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Familial component of early-onset colorectal cancer: opportunity for prevention

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Abstract

Background: Individuals with a non-syndromic family history of colorectal cancer are known to have an increased risk. There is an opportunity to prevent early-onset colorectal cancer (age less than 50 years) (EOCRC) in this population. The aim was to explore the proportion of EOCRC that is preventable due to family history of colorectal cancer.

Methods: This was a retrospective multicentre European study of patients with non-hereditary EOCRC. The impact of the European Society of Gastrointestinal Endoscopy (ESGE), U.S. Multi-Society Task Force (USMSTF), and National Comprehensive Cancer Network (NCCN) guidelines on prevention and early diagnosis was compared. Colorectal cancer was defined as potentially preventable if surveillance colonoscopy would have been performed at least 5 years before the age of diagnosis of colorectal cancer, and diagnosed early if colonoscopy was undertaken between 1 and 4 years before the diagnosis.

Results: Some 903 patients with EOCRC were included. Criteria for familial colorectal cancer risk in ESGE, USMSTF, and NCCN guidelines were met in 6.3, 9.4, and 30.4 per cent of patients respectively. Based on ESGE, USMSTF, and NCCN guidelines, colorectal cancer could potentially have been prevented in 41, 55, and 30.3 per cent of patients, and diagnosed earlier in 11, 14, and 21.1 per cent respectively. In ESGE guidelines, if surveillance had started 10 years before the youngest relative, there would be a significant increase in prevention (41 *versus* 55 per cent; $P = 0.010$).

Conclusion: ESGE, USMSTF, and NCCN criteria for familial colorectal cancer were met in 6.3, 9.4, and 30.4 per cent of patients with EOCRC respectively. In these patients, early detection and/or prevention could be achieved in 52, 70, and 51.4 per cent respectively. Early and accurate identification of familial colorectal cancer risk and increase in the uptake of early colonoscopy are key to decreasing familial EOCRC.

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Introduction

Early-onset colorectal cancer (EOCRC), defined as cancer diagnosed before the age of 50 years, accounts for 10–12 per cent of all new colorectal cancer diagnoses. The incidence of colorectal cancer in individuals aged less than 50 years has been increasing since the mid-1990s, driven largely by rectal tumours, and is expected to increase by over 140 per cent by 2030[1,2]. The reasons for these increasing trends in EOCRC are uncertain, although the exposome, defined as the totality of human environmental exposures from conception onwards, has been hypothesized as one of the main causes[3–5].

The familial and hereditary component of EOCRC has been explored in several studies. Germline pathogenic variants in known cancer predisposition genes are present in ≈ 13 per cent (range 9–26 per cent) of patients with EOCRC, and in ≈ 28 per cent (range 13–33 per cent) with a family history of colorectal cancer[6,7]. Individuals with a non-syndromic family history of colorectal cancer are known to have an increased risk of this cancer, and most guidelines recommend starting surveillance at age 40 years with a 5-year interval[8–10]. However, there is variability in the definition of familial risk. According to the European Society of Gastrointestinal Endoscopy (ESGE)[11], this risk is considered to be clinically meaningful in those with at least one first-degree relative (FDR) diagnosed before the age of 50 years, and in individuals with two or more FDRs with colorectal cancer. On the other hand, the U.S. Multi-Society Task Force (USMSTF) guideline[12,13] defines familial risk as the presence of at least one FDR with colorectal cancer or advanced adenoma diagnosed before the age of 60 years, or having two or more FDRs. Finally, the National Comprehensive Cancer Network (NCCN) 2022 guideline[14] includes the presence of at least one FDR with colorectal cancer or advanced adenoma or advanced sessile serrated polyp regardless of age, and having second- and third-degree relatives with colorectal cancer at any age.

Stanich *et al.* recently showed in the Ohio Colorectal Cancer Prevention Initiative that, if current US screening guidelines were followed, more than 45 per cent of familial EOCRCs could be prevented, based on the assumption that a colonoscopy performed 5 years or more before the age of diagnosis of colorectal cancer could have prevented the cancer[15]. Furthermore, Gupta *et al.*[16] showed, among patients with EOCRC aged 40–49 years (which represents over 70 per cent of all EOCRCs), that one in four in met family history-based early screening criteria, and that 98.4 per cent of them could have been recommended screening initiation at an age younger than the observed age of diagnosis.

However, there is still uncertainty about the proportion of non-hereditary EOCRCs that could potentially be prevented by applying current familial colorectal cancer risk guidelines. This information would be of great interest to improve early diagnosis and prevention of EOCRC. The main aim of this study was to explore the proportion of EOCRCs that could be preventable based on a family history of colorectal cancer in two large multicentre European consortiums.

