


# BMJ Open 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

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## ABSTRACT

**Purpose** The Spanish Early-onset Colorectal Cancer (SECOC) study is a multicentre prospective cohort established in Spain to investigate the molecular basis of early-onset colorectal cancer (EOCRC), including metabolic alterations.

**Participants** 220 patients with EOCRC have been enrolled since January 2019 through 18 centres across Spain. Individual-level data were collected by questionnaire, including lifestyle and other colorectal cancer-related factors. Medical record review was performed to capture clinical, histopathological and familial cancer history data. Biospecimen collection (blood, stool, tissue) at diagnosis and at various time points across treatment, as applicable, is also completed.

**Findings to date** Participants had a median age of 44 years (range 14–49), and the majority are men (60%), with individuals age 40–49 years at EOCRC diagnosis being over-represented. Forty-three per cent of participants were diagnosed with a tumour in the rectosigmoid junction/rectum. Nearly two-thirds of EOCRC cases (64%) were diagnosed with advanced stage (III–IV) disease, and 28% of cases had no reported familial history of cancer.

**Future plans** We are actively recruiting and observing participants; we plan to administer follow-up questionnaires and perform additional biospecimen collection. This prospective cohort offers a unique, rich resource for research on EOCRC aetiologies and will contribute to larger international efforts to disentangle the rising disease burden.

## Strengths and limitations of this study

- One of the main strengths of Spanish Early-onset Colorectal Cancer study is the prospective cohort design, which reduces different type of bias.
- The demographic composition of this cohort is predominantly European white, being at the same time a weakness, leaving aside ethnic minorities to take into account in Spain (Latino, etc), but it can also be a strength, by minimising any potential difference in the findings due to the marked disparities of the early-onset colorectal cancer (EOCRC).
- The cohort covers a wide range of aspects of the EOCRC (clinical, family, histological features), important when analysing their relationships with the molecular analyses to be developed.
- The collaboration with patient advocacy organisations in Spain and Europe confers an essential perspective on the priorities for patients.

## INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide (10% of all new cases, excluding non-melanoma skin cancer), and ranks as the second leading cause of cancer-related deaths.<sup>1</sup> Despite a reduction in the absolute numbers of patients diagnosed with CRC, mainly due to advances and uptake in screening modalities—particularly in developed countries—there has



## Box 1 Overview of questionnaire data collected for the Spanish Early-onset Colorectal Cancer cohort

### Questionnaire

#### Demographic information

- ▶ Race/ethnicity.
- ▶ Country of birth (duration of residence in Spain).

#### Anthropometrics

- ▶ Body mass index (at diagnosis, at age 18 years).
- ▶ Area of the body where fat accumulates with weight gain.

#### Lifestyle characteristics during childhood and adulthood

- ▶ Smoking.
- ▶ Alcohol use.
- ▶ Physical activity.
- ▶ Medication history (anti-inflammatory drugs, steroids, antibiotics, probiotics).

#### Dental history

#### Dietary intake in the last 2 years

- ▶ Food frequency.
- ▶ Significant changes to diet in previous decade.

#### Medical history

- ▶ Pathologies or diseases (type and duration).
- ▶ Medications or environmental allergies.
- ▶ Previous surgeries.

#### Familial history

- ▶ Diseases not related to cancer (type, relationship, age, death).
- ▶ Cancer (type, relationship, age, death).

#### Reproductive health (women)

- ▶ Menarche.
- ▶ Menopausal status.
- ▶ Pregnancy, childbirth history and conditions.
- ▶ Children.
- ▶ Oral contraceptive use (age, duration, type).

## Data collection

### Questionnaire data

An outline of the topics included in the SECOC baseline questionnaire, administered prior to CRC surgery, are listed in [box 1](#). Briefly, these include demographic characteristics, medical history, anthropometrics including body mass index (BMI) at diagnosis and age 18 years, lifestyle-related factors (eg, smoking, alcohol, drug/medication use, dental history, physical activity), dietary intake, familial cancer and medical history, as well as reproductive health for women. For familial cancer history, pedigrees were collected with at least two additional generations from the proband and classified into first and second degree relatives. For each category, cases were classified according to the presence of: CRC family history; digestive cancers other than CRC; gynaecologic and/or breast cancers; urinary tract and prostate cancers; and other tumour type. Cases were defined as having a second degree relative when only this fact was present and none in first degree relative presented cancer. In addition, on identification of a family cancer history, data

were captured to ascertain presence/absence of early-onset cancers (<50 years of age). And finally, cases were classified as sporadic if they did not present with any first or second degree relatives with a history of cancer.

