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Original Article

Regional patterns of early-onset colorectal cancer from the GEOCODE (Global Early-Onset COlorectal Cancer DatabasE)-European consortium: retrospective cohort study

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Abstract

Background: The incidence of early-onset colorectal cancer is increasing, but in Europe this growth shows a heterogeneous pattern in different countries and regions.

Methods: Patients from six countries who participated in the Global Early-Onset COlorectal Cancer DatabasE (GEOCODE)-Europe group were included. The inclusion criteria were patients with colorectal adenocarcinoma diagnosed between 18 and 49 years of age, between January 2010 and December 2017, with at least 3 years of follow-up. Patients with inherited colorectal cancer syndromes were excluded.

Results: A total of 851 patients were included with almost equal sex distribution, most were diagnosed at age 39 years or older and 42% of patients were overweight or obese. Diagnoses were predominantly at later stages (62.5% stage III–IV) and tumours were predominantly located in the distal colon (76.9% left colon and rectum). Comparative analysis between countries demonstrated that the UK had a younger age at diagnosis and the Italian cohort had a higher prevalence of being overweight or obese. Patients from Luxembourg had more advanced stage diagnoses and those from The Netherlands had more polyps. Patients from the UK had a greater family history

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of colorectal cancer. Comparison of Mediterranean *versus* non-Mediterranean countries showed significant differences in the age at diagnosis and body mass index. The prevalence of early-onset colorectal cancer over the age of 40 years in Mediterranean *versus* non-Mediterranean countries was 71.4% *versus* 62.1% ($P = 0.002$), and early-onset colorectal cancer was diagnosed at a more advanced stage in Mediterranean countries *versus* non-Mediterranean countries (65.3% *versus* 54.7%; $P = 0.033$). Family history of colorectal cancer in a first-degree relative was more common in non-Mediterranean *versus* Mediterranean countries (19.1% *versus* 11.4%; $P < 0.001$).

Conclusion: This study highlights significant geographical disparities in the clinical, pathological and familial features of early-onset colorectal cancer across European countries.

Introduction

Colorectal cancer (CRC) incidence and mortality rates differ markedly around the world. Globally, colorectal cancer is the third most diagnosed cancer in males and the second in females[1]. The regional incidence of colorectal cancer varies over 10-fold, with the highest incidence rates in Australia and New Zealand, Europe and the USA, and the lowest rates in Africa and South-Central Asia[2]. These geographic differences seem to be attributable to variations in exposures (dietary and environmental) together with a background of genetic susceptibility[3,4].

There has been a reduction in the incidence and mortality rate of colorectal cancer in recent years, mostly attributed to colorectal cancer screening programmes and therapeutic advances[5,6]. However, the incidence of colorectal cancer in individuals diagnosed before the age of 50 years has been rising over the last three decades[4,6]. Currently, nearly 1 in every 10 patients with colorectal cancer is younger than 50 years at diagnosis (that is early-onset colorectal cancer; EOCRC). Incidence rates for colon and rectal cancers in the USA are estimated to increase by 90.0% and 124.2% respectively, for patients aged 20 to 34 years, and by 27.7% and 46.0% respectively, for patients aged 35 to 49 years by 2030[7,8]. However, the incidence of EOCRC in the USA is significantly higher than in Europe[9], where the incidence of EOCRC displays a heterogeneous pattern across different countries and geographical regions. While the overall incidence of EOCRC has generally continued to rise in Germany, the UK, Denmark, Slovenia and Sweden (countries with a stable or declining trend among adults older than 50 years), the incidence of EOCRC has declined in several European countries (Italy, Austria and Lithuania)[8,10]. In European countries with an increasing colorectal cancer incidence among adults older than 50 years of age (including Cyprus, The Netherlands and Norway), the incidence of colorectal cancer in younger adults has increased twice as rapidly compared with older-onset cases[8,10]. Studies of more defined geographical areas have allowed better estimation of the differences in incidence[11,12]. These geographical differences in EOCRC incidence are also reflected in other factors such as sex and race/ethnicity distribution, as well as survival[13–16]. These disparities are likely explained by environmental factors, and intrinsic genetic variants. This unique epidemiology of EOCRC has increased focus on understanding the aetiologies predisposing to EOCRC and in developing clinical approaches tailored to younger patients—including updated guidelines to start average-risk screening at age 45 years in the USA[17–19]. Understanding the epidemiology of EOCRC in different countries is key to implementing additional effort to tackle this problem.

GEOCODE (Global Early-Onset COlorectal Cancer DatabasE) is a consortium aimed at exploring and analysing clinical and translational aspects of EOCRC worldwide. The confirmation of geographical differences would serve not only as a starting point for an adequate characterization of the disease, but also to understand its molecular basis and define personalized management. The present study focuses on geographical variations across several European countries in relation to the clinical, pathological and familial characteristics of EOCRC.