Methods

Study design and data sources

This retrospective, descriptive, multicentre European study included patients enrolled in two consortiums focused on EOCRC: Global Early-Onset Colorectal Cancer Database (GEOCODE) and Spanish Early-onset Colorectal Cancer Cohort (SECOC)[17]. GEOCODE is a worldwide consortium study with the main aim of exploring global patterns of EOCRC, and for this study data were collected on patients from participants from the following European countries: Spain, Italy, England, the Netherlands, Luxembourg, and Poland. SECOC is a Spanish group that integrates hospitals from Madrid, Barcelona, Basque Country, Castilla y Leon, and Navarra, all in Spain. Data from GEOCODE and SECOC were curated to avoid duplicates.

Study population

The study population consisted of patients with non-polyposis colorectal cancer diagnosed before the age of 50 years. Exclusion criteria were: known or suspected cancer predisposition syndromes; inflammatory bowel disease; and histological diagnoses other than adenocarcinoma. A database was developed with patients diagnosed with EOCRC from January 2010 to December 2020. Baseline patient characteristics, tumour characteristics, and family history of colorectal cancer with age at diagnosis (from proband and FDRs (children, siblings, parents)) and the degree of kinship (first, second, and third degree) were collected.

To rule out Lynch syndrome, patients with mismatch repair (MMR) deficiency, defined as either microsatellite instability and/or loss of MLH1, MSH2, MSH6 or PMS2 protein expression by immunohistochemistry, were excluded. Patients with sporadic MMR deficiency due to *MLH1* promoter hypermethylation were not excluded from the analysis. Patients with a (likely) pathogenic MMR germline variant in a cancer predisposition gene were also excluded. Studies undertaken in the population to excluded cancer predisposition syndromes are detailed in *Table S1*.

Statistical analysis

The prevalence of family history of colorectal cancer in the EOCRC population was analysed in subgroups. To evaluate the impact of family history on colorectal cancer prevention, following the statistical analysis carried out by Stanich *et al.*[15], it was assumed that surveillance colonoscopy performed at least 5 years before the patient's age at diagnosis would have prevented colorectal cancer, and undertaking colonoscopy 1–4 years before the colorectal cancer diagnosis would have led to an earlier diagnosis. The impact on prevention and early detection of colorectal cancer if ESGE, USMSTF and NCCN guidelines (*Table 1*) were applied correctly in this cohort, considering that the main difference in the recommendation is that the USMSTF and NCCN guidelines recommend starting screening at age 40 years or 10 years earlier than the youngest relative with colorectal cancer, whichever comes first (as opposed to age 40 years for all individuals in the ESGE guideline). The difference in age at which the colorectal cancer was diagnosed with respect to the potential age at which surveillance colonoscopy should have been performed based on family history was analysed.

A descriptive analysis was carried out first. The χ^2 test (independence test) and Fisher's test (when necessary) were used, and $P < 0.050$ was considered statistically significant. ANOVA (ANOVA or Kruskal–Wallis test) was used for quantitative variables. All analyses were done using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Table 1 Practice guidelines recommending early initiation of screening before age 50 years based on family history of colorectal cancer used in this study

Practice guideline	Criteria	Recommendation
European Society of Gastrointestinal Endoscopy[11]	≥ 1 FDR diagnosed with CRC before the age of 50 years 2 or more FDRs with CRC at any age	Colonoscopy at age 40 years
U.S. Multi-Society Task Force[12,13]	≥ 1 FDR with CRC or advanced adenoma diagnosed before the age of 60 years 2 or more FDRs with colorectal cancer at any age	Colonoscopy at age 40 years or 10 years before earliest diagnosis of CRC, whichever is first
National Comprehensive Cancer Network[14]	≥ 1 FDR with CRC or advanced adenoma/ advanced sessile serrated polyps at any age	Colonoscopy at age 40 years or 10 years before earliest diagnosis of CRC (or age of onset of adenoma in relative), whichever is first
	SDRs and TDRs with CRC at any age	Colonoscopy at age 45 years

FDR, first-degree relative; CRC, colorectal cancer; SDR, second-degree relative; TDR, third-degree relative.

