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Hereditary evaluation and genetic counselling in young individuals with colorectal cancer in a population-based cohort

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A B S T R A C T

Aim: Early-onset colorectal cancer should raise suspicions of a hereditary colorectal cancer (CRC) syndrome, including Lynch syndrome (LS) and Familial Adenomatous Polyposis (FAP). Collection of family history and genetic counselling (GC) is mandatory but previous studies have revealed low awareness of hereditary CRC among clinicians why there has been an incentive to implement universal LS screening. In this population-based cohort study, we aimed to observe the uptake of GC in the Swedish South-Eastern medical care region for young CRC patients and to investigate the frequency of patients diagnosed with LS.

Methods: Patients below 50 years of age diagnosed with CRC between 2008 and 2017 were identified from the national Swedish Colorectal Cancer Registry. Medical records were reviewed regarding family history, co-morbidity and referral for GC, with a follow-up time of at least three years.

Results: The analysis included 278 patients with 287 tumours, 108 (38%) located in rectum and 179 (62%) in colon. One hundred sixteen (42%) individuals were referred to the Regional Clinical Genetics service, whereof 74 (27%) underwent complete investigation. Thirteen (18%) patients were identified with a mutation, eleven (15%) had LS and two (3%) FAP. The remaining 61 (82%), without proven mutation, were considered as familial CRC. Younger age correlated with a higher chance of referral for GC.

Conclusion: The study found that only a minority of young CRC patients underwent genetic counselling, contrary to clinical guidelines. Hereditary CRC is therefore probably underdiagnosed even among young individuals.

1. Introduction

Colorectal cancer (CRC) is the third most common malignancy both globally and in Sweden and the second leading cause of cancer related death [1,2]. A family history of CRC is a strong risk factor for developing CRC and early detection is of great importance for long time survival [3,4]. Although most CRC appears to be sporadic, hereditary syndromes such as Lynch syndrome (LS) and Familial Adenomatous Polyposis (FAP), may account for 2–5% of all CRC and as much as 14–30% of early-onset CRC (EOCRC), here defined as diagnosed before 50 years of age [5–7]. In addition to these well-defined hereditary syndromes, another 20% of EOCRC patients shows a familial aggregation although a specific mutation is undetectable with current knowledge [5]. In general, EOCRC is associated with more advanced tumour stage, poor cell differentiation and left-sided- or rectal location. Early-onset CRC remains a challenge to healthcare since the age of 50 years is the cut-off limit for the start of many CRC screening programs [8]. Of concern, the incidence of EOCRC seems to be increasing in developed countries [9].

Lynch syndrome is a hereditary tumour predisposition syndrome with a lifetime risk of CRC up to 70% [10]. In this condition, germline variants in *MLH1, MSH2, MSH6 or PMS2* genes predispose to development of tumours characterized by deficient mismatch repair pathway (dMMR). The second most common hereditary syndrome is Familial Adenomatous Polyposis (FAP), characterized by numerous adenomatous polyps in the gastrointestinal tract and EOCRC [11]. Early onset of cancer is a hallmark of LS and FAP, so collection of family history of cancer is an important routine diagnostic tool in the work-up of a new CRC patient [12] helping to evaluate cancer burden in the family. It should include type of cancer and age at diagnosis for both first-degree relatives (FDR) like parents, siblings and children and second-degree relatives like grandparents, aunts and nephews, in order. LS can be suspected through microsatellite instability (MSI) analysis or immunohistochemistry for MMR-proteins (IHC-MMR) in tumour tissue and

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confirmed by screening of MMR-genes in constitutional DNA.

During the last decades, there have been several attempts to create sensitive and specific diagnostic criteria of Lynch syndrome, such as the Amsterdam and Bethesda criteria and respective revised versions [13–16]. The Swedish recommendations for hereditary CRC applied in 2008–2017 were based upon the revised Bethesda guidelines, first stating that CRC diagnosed in a patient <50 years is itself sufficient to refer the patient for genetic counselling (GC) [17].

