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Risk of colorectal cancer associated with frequency of colorectal polyp diagnosis in relatives

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ABSTRACT (260 WORDS, LIMIT 260)

Background & Aims: We aimed to evaluate the association of frequency of polyp diagnosis in relatives with the risk of overall and early-onset colorectal cancer (CRC).

Methods: We leveraged data from nationwide Swedish family cancer datasets (1964-2018) to calculate standardized incidence ratios (SIRs) for individuals with a family history of polyp by frequency of polyp diagnosis in family members.

Results: We followed up 11,676,043 individuals 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 FDR with one-time polyp diagnosis [95%CI=1.3-1.4, N=11,035; early-onset SIR: 1.4 (1.3-1.5), N=742]. The risk was significantly higher in individuals with 1 FDR with ≥2 times (frequent) polyp diagnoses [overall CRC: 1.8 (1.8-1.9); early-onset CRC=2.3 (2.0-2.6)]. A rather similar risk was observed for individuals with ≥2 FDRs with one-time polyp diagnosis [overall CRC: 1.9 (1.7-2.1); early-onset CRC: 2.2 (1.5-2.9)]. Individuals with ≥2 FDRs with frequent polyp diagnoses had a 2.4-fold overall risk (2.2-2.7) and a 3.9-fold early-onset risk (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

INTRODUCTION

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 from polyp to CRC.[2] Colonoscopy screening and subsequent polypectomy have been shown 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 with a recent shift to 45 in the US.[4-6] However, there has been a notable increase in early-onset CRC (diagnosed before the age of 50), 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 to 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 the number of first-degree relatives (FDRs) diagnosed with polyp and the age at diagnosis in relatives.[16] However, that study did not differentiate between 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 is reported to be 55%, whereas in Europe this rate is reported to be at least 41%.[17-18] More importantly, the prevalence of frequent colorectal polyp was reported to be 1% to 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 are 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 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

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 four 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 together 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 7th Revision of International Classification of Diseases (ICD-7) codes and later revisions. The Population Register provides vital information about individuals' births, deaths, migration records, and socioeconomic measures for the entire study period. The above datasets are updated periodically and the last update in 2020, which is used for this study, includes over 13 million individuals that were followed up to the end of 2018, with an overall completeness of cancer data estimated at 96% or higher.[23]

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 one 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 colorectal cancer (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 CRC and benign colorectal polyp

Sweden issued colorectal cancer screening guidelines in 2014, but it did not launch a nationwide screening program until September 2022.[24] Before this, there were some regional screening trials in Sweden, generally starting at age 60.[25-27] More details are presented in the online supplementary eMethods. For individuals with FDR(s) who had early-onset colorectal cancer, Sweden recommended starting screening at age 55.[28] They did not mention any specific recommendation for family members of patients with colorectal polyp. Data on CRC patients were extracted from the Swedish Cancer Registry dataset using the following ICD-7 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, ICD-9, and ICD-10 coding systems (**Supplementary Table S1)**.

Family history of polyp

The 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 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 two 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 two categories: those diagnosed once and those with frequent diagnoses. A frequent polyp diagnosis was defined as at least two 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 three groups: <50, 50-59, and ≥60 years. 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 five-year age groups, sex, calendar year (ranging from 1964 to 2018 in intervals of five 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 one-time polyp only from one 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% confidence intervals (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 (one-time polyp diagnosis, and ≥2 times polyp diagnoses), number of relatives with polyp (1 FDR + 0 SDR, ≥2 FDRs + 0 SDR, 0 FDR + 1 SDR, and 0 FDR + ≥2 SDRs), and youngest age at polyp diagnosis (<50, 50-59, ≥60 years). 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 one known FDR were included in this study (**Table 1**). Of these, 51% (n=5,934,544) were men, the 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 one colonoscopy, and the median age at their first colonoscopy was 63 (49-74) years. Among relatives diagnosed with colorectal polyp (N=196,910), 162,769 had only one-time polyp diagnosis (70.7% of them underwent only one colonoscopy), and 34,141 had frequent (≥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.