Table 2 Characteristics of cohort

	No. of patients	Age at diagnosis of CRC (years), mean(s.d.)
Whole cohort	903 (100)	41.8(6.5)
Sex		
F	448 (49.6)	41.4 (6.6)
M	455 (50.3)	42.3 (6.4)
Tumour location*		
Right colon	217 (24.8)	
Left colon	317 (36.2)	
Rectum	342 (39)	
TNM stage at diagnosis		
I	138 (16.2)	
II	180 (21.1)	
III	295 (34.7)	
IV	238 (28)	
Family history of colorectal cancer		
Yes	275 (30.4)	41.5 (6.4)
No	628 (69.6)	41.9 (6.5)
Family relationship†		
First-degree relative		
≥ 1	155 (17.2)	42.4 (6.1)
≥ 1 aged < 50 years	37 (4.1)	39.7 (7.3)
≥ 1 aged < 60 years	68 (7.5)	41.1 (6.5)
≥ 2	33 (3.6)	43.3 (5.5)
Second-degree relative		
1	150 (16.6)	40.8 (6.9)
≥ 2	35 (3.9)	40.1 (7.1)
Third-degree relative		
≥1	29 (3.2)	41.4 (7.1)

Values are *n* (%) unless otherwise indicated.
*Right colon includes caecum, ascending colon, hepatic flexure, and transverse colon; left colon includes splenic flexure, descending colon, and sigmoid colon; rectum includes rectosigmoid junction and rectum.
†Calculated based on total number of patients, including those with more than one relative. CRC, colorectal cancer.

Results

Cohort description and prevalence of family history of colorectal cancer

A total of 903 patients with EOCRC were included. Characteristics of the cohort are summarized in *Table 2*. The mean(s.d.) age at diagnosis was 41.8(6.5) years, and there were similar numbers of men and women. Regarding tumour location, the majority of cancers were located in the rectum (39 per cent), followed by the left colon (36 per cent) and right colon (25 per cent); 63 per cent were diagnosed at an advanced stage (stages III and IV).

A family history of colorectal cancer was noted in 275 patients (30.4 per cent). Details of kinship and age at colorectal cancer diagnosis in relatives are provided in *Tables 2* and *S2*. The prevalence of at least one FDR, at least one FDR diagnosed before the age of 50 years, and two or more FDRs with colorectal cancer was 17.2, 4.1, and 3.6 per cent respectively. Overall, the presence of a family history was not associated with early age at diagnosis ($P = 0.7$, ANOVA), but there was a significant difference between those who had at least one FDR diagnosed when aged less than 50 years *versus* those with at least two FDRs (mean age 39.7 *versus* 43.3 years; $P = 0.04$) (*Table 2*).

Familial colorectal cancer risk based on ESGE, USMSTF, and NCCN criteria

Altogether, 57 of the 903 patients (6.3 per cent) met the ESGE criteria for familial colorectal cancer risk, with a mean(s.d.) age of 41.4(6.7) years at colorectal cancer diagnosis. The distribution of patients according to the specific criteria is detailed in *Table 3*. Although patients with only one FDR diagnosed with colorectal cancer at age less than 50 years were younger than those with two or more FDRs (mean 39.4 *versus* 44 years), the difference was not statistically significant ($P = 0.07$). Interestingly, the mean age at diagnosis of the youngest relative was lower in the group of patients with only one FDR with colorectal cancer aged less than 50 years than among patients with only two or more FDRs (44.1 *versus* 64.7 years; $P = 0.001$). Patients fulfilling the ESGE criteria did not differ from those without familial colorectal cancer risk in either sex distribution or tumour location (*Table S3*). However, patients with colorectal cancer fulfilling the familial colorectal cancer risk criteria had earlier-stage tumours (stage I–II: 56 *versus* 36 per cent; $P = 0.002$).

Fulfilment of the USMSTF and NCCN criteria for familial colorectal cancer risk was analysed, taking into account that the prevalence of advanced polyps in relatives was not collected systematically. USMSTF and NCCN criteria were met by 85 of 903 (9.4 per cent) and 275 of 903 (30.4 per cent) respectively. Mean age at colorectal cancer presentation was 41.9(6.3) and 41.5(6.5 years) respectively. The distribution of patients according to the specific USMSTF and NCCN criteria is shown in *Table 3*. There was no difference in the age at colorectal cancer diagnosis between criteria, although, as for the USMSTF criteria, the relatives of patients with only one FDR aged less 60 years were younger than those of patients with only two or more FDRs (mean 50.3 *versus* 69.5 years; $P = 0.001$). Patients fulfilling the USMSTF or NCCN criteria did not differ from those without familial colorectal cancer risk in either sex ratio or tumour location (*Table S3*). As observed for ESGE criteria, there was an association between early stage at diagnosis and patients meeting USMSTF criteria (stage I–II: 59 *versus* 35 per cent; $P = 0.003$) and NCCN criteria (46.5 *versus* 33 per cent; $P < 0.001$).