Previous studies from other countries found that family history in medical records often is either missing or lack in quality, but there is limited data from Sweden [18–20]. Two reports from Norway and the UK, representing two hospitals each, found low compliance to the revised Bethesda guidelines as well as low awareness of LS among their surgeons. Consequently, GC was not offered frequently enough in those countries.

Reflex LS screening with IHC has been proposed in recent years for all CRC patients regardless of age [21,22]. This approach has limitations since results need to be interpreted by the referring doctor and patients can still be reluctant to undergo GC. Furthermore, reflex screening alone, without evaluation of family history, will exclude the major portion of patients with familial CRC [23–25]. A Swedish study estimated that more than 75% of the expected LS patients in Sweden remain unidentified [26]. Yet, little is known about the uptake of GC among EOCRC patients in large and well-defined populations. In this ten-year population-based cohort study of patients <50 years of age, we aim to evaluate the awareness of hereditary CRC, described as the number of referrals for GC, and examine the frequency of diagnosed hereditary CRC syndromes.

2. Methods

2.1. Patient selection

Patients in the Swedish South-Eastern medical care region diagnosed with CRC before 50 years of age during the period January 1, 2008 and December 31, 2017 were identified in the Swedish Colorectal Cancer Registry (SCRCR) and included in the study. Information regarding tumour stage (TNM), localization and dates of diagnosis and surgery were obtained from the SCRCR together with comparative data on patients diagnosed at 50 years or older. The national Swedish registry (today the SCRCR), once started with rectal cancers in 1995 while colon cancers were included from 2007 [27,28]. The use of a unique Personal Identification Number makes it possible to follow patients over time in the SCRCR [29]. A previous validation of SCRCR including most of the study period found that only 1.5% and 1.2% of colon and rectal cancers, respectively, were missing in comparison to the Swedish Cancer Registry which is a register compulsory to report to according to Swedish law [30].

The Swedish South-Eastern medical care region comprises three counties (Östergötland, Jönköping and Kalmar) with approximately 1.1 million (2020) inhabitants allocated at seven hospitals managing CRC, all of them public and run by the counties [31]. These include the University hospital in Linköping that serves the region with advanced cancer care and genetic counselling.

2.2. Genetic counselling

A referral for GC initiated an individual process where a pedigree establishment was mandatory in order to go further with molecular analyses. This followed with either IHC-MMR if the pedigree indicated a very low grade of heredity, a CRC gene panel analysis (at minimum including MLH1, MSH2, MSH6 and PMS2) alone or both. Given the ten-year observation period, collaboration with laboratory departments and analytic methodology evolved over time. During 2015 through 2017, many patients were included in a separate research project (not yet published) providing a broader CRC gene panel.

2.3. Medical records

Electronic medical records were available for most patients and requested in paper form when necessary. Medical records were systematically reviewed for all included patients in order to obtain information that was unavailable from the registry, i.e., documentation of family history, co-morbidity, date of referral for GC and results from genetic investigations. A family history of CRC, or another LS-related tumour (e.g. endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract [16]), in a first or second-degree relative classified patients as having a positive family history. Information on IHC-MMR and MSI-analysis were sought after in the department of pathology in each county. The reviews took place from May 2018 until February 2019 and included all notes, both primary and hospital health care, from the first time of presentation until date of review. A last check for a GC referral was performed in March 2021, allowing at least three years of follow-up after diagnosis for all included patients.

Patients were characterized whether they were referred to GC and the origin of such referral (surgeon, oncologist or other). Genetic counselling was defined as complete when an established pedigree was combined with molecular analysis and aborted if the patient, after reminders, did not return the initial family history forms, actively declined GC or expired close to referral. The clinical genetics local registry (RGR) was used to validate that all patients referred for GC were identified.

2.4. Statistical analyses

Comparisons between patients referred to GC and those not referred were performed using Mann Whitney *U* test, Chi-squared test, Fishers exact test, and Pearson correlation test as appropriate. Numbers are presented as median and range unless otherwise stated.