***Overall* risk of CRC 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 to those without any family history, individuals with 1 FDR with a history of one-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 one-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 one-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 confidence intervals (**Table 2**). When an FDR was diagnosed only once with polyp before age 50 years or at age 50-59, the risk was about 1.50-fold, which was significantly higher than the 1.28-fold risk for polyp diagnosis at age≥60. The risk was 2.30-fold when an FDR was diagnosed with frequent polyp before age 50, 2.08-fold for age 50-59, and 1.66-fold for age≥60. A similar trend was observed for those individuals with ≥2 FDRs with one-time polyp diagnoses (SIR trend 2.12, 2.16, and 1.69). In individuals with ≥2 FDRs with frequent polyp diagnoses and the youngest age of diagnosis below 50 (3.43-fold) was significantly higher than that for youngest age≥60 (2.10-fold). We did not find any meaningful risk trend by age at polyp diagnosis in SDRs (**Supplementary Table S2**).

Risk of early-onset CRC 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 to 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 to the 1.82-fold increased risk (95% CI 1.76-1.88) for overall CRC. Similarly, individuals with ≥2 FDRs with one-time polyp diagnosis had a 2.16-fold increased risk of early-onset CRC (95% CI 1.55-2.93) compared to 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, with a downward trend as the age at diagnosis increased (**Table 3**). When an FDR was diagnosed only once with polyp at age 50, 50-59, and age≥60 years, 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, 2.52-fold for age 50-59 (95% CI 1.87-3.32), and at 1.78-fold for age≥60 (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 or younger, 2.71-fold (95% CI 1.17-5.33) for age 50-59, and 1.94-fold (95% CI 0.88-3.68) for age≥60.

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 Table S3 and Table S4**). In a sensitivity analysis excluding individuals with relatives diagnosed as

one time polyp only from one colonoscopy, the risk of overall and early-onset CRC increased slightly but remained robust (**Supplementary Table S5 and Table S6**).

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 one FDR had frequent polyp diagnoses and when multiple FDRs had a one-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. While the incidence and mortality of late-onset CRC in the US have declined by approximately 50% mostly due to the widespread implementation of colorectal screening,[29, 30] the increasing incidence of early-onset CRC remains a global concern due to its unknown etiology and poorer prognosis.[31] 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 accurately 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 times) in relatives should be included in risk-adapted colorectal cancer screening guidelines Further studies are warranted focusing on recommending the optimal age of screening initiation, screening intervals, and screening modalities for individuals with a family history of polyp with 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 the reduction of 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 to those with a one-time polyp diagnosis, leading to an increased risk of both overall and early-onset CRC in the family members.[32, 33] Although prior research has identified some factors associated with polyp frequency, including age,[34] lifestyle factors,[35] polyp characteristics at first colonoscopy,[36-38] and obesity,[35] 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 the US Multi-Society Task Force Guidelines provide specific recommendations, suggesting that screening should be initiated 10 years prior to the youngest age at polyp diagnosis in FDRs.[39, 40] 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) to 8.04 (having multiple FDRs with frequent polyp diagnoses, the first polyp diagnosed before age 50). A prior study concluded that CRC-associated genetic variants are more strongly associated with early-onset than late-onset CRC.[41] 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.[42]

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 that 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 for the first time 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 FDR(s) with frequent polyp diagnoses, played a more important role in early-onset CRC compared 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 of 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 histological 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 reported no significant differences in the association between polyp histological type in relatives and the risk of CRC.[16] As our study population largely overlaps with that of Song et al., we believe that our results are valid across different histological types of polyps. While the lack of information on the number, histology, and size of polyps is indeed a weakness, this may better reflect real-world practice, where people rarely know the detailed characteristics of polyps in their relatives, but more likely know whether they have had one-time colonoscopy with polyp removal or more than once. Secondly, we were unable to adjust for certain potential confounders/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 is 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 anyway. 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-tech 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.

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Author names in bold designate shared co-first authorship.