Impact of familial colorectal cancer risk on early diagnosis and prevention

The impact of application of guidelines on the prevention and early detection of colorectal cancer was evaluated by calculating

Table 3 Differences between age at diagnosis of colorectal cancer of patients and relatives according to ESGE, USMSTF, and NCCN guidelines

	Proportion of entire cohort with CRC	Proportion of those with CRC who meet family risk criteria	Age (years) at diagnosis of CRC, mean(s.d.)	
			Patient	Youngest FDR
ESGE criteria	57 of 903 (6.3)	57 (100)	41.4 (6.7)	49.6(12.9)
Only 1 FDR aged < 50 years	26 of 903 (2.9)	26 of 57 (46)	39.4 (7.5)	44.1(5)
Only ≥ 2 FDRs	23 of 903 (2.5)	23 of 57 (40)	44.0 (4.6)	64.7(8.8)
Both criteria (≥ 1 FDR aged < 50 years and ≥ 2 FDRs)	8 of 903 (0.9)	8 of 57 (14)	41.0 (7.6)	37.37(10.9)
USMSTF criteria	85 of 903 (9.4)	85 (100)	41.9 (6.3)	52.0(11.1)
Only 1 FDR aged < 60 years	53 of 903 (5.9)	53 of 85 (62)	41.1 (6.6)	50.3(7.7)
Only ≥ 2 FDRs	19 of 903 (2.1)	19 of 85 (22)	43.9 (4.8)	69.5(13.1)
Both criteria (≥ 1 FDR aged < 60 years and ≥ 2 FDRs)	13 of 903 (1.4)	13 of 85 (15)	42.3 (6.6)	43.8(12.1)
NCCN criteria	275 of 903 (30.4)	275 (100)	41.5 (6.5)	n.a.
≥ 1 FDR at any age	155 of 903 (17.2)	155 of 275 (53.4)	42.4 (6.1)	59.6(13)
Any SDR and/or TDR	120 of 903 (13.2)	120 of 275 (43.6)	40.4 (6.7)	n.a.

Values are *n* (%) unless otherwise indicated. CRC, colorectal cancer; ESGE, European Society of Gastrointestinal Endoscopy; FDR, first-degree relative; USMSTF, U.S. Multi-Society Task Force; NCCN, National Comprehensive Cancer Network; n.a., not available; SDR, second-degree relative; TDR, third-degree relative.