### Clinicopathological data

Clinicopathological and pathological characteristics were ascertained from detailed medical record review. Variables include age at CRC diagnosis, sex, anatomical tumour location, tumour grade, mucin production, signet ring cells, perineural and vascular invasion, tumour budding, tumour infiltrating lymphocytes, tumour stage lymph node involvement, metastasis site(s), CRC treatments, BMI at diagnosis, medical and detailed information on colorectal polyps detected before/at EOCRC diagnosis. Presence of multiple primary neoplasms (eg, synchronous and metachronous CRC) was also captured and defined as follow: (i) Synchronous CRC was defined as two or more histologically different CRCs that developed simultaneously or within 6 months of detection of the first CRC diagnosis; and (ii) Metachronous CRC was defined on presence of a secondary neoplasm detected distant from the anastomosis area, greater than 6 months after first CRC diagnosis.

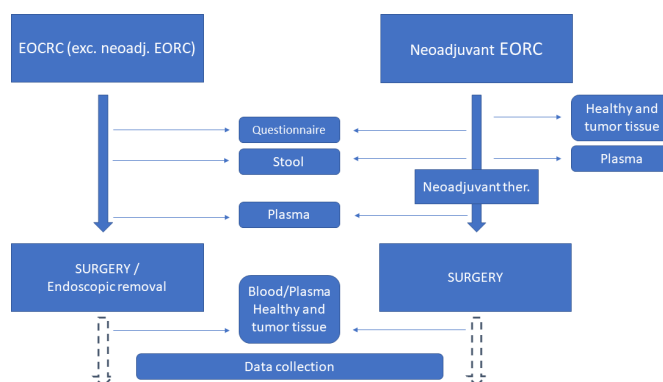
### Follow-up data ascertainment

Follow-up is completed for all EOCRC cases in SECOC every 6 months. In addition to surveillance for disease outcomes, cases are followed for the presence of colorectal polyps after EOCRC diagnosis.<sup>16</sup>

### Biological sample collection

Given the overarching goal of SECOC to characterise the molecular basis of EOCRC, biological fresh samples are collected at multiple time points in this study. Timing and types of sample collection for SECOC are depicted in [figure 2](#). Notable, early-onset rectal cancer cases who receive neoadjuvant therapy have a distinct biological sample collection pattern in order to collect samples prior to tumour therapy.

The collection of faecal (stool) samples from patients with EOCRC affords a unique opportunity to study the



**Figure 2** Study data and biospecimen collection diagram. EOCRC, early-onset colorectal cancer; EORC, early-onset rectal cancer.



microbial diversity within this patient population by 16S and/or metagenomic sequencing. The collection of stool is assembled as far out as possible from the diagnostic colonoscopy, and prior to admission for CRC treatment, to avoid possible contamination from bowel preparations. Blood collection includes whole blood as well as plasma samples for future molecular-omics studies. Routine tissue collection includes both normal (healthy) colon and tumour tissue collected during endoscopy or surgery (the main proportion of samples).

As mentioned before, different protocol will be assessed for rectal cancer cases receiving neoadjuvant therapy. In this case, an additional sample collection will be defined prior to that therapy, collecting both tumour and healthy colon tissues and plasma sample. In these cases, stool collection will be made also before neoadjuvant therapy.

Finally, as we progress in the recruitment and based on the preliminary results, the consequent sample calculations will be carried out, and thus the different types of samples and necessary data will be able to be carried out.

### Definition and collection of control group

The control group is being selected in a ratio of 2:1 in relation to cases. They are healthy subjects under 50 years of age and matched with the cases in defined characteristics. The match process is defined by the following case variables: age at the EOCRC diagnosis, sex, race and geographical area of diagnosis. In addition, all colonic pathology (inflammatory bowel disease, etc) will be exclusion criteria for cases, as well as any diagnosis of cancer in the controls, or suspicion of hereditary syndrome in the family. For controls, initially stool samples is being also collected, as well as they fulfil the lifestyles questionnaire.