Ethical approval

The regional board of research ethics committee in Linköping (DNR 2017-458-31) approved the study.

3. Results

From 2008 to 2017 the South-Eastern medical care region registered 6741 CRC patients, corresponding 11.3% of the total numbers of CRC patients in Sweden. Among them, 278 (4%) were <50 years at diagnosis and included in the analysis. In the study population, genders distributed equally ($p = 0.41$) with 51% colon cancer and 46% rectal cancer in women. Synchronous tumours were registered in eight (3%) patients, gaining 287 tumours in total. Rectal cancer was overrepresented in the younger age group ($p = 0.026$) compared to patients >50 years of age at diagnosis. EOCRC patients also showed significantly less frequent stage II disease ($p = 0.001$) and more stage IV ($p < 0.001$). Further patient characteristics are displayed in Table 1.

Medical records held some information of family history of cancer in 188 (68%) of 278 patients and of these, 107 (57%) had a positive family history of colorectal tumours or Lynch-related tumours. Ninety (32%) patients had no documentation of family history, 19 of those (21%) were referred to GC. Patients referred to GC were more likely to have a positive family history documented (Table 1), but information on family history was often vague and unspecific regarding cancer type and age at diagnosis in relatives.

Fig. 1 displays results of referral frequency to genetic counselling and results of genetic investigations in the 116 (42%) patients referred to the Regional Clinical Genetics service. Seventy-four (64%) patients underwent complete GC, including pedigree and molecular analysis. Pathogenic variants were identified in 13 (18%) of the investigated patients, eleven (15%) with LS and two (3%) with FAP. In three patients confirmed with LS, there was already a known mutation in the family. In the remaining 61 (82%) patients there were no mutation detected but a

Table 1
Colorectal cancer patients in the Swedish South-Eastern medical care Region, 2008–2017.

		Patients ≥50 years of age n = 6463, n (%)	Patients <50 years of age n = 278		*p-value, referred vs not referred patients*	*p-value, patients <50 vs ≥ 50 years of age*
			Referred to RCG n = 116, n (%)	Not referred n = 162, n (%)		
Tumours		6719	119	168	0.949	
Age	Median	74ys,	42ys,	46ys,	<0.001	
	IQR	67-81ys	37-46ys	41-48ys		
Sex	Male	3434 (53)	55 (47)	87 (54)	0.301	0.502
	Female	3029 (47)	61 (53)	75 (46)		
Tumour localization	Rectum	2110 (31)	46 (38)	62 (37)	0.763[a]	0.026[a]
	Colon	4609 (69)	73 (61)	106 (63)		
Localization in colon	*Right side*				0.011[a]	0.372[a]
	Appendix	69 (1)	1 (1)	7 (7)		
	Caecum	1008 (22)	16 (22)	9 (9)		
	Ascending	830 (18)	13 (18)	16 (15)		
	Hepatic flexure	244 (5)	5 (7)	5 (5)		
	Transverse	449 (10)	11 (15)	11 (10)		
	Left side					
	Splenic flexure	144 (3)	1 (1)	9 (8)		
	Descending	214 (5)	3 (4)	11 (10)		
	Sigmoid	1644 (36)	21 (29)	38 (36)		
	Missing data	7 (0)	2 (3)	-		
Stage[b]	Stage I	943 (15)	15 (13)	20 (12)	0.885	0.196
	Stage II	1956 (30)	27 (23)	36 (22)	0.836	0.001
	Stage III	1972 (31)	41 (35)	56 (35)	0.893	0.368
	Stage IV	1233 (18)	33 (28)	50 (31)	0.664	<0.001
	Missing data	359 (6)	-	-		
Documented family history		N/A	97 (84)	91 (56)	<0.001	
Positive family history[c]		N/A	75 (65)	32 (20)	<0.001	

RCG, Regional Clinical Genetics,
IQR, Inter Quartile Range.
Mann-Whitney *U* test, Fisher's exact test and Chi-square test used as appropriate.
[a] p-value based on number of tumours.
[b] Synchronous and metachronous tumours based on worst stage.
[c] Any family history on colorectal cancer or Lynch-related tumours documented.