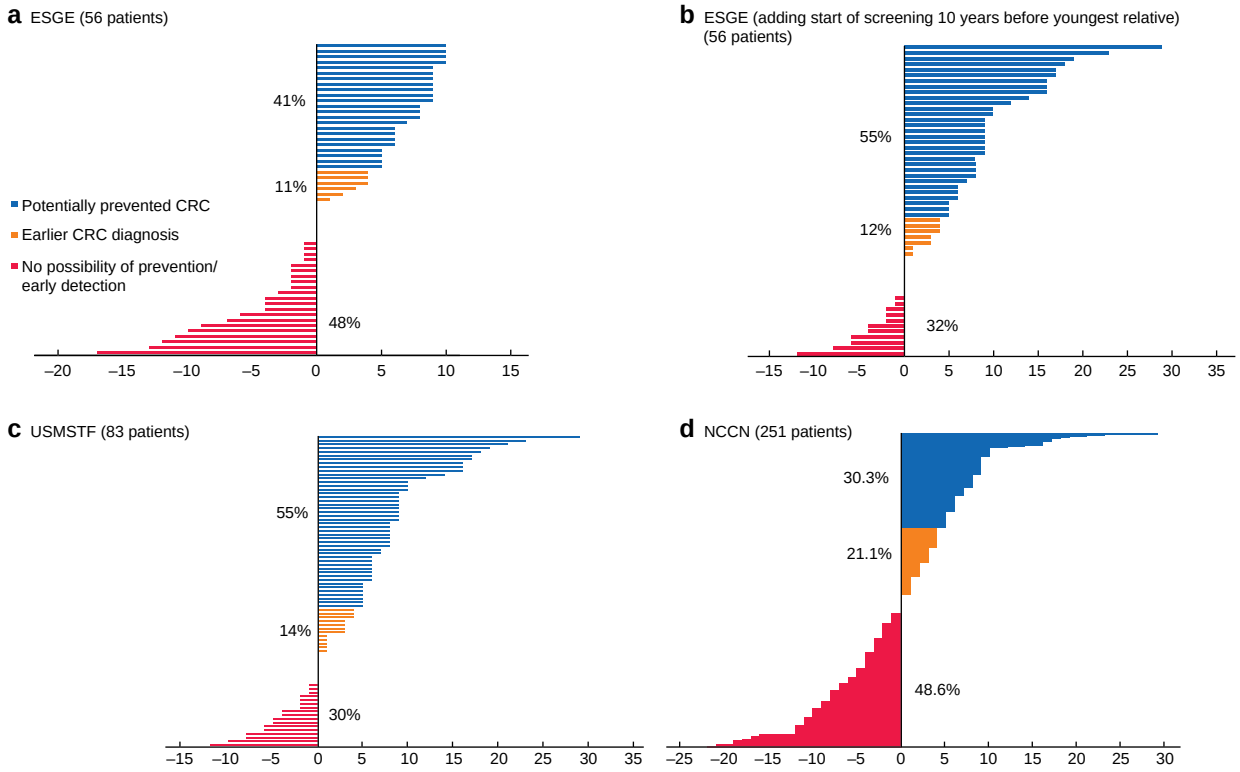

Fig. 1 Impact of application of European Society of Gastrointestinal Endoscopy, U.S. Multi-Society Task Force, and National Comprehensive Cancer Network guidelines on colorectal cancer prevention and early detection
Impact of **a** European Society of Gastrointestinal Endoscopy (ESGE), **b** modified ESGE, **c** U.S. Multi-Society Task Force (USMSTF), and **d** National Comprehensive Cancer Network (NCCN) guidelines, showing cases of colorectal cancer (CRC) that could have been prevented (difference between age recommended for screening based on guidelines and age of CRC diagnosis 5 years or more), diagnosed earlier (difference between age recommended for screening based on guidelines and age of CRC diagnosis 1–4 years), or neither prevented nor diagnosed earlier (difference between age recommended for screening based on guidelines and age of CRC diagnosis less than 1 year). The number of patients with early-onset CRC meeting the criteria for each guideline for early screening is shown. Data are based on patients for whom the age of colorectal cancer in relatives was available. Difference between age recommended for screening based on guidelines and age of CRC diagnosis. A negative result value indicate that the recommended age for screening colonoscopy is after CRC diagnosis.

the differential between the theoretical age of initiation of surveillance colonoscopy based on family history and the age at colorectal cancer diagnosis.

If the ESGE guidelines were applied, colorectal cancer could have been potentially preventable in 41 per cent and diagnosed earlier in 11 per cent of those meeting the criteria for a family history of colorectal cancer (*Fig. 1*). Importantly, neither prevention nor early diagnosis could have been achieved in 48 per cent of those meeting the ESGE criteria for family history. The highest percentage of potential prevention was predicted to have occurred in those who met the criteria of having two or more FDRs (50 per cent) (*Table 4*).

The effect of adding the criterion of starting 10 years before the diagnosis of colorectal cancer in the youngest relative to the

Table 4 Impact of application of familial colorectal cancer guidelines on prevention of colorectal cancer

	No possibility of prevention/early detection	Earlier CRC diagnosis	Potentially prevented CRC
Guidelines			
ESGE	27 of 56 (48)	6 of 56 (11)	23 of 56 (41)
ESGE modified	18 of 56 (32)	7 of 56 (12)	31 of 56 (55)
USMSTF	25 of 83 (30)	12 of 83 (14)	46 of 83 (55)
NCCN	122 of 251 (48.6)	53 of 251 (21.1)	76 of 251 (30.3)
ESGE criteria			
Only 1 FDR aged < 50 years	14 of 26 (54)	3 of 26 (11)	9 of 26 (35)
Only ≥ 2 FDRs	9 of 22 (41)	2 of 22 (9)	11 of 22 (50)
≥ 1 FDR aged < 50 years and ≥ 2 FDRs	4 of 8 (50)	1 of 8 (12)	3 of 8 (37)
ESGE modified criteria			
Only 1 FDR aged < 50 years	8 of 26 (31)	4 of 26 (15)	14 of 26 (54)
Only ≥ 2 FDRs	9 of 22 (41)	2 of 22 (9)	11 of 22 (50)
≥ 1 FDR aged < 50 years and > 2 FDRs	1 of 8 (12)	1 of 8 (12)	6 of 8 (75)
USMSTF criteria			
Only 1 FDR aged < 60 years	15 of 51 (29)	9 of 51 (18)	27 of 21 (53)
Only ≥ 2 FDRs	7 of 19 (37)	2 of 19 (10)	10 of 19 (53)
≥ 1 FDR aged < 60 years and ≥ 2 FDRs	3 of 13 (23)	1 of 13 (8)	9 of 13 (69)
NCCN criteria			
≥ 1 FDR at any age	37 of 131 (28.2)	20 of 131 (15.2)	74 of 131 (56.4)
Any SDR or TDR	85 of 120 (70.8)	33 of 120 (27.5)	2 of 120 (1.6)

