–1.32). The 1.20-fold increased risk in individuals with multiple SDRs with frequent polyp diagnoses was not statistically significant.

Further stratification by the youngest age at polyp diagnosis in relatives showed significantly increased SIRs and an age-dependent risk trend only in those with FDR diagnosed with polyp, although mostly with overlapping CIs (Table 2). When an FDR was diagnosed only once with polyp before age 50 years or at age 50–59 years, the risk was approximately 1.50-fold, which was significantly higher than the 1.28-fold risk for polyp diagnosis at age 60 years and older. The risk was 2.30-fold when an FDR was diagnosed with frequent polyp before age 50 years, 2.08-fold for age 50–59 years, and 1.66-fold for age 60 years and older. A similar trend was observed for those individuals with ≥2 FDRs with 1-time polyp diagnoses (SIR trend, 2.12, 2.16, and 1.69). In individuals with ≥2 FDRs with frequent polyp diagnoses, the SIR was

Table 2. Overall Risk of Colorectal Cancer in Relatives of Patients Diagnosed With Colorectal Polyp

No. of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, *y*	n[a]	Incidence/100,000 person-years	SIR[b]	95% CI
No FDR, no SDR	0	NA	142,234	44	Reference	Reference
1 FDR, no SDR	1	All ages	11,035	60	**1.35**	1.32–1.38
		<50	1541	53	**1.49**	1.42–1.57
		50–59	2072	71	**1.52**	1.46–1.59
		≥60	7421	59	**1.28**	1.25–1.31
	≥2	All ages	3144	84	**1.82**	1.76–1.88
		<50	472	96	**2.30**	2.10–2.51
		50–59	725	102	**2.08**	1.93–2.24
		≥60	1946	76	**1.66**	1.58–1.73
≥2 FDRs, no SDR	1	All ages	515	80	**1.89**	1.73–2.06
		<50	117	66	**2.12**	1.75–2.54
		50–59	144	94	**2.16**	1.82–2.54
		≥60	254	81	**1.69**	1.48–1.91
	≥2	All ages	382	106	**2.44**	2.20–2.69
		<50	109	111	**3.43**	2.81–4.14
		50–59	103	106	**2.33**	1.90–2.82
		≥60	170	103	**2.10**	1.80–2.45
1 SDR, no FDR	1	All ages	2846	17	1.00	0.96–1.03
	≥2	All ages	490	15	**1.21**	1.10–1.32
≥2 SDRs, no FDR	1	All ages	85	7	1.11	0.88–1.37
	≥2	All ages	47	8	1.20	0.88–1.60

NA, not applicable.
[a]Number of observed patients with CRC.
[b]Adjusted for age, sex, calendar year, region, socioeconomic status, and history of diabetes mellitus. Bold indicates statistically significant (95% CIs did not include 1.00).

significantly higher when the polyp in at least one FDR was diagnosed before age 50 (3.43-fold) compared with the SIR when all polyps were diagnosed after age 59 (2.10-fold). We did not find any meaningful risk trend by age at polyp diagnosis in SDRs (Supplementary Table 2).

Risk of Early-Onset Colorectal Cancer in Relatives of Patients With Polyp Diagnosis

We observed an even stronger association between family history of polyp (number of affected FDRs, youngest age at polyp diagnosis, and frequency of polyp diagnosis in relatives) and early-onset CRC compared with overall CRC (Table 3). A history of frequent polyp diagnoses in 1 FDR was associated with a significantly higher risk of early-onset CRC (SIR, 2.27; 95% CI, 1.99–2.58) compared with the 1.82-fold increased risk (95% CI, 1.76–1.88) for overall CRC. Similarly, individuals with ≥2 FDRs with 1-time polyp diagnosis had a 2.16-fold increased risk of early-onset CRC (95% CI, 1.55–2.93) compared with a 1.89-fold increased risk (95% CI, 1.73–2.06) for overall CRC with overlapping CIs. The difference was even more evident in individuals with ≥2 FDRs diagnosed with frequent polyp, in whom the risk of early-onset CRC was 3.92-fold (95% CI, 2.83–5.30), which was significantly higher than the 2.44-fold increased risk (95% CI, 2.20–2.69) for overall CRC.