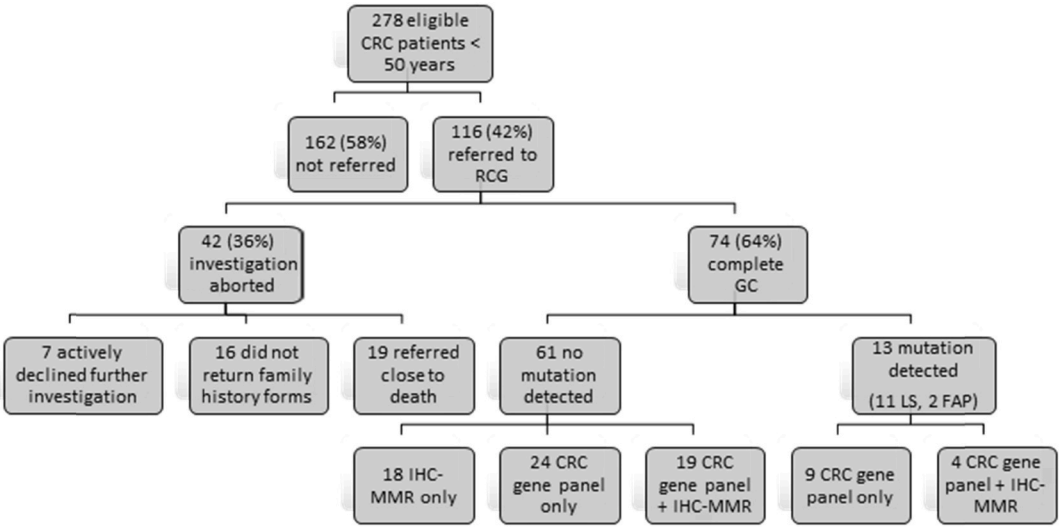

Fig. 1. Flow chart of genetic counselling for all 278 patients in the Swedish South-Eastern medical care region 2008–2017 diagnosed.with early onset colorectal cancer diagnosed (<50 years age).

possible family predisposition to CRC were considered by the RCG due to low age at diagnosis. Thus, their first-degree relatives were advised regular colonoscopies with five-year intervals starting 5–10 years before reaching the age of the earliest case of CRC in the family. Twenty-three (20%) individuals initially referred either actively declined further investigation or refrained to return the family history forms. Another 19 (16%) patients referred in late-stage disease left blood samples for later analysis and in seven cases, a close relative continued the genetic investigation, of which the results are out of scope of this study. Except for GC, we found only three patients that underwent IHC-MMR.

Referrals for GC varied from 18% to 50% among the seven hospitals within the region (p = 0.33). Surgical units sent 50 (43%) persons to GC, equally to oncological units (43%) and a small part came from patients own initiative (3%) or other units (10%). Low age correlated with higher

frequency of referrals ($p < 0.001$), with 61% referral frequency in those aged 18–29 years, 58% in 30–39, and 36% in 40–49. Patients with right-sided colon tumours were more often referred (Table 1) but no statistically significant differences regarding sex or tumour stage could be seen. Over time, referral frequency varied from 32% (2008) to 59% (2014) and showed a non-significant tendency to increase over the study period ($p = 0.161$) (Fig. 2). Time gap from diagnosis to GC ranged from minus 13 months (patient's own referral) to 101 months, median 8 months. Notably, 33 (28%) referrals were sent more than two years after diagnosis. Only three of the eight patients with synchronous EOCRC tumours underwent GC. Overall, 15 (5%) individuals had a coexisting diagnose of inflammatory bowel disease (IBD) and one of them underwent GC. Except from IBD diagnosis, we found major co-morbidity in another 25 (9%) patients of which six had severe cerebral disorders, 16 developmental disorders or severe psychiatric disease and three alcohol- or drug abuse, whereof three (3/25) underwent GC.