Values are *n* (%) unless otherwise indicated. Data are based on patients for whom the age of colorectal cancer in relatives was available. CRC, colorectal cancer; ESGE, European Society of Gastrointestinal Endoscopy; ESGE modified, with addition of the criterion of starting surveillance 10 years before youngest relative; USMSTF, U.S. Multi-Society Task Force; NCCN, National Comprehensive Cancer Network; FDR, first-degree relative; SDR, second-degree relative; TDR, third-degree relative.

current ESGE guidelines was explored. If this criterion had been applied, the mean(s.d.) recommended age for initiation of colonoscopy would have been 34.9(6.9) years, and, remarkably, there was a clear increase in the proportion of preventable colorectal cancer (55 *versus* 41 per cent; $P = 0.01$), with a slight increase in early diagnosis (12 *versus* 11 per cent; $P = 0.01$) (*Fig. 1*). Notably, in the subgroup of patients meeting both criteria for familial colorectal cancer risk, 75 per cent of cases could have been prevented (*Table 4*).

If the USMSTF guidelines were applied, the mean recommended age for initiation of colonoscopy would have been 36.6(6.1) years. Compared with the ESGE guidelines, USMSTF criteria encompassed a higher percentage of preventable cases (55 per cent) and early diagnoses (14 per cent) (*Fig. 1*). The highest proportion of prevention could have been achieved among who met both clinical criteria (69 per cent) (*Table 4*).

Regarding the NCCN guidelines, the mean recommended age for initiation colonoscopy was 38(4.9) years for those with at least one FDR with colorectal cancer (age at diagnosis of second- and third-degree relatives was not available). Overall, the impact on colorectal cancer prevention was smaller than that of the other two guidelines; in only 30.3 per cent of patients would early screening have prevented colorectal cancer. However, for patients with at least one FDR, the percentage of preventable colorectal cancer (56.4 per cent) was similar to that for ESGE and USMSTF guidelines (*Table 4*). Of note, in only 1.6 per cent of patients with at least one second- or one third-degree relative, would early screening have prevented colorectal cancer.

Discussion

The incidence of EOCRC is increasing and is of urgent concern. Although most cases are estimated to be related to the exposome, up to 30 per cent have a family history, and only a minority have a hereditary origin[7,18–20]. In non-syndromic cases, application of colorectal cancer prevention guidelines based on family history is one of the strategies to reduce the incidence of EOCRC. However, the impact of applying current guidelines remains poorly understood. This study, using a large European multicentre cohort of patients with EOCRC, evaluated the potential for prevention if the ESGE, USMSTF, and NCCN guidelines were applied[10,12]. Family-based criteria for early screening in ESGE, USMSTF, and NCCN guidelines were met in 6.3, 9.4, and 30.4 per cent of patients respectively. Early detection and/or prevention could be achieved in 52, 70, and 51.4 per cent of patients fulfilling these criteria respectively. Interestingly, within the ESGE guidelines, the addition of starting 10 years before the diagnosis of colorectal cancer in the youngest relative led to a significant increase in the potential prevention of EOCRC. Overall, the results indicate that the proportion of EOCRCs that meet the family history-based criteria for earlier colorectal cancer screening differs between guidelines. Strikingly, in a meaningful proportion of these patients, early screening would not affect the diagnosis and prevention of EOCRC. It is crucial to ensure that recommendations for patients with familial colorectal cancer risk are delivered in order to prevent EOCRC in these patients.

Once a known inherited disorder has been ruled out, family history of colorectal cancer is a well established risk factor for developing this tumour. The age at diagnosis and number of relatives affected, and the degree of kinship are the main factors that determine this risk. According to various guidelines, individuals with a family history of colorectal cancer should undergo more intensive surveillance than the general population, starting at an earlier age. However, the definitions of patients qualifying for more intensive surveillance differ between countries. Guidelines differ mainly in the age cut-off for the youngest relative's diagnosis (50 *versus* 60 years), the age of initiation of surveillance (40 years *versus* early initiation if affected relative is younger than 50 years), and consideration of advanced polyps in relatives[10,12]. In the present study, which focused on EOCRC, the mean age at colorectal cancer diagnosis in patients with a familial colorectal cancer risk was 41.5 years, which is close to the recommended starting age for surveillance. Interestingly, although the mean age at diagnosis of familial EOCRC did not differ from that of non-familial cases, in the subgroup of patients with at least one FDR diagnosed before the age of 50 years, the age at diagnosis in patients and relatives