### Patient and public involvement

No patient involved until now, but the immediate steps will be to include in the coordinating committee of the cohort both representation of patients, as well as patient organisations, not only from Spain, but also European, in order to make the results known constantly, and expand the knowledge accordingly, but also to receive feedback on the needs of those to adapt future studies in this regard. For this reason, Digestive Cancers Europe ([www.digestive-cancers.eu](http://www.digestive-cancers.eu)), the European umbrella organisation of a large group of national members representing patients with digestive cancer—colorectal, gastric, pancreatic and rare cancers, has been already contacted. In addition, there will be a need to expand the results not only scientifically but publicly to raise awareness of this problem in society, as well as the importance of future educational strategies both in the medical community and in society in general.

## FINDINGS TO DATE

### Baseline demographic characteristics

Individual and clinicopathological characteristics for a subset (n=176 of 220) of currently enrolled EOCRC cases

with annotated data in SECOC are provided in [table 1](#). Among these cases, the majority (60.3%) were men—which is aligned with a higher incidence of CRC among men. At baseline, patients with EOCRC in SECOC have a median age of 44 years, with a large proportion of the cohort diagnosed between ages 40 and 49 years (74%). Four out of every 10 patients with EOCRC in SECOC (42.6%) had a BMI classified as overweight or obese. Less than one-third of cases (28.4%) had no family history of cancer, while another one-third (31.3%) of cases had positive family CRC history.

### EOCRC clinicopathology

The most frequent tumour location among cases was the rectum (42.6%), followed by tumours in the left colon and then right colon (32.4% and 25%, respectively). Nearly two-thirds of cases (64.2%) were diagnosed with advanced stage disease (stage III–IV). Twenty-one per cent of colorectal adenocarcinomas among patients with EOCRC harboured a mucinous component.

### Molecular characterisation of EOCRC

Given the emerging role of metabolic dysregulation in EOCRC,<sup>7</sup> the first molecular characterisation of case in SECOC is to assess metabolic alterations, including carbohydrate metabolism, in EOCRC via transcriptomic (RNA-sequencing) profiling paired with detailed lifestyle-related data. Profiling of tumorous tissues is currently underway and anticipated to be paired with additional omics profiles in the future to provide a multidimensional characterisation of the molecular basis of EOCRC.

## STRENGTHS AND LIMITATIONS

We established the SECOC cohort, the largest prospective study on EOCRC with a nationwide distribution in Spain. The detail and breadth of data on various exposures and biological samples collected is presented in this paper. This uniform collection enables unique and in-depth molecular characterisation of EOCRC, and more complex multiomics analyses, in order to elucidate underlying aetiologies of this rising disease burden. In addition, our ongoing partnership with patient advocacy organisations in Spain and Europe provides a unique perspective and insight on the priorities and needs for patients in order to tailor SECOC and expand the impact of this study moving forward.

Another strength of SECOC is the prospective cohort design, which reduces selection and recall bias among EOCRC cases. Moreover, identical protocols/data and biospecimen collection across all 18 centres in SECOC allows for uniform data pooling and harmonisation, as well as the ability to assess geographical heterogeneity of EOCRC across Spain.<sup>13</sup> This is particular advantage for biospecimen collection, as it will allow for the characterisation and integration of molecular assays and analyses to deepen our understanding of the molecular basis of EOCRC. However, future expansion of biological sample

**Table 1** Baseline characteristics of the patients with early-onset CRC cohort: Spanish Early-onset Colorectal Cancer (SECOC) Consortium