4. Discussion and conclusions

In this population-based cohort of 278 EOCRC patients, from South-East Sweden (1.1 million inhabitants representing approximately ten percent of Sweden), we evaluated documentation of family history in medical records and the uptake and results of genetic counselling for hereditary CRC. The main finding is that less than half of the study group (42%) underwent genetic counselling, and we conclude that a significant number of patients and their families are withheld from having their genetic risk valued as mandated by present guidelines [17]. Previous publications of newly diagnosed CRC patients have shown similar shortcomings when it comes to screening for LS[19 20]. Most patients (68%) had their family history documented but information was often scarce.

The study covered CRC patients <50 years diagnosed over ten years with a follow-up time of at least three years in a well-defined population. Even though the study design limited the cohort size, the long observational period validates the result. In line with previous studies of EOCRC patients, rectal cancer and late stage disease were significantly overrepresented in this cohort [32]. Given a nearly complete reporting rate to the national Swedish Colorectal Cancer Registry and that all healthcare in the Swedish South-Eastern medical care region is public, inclusion of EOCRC patients from the studied population is optimized [30]. Genetic counselling in Sweden is organized in six centres, readily available to every CRC patient as indicated. In 2016 the mutation spectrum of Swedish LS population was reported with 201 unique disease-predisposing MMR gene mutations in 369 families, assumed to constitute just a small portion of the overall LS mutation carriers in the country [26]. We contacted the five remaining clinical genetics services in Sweden by phone and mail in January 2021 to compare our findings nationally. However, no recent similar studies on collection of family history and uptake of GC had been conducted in the other regions. In our study, a substantial proportion (17.6%) of the patients that underwent complete GC had a confirmed hereditary syndrome, which is consistent with what has been previously reported [5 8]. Since 58% of our cohort lacked referral during follow-up, it is probable that a substantial number of individuals with hereditary CRC are left undiagnosed.

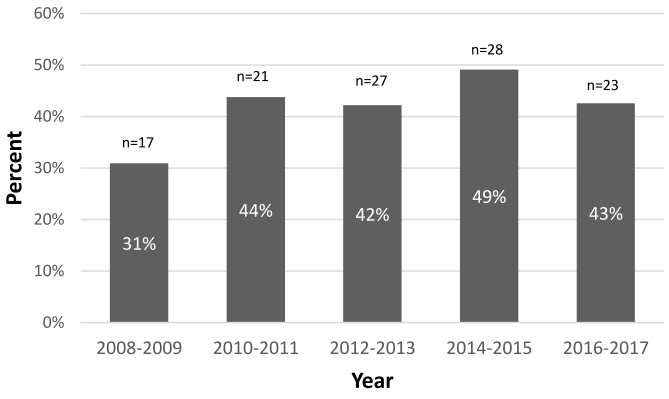

Fig. 2. Frequency of referrals for genetic counselling. Patients diagnosed with early onset colorectal cancer (<50 years of age) in the Swedish South-Eastern medical care region 2008–2017.

During the review of medical records of EOCRC patients who were not referred for GC, we found only a few examples that the question regarding GC had been documented by the clinician. We cannot rule out that such a discussion had taken place in more cases and that such patients declined GC, but still, it is not documented. Another difficulty with medical records was to interpret documented family history. Not surprisingly, some patients had problems recalling cancer type or age at diagnose in relatives. Regarding clinicians' awareness of hereditary CRC, we found that the youngest EOCRC patients were more probable to be referred for GC. There was also a higher degree of right-sided colon tumours among referred patients. The latter can be a coincidence or due to awareness among clinicians that LS has a predilection for right-sided colon tumours [10].