We did not find a substantial association between an increased risk of early-onset CRC and having SDRs with polyp diagnosis except for a 1.65-fold increased risk of CRC associated with having ≥2 SDRs with frequent polyp diagnoses (95% CI, 1.00–2.57).

Stratification by age at polyp diagnosis in FDRs showed that the risk of polyp diagnosis was highest in individuals with an FDR diagnosed before the age of 50 years, with a downward trend as the age at diagnosis increased (Table 3). When an FDR was diagnosed only once with polyp at age 50 years, 50–59 years, and 60 years and older, the risk was 2.17-fold (95% CI, 1.86–2.52), 1.75-fold (95% CI, 1.47–2.06), and 1.21-fold (95% CI, 1.09–1.33) increased, respectively. The risk was 4.47-fold (95% CI, 3.42–5.74) when an FDR was diagnosed with frequent polyp before age 50 years, 2.52-fold for age 50–59 years (95% CI, 1.87–3.32), and at 1.78-fold for age 60 years and older (95% CI, 1.48–2.11). A similar trend was observed for individuals with ≥2 FDRs with frequent polyp diagnoses, in whom the risk was 8.04-fold (95% CI, 5.20–11.87) for age 49 years or younger, 2.71-fold (95% CI, 1.17–5.33) for age 50–59 years, and 1.94-fold (95% CI, 0.88–3.68) for age 60 years and older.

In sensitivity analyses, additionally adjusted for history of hospitalization for obesity, alcoholism, and chronic obstructive pulmonary disease (as a proxy for heavy smoking), the main results of the overall and early-onset CRC risk remained robust (Supplementary Tables 3 and 4). In a sensitivity analysis excluding individuals with relatives diagnosed as 1-time polyp only from 1 colonoscopy, the risk of overall and early-onset CRC increased slightly but remained robust (Supplementary Tables 5 and 6).

Table 3. Risk of Early-Onset Colorectal Cancer in Relatives of Patients Diagnosed With Colorectal Polyp

No. of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, *y*	n[a]	Incidence/100,000 person-years	SIR[b]	95% CI
No FDR, no SDR	0	NA	8480	4	Reference	Reference
1 FDR, no SDR	1	All ages	742	6	**1.44**	1.34–1.55
		<50	172	8	**2.17**	1.86–2.52
		50–59	143	7	**1.75**	1.47–2.06
		≥60	427	5	**1.21**	1.09–1.33
	≥2	All ages	237	10	**2.27**	1.99–2.58
		<50	61	18	**4.47**	3.42–5.74
		50–59	50	11	**2.52**	1.87–3.32
		≥60	126	8	**1.78**	1.48–2.11
≥2 FDRs, no SDR	1	All ages	41	10	**2.16**	1.55–2.93
		<50	21	16	**3.88**	2.40–5.93
		50–59	6	6	**1.28**	0.47–2.80
		≥60	14	7	**1.58**	0.86–2.65
	≥2	All ages	42	18	**3.92**	2.83–5.30
		<50	25	35	**8.04**	5.20–11.87
		50–59	8	13	**2.71**	1.17–5.33
		≥60	9	9	**1.94**	0.88–3.68
1 SDR, no FDR	1	All ages	328	2	0.97	0.87–1.08
	≥2	All ages	69	2	1.11	0.86–1.40
≥2 SDRs, no FDR	1	All ages	22	2	1.00	0.62–1.50
	≥2	All ages	19	3	**1.65**	1.00–2.57

NA, not applicable.
[a]Number of observed patients with CRC.
[b]Adjusted for age, sex, calendar year, region, socioeconomic status, and history of diabetes mellitus. Bold indicates statistically significant (95% CIs did not include 1.00).

Discussion

Our study indicated a significant association between the frequency of polyp diagnosis (once or frequent) in FDRs and the risk of CRC, particularly early-onset CRC, by leveraging the largest family-cancer datasets in the world. This association was independent of the number of relatives with polyp and their age at polyp diagnosis. Interestingly, a similar increased CRC risk was observed when 1 FDR had frequent polyp diagnoses and when multiple FDRs had a 1-time polyp diagnosis.