Table 1. Characteristics of included individuals

Characteristics	Numbers
Total	11,676,043
Male	5,934,544 (50.8%)
Median age (25th and 75th percentile), y	49 (24-71)
Colorectal cancer diagnosis	162,927
Individuals with at least 1 colonoscopy	850,198
Median age at first colonoscopy (25th and 75th percentile), y	63 (49-74)
Relatives with one-time polyp diagnosis	162,769
Underwent only 1 colonoscopy	115,090 (70.7%)
Underwent >1 colonoscopy	47,679 (29.3%)
Relatives with frequent polyp diagnoses	34,141
Underwent only 2 colonoscopies	14,694 (43.0%)
Underwent >2 colonoscopies	19,447 (57.0%)

Table 2. Overall risk of colorectal cancer in relatives of patients diagnosed with colorectal polyp

Number of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, y	N	Incidence /100,000 person-years	SIR	95% CI
No FDR, no SDR	0	NA	142,234	44	**Reference**	
1 FDR, no SDR	1	All ages	11,035	60	**1.35**	1.32-1.38
		<50	1,541	53	**1.49**	1.42-1.57
		50-59	2,072	71	**1.52**	1.46-1.59
		≥60	7,421	59	**1.28**	1.25-1.31
	≥2	All ages	3,144	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	1,946	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	2,846	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

CI=Confidence interval; FDR=First-degree relative; SDR=Second-degree relative; N: Number of observed colorectal cancer patients; NA=Not applicable; SIR=Standardized incidence ratio adjusted for age, sex, calendar year, region, socioeconomic status, and history of diabetes mellitus. Bold SIR indicates statistically significant (95% CIs did not include 1.00).

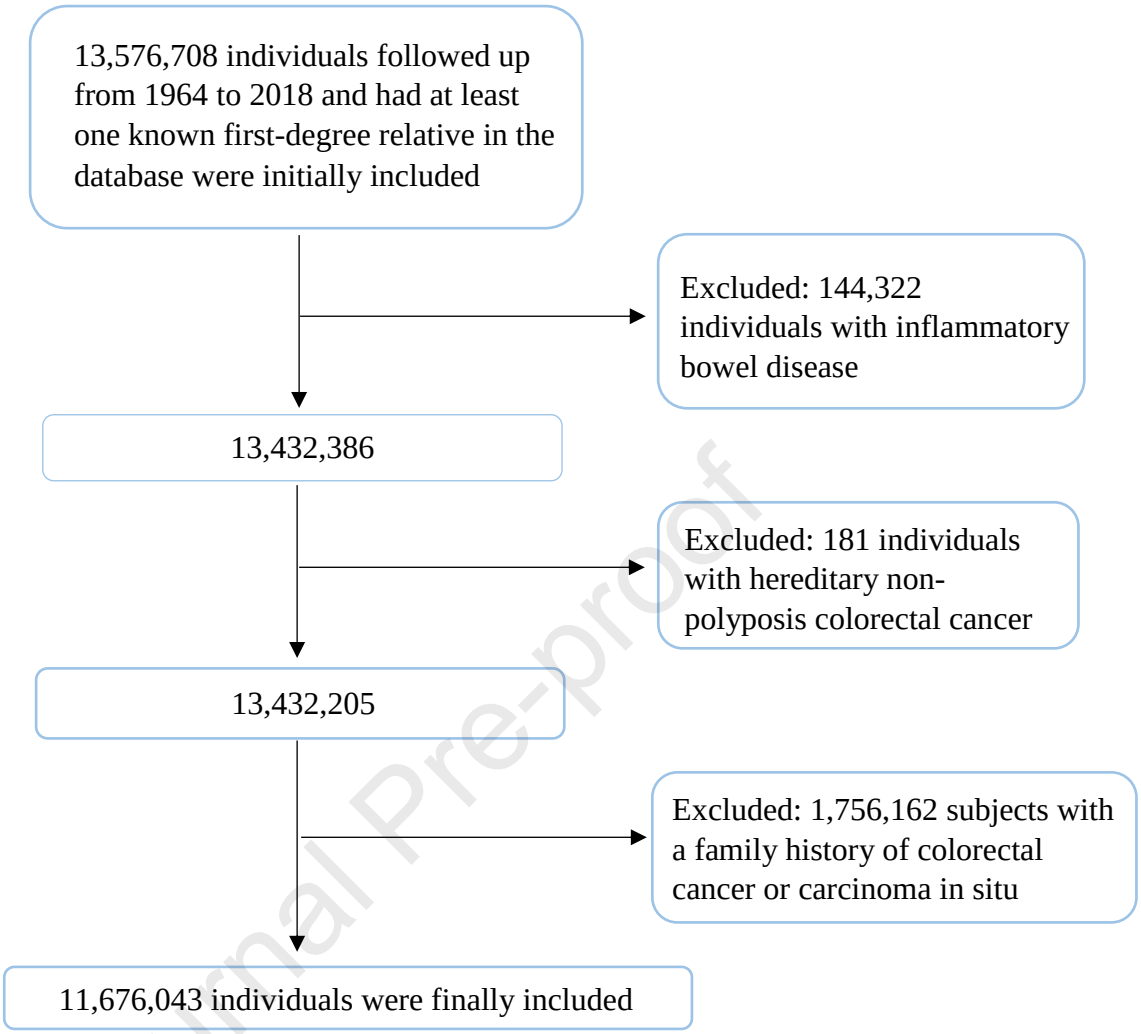
Table 3. Risk of <u>early-onset</u> colorectal cancer in relatives of patients diagnosed with colorectal polyp