was significantly lower. Therefore, it seems that starting surveillance earlier could have a more important preventive effect in the presence of EOCRC in a relative. This is confirmed in the present data for the following observations: the theoretical starting age based on application of the USMSTF and NCCN guidelines was 36.6 and 38 years respectively, showing a greater potential for prevention than the ESGE guidelines; and applying the criterion of starting surveillance 10 years before the youngest familial case in the ESGE guideline would have achieved significantly greater preventive potential (starting age 35 years). Accordingly, an early start seems crucial for prevention of EOCRC. Indeed, the American Cancer Society, American College of Gastroenterology, and US Preventive Services Task Force have recently endorsed the recommendation of screening in average-risk persons aged 45 years[12,21,22]. In the present cohort, with a mean(s.d.) age at diagnosis of 41.8(6.5 years), 41 of 903 cases (4.5 per cent) could have been prevented and 289 (32 per cent) could have been diagnosed earlier if colonoscopy had been performed at age 45 years, regardless of family history. Accordingly, it is important to note that the impact of lowering the starting age of screening exceeds the impact of implementation of family-based earlier colorectal cancer screening.

The impact of family history on EOCRC prevention has been assessed recently by Stanich *et al*. in the Ohio Colorectal Cancer Prevention Initiative[15]. In that study, tumours in 45.4 per cent of patients with a family history of colorectal cancer would possibly have been prevented if the USMSTF guideline had been applied. In addition, Gupta *et al.*[16] conducted a case–control study focused on EOCRC in patients aged 40–49 years in the Colon Cancer Family Registry, with a mean age of 45.3 years. In that study, 37 per cent of the population had any family history of colorectal cancer, and 25 per cent met the family history-based criteria for early screening. Interestingly, 98.4 per cent of patients with EOCRC who met early screening criteria could have been recommended screening initiation at an age younger than the observed age of diagnosis, which is much higher than in the present study. The authors believe that the main reason for this difference is the fact that Gupta *et al.*[16] specifically focused on EOCRCs diagnosed at between 40 and 49 years of age. Remarkably, when the present data for patients with EOCRC aged 40–49 years were analysed (617 of 903, 68.3 per cent of the population), the impact of implementation of the guidelines was much greater, with figures for early detection and/or prevention of 82.8, 88.3, and 72.5 per cent for ESGE, USMTSF, and NCCN guidelines respectively (*Table S4*). Overall, this analysis indicates that the impact of the implementation of family history-based criteria is greater among individuals aged 40–49 years than for those with earlier-onset disease (respective figures for the population aged less than 40 years were 0, 37.5, and 10.6 per cent). Overall, this suggests that effort is needed to increase both the identification of family history of colorectal cancer in the general population, and the uptake of early colonoscopy. Interestingly, the potential benefit of early screening was mostly seen in patients diagnosed between the age of 40 and 49 years.

The present study has several strengths. This is one of the largest EOCRC cohorts in a European multicentre study with systematic collection of family history. Although not all patients had a germline genetic study, Lynch syndrome, the most common form of inherited EOCRC, was ruled out, by at least tumour MMR deficiency analysis. However, the following limitations must be acknowledged. First, this study is subject to ascertainment bias because all patients were recruited after diagnosis of colorectal cancer and the type of surveillance colonoscopy they had is not known. Accordingly, the potential effect of the application of familial colorectal cancer risk guidelines is only partially seen as cancers that were prevented are not captured in the study. Second, the comparison with the USMSTF and NCCN guidelines is limited by the fact that a family history of advanced polyps was not recorded. Third, the study is based on the assumption that a colonoscopy performed 5 years or more before the patient's age at diagnosis would be potentially preventive. Although arbitrary, this observation is based on the estimates of effectiveness of polypectomy and has been used by Stanich *et al.* recently[13]. No economic or cost-effectiveness analyses of all the strategies were undertaken, as they were beyond the scope of the present investigation.

In summary, EOCRCs fulfilling the criteria for family history-based earlier screening differed among guidelines and a clinically meaningful proportion of cases could be prevented if early surveillance were initiated. The impact of the current ESGE guidelines would be much greater if the starting age was based on earlier diagnosis among the relatives. Although the absolute impact of family history on EOCRC incidence is small, special efforts should be made to increase adherence and the timely implementation of current guidelines.

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Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The raw data for this article is available upon request.