Methods

Study population

Inclusion criteria in the GEOCODE study were patients diagnosed with colorectal adenocarcinoma aged between 18 and 49 years between January 2010 and December 2017, and with at least 3 years of follow-up. Each centre obtained acceptance for the study according to the regulations of the corresponding country and institution. Patients were defined as the index case for each family. In this study, the focus was on sporadic EOCRC, in which the environmental component is assumed to be more relevant. Accordingly, patients with EOCRC diagnosed with inflammatory bowel disease, familial adenomatous polyposis, polyposis (defined as the presence of more than 10 polyps accumulated over time), *MUTYH* (*MutY DNA glycosylase*)-associated polyposis, Lynch syndrome or any other already known inherited syndrome were excluded. Patients with tumours exhibiting mismatch repair deficiency, defined as either microsatellite instability and/or loss of mismatch repair (MMR) protein expression by immunohistochemistry were excluded (in whom neither *MLH1* (*MutL Homolog 1*) methylation nor biallelic somatic mutations had been analysed (and accordingly Lynch syndrome could be present)). Patients with sporadic mismatch repair deficiency due to *MLH1* promoter hypermethylation were not excluded from the analysis. Institutions and countries participating in the GEOCODE-Europe arm are shown in *Fig. 1*, distributed as follows: Humanitas Clinical and Research Centre, Rozzano, Milan, Italy; Centre Hospitalier de Luxembourg, Luxembourg; Leiden University Medical Centre, Leiden, The Netherlands; Bielanski Hospital, Warsaw, Poland; Orlowski Hospital, Warsaw, Poland; Hospital Clínic, Barcelona, Spain; Vall d'Hebron University Hospital, Barcelona, Spain; 12 de Octubre University Hospital, Madrid, Spain; Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK; St. Mark's Hospital, Harrow, UK; West Middlesex University Hospital, London, UK.

This study received approval from the ethical boards of each participating institution and all patients provided written informed consent for participation in this study.

This study is registered in accordance with the declaration of Helsinki and has been reported in line with the STROCSS (Strengthening the Reporting of Cohort Studies in Surgery) criteria[20].

Demographic and clinical features of EOCRC patients

Personal and clinicopathological information was obtained from each EOCRC index patient, including age at diagnosis, sex, body mass index (BMI) at diagnosis (overweight was defined as BMI >25 kg/m² and obesity as BMI >30 kg/m²), tumour location (right colon: caecum, ascending and transverse colon; left colon: splenic flexure, descending and sigmoid colon; and rectum);

