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Recommendations to improve identification of hereditary and familial colorectal cancer in Europe

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Abstract Familial colorectal cancer (CRC) accounts for 10–15% of all CRCs. In about 5% of all cases, CRC is associated with a highly penetrant dominant inherited syndrome. The most common inherited form of non-polyposis CRC is the Lynch syndrome which is responsible for about 2–4% of all cases. Surveillance of individuals at high risk for CRC prevents the development of advanced CRC. About 1 million individuals in Western Europe are at risk for Lynch syndrome. We performed a survey to evaluate the strategies currently used to identify individuals at high risk for CRC in 14 Western European countries. Questionnaires were distributed amongst members of a European collaborative group of experts that aims to improve the prognosis of families with hereditary CRC. The survey showed that in all countries obtaining a family

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history followed by referral to clinical genetics centres of suspected cases was the main strategy to identify familial and hereditary CRC. In five out of seven countries with a (regional or national) CRC population screening program, attention was paid in the program to the detection of familial CRC. In only one country were special campaigns organized to increase the awareness of familial CRC among the general population. In almost all countries, the family history is assessed when a patient visits a general practitioner or hospital. However, the quality of family history taking was felt to be rather poor. Microsatellite instability testing (MSI) or immunohistochemical analysis (IHC) of CRC are usually recommended as tools to select high-risk patients for genetic testing and are performed in most countries in patients suspected of Lynch syndrome. In one country, IHC was recommended in all new cases of CRC. In most countries there are no specific programs on cancer genetics in the teaching curriculum for medical doctors. In conclusion, the outcome of this survey and the discussions within an European expert group may be used to improve the strategies to identify individuals at high risk of CRC. More attention should be given to increasing the awareness of the general population of hereditary CRC. Immunohistochemical analysis or MSI-analysis of all CRCs may be an effective tool for identifying all Lynch syndrome families. The cost-effectiveness of this approach should be further evaluated. All countries with a CRC population screening program should obtain a full family history as part of patient assessment.

Keywords Lynch syndrome · Identification · Family history · Hereditary colorectal cancer · Familial colorectal cancer · Microsatellite instability · Immunohistochemical analysis · Prevention

Introduction

Environmental factors play a dominant role in the etiology of most colorectal cancers (CRC). However, hereditary factors are significant in 10–15% of the cases. In about 5% of all cases, CRC is associated with a highly penetrant dominant inherited syndrome [1, 2]. The most common inherited form of CRC is the Lynch syndrome (LS) which is responsible for about 2–4% of all cases [3]. Familial adenomatous polyposis is another well-described inherited syndrome and is responsible for <1% of all cases. Families with two cases of CRC or one case diagnosed at a young age (<50 years), are usually referred to as familial CRC.

Lynch syndrome (LS) is caused by an inherited defect in one of the DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6 and PMS2*). It is characterized by the development of CRC, endometrial cancer and other malignancies at an unusual young age [4, 5]. The hallmark of Lynch syndrome is the presence of microsatellite instability in the tumors as a consequence of deficient mismatch repair.

How many individuals in the general population are at risk for Lynch syndrome or familial colorectal cancer is not

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exactly known. In most Western countries, the lifetime risk of developing CRC is about 5%. As mentioned above, 2–4% of all CRC cases are caused by a defect in the MMR-genes. Based on these figures, it can be estimated that 1–2 per 1,000 individuals in the general population are at risk of developing CRC on the basis of a MMR-defect. This means that in Western Europe with a population of 500 million, we have 1 million individuals at risk for Lynch syndrome. A recent study from the Netherlands indicated that 2% of individuals aged between 45 and 70 years have a significant family history compatible with familial colorectal cancer (relative risk of at least four) [6]. Based on this estimate, we calculate that there must be 3 million people aged between 45 and 70 years in Europe at risk for familial colorectal cancer.

Identification of these high-risk groups is important, because it allows at risk individuals to take preventive measures and to undergo colonoscopic surveillance. Several studies have shown that surveillance of Lynch syndrome families reduces the development of CRC by 60% and also decreases mortality [7, 8]. Although the effect of surveillance in familial colorectal cancer on mortality is unknown, various studies have reported a high yield of advanced adenomas in these families when compared to surveillance of average risk individuals [9]. These findings which are in agreement with the reported increased relative risk of developing CRC may outweigh the possible disadvantages of surveillance in familial CRC including complications of colonoscopy such as perforation and bleeding.

Patients with familial adenomatous polyposis (FAP) are easily recognized because of the presence of multiple adenomas in the colon. In patients with ten or more colorectal adenomas, FAP should be considered and the patient should be referred for mutation analysis of the polyposis genes (*MUTYH*, *APC*). However, the diagnosis of familial and hereditary CRC is more complex because it is based on personal features (early onset CRC, multiple CRC) and family data (number of relatives with CRC). This might be the reason that many families remain undetected.

Therefore, a major challenge is, to develop appropriate tools to identify all individuals at high risk. The aims of the present study were (a) to evaluate the current strategies that are used in Western Europe for the identification of high-risk groups and (b) to discuss how identification can be improved.

Methods

The study was conducted by a collaborative European group, named the Mallorca group. This group consists of about 30 experts in hereditary CRC from 14 European countries. The aims of the group are to improve the management of families with an inherited predisposition for CRC, to develop guidelines [5, 10] and to conduct collaborative studies.

The first step in the current study was to make an inventory of all possible strategies for identification. Discussion within the group and with experts outside the group revealed the following strategies. There are strategies directed at the general population, and those that aim to identify families through case finding. Strategies directed at the general population include efforts to increase the awareness of familial/hereditary CRC for example by television programs or advertisements, information provided through the internet, news papers or special health programs with counselling on environmental and genetic risk factors in the work place. Another strategy directed at the general population might be to evaluate the family history when offering population screening for CRC.