Our study provides the first solid evidence of a significant association between the frequency of polyp diagnosis in FDRs and an increased risk of CRC, with a stronger association observed for early-onset CRC. This novel independent association was in addition to the association with the number of close relatives with polyp and the youngest age at polyp diagnosis. Although the incidence and mortality of late-onset CRC in the United States have declined by approximately 50%, mostly due to the widespread implementation of colorectal screening,[33,34] the increasing incidence of early-onset CRC remains a global concern due to its unknown etiology and poorer prognosis.[35] Current screening strategies for individuals with a family history of polyp are not only highly inconsistent, but also overlook those with a family history of frequent polyp diagnoses. Our results suggest that screening guideline developers and clinicians should recognize the elevated CRC risk in those with a family history of polyp, especially those with a family history of frequent polyp diagnoses and develop tailored screening strategies for this population. For individuals with a family history of polyp, frequency of polyp diagnosis (once or 2 or more times) in relatives should be included in risk-adapted CRC screening guidelines. Further studies are warranted focusing on recommending the optimal age at screening initiation, screening intervals, and screening modalities for individuals with a family history of polyp, with an emphasis on the frequency of such polyp diagnoses, in addition to number of affected relatives and their age at polyp diagnoses. In brief, our findings can be used to inform CRC screening guidelines and help design a more tailored approach to screening. Furthermore, understanding the mechanism behind the association between the frequency of polyp diagnosis in FDRs and an increased risk of CRC may help reduce the incidence and mortality of both overall and early-onset CRC. We suspect that relatives with frequent polyp diagnoses may have some familial genetic mutations and/or exposure to a shared environmental carcinogen compared with those with a 1-time polyp diagnosis, leading to an increased risk of both overall and early-onset CRC in the family members.[36,37] Although prior research has identified some factors associated with polyp frequency, including age,[38] lifestyle factors,[39] polyp characteristics at first colonoscopy,[40,41] and obesity,[42] the etiology behind these associations is still largely unknown and the clinical implications remain unclear. Further research is warranted to investigate the frequency of polyp from both genetic and environmental perspectives.

Our study corroborates previous findings of an age-dependent trend in CRC risk in individuals with an FDR diagnosed with polyp.[16] We observed a more pronounced trend in the risk of early-onset CRC, suggesting that individuals with FDRs diagnosed with polyp at a younger age may have an increased overall and early-onset CRC risk. Despite the observed age-dependent trend in CRC risk in individuals with a family history of polyp, specific screening guidelines by the age of onset in FDRs remain limited. The German and US Multi-Society Task Force Guidelines provide specific recommendations, suggesting that screening should be initiated 10 years before the youngest age at polyp diagnosis in FDRs.[43,44] Our findings suggest that the age at diagnosis of polyp in FDRs should be considered when enacting risk-adapted screening strategies, including tailored starting ages and intervals.

In addition, our study identified a subset of individuals at very high risk of early-onset CRC, with an estimated SIR ranging from 4.47 (having an FDR with frequent polyp diagnoses, the first one diagnosed before age 50 years) to 8.04 (having multiple FDRs with frequent polyp diagnoses, the first polyp diagnosed before age 50 years). A prior study concluded that CRC-associated genetic variants are more strongly associated with early-onset than late-onset CRC.[45] As such, genetic testing and consulting may be considered for those at high risk of early-onset CRC, and personalized surveillance should be applied to these individuals.[46]

Our study has some notable strengths. Firstly, by using the nationwide register-based, high-quality, family cancer data to extract information on the family relationship and polyp in the family members, we were able to avoid some common biases, such as selection bias and recall bias, which are common in smaller studies with self-reported family history. Secondly, our study leveraged some of the largest family cancer datasets, comprising more than 11 million individuals with up to 54 years of follow-up, thus providing sufficient power and robust evidence to identify associations between exposure and outcome. Thirdly, we discovered a significant correlation between the frequency of polyp diagnosis in relatives and the risk of both overall and early-onset CRC, independent of the number of relatives with polyp and their age at diagnosis. Our findings suggest that the frequency of polyp diagnosis in relatives should be taken into account when developing risk-adapted CRC screening strategies for individuals with a family history of polyp. Furthermore, our results demonstrated that family history of polyp, especially multiple FDRs with polyp and/or FDRs with frequent polyp diagnoses, is more strongly associated with early-onset CRC than with late-onset CRC. We also observed an age-dependent trend in CRC risk in individuals with FDRs diagnosed with polyp, highlighting the importance of considering the age at polyp diagnosis in relatives when screening those with a family history of polyp. Finally, we identified several high-risk groups for early-onset CRC that have not been adequately addressed by current screening guidelines.