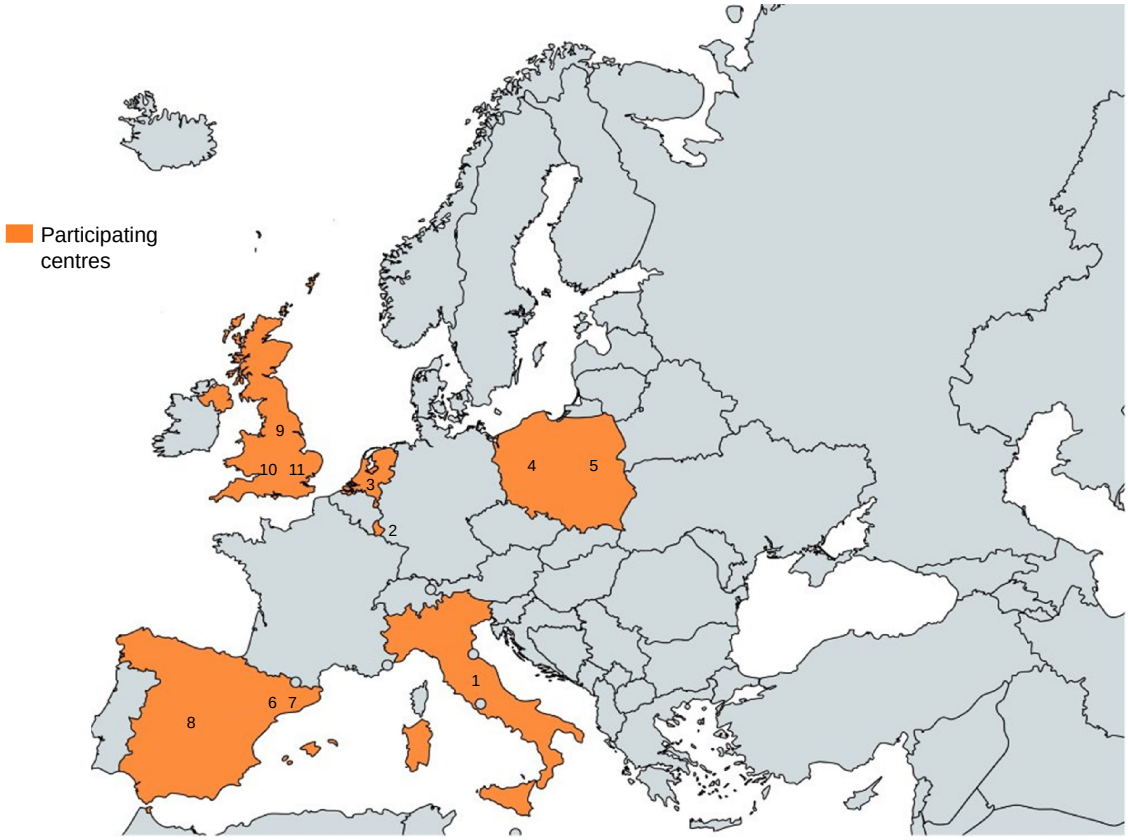

Fig. 1 Distribution of the participating centres in the corresponding countries in GEOCODE-Europe
1. Humanitas Clinical and Research Centre, Rozzano Milan (Italy). **2.** Centre Hospitalier de Luxembourg (Luxembourg). **3.** Leiden University Medical Centre, Leiden, The Netherlands. **4.** Bielanski Hospital, Warsaw, Poland. **5.** Orlowski Hospital, Warsaw, Poland. **6.** Hospital Clínic, Barcelona, Spain. **7.** Vall d´Hebron University Hospital, Barcelona, Spain. **8.** 12 de Octubre University Hospital, Madrid, Spain. **9.** Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK. **10.** St. Mark's Hospital, Harrow, UK. **11.** West Middlesex University Hospital, London, UK. GEOCODE, Global Early-Onset COlorectal Cancer DatabasE.

histological features, including cell differentiation grade (low, medium or high), presence of mucinous component, and presence of 'signet ring' cell tumours; tumour stage (TNM); presence of metastatic disease (location and number); multiple primary neoplasms including the diagnosis of synchronous and/or metachronous colorectal cancer; and other primary neoplasms different from colorectal cancer; finally, the presence of previous or synchronous colorectal polyps was evaluated.

For the analysis of family history of cancer, the authors included data from first- and second-degree relatives. The cancer subtypes were defined and identified as follows (not exclusive): colorectal cancer, extracolonic gastrointestinal tumours (that is non-colorectal cancer), gynaecologic and breast cancers, urinary and prostate cancers, and other tumours different than the ones described. We also described the presence of any early-onset cancer cases in the family (younger than 50 years of age).

Study objective

The primary aim was to investigate whether EOCRC displays geographical differences in several clinicopathological and familial features. The data was analysed with two approaches: first, comparing all the countries with each other; and second, analysing the countries according to a defined geographical area: 'Mediterranean' countries (Spain and Italy) and 'non-Mediterranean' countries (the other four countries), which overall had equivalent sample sizes.

Statistical analyses

Countries and regions were compared for continuous variables using the Kruskal–Wallis test from the stats package in R (v.4.0.4). The association between regions/countries and categorical variables was analysed using the chi-square test and the probability level (*P* values) was computed by a Monte Carlo simulation with 106 replicates.

Patient and public involvement statement

Within the GEOCODE consortium there are patient associations involved, depending on the geographical area. For the European part, the Digestive Cancers Europe (DICE) association is continuously updated on the progress of the project, as well as taking part in the critical review and formulation of new needs and gaps to be solved. In addition, it is intended that the results obtained are made public by different means, such as social networks or the media, to respond to one of the immediate needs that the EOCRC problem entails, such as increasing awareness.

Results

Baseline characteristics

Baseline characteristics of EOCRC patients included in this study are presented in *Table S1*. A total of 851 patients were collected. Overall, the cohort showed almost equal sex distribution, the