Characteristic	Total N (%)
Total	176
Sex	
Female	70 (39.7)
Male	106 (60.3)
Age at diagnosis	
<30 years	6 (3.4)
30–39 years	39 (22.2)
40–49 years	131 (74.4)
Mean (std), years	42.7 (6.2)
Median (range), years	44 (14–49)
Body mass index	
Underweight (<18.5 kg/m <sup>2</sup> )	9 (5.1)
Normoweight (18.5–<25 kg/m <sup>2</sup> )	62 (35.2)
Overweight (25–<30 kg/m <sup>2</sup> )	56 (31.8)
Obese (30+ kg/m <sup>2</sup> )	19 (10.8)
Unknown	30 (17.1)
Mean (std), kg/m <sup>2</sup>	25.6
Median (range), kg/m <sup>2</sup>	25.2 (14.2–43)
Tumour stage at diagnosis	
I	26 (14.8)
II	29 (16.5)
III	75 (42.6)
IV	38 (21.6)
Unknown	8 (4.5)
Tumour site	
Right colon	44 (25)
Left colon	57 (32.4)
Rectosigmoid junction/rectum	75 (42.6)
Histological features*	
Mucinous	34/162 (21)
'Signet ring' cells	7/162 (4.3)
Unknown	14 (8)
Grade of differentiation*	
Low	18 (10.2)
Medium	84 (47.7)
High	62 (35.2)
Unknown	12 (6.8)
History of polyps	
None	113 (64.2)
Yes	57 (32.4)
Adenomatous	33 (57.9)
Hyperplastic	8 (14)
Serrated	3 (5.3)
Mixed	11 (19.3)
Unknown	2 (3.5)
Unknown	6 (3.4)

Continued

**Table 1** Continued

Characteristic	Total N (%)
Multiple primary neoplasms	
Synchronous CRC	6 (3.4)
Other	13 (7.4)
Familial CRC history	
Yes	55 (31.3)
No	113 (64.2)
Unknown	8 (4.5)
Familial cancer history	
Yes	50 (28.4)
No	122 (69.3)
Unknown	4 (2.3)
Microsatellite instability	
MSS	112 (63.6)
MSI	16 (9.1)
Unknown	48 (27.3)

\*Cases with only a biopsy due to palliative care are excluded from tumour histology/grade. CRC, colorectal cancer; MSI, microsatellite instability; MSS, microsatellite stability.

collection—including among cases receiving adjuvant therapy, will expand the potential of SECOC to define changes in molecular features caused by these therapies and may yield insight into potential biomarkers for disease recurrence and prognostic outcomes. This will also afford a unique opportunity to continue building a robust cohort size with sufficient statistical power that will allow for clinical translation of our findings in the future (eg, liquid biopsy).

While SECOC is the first-of-its-kind cohort across Spain, it should be noted that the demographic composition of this cohort is predominantly comprised of European whites. While this will minimise any potential differences in biological findings due to the marked EOCRC racial/ethnic disparities,<sup>15 17</sup> collaborations with other studies worldwide that include an over-representation of diverse population subgroups will be essential in order to better understand the disproportionate burden of EOCRC moving forward. In addition, the inclusion of SECOC in larger, international consortium efforts will also overcome this emerging limitation and allow for and increased sample size of EOCRC cases.

## COLLABORATIONS

The SECOC multicentre prospective cohort will continue to collect a robust set of data, including follow-up, and biological samples. Researchers interested in collaboration are invited to propose EOCRC research based on the data/biospecimen available within SECOC or submit a request for additional data collection. Requests can be submitted to JP (josepereag@hotmail.com) and will be

reviewed by the SECOC committee. Moreover, SECOC is a contributing cohort to the Global Early-Onset Colorectal Cancer (GEOCODE) Consortium—in order to define the burden and patterns of EOCRC worldwide, including EOCRC disparities, and is open to further collaborations with other EOCRC cohorts toward this objective. Other ongoing EOCRC projects, like BEYOND project (BETter understanding of Young-ONset ColoRectal Cancer),<sup>18</sup> with a similar range of sample collection, could be good candidates to explore synergies in the discovery of the mechanistic of the EOCRC and its molecular bases.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Cohort description section for further details.

**Patient consent for publication** Not applicable.

**Ethics approval** This study was approved by the Fundación Jiménez Díaz University Hospital Ethics Board (PI20/00974), and the contributing centres to SECOC were approved by all local research ethics review committees, and participants signed and informed consent for SECOC prior to enrolment. Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available upon reasonable request. Data will be available on reasonable request. Researchers may request access data

by applying to the SECOC access committee. Nowadays, the best approach is connecting with the author for correspondence. Data also will be distributed in the corresponding repositories, according to each type of sample and analysis.

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