It has previously been shown that EOCRC patients with a known history of hereditary CRC had less advanced CRC at time of diagnosis compared with young patients without a family history (OR = 0.71, 95% CI: 0.56–0.89, P = 0.004) [7]. More so, individuals with hereditary CRC also had lower excess mortality rate (EMR) after adjusting for cancer stage (EMR = 0.63, 95% CIs: 0.47–0.84, P = 0.002) compared to those without, indicating that a family history of CRC may be associated with a greater CRC awareness, leading to earlier diagnosis and better prognosis [7]. It is however important to remember that there can be many barriers for patients to undergo GC. Financial issues like patient fees and traveling costs are described even though it should not be a concern in a publicly financed healthcare system. The time and effort needed to undergo GC can be a barrier and patients may feel overwhelmed at the time of referral by their own cancer diagnosis [33]. This could possibly explain why, in our material, 20% of referred individuals either actively declined or failed to show up. Patients might also be unaware of the service or their eligibility, emphasizing the importance of a well-informed clinician raising the question of GC [34]. Halverson et al. explored reasons for patients not to undergo GC and found that 67% would have been willing to undergo GC if the clinician had "mentioned it again", implicating that more information and patient education can be one target to increase GC for CRC [35]. Our study shows that a long-time gap between diagnose of CRC to referral for GC was frequent, a possible result of the above-mentioned reasons.

Underlying severe co-morbidity is possibly another barrier for GC since only three (12%) of 25 patients with drug or alcohol abuse or cerebral, psychiatric, and developmental disorders underwent GC. However, in a previous study of breast cancer patients eligible for genetic testing, uptake of GC was not impaired by mental health disorders [36]. Surprisingly, only one of 15 (7%) IBD patients underwent GC. Even if the combination of LS and IBD is rare and pathways for tumour genesis differs, IBD should not exclude a patient from screening for LS. Endoscopic surveillance is recommended in 8–10 years after onset of UC or Crohn's colitis [37]. However, observational studies reported that 12.5% of IBD patients develop cancer before the scheduled start of endoscopic surveillance and that family history of CRC in IBD patients is a strong risk factor for CRC [38,8]. In addition, very young age-onset of IBD, <16 years of age, can be an indication for GC in its own right [39].

As of 2020 IHC-MMR is recommended as a screening test for all CRC patients, regardless of age, in the Swedish national guidelines and is established as a cost-effective strategy[17 21]. However, this requires good knowledge of genetic issues and the complexities of genetic testing among clinicians in order to benefit the patient [34,40]. In an Australian study only 30% with abnormal results attended GC of reflex IHC-MMR testing among CRC patients, with higher compliance (62%) for patients <50 years of age. Even though reflex testing has the chance to

increase the identification of patients with possible LS, it still requires a well-informed clinician to interpret the result and translate knowledge into every patient with possible hereditary CRC[23 25].

In conclusion, the present study found that only four out of ten patients diagnosed with colorectal cancer below 50 years of age were referred to genetic counselling as mandated by national guidelines. This raises concerns about the awareness of hereditary colorectal cancers among clinicians. To improve their knowledge of hereditary CRC in young persons and increase referrals for GC, more should be done. In addition to reflex IHC-MMR testing we suggest collection of family history documentation as a quality measure variable in the SCRCR and GC referral as a mandatory point of discussion in the multi-disciplinary team conference. However, if this will be enough to improve the identification of young individuals with hereditary CRC remains to be seen.

Author statement

Erik Lundqvist: Investigation, Formal analysis, Writing original draft, Funding acquisition. Ekaterina Kuchinskaya: Investigation, Writing - Review. Editing Kalle Landerholm: Investigation, Writing - Review & Editing. Jeanette Assarsson: Investigation, Writing - Review & Editing. Anna Benckert: Investigation, Writing - Review & Editing. Pär Myrelid: Supervision, Formal analysis, Writing- Reviewing and Editing. Staffan Haapaniemi: Conceptualization, Investigation, Writing- Reviewing and Editing.

Declaration of competing interest

No conflicts of interest.

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