Table 1 Characteristics of the whole cohort and comparison between countries

Feature	Study cohorts by country						
	Italy 188 (22.1)	Luxembourg 32 (3.8)	The Netherlands 104 (12.2)	Poland 61 (7.2)	Spain 259 (30.4)	UK 207 (24.3)	P
Sex							
Female	89 (47.3)	15 (46.9)	53 (51)	32 (52.5)	135 (52.1)	91 (44)	0.578
Male	99 (52.7)	17 (53.1)	51 (49)	29 (47.5)	124 (47.9)	116 (56)	
Age at diagnosis (years)							
<30 years	10 (5.3)	1 (3.1)	6 (5.8)	8 (13.1)	10 (3.9)	23 (11.1)	0.002
≥30 to ≤39 years	46 (24.5)	9 (28.1)	21 (20.2)	15 (24.6)	62 (23.9)	70 (33.8)	
≥40	132 (70.2)	22 (68.8)	77 (74)	38 (62.3)	187 (72.2)	114 (55.1)	
Mean(s.d.) (years)	42.1(6.6)	41.5(6.3)	42.8(6.2)	40.3(8.0)	42.1(5.9)	39.8(7.4)	0.003
BMI (kg/m^2)							
Underweight (≤18.5 kg/m^2)	4 (2.1)	2 (6.3)	2 (1.9)	4 (6.6)	12 (4.6)	3 (1.4)	0.006
Normal weight (>18.5 to ≤25 kg/m^2)	99 (52.7)	23 (71.9)	36 (34.6)	36 (59)	104 (40.2)	21 (10.1)	
Overweight (>25 to ≤30 kg/m^2)	61 (32.4)	6 (18.8)	18 (17.3)	16 (26.2)	50 (19.3)	6 (2.9)	
Obesity (>30 kg/m^2)	23 (12.2)	1 (3.1)	9 (8.7)	4 (6.6)	52 (20.1)	8 (3.9)	
Unknown	1 (0.5)	0 (0)	39 (37.5)	1 (1.6)	41 (15.8)	169 (81.6)	
Tumour stage at diagnosis							
I	31 (16.5)	2 (6.3)	10 (9.6)	15 (24.6)	48 (18.5)	41 (19.8)	0.001
II	27 (14.4)	5 (15.6)	19 (18.3)	15 (24.6)	49 (18.9)	46 (22.2)	
III	74 (39.4)	16 (50)	32 (30.8)	19 (31.1)	81 (31.3)	70 (33.8)	
IV	56 (29.8)	9 (28.1)	39 (37.5)	8 (13.1)	81 (31.3)	28 (13.5)	
Unknown	0 (0)	0 (0)	4 (3.8)	4 (6.6)	0 (0)	22 (10.6)	
Tumour site							
Right colon	31 (16.5)	9 (28.1)	23 (22.1)	14 (23)	68 (26.3)	46 (22.2)	0.212
Left colon	80 (42.6)	7 (21.9)	33 (31.7)	19 (31.1)	98 (37.8)	65 (31.4)	
Rectosigmoid junction/rectum	74 (39.4)	16 (50)	44 (42.3)	28 (45.9)	93 (35.9)	81 (39.1)	
Histological features							
Mucinous	25 (13.3)	11 (34.4)	12 (11.5)	11 (18)	39 (15.1)	24 (11.6)	0.028
'Signet ring' cells	2 (1.1)	1 (3.1)	2 (1.9)	0 (0)	13 (5)	8 (3.9)	0.091
Grade of differentiation							
Low	44 (23.4)	4 (12.5)	20 (19.2)	2 (3.3)	38 (14.7)	26 (12.6)	0.001
Medium	65 (34.6)	22 (68.8)	58 (55.8)	27 (44.3)	140 (54.1)	88 (42.5)	
High	78 (41.5)	6 (18.8)	14 (13.5)	29 (47.5)	58 (22.4)	87 (42)	
Metastasis sites at diagnosis							
Total cases	56 (29.8)	9 (28.1)	39 (37.5)	8 (13.1)	81 (31.3)	29 (14)	0.001
Liver	51 (27.1)	8 (25)	29 (27.9)	7 (11.5)	56 (21.6)	18 (8.7)	
Lung	3 (1.6)	1 (3.1)	4 (3.8)	0 (0)	20 (7.7)	5 (2.4)	
Peritoneal	6 (3.2)	1 (3.1)	6 (5.8)	2 (3.3)	24 (9.3)	4 (1.9)	
Other	6 (3.2)	0 (0)	12 (11.5)	2 (3.3)	18 (6.9)	8 (3.9)	
Previous polyps							
None	172 (91.5)	31 (96.9)	99 (95.2)	49 (80.3)	246 (95)	187 (90.3)	0.001
Yes	16 (8.5)	1 (3.1)	5 (4.8)	12 (19.7)	11 (4.2)	15 (7.2)	
Synchronous polyps							
Yes	23 (12.2)	4 (12.5)	21 (20.2)	6 (9.8)	55 (21.2)	66 (31.9)	0.001
No	165 (87.8)	28 (87.5)	83 (79.8)	55 (90.2)	202 (78)	136 (65.7)	
Multiple primary neoplasms (MPN)							
Synchronous CRC	5 (2.7)	1 (3.1)	0 (0)	0 (0)	5 (1.9)	7 (3.4)	0.312
Metachronous CRC	0 (0)	1 (3.1)	1 (1)	1 (1.6)	4 (1.5)	0 (0)	0.159
Other MPN	7 (3.7)	2 (6.3)	3 (2.9)	1 (1.6)	11 (4.2)	3 (1.4)	0.470
Familial cancer history (first degree)							
Colorectal cancer	18 (9.6)	2 (6.3)	8 (7.7)	2 (3.3)	33 (12.7)	65 (31.4)	0.001
Digestive cancers different from CRC	10 (5.3)	0 (0)	7 (6.7)	0 (0)	6 (2.3)	8 (3.9)	0.007
Gynaecologic and breast cancer	10 (5.3)	0 (0)	9 (8.7)	1 (1.6)	13 (5)	9 (4.3)	0.010
Urinary tract and prostate cancer	8 (4.3)	0 (0)	3 (2.9)	1 (1.6)	10 (3.9)	11 (5.3)	0.688
Early-onset cancers in family (<50 years of age)							
Yes	9 (4.8)	0 (0)	18 (17.3)	1 (1.6)	20 (7.7)	38 (18.4)	0.001
No	134 (71.3)	30 (93.8)	35 (33.7)	54 (88.5)	206 (79.5)	117 (56.5)	