We did not have information on polyp characteristics, such as size, number, and histologic classification, and were therefore unable to assess the association between these factors in relatives and the risk of CRC. However, a previous study by Song et al[16] reported no significant differences in the

association between polyp histologic type in relatives and risk of CRC.[16] As our study population largely overlaps that of Song et al, we believe that our results are valid across different histologic types of polyps. Although the lack of information on the number, histology, and size of polyps is indeed a weakness, this may better reflect real-world practice, when people rarely know the detailed characteristics of polyps in their relatives, but more likely know whether they have had 1 colonoscopy with polyp removal or more than one. Secondly, we were unable to adjust for certain potential confounders and modifiers, such as smoking and physical activity. However, as the results of our sensitivity analysis by further adjustment for hospitalization for chronic obstructive pulmonary disease (as proxy to heavy smoking), obesity, and alcoholism were quite similar to our main results, the potential impact of these residual factors on our results is likely minimal. Our sample size was also limited in some subgroups, particularly for second-degree relatives. Finally, the long-term follow-up in this study was a clear strength. However, the spanning of many generations of colonoscopy efficacy and technology may result in some unidentified polyps being assigned to the reference group (those without a polyp in a relative). This is a limitation that must be acknowledged. Nevertheless, this limitation does not affect the identified high-risk group with frequent polyp diagnoses, as they were diagnosed with even older technologies. This limitation inevitably leads to an underestimation of the actual risk. It is therefore likely that our newly identified high-risk group has an even higher risk than what we would have found if all reference groups had undergone high-technology colonoscopy. It is still imperative that this newly identified high-risk group be given special attention in screening strategies.

Based on some of the largest family-cancer datasets in the world, our study found that the frequency of colorectal polyp diagnosis in relatives (once or frequent) is associated with risk of CRC, particularly early-onset CRC, independent of number of close relatives with polyp and youngest age at polyp diagnosis. Therefore, frequency of colorectal polyp diagnosis in relatives should be considered as important as number of relatives with colorectal polyp when developing CRC screening strategies.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.12.030.

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The authors disclose no conflicts.

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Data Availability
No additional data are available. The lead author (M.F.) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Supplementary Materials and Methods

Screening Programs and Guidelines in Sweden

A population-based screening program for colorectal cancer in Stockholm-Gotland. In 2008–2009, the regions of Stockholm and Gotland, as the only 2 of 21 regions in Sweden (these 2 regions comprise nearly 20% of the total Swedish population), started implementing an organized screening program using biennial guaiac fecal occult blood tests (FOBTs).[29,30] Individuals aged 60–69 years (birth year cohorts from 1940) were gradually enrolled in the screening program. Invitations were sent randomly to selected birth-year cohorts every year, along with information about the screening, test instructions, and a prepaid return envelope. Individuals with positive tests were invited to a colonoscopy examination at a local clinic. New screening invitations were sent every 2 years, irrespective of prior participation. By 2011, seven cohorts (ie, individuals born in 1940, 1942, 1943, 1944, 1946, 1949, and 1950) had been enrolled in the program and the first of the invited birth cohorts (1940) progressed to the post-screening age interval (ie, age 70 years and older). In 2015, the guaiac FOBTs was replaced with fecal immunochemical tests (FITs). Participation rates were estimated to be up to 64% during the first 5 years of screening in the regions of Stockholm–Gotland, with approximately 86%–92% compliance with colonoscopy after a positive test result.