References

1. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS *et al.* Colorectal cancer incidence patterns in the United States, 1974–2013. *J Natl Cancer Inst* 2017; **109**:djw22
2. Mauri G, Sartore-Bianchi A, Russo AG, Marsoni S, Bardelli A, Siena S. Early-onset colorectal cancer in young individuals. *Mol Oncol* 2019;**13**:109–131
3. Lui RN, Tsoi KKF, Ho JMW, Lo CM, Chan FCH, Kyaw MH *et al.* Global increasing incidence of young-onset colorectal cancer across 5 continents: a joinpoint regression analysis of 1 922 167 cases. *Cancer Epidemiol Biomarkers Prev* 2019;**28**:1275–1282
4. Akimoto N, Ugai T, Zhong R, Hamada T, Fujiyoshi K, Giannakis M *et al.* Rising incidence of early-onset colorectal cancer—a call to action. *Nat Rev Clin Oncol* 2021;**18**:230–243
5. Hofseth LJ, Hebert JR, Chanda A, Chen H, Love BL, Pena MM *et al.* Early-onset colorectal cancer: initial clues and current views. *Nat Rev Gastroenterol Hepatol* 2020;**17**:352–364
6. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. *Gastroenterology* 2010;**138**:2044–2058
7. Alvarez M D, Quintana I, Terradas M, Mur P, Balaguer F, Valle L. The inherited and familial component of early-onset colorectal cancer. *Cells* 2021;**10**:710
8. Wong MCS, Chan CH, Lin J, Huang JLW, Huang J, Fang Y *et al.* Lower relative contribution of positive family history to colorectal cancer risk with increasing age: a systematic review and meta-analysis of 9.28 million individuals. *Am J Gastroenterol* 2018;**113**:1819–1827
9. Armelao F, de Pretis G. Familial colorectal cancer: a review. *World J Gastroenterol* 2014;**20**:9292–9298
10. Monahan KJ, Bradshaw N, Dolwani S, Desouza B, Dunlop MG, East JE *et al.* Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/UK Cancer Genetics Group (UKCGG). *Gut* 2020;**69**:411–444
11. van Leerdam ME, Roos VH, van Hooft JE, Balaguer F, Dekker E, Kaminski MF *et al.* Endoscopic management of Lynch syndrome and of familial risk of colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* 2019;**51**:1082–1093
12. Shaukat A, Kahi CJ, Burke CA, Rabeneck L, Sauer BG, Rex DK. ACG clinical guidelines: colorectal cancer screening 2021. *Am J Gastroenterol* 2021;**116**:458–479
13. Rex DK, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T *et al.* Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2017;**153**:307–323
14. Ness RM, Llor X, Abbadessa B, Chen CT, Cooper G, Early DS *et al.* NCCN Clinical practice guidelines in oncology (NCCN guidelines®) colorectal cancer screening. Version 1. *J Natl Comprehens Cancer Netw* 2022;**20**:603–606
15. Stanich PP, Pelstring KR, Hampel H, Pearlman R. A high percentage of early-age onset colorectal cancer is potentially preventable. *Gastroenterology* 2020;**160**:1850–1852
16. Gupta S, Bharti B, Ahnen DJ, Buchanan DD, Cheng IC, Cotterchio M *et al.* Potential impact of family history-based screening guidelines on the detection of early-onset colorectal cancer. *Cancer* 2020;**126**:3013–3020
17. Perea J, Marti M, Espin E, Hernandez-Villafranca S, Orihuela P, Vidal Tocino R *et al.* Cohort profile: the Spanish Early-onset Colorectal Cancer (SECOC) cohort: a multicentre cohort study on the molecular basis of colorectal cancer among young individuals in Spain. *BMJ Open* 2021;**11**:e055409
18. Pearlman R, Frankel WL, Swanson B, Zhao W, Yilmaz A, Miller K *et al.* Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. *JAMA Oncol* 2017;**3**:464–471
19. Stoffel EM, Koeppe E, Everett J, Ulintz P, Kiel M, Osborne J *et al.* Germline genetic features of young individuals with colorectal cancer. *Gastroenterology* 2018;**154**:897–905.e1
20. Mikaeel RR, Young JP, Li Y, Smith E, Horsnell M, Uylaki W *et al.* Survey of germline variants in cancer-associated genes in young adults with colorectal cancer. *Genes Chromosomes Cancer* 2022;**61**:105–113
21. Wolf AMD, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ *et al.* Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin* 2018;**68**:250–281
22. Davidson KW, Barry MJ, Mangione CM, Cabana M, Caughey AB, Davis EM *et al.* Screening for colorectal cancer: US preventive services task force recommendation statement. *JAMA* 2021; **325**:1965–1977