Number of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, y	N	Incidence /100,000 person-years	SIR	95% CI
No FDR, no SDR	0	NA	8,480	4		**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

CI=Confidence interval; FDR=First-degree relative; SDR=Second-degree relative; N: Number of observed colorectal cancer patients; NA=Not applicable; SIR=Standardized incidence ratio adjusted for age, sex, calendar year, region, socioeconomic status, and history of diabetes mellitus. Bold SIR indicates statistically significant (95% CIs did not include 1.00).

Legend of figure:

Figure 1. Flowchart of study population



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

- We lacked information on specific polyp characteristics, including size, number, and histological classification. This limitation reflects real-world scenarios where 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.

Lay summary

A higher frequency of colorectal polyp diagnoses among relatives is associated with a greater risk of (early-onset) colorectal cancer, even when considering the number of affected relatives and age at polyp diagnosis.

Risk of colorectal cancer associated with frequency of colorectal polyp diagnosis in relatives

Yuqing Hu; Elham Kharazmi; Qunfeng Liang; Kristina Sundquist; Jan Sundquist; Mahdi Fallah

Supplementary materials

eMethods

Screening programs and guidelines in Sweden

A population-based screening program for colorectal cancer in Stockholm-Gotland[1, 2]: In 2008–2009, the regions of Stockholm and Gotland, as the only two of the 21 regions in Sweden (these two regions comprise nearly 20% of the total Swedish population), started implementing an organized screening program using biennial guaiac fecal occult blood tests (gFOBT). Individuals aged 60–69 (birth year cohorts from 1940) were gradually enrolled in the screening program. Invitations were randomly sent to selected birth-year cohorts every year, along with information about the screening, test instructions, and a pre-paid return envelope. Individuals with positive tests were invited to a colonoscopy examination at a local clinic. New screening invitations were made every two years, irrespective of prior participation. By 2011, seven cohorts (individuals were 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 (i.e., age≥70 years). In 2015, the gFOBT was replaced by fecal immunochemical tests (FIT). Participation rates were estimated to be up to 64% during the first five years of screening in the regions of Stockholm–Gotland with around 86%–92% compliance to colonoscopy following a positive test result.

Swedish colorectal cancer screening trial (SCREESCO)[3]: They conducted a randomized controlled trial in 18 out of 21 regions in Sweden (excluding Stockholm, Gotland, and Västernorrland) as of the SCREESCO study. This covered 74.5% of the national population, where colorectal cancer 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 either a one-time colonoscopy, two rounds of FIT screening (conducted two 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:[4] By September 2022, all 21 health care regions in Sweden had initiated a nationally synchronized screening program for colorectal cancer: All residents of Sweden, 60-74 years old, are offered participation by mail every second year.

Screening guidelines in Sweden[4]: In 2014, the National Board of Health and Welfare recommended screening with FOBT test for the age group 60-74 years every two years. In 2017, the Regional Cancer Center South proposed FOBT-based screening for the age group 50-74 years.

Swedish screening guidelines for individuals with a hereditary increased risk without a proven pathogenic variant are recommended colonoscopy checks according to following family history**:**[5]

1. One first-degree relative with colorectal cancer diagnosed before age 50 years: Single colonoscopy at age 55 years
2. One first-degree relative with colorectal cancer diagnosed at age ≥50: No colonoscopy

Child/sibling/parent of cluster of two first-degree relatives with colorectal cancer: Single colonoscopy at age 55

3. Child/sibling/parent of cluster of three first-degree relatives with colorectal cancer: Colonoscopy every five years starting five years before the youngest age at diagnosis of affected family members.