Swedish Colorectal Cancer Screening trial. A randomized controlled trial in 18 of 21 regions in Sweden (excluding Stockholm, Gotland, and Västernorrland) was conducted (SCREESCO [Swedish Colorectal Cancer Screening] study).[31] This covered 74.5% of the national population, where CRC screening was not previously offered. Residents who were 60 years old at the time of randomization were identified from a population register maintained by the Swedish Tax Agency. Eligible individuals were randomly assigned to a 1-time colonoscopy, 2 rounds of FIT screening (conducted 2 years apart), or a control group (no intervention; standard diagnostic pathways). Between March 1, 2014 and December 31, 2020, a total of 278,280 people were included in the study: 31,140 were assigned to the colonoscopy group, 60,300 to the FIT group, and 186,840 to the control group.

Swedish National Screening Program. By September 2022, all 21 health care regions in Sweden had initiated a nationally synchronized screening program for colorectal cancer[28]: All residents of Sweden, aged 60–74 years, are offered participation by mail every second year.

Screening guidelines in Sweden. In 2014, the National Board of Health and Welfare recommended screening with FOBT test for the age group 60–74 years every 2 years. In 2017, the Regional Cancer Center South proposed FOBT-based screening for the age group 50–74 years.[28]

Swedish screening guidelines for individuals with a hereditary increased risk without a proven pathogenic variant are recommended colonoscopy checks according to following family history[32]:

1. One FDR with CRC diagnosed before age 50 years: Single colonoscopy at age 55 years
2. One FDR with CRC diagnosed at age 50 years or older: No colonoscopy
3. Child/sibling/parent of cluster of 2 FDRs with CRC: Single colonoscopy at age 55 years
4. Child/sibling/parent of cluster of 3 FDRs with CRC: Colonoscopy every 5 years starting 5 years before the youngest age at diagnosis of affected family members

They have not yet provided any specific CRC screening recommendations for individuals with a family history of colorectal polyp.

Quality of Colonoscopies in Sweden

Data from the SCREESCO demonstrated that the adenoma detection rate was 23.9% and 37.8% in colonoscopy and FIT arms, respectively. Lesion detectability in SCREESCO was mostly acceptable, with room for improvement.[e1,e2]

Supplementary Discussion

We excluded the patients with potential hereditary nonpolyposis CRC (HNPCC) according to Amsterdam II criteria.[e3] We may have missed a few patients with HNPCC that could not be identified by these criteria. However, HNPCC is a familial hereditary condition. In our study, we excluded all individuals with a family history of CRC. As a result of this exclusion, we believe that we excluded most of the patients with HNPCC in the first place, before entering our study focusing only on family history of polyp diagnosis without any family history of CRC. That is why the prevalence of HNPCC is very low in our study population, but not in our original database.

Supplementary References

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Supplementary Table 1. Colorectal Polyp Codes From International Classification of Diseases Systems

ICD version	Year	Codes
ICD-7[23]	1964–1968	211
ICD-8[24]	1969–1986	211.3, 211D, 211.4, and 211E
ICD-9[25]	1987–2005	569, 569A, 556.4, V12.72, V12H, 211.3, 211D, 211.4, and 211E
ICD-10[26]	2006–2018	K63.5, K62.1, K51.4, JFA15, JGA05, and D12

Supplementary Table 2. Risk of Colorectal Cancer in Second-Degree Relatives of Patients Diagnosed With Colorectal Polyp by Youngest Age at Polyp Diagnosis

CRC risk	No. of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, *y*	n[a]	Incidence/100,000 person-years	SIR[b]	95% CI
Overall	No SDR, no FDR	0	NA	142,234	44	Reference	Reference
	1 SDR, no FDR	1	<50	1792	47	0.99	0.94–1.03
			50–59	549	23	1.00	0.92–1.08
			≥60	504	5	1.03	0.94–1.12
		≥2	<50	301	53	**1.21**	1.08–1.36
			50–59	101	19	**1.38**	1.12–1.67
			≥60	88	4	1.04	0.83–1.28
	≥2 SDRs, no FDR	1	<50	45	16	1.05	0.76–1.40
			50–59	17	7	1.21	0.70–1.93
			≥60	23	4	1.17	0.74–1.76
		≥2	<50	19	13	0.84	0.50–1.31
			50–59	7	4	1.00	0.40–2.06
			≥60	21	**7**	**2.23**	1.38–3.41
Early-onset	0 SDR, no FDR	0	NA	8480	4	Reference	Reference
	1 SDR, no FDR	1	<50	87	3	0.95	0.76–1.17
			50–59	31	2	0.72	0.49–1.02
			≥60	209	2	1.04	0.90–1.19
		≥2	<50	17	4	1.35	0.78–2.15
			50–59	12	2	1.28	0.66–2.23
			≥60	40	2	0.99	0.71–1.35
	≥2 SDRs, no FDR	1	<50	6	2	1.15	0.42–2.51
			50–59	4	2	0.91	0.25–2.32
			≥60	12	2	0.96	0.49–1.67
		≥2	<50	3	2	1.19	0.25–3.48
			50–59	4	3	1.36	0.37–3.49
			≥60	12	4	**1.97**	1.02–3.44