Values are *n* (%) unless otherwise indicated. CRC, colorectal cancer; s.d., standard deviation; BMI, body mass index.

majority with an age at diagnosis older than 39 years (67%) and a 42% prevalence of overweight/obesity. Diagnoses were predominantly at later stages (stage III, 292 (35.6%); stage IV, 221 (26.9%) respectively). Tumour location was predominantly distal, displaying involvement of the left colon and rectum (638 patients (76.4%)), with 122 (14.3%) patients with mucinous features. In 175 (20.7%) of the population, synchronous polyps were identified, and the proportion of multiple primary neoplasms was in total 6.1%. Finally, regarding familial cancer history, the most frequent type of neoplasm in first- and second-degree relatives was colorectal cancer (15% and 11.3% respectively), and the next most frequent groups were breast and gynaecological (6.5 and 5% respectively) and in 86 (12.9%) cases at least one additional case of early-onset tumour in the family was present.

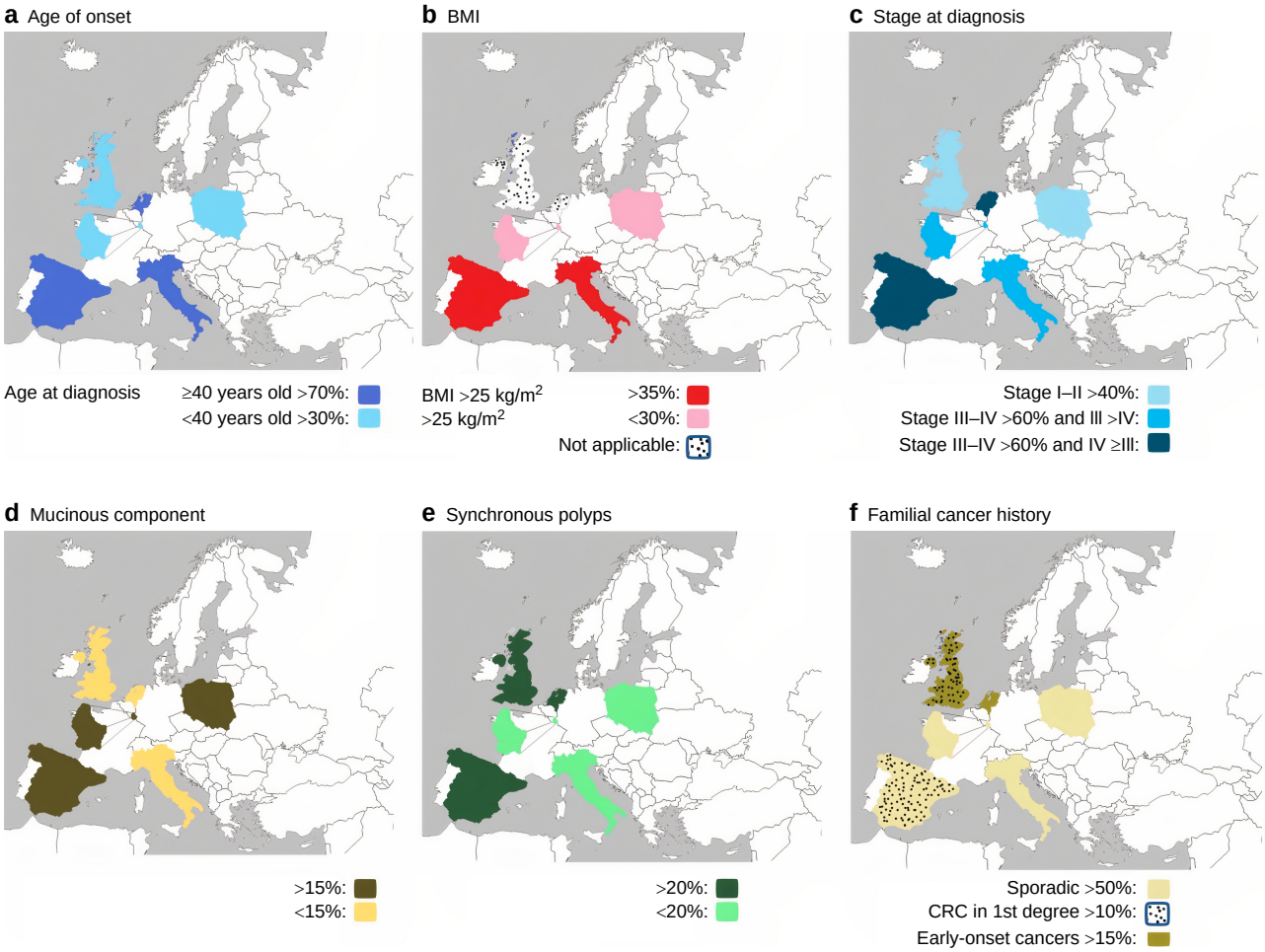

Fig. 2 Characteristics according to the different variables of each country
a Age of onset. **b** Body mass index (BMI). **c** Stage of diagnosis. **d** Mucinous component. **e** Synchronous polyps. **f** Familial cancer history. CRC, colorectal cancer.