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

Quality of colonoscopies in Sweden[6, 7]

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.

eDiscussion

We excluded the potential HNPCC patients according to Amsterdam II criteria.9 We may have missed a few HNPCC patients 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 colorectal cancer. As a result of this exclusion, we believe that we excluded the majority of HNPCC patients 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.

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Author names in bold designate shared co-first authorship.

Supplementary Table S1. Colorectal polyp codes from International Classification of Diseases systems

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

ICD=International Classification of Diseases.

Supplementary Table S2. Risk of colorectal cancer in second-degree relatives of patients diagnosed with colorectal polyp by youngest age at polyp diagnosis

CRC risk	Number of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, y	N	Incidence /100,000 person-years	SIR	95% CI
Overall	**No SDR, no FDR**	0	NA	142,234	44	Reference	
	1 SDR, no FDR	1	<50	1,792	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	8,480	4	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

CI=Confidence interval; FDR=First-degree relative; SDR=Second-degree relative; N: Number of observed colorectal cancer patients; SIR=Standardized incidence ratio adjusted for age, sex, calendar year, region, socioeconomic status, and history of diabetes mellitus. Bold SIR indicates statistically significant (95% CIs did not include 1.00).

Supplementary Table 33. 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

Number of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, y	N	Incidence /100,000 person-years	SIR	95% CI
No FDR, no SDR	0	NA	142,234	44		Reference
1 FDR, no SDR	1	All ages	11,035	59	**1.35**	1.33-1.38
		<50	1,541	51	**1.49**	1.42-1.57
		50-59	2,072	70	**1.53**	1.46-1.59
		≥60	7,421	59	**1.29**	1.26-1.32
	≥2	All ages	3,144	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	1,946	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	2,846	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

CI=Confidence interval; FDR=First-degree relative; SDR=Second-degree relative; N: Number of observed colorectal cancer patients; NA=Not applicable; SIR=Standardized incidence ratio 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 SIR indicates statistically significant (95% CIs did not include 1.00).

Supplementary Table 34: 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

Number of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, y	N	Incidence /100,000 person-years	SIR	95% CI
No FDR, no SDR	0	NA	8,480	4	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

CI=Confidence interval; FDR=First-degree relative; SDR=Second-degree relative; N: Number of observed colorectal cancer patients; NA=Not applicable; SIR=Standardized incidence ratio 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 SIR indicates statistically significant (95% CIs did not include 1.00).

Supplementary Table 35. Risk of overall colorectal cancer in relatives of patients diagnosed with colorectal polyp excluding relatives with one-time polyp diagnosis from only one colonoscopy

Number of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, y	N	Incidence /100,000 person-years	SIR	95% CI
No FDR, no SDR	0	NA	142,234	44	**Reference**	
1 FDR, no SDR	1	All ages	3,757	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	2,467	59	**1.38**	1.33-1.44
	≥2	All ages	3,090	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	1,933	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

CI=Confidence interval; FDR=First-degree relative; SDR=Second-degree relative; N: Number of observed colorectal cancer patients; NA=Not applicable; SIR=Standardized incidence ratio adjusted for age, sex, calendar year, region, socioeconomic status, and history of diabetes mellitus. Bold SIR indicates statistically significant (95% CIs did not include 1.00).

Supplementary Table 3b. Risk of early-onset colorectal cancer in relatives of patients diagnosed with colorectal polyp excluding relatives with one-time polyp diagnosis from only one colonoscopy

Number of relatives with polyp	Frequency of polyp diagnosis	Youngest age at polyp diagnosis, y	N	Incidence /100,000 person-years	SIR	95% CI
No FDR, no SDR	0	NA	8,480	4		**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

CI=Confidence interval; FDR=First-degree relative; SDR=Second-degree relative; N: Number of observed colorectal cancer patients; NA=Not applicable; SIR=Standardized incidence ratio adjusted for age, sex, calendar year, region, history of diabetes mellitus, and socioeconomic status. Bold SIR indicates statistically significant (95% CIs did not include 1.00).