NA, not applicable.
[a]Number of observed patients with CRC.
[b]Adjusted for age, sex, calendar year, region, socioeconomic status, and history of diabetes mellitus. Bold indicates statistically significant (95% CIs did not include 1.00).

Supplementary Table 3. Risk of Overall Colorectal Cancer in Relatives of Patients Diagnosed With Colorectal Polyp Additionally Adjusting for History of Hospitalization for Obesity, Alcoholism, and Chronic Obstructive Pulmonary Disease

No. of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, *y*	n[a]	Incidence/100,000 person-years	SIR[b]	95% CI
No FDR, no SDR	0	NA	142,234	44	Reference	Reference
1 FDR, no SDR	1	All ages	11,035	59	**1.35**	1.33–1.38
		<50	1541	51	**1.49**	1.42–1.57
		50–59	2072	70	**1.53**	1.46–1.59
		≥60	7421	59	**1.29**	1.26–1.32
	≥2	All ages	3144	82	**1.82**	1.76–1.89
		<50	472	90	**2.30**	2.10–2.52
		50–59	725	99	**2.09**	1.94–2.25
		≥60	1946	76	**1.66**	1.59–1.73
≥2 FDRs, no SDR	1	All ages	515	89	**1.89**	1.73–2.06
		<50	117	91	**2.12**	1.75–2.54
		50–59	144	113	**2.17**	1.83–2.56
		≥60	254	83	**1.69**	1.49–1.91
	≥2	All ages	382	118	**2.45**	2.21–2.71
		<50	109	144	**3.44**	2.82–4.15
		50–59	103	143	**2.34**	1.91–2.84
		≥60	170	104	**2.12**	1.81–2.46
1 SDR, no FDR	1	All ages	2846	17	1.00	0.96–1.04
	≥2	All ages	490	14	**1.21**	1.10–1.32
≥2 SDRs, no FDR	1	All ages	85	8	1.10	0.88–1.37
	≥2	All ages	47	8	1.20	0.88–1.60

NA, not applicable.
[a]Number of observed patients with CRC.
[b]Adjusted for age, sex, calendar year, region, socioeconomic status, history of diabetes mellitus, and history of hospitalization, obesity, alcoholism and chronic obstructive pulmonary disease. Bold indicates statistically significant (95% CIs did not include 1.00).

Supplementary Table 4. Risk of Early-Onset Colorectal Cancer in Relatives of Patients Diagnosed With Colorectal Polyp Additionally Adjusting for History of Hospitalization for Obesity, Alcoholism, and Chronic Obstructive Pulmonary Disease

No. of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, *y*	n[a]	Incidence/100,000 person-years	SIR[b]	95% CI
No FDR, no SDR	0	NA	8480	4	Reference	Reference
1 FDR, no SDR	1	All ages	742	6	**1.45**	1.34–1.55
		<50	172	8	**2.18**	1.87–2.54
		50–59	143	7	**1.77**	1.49–2.08
		≥60	427	5	**1.21**	1.10–1.33
	≥2	All ages	237	9	**2.28**	2.00–2.59
		<50	61	16	**4.49**	3.43–5.77
		50–59	50	11	**2.54**	1.89–3.35
		≥60	126	8	**1.79**	1.49–2.13
≥2 FDRs, no SDR	1	All ages	41	12	**2.19**	1.57–2.97
		<50	21	21	**3.96**	2.45–6.05
		50–59	6	13	**1.30**	0.48–2.84
		≥60	14	10	**1.58**	0.87–2.66
	≥2	All ages	42	20	**3.94**	2.84–5.32
		<50	25	60	**8.11**	5.25–11.97
		50–59	8	17	**2.73**	1.18–5.38
		≥60	9	11	1.93	0.88–3.67
1 SDR, no FDR	1	All ages	328	2	0.98	0.87–1.09
	≥2	All ages	69	2	1.11	0.86–1.40
≥2 SDRs, no FDR	1	All ages	22	2	0.99	0.62–1.50
	≥2	All ages	19	3	1.64	0.99–2.57