Overall comparison between countries

Characteristics of EOCRC across the European countries included in the study are summarized in *Table 1*. Overall, there were significant differences in several features including age at diagnosis, BMI, tumour stage, tumour differentiation and family history of cancer. According to the differential variables (that is age, BMI, stage, pathological features), countries were categorized and are represented in *Fig. 2a–f*.

There were no differences in the sex distribution across countries. However, age at diagnosis was highly heterogenous, evidenced by the fact that The Netherlands, Spain and Italy comprised a higher proportion of individuals older than 40 years (74%, 72.2% and 70.2% respectively), compared with the UK, where the age at diagnosis at >40 years was 55%. Strikingly, we observed important differences in the BMI, showing a higher percentage of overweight and obesity in Italy, Spain and Poland (44.6%, 39.4% and 32.8% respectively), compared with the rest of the countries, where it is lower than 26%.

Considering tumour characteristics, in Luxembourg, Italy, The Netherlands and Spain, EOCRC was diagnosed at a more advanced stage (stage III–IV, 78.1%, 69.2%, 68.3%, 62.6% respectively), in contrast to Poland and the UK, where it was less than 48%. There were no significant differences in tumour location. There was a higher incidence of mucinous tumours in Luxembourg at 34.4%, compared with the rest of the countries: less than 18%. Additionally, there was a higher prevalence of poorly differentiated tumours in Poland, the UK and Italy (47.5%, 42% and 41.5% respectively), compared with Luxembourg, The Netherlands and Spain, where it was less than 22%. Furthermore, significant differences were observed regarding the presence of polyps before cancer diagnosis, with approximately 20% in The Netherlands, compared with the rest of the countries where it ranged from 3 to 9%.

Regarding family history of cancer, statistically significant differences were observed in the proportion of cases with first-degree relatives with a history of colorectal cancer (UK: 31.4%, compared with the rest of the countries where it ranged from 3 to 13%). Finally, the presence of early-onset cancer in the family also showed large differences across countries, with rates of 18.4% in the UK and 17.3% in The Netherlands, contrasting with the rest of the countries, where it ranged from 0 to 8%.

Comparison of Mediterranean versus non-Mediterranean regions

The results of these analyses are summarized in *Fig. 3*, *Table 2* and *Fig. S1*.

Patient characteristics

There were differences in the age at diagnosis and BMI between these two regions. The prevalence of EOCRC over the age of 40 years in Mediterranean *versus* non-Mediterranean countries was

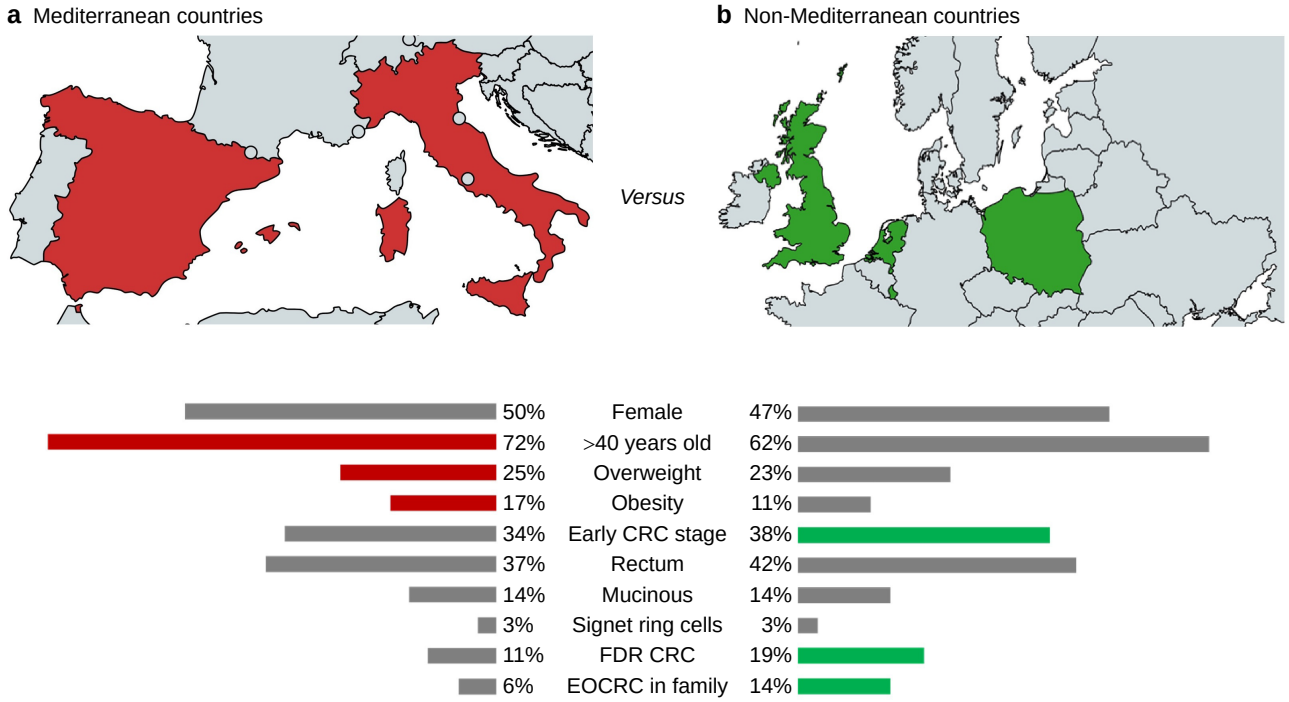

Fig. 3 Characteristics according to the different variables between a Mediterranean and b non-Mediterranean countries
CRC, colorectal cancer; FDR, first-degree relative; EOCRC, early-onset colorectal cancer; early CRC stage, tumour stage at diagnosis I or II.

71.4% *versus* 62.1% respectively ($P = 0.002$; mean(s.d.) age 42.1(6.2) years old *versus* 40.8(7.2) respectively; $P = 0.03$). The prevalence of overweight/obesity was higher in Mediterranean *versus* non-Mediterranean countries (mean BMI 24.9 (14.5–40) kg/m^2 *versus* 23.5 (13.7–62.9) respectively; $P = 0.001$).

Tumour characteristics

EOCRC was diagnosed at a more advanced stage in Mediterranean countries *versus* non-Mediterranean countries, 65.3% *versus* 54.7% in advanced stage (stage III and IV) ($P = 0.033$). There were no differences in tumour location or histological features between the two regions.

Family history

Family history of colorectal cancer in a first-degree relative was more common in non-Mediterranean *versus* Mediterranean countries (19.1% *versus* 11.4% respectively; $P < 0.001$). There were no significant differences in family history of colorectal cancer in patients with only second-degree relatives with colorectal cancer. Family history of other gastrointestinal, gynaecological, breast, urinary tract and prostate cancers did not differ between the two regions. Early-onset cancer (<50 years of age) in relatives was more frequent in non-Mediterranean than in Mediterranean countries (14.1% *versus* 6.5% respectively; $P < 0.001$). There was no difference in the proportion of EOCRC considered as sporadic based on family history between regions ($P = 0.175$).

Discussion

This European multicentre study within the GEOCODE consortium describes the existence of striking phenotypic geographical differences in EOCRC. The comparative analysis between countries demonstrates that the phenotype of colorectal cancer in young adults presents differences according to the geographical area analysed, such as mean age of onset (younger age at diagnosis is observed in the UK), BMI (higher overweight and obesity rates are observed in Italy), staging (more advanced stages at diagnosis are observed in Luxembourg), associated polyps (mainly in The Netherlands) or family history of cancer (higher percentage of family history of colorectal cancer in the UK). In summary, our study highlights substantial geographical disparities in clinicopathological features of EOCRC across European countries.

EOCRC in patients from Mediterranean countries are more frequently associated with overweight/obesity, older age at diagnosis and a lower frequency of family history of colorectal cancer than non-Mediterranean countries. Conversely, non-Mediterranean countries were more closely associated with a family history of colorectal cancer and early-onset cancers, together with an earlier age of onset of colorectal cancer compared with Mediterranean countries. This suggests a more predominant lifestyle and environmental component in the Mediterranean population. Factors such as exposure to environmental carcinogens, which may vary significantly between regions due to industrial activity or pollution, differences in lifestyle including dietary habits, physical activity levels and smoking rates, as well as disparities in healthcare access and preventive screening practices, likely contribute to the regional variations observed in EOCRC. Established risk factors for EOCRC include male sex, race and ethnicity, obesity, diabetes, alcohol consumption and hyperlipidaemia[21–24]. Unfortunately, data were only collected on BMI, revealing a noteworthy observation of 42% prevalence of overweight/obesity. Obesity is known to be a risk factor for several major cancers, including colorectal cancer and EOCRC[25]. Wei *et al.*[9] recently described how obesity likely explains the higher incidence of EOCRC in the USA compared with Europe. At present, the incidence and prevalence of obesity is very similar across Europe, with an increased incidence in people over the age of 40 years[26]. However, recent data shows that childhood obesity

Table 2 Characteristics analysis comparing Mediterranean *versus* non-Mediterranean countries