NA, not applicable.
[a]Number of observed patients with CRC.
[b]Adjusted for age, sex, calendar year, region, socioeconomic status, history of diabetes mellitus, and history of hospitalization, obesity, alcoholism, and chronic obstructive pulmonary disease. Bold indicates statistically significant (95% CIs did not include 1.00).

Supplementary Table 5. Risk of Overall Colorectal Cancer in Relatives of Patients Diagnosed With Colorectal Polyp, Excluding Relatives With 1-Time Polyp Diagnosis From Only 1 Colonoscopy

No. of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, *y*	n[a]	Incidence/100,000 person-years	SIR[b]	95% CI
No FDR, no SDR	0	NA	142,234	44	Reference	Reference
1 FDR, no SDR	1	All ages	3757	66	**1.48**	1.43–1.52
		<50	495	53	**1.67**	1.52–1.82
		50–59	795	71	**1.71**	1.59–1.83
		≥60	2467	59	**1.38**	1.33–1.44
	≥2	All ages	3090	83	**1.81**	1.75–1.88
		<50	451	96	**2.30**	2.10–2.53
		50–59	706	102	**2.07**	1.92–2.23
		≥60	1933	76	**1.65**	1.58–1.73
≥2 FDRs, no SDR	1	All ages	77	103	**2.37**	1.87–2.97
		<50	13	66	**2.16**	1.15–3.69
		50–59	30	94	**3.02**	2.04–4.31
		≥60	34	81	**2.06**	1.43–2.88
	≥2	All ages	194	133	**3.04**	2.62–3.50
		<50	60	111	**4.65**	3.55–5.99
		50–59	56	106	**2.96**	2.24–3.85
		≥60	78	103	**2.43**	1.92–3.03
1 SDR, no FDR	1	All ages	915	18	1.01	0.95–1.08
	≥2	All ages	480	15	**1.20**	1.10–1.31
≥2 SDRs, no FDR	1	All ages	8	6	0.87	0.37–1.71
	≥2	All ages	19	8	1.10	0.66–1.71

NA, not applicable.
[a]Number of observed patients with CRC.
[b]Adjusted for age, sex, calendar year, region, socioeconomic status, and history of diabetes mellitus. Bold indicates statistically significant (95% CIs did not include 1.00).

Supplementary Table 6. Risk of Early-Onset Colorectal Cancer in Relatives of Patients Diagnosed With Colorectal Polyp Excluding Relatives With 1-Time Polyp Diagnosis From Only 1 Colonoscopy

No. of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, *y*	n[a]	Incidence/100,000 person-years	SIR[b]	95% CI
No FDR, no SDR	0	NA	8480	4	Reference	Reference
1 FDR, no SDR	1	All ages	255	7	**1.62**	1.43–1.84
	≥2	All ages	234	10	**2.26**	1.98–2.56
≥2 FDRs, no SDR	1	All ages	6	12	**2.73**	1.00–5.95
	≥2	All ages	19	20	**4.40**	2.65–6.87
1 SDR, no FDR	1	All ages	95	2	0.96	0.77–1.67
	≥2	All ages	68	2	1.10	0.85–1.39
≥2 SDRs, no FDR	1	All ages	1	1	0.43	0.01–2.41
	≥2	All ages	8	4	1.91	0.83–3.78

NA, not applicable.
[a]Number of observed patients with CRC.
[b]Adjusted for age, sex, calendar year, region, history of diabetes mellitus, and socioeconomic status. Bold indicates statistically significant (95% CIs did not include 1.00).