Characteristic	Study cohorts by region		
	Mediterranean countries 447 (52.53)	Non-Mediterranean countries 404 (47.47)	P
Sex			
Female	224 (50.1)	191 (47.3)	0.410
Male	223 (49.9)	213 (52.7)	
Age at diagnosis (years)			
<30 years	20 (4.5)	38 (9.4)	0.002
≥30 to ≤39 years	108 (24.2)	115 (28.5)	
≥40	319 (71.4)	251 (62.1)	
Mean(s.d.) (years)	42.1(6.2)	40.8(7.2)	0.030
BMI (kg/m^2)			
Underweight (≤18.5 kg/m^2)	16 (3.9)	11 (5.6)	0.045
Normal weight (>18.5 to ≤25 kg/m^2)	203 (50.1)	116 (59.5)	
Overweight (>25 to ≤30 kg/m^2)	111 (27.4)	46 (23.5%)	
Obesity (>30 kg/m^2)	75 (18.5)	22 (11.2)	
Tumour stage at diagnosis			
I	79 (17.7)	68 (16.8)	0.033
II	76 (17)	85 (21)	
III	155 (34.7)	137 (33.9)	
IV	137 (30.6)	84 (20.8)	
Unknown	0 (0)	30 (7.4)	
Tumour site			
Right colon	99 (22.1)	92 (22.8)	0.056
Left colon	178 (39.8)	124 (30.7)	
Rectosigmoid junction/rectum	167 (37.4)	169 (41.8)	
Unknown	3 (0.7)	19 (4.7)	
Rectum site			
Yes	167 (37.4)	169 (41.8%)	0.066
No	277 (61.9)	216 (53.5%)	
Unknown	3 (0.7)	19 (4.7%)	
Histological features			
Mucinous	64 (14.3)	58 (14.4)	1
'Signet ring' cells	15 (3.4)	11 (2.7)	0.691
Grade of differentiation			
Low	82 (18.3)	52 (12.9)	0.083
Medium	205 (45.9)	195 (48.3)	
High	136 (30.4)	136 (33.7)	
Unknown	24 (5.4)	21 (5.2)	
Familial cancer history (first degree)			
Colorectal cancer (CRC)	51 (11.4)	77 (19.1)	<0.001
Digestive cancers different from CRC	16 (3.6)	15 (3.7)	0.712
Gynaecologic and breast cancer	23 (5.1)	19 (4.7)	1
Urinary tract and prostate cancer	18 (4)	15 (3.7)	1
Early-onset cancers in family			
Yes	29 (7.8)	57 (19.4)	<0.001
No	340 (92.2)	236 (80.6)	

Values are *n* (%) unless otherwise indicated. BMI, body mass index.

is most prevalent across southern European countries. Experts have attributed this change of tendency to the loss of the traditional Mediterranean diet, traditionally linked to a diet rich in olive oil, fruits, vegetables and whole grains, and an increase of processed and artificial foods that have gradually replaced healthier habits[27]. However, when analysing this data across Mediterranean and non-Mediterranean countries, caution is warranted in suggesting a definitively higher prevalence of obesity in the Mediterranean region. The regional variations in lifestyle, dietary habits and genetic predispositions requires careful interpretation. Contemporary shifts in dietary patterns towards more processed foods and sedentary lifestyles may likely contribute to an increased prevalence of obesity[9,24,27,28]. Acknowledging these multifaceted elements is essential in understanding the complex interplay between lifestyle, diet and obesity prevalence in Mediterranean countries. It is important to highlight that known hereditary forms were ruled out in the analysed population. The observed differences might be related to a combination of genetic background of low- and/or high-penetrance alleles. More granular data on the contribution of these factors would be needed to draw any conclusion.

Previous evidence has shown that EOCRC is particularly frequent in the rectum, closely followed by the distal colon. Over 70% of these cancers manifest in the left colon on initial presentation[29–33]. This study aligns with these findings, demonstrating that in all countries examined, more than 70% of EOCRC cases are situated in the distal colon, encompassing both the left colon and rectum. Concerning tumour stage, prior studies have consistently suggested that EOCRC patients tend to have a higher incidence of stage III or IV compared with those with later-onset disease[32,33]. Over 60% of patients from Italy, Spain, Luxembourg and The Netherlands had disease at an advanced stage. However, notable variations exist, such as in the UK and Poland, where diagnoses are evenly distributed between advanced and early stages.

The main strengths of this study are its large sample size, its multicentre nature with detailed and centralized information on several clinical, pathological factors and family history of

cancer. However, significant limitations are noted: the GEOCODE cohort is not selected from whole population national colorectal cancer registries and accordingly, suffers from a potential selection and/or referral bias and additionally, considering the regional differences, there may be a potential publication bias. However, centres involved in the study systematically recruited all EOCRC presenting during the study interval and are reference centres from representative population areas in the countries. However, our results should be interpreted carefully and may not be representative of the entire European population; it was not possible to account for various potential confounding factors, including carcinogen exposure, dietary and lifestyle choices, socioeconomic status and healthcare access. This limitation prevents us from drawing definitive conclusions about the causes behind the observed disparities; and one of the limitations of including a long interval recruitment time is that some of the already known prognostic factors for recurrence were not collected systematically, such as perineural and/or perivascular invasion.

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Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The entire database is available upon request to interested researchers from the corresponding author.

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