The second main strategy is case finding. Examples are an assessment of the family history when patients visit the general practitioner or hospital or analysis of the colorectal cancer for the presence of microsatellite instability, the hallmark of Lynch syndrome.

The questionnaire that was developed addressed all these questions and is shown in Table 1. All members of the Mallorca group including a few other experts from countries that were not yet represented in the group were invited to participate in the study and to complete the questionnaire.

Results

The response rate was 100%. Information was received from 14 countries. A summary of the results are shown in Tables 2 and 3. The main strategy for identification in 13 out of the 14 countries was obtaining family history and referral to a clinical genetics centre if the family history was suspicious for hereditary CRC. In one country (Denmark) the national recommendation is to test all new CRCs for MMR deficiency by immunohistochemical analysis of the MMR-proteins. In only one country (Germany) were special campaigns (television programs/advertisements) organized at regular intervals aiming to increase the awareness of the general population of (familial) CRC and the possibility of early detection. Also, in only two countries, were special health programs organised in the work place by some companies to provide information about environmental and genetic risk factors. In five out of seven countries with a (regional or national) CRC population screening program (usually faecal occult blood testing), attention was paid in the program to the detection of familial CRC. In almost all countries, a family history is

Table 1 Questionnaire: inventory of strategies in Europe

General population		
What is the most common strategy for the identification of familial and hereditary CRC in your country?		
Are you aware of special campaigns in your country that focus on the identification of high-risk groups for development of CRC? (TV-spots, Internet?)	☐ Yes If yes, please describe:	☐ No
Are you aware of projects for the identification of high-risk (CRC) individuals in the setting of workplace?	☐ Yes If yes, please describe:	☐ No
Are the usual CRC population screening program (e.g. FOBT) include questions on familial history for CRC?	☐ Yes	☐ No
Patients visiting GP/specialists		
Is a family history obtained at the beginning of a patient career?	☐ Yes	☐ No
What is the quality of this evaluation of family history?		
Who is mostly responsible for the identification of familial CRC?	☐ GP ☐ Gastroenterologist ☐ All	☐ Surgeon ☐ Internist
Who is mostly responsible for the identification of hereditary CRC?	☐ GP ☐ Gastroenterologist ☐ All	☐ Surgeon ☐ Internist
Is MSI or IHC offered only to patients with CRC if they meet specific criteria (revised Bethesda or national criteria)?	☐ Yes	☐ No
Is MSI or IHC offered to all patients with CRC?	☐ Yes	☐ No
Are guidelines available that describe the application of these tests?	☐ Yes	☐ No
Do GPs have guidelines for referral individuals with a possible increased risk for CRC to clinical genetic centres?	☐ Yes	☐ No
Do specialists have guidelines for referral individuals with a possible increased risk for CRC to clinical genetic centres?	☐ Yes	☐ No
Do general patient information pamphlets on CRC contain information about the possibility of hereditary cancer?	☐ Yes	☐ No
Is special attention given to familial and hereditary CRC in the education of GP/specialists?	☐ Yes	☐ No
Related issues		
Is there a patient association on hereditary CRC (Lynch syndrome) in your country?	☐ Yes If yes please provide email address:	☐ No
Is genetic testing available in your country?	☐ Yes	☐ No

assessed when a patient visits a general practitioner or hospital. However, all responders indicated that the quality of the family history was either poor or very poor. Microsatellite instability testing (MSI) or immunohistochemical analysis (IHC) of CRC, is usually recommended as a tool to select high-risk CRC-patients for genetic testing to diminish the costs associated with mutation analysis [5]. The survey showed that the Bethesda criteria (a specific set of clinical criteria that raise the suspicion of LS) [11] are used in most countries to select CRC-patients for MSI- or IHC-analysis. In one country, IHC was performed in all new cases of CRC. In almost all countries, specialists have guidelines for the referral of patients suspected of inherited CRC to clinical genetics centres. However, only in about half of the countries do general practitioners have such guidelines. In nine of the 14 countries, general patient information brochures on CRC also include information on hereditary CRC. In most countries there are no specific programs in the curriculum for medical doctors on cancer genetics.

Discussion

Identification of individuals at high risk of developing CRC is extremely important because it allows individuals to take appropriate measures in order to prevent early mortality from metastatic disease. Such strategies include those directed at the general population and those that aim to identify families through case finding. The current study demonstrates that in Western Europe almost no attention is given to increasing the awareness of hereditary CRC in the general population. Although family history is assessed during primary contacts between patients and doctors in

Table 2 Identification of high-risk groups for colon cancer (CRC) through the general population

Strategies	Countries (total 14)
Special campaigns (television/ Internet)	1
Health programs on work place that addresses genetic risk factors	2
Assessment of family history via CRC screening programs	In 5 out 7 countries with CRC screening program

most countries, all participants indicated that the quality of family history taking in their respective countries was poor. Finally, it was reported that the family history was not always addressed during population CRC screening program.

The limitations of the survey are that a relatively small number of experts were involved in the study. On the other hand all experts that were invited agreed to participate and a large number of Western European countries were represented.

How can we improve the identification of these high-risk groups in view of the outcome of this study? First of all, more attention should be given to increase the awareness of familial and hereditary CRC in the general population. The role of hereditary factors in the development of CRC and the availability of an effective screening tool can be made public in programs or advertisements on television or discussed in newspapers or magazines. Experience has shown that such campaigns have to be repeated at regular intervals.

Family history is the most important tool for the identification of hereditary CRC. It should therefore be assessed during all primary contacts between doctors and patients. The minimum information that should be collected is the size of the family and the number of first-degree relatives (and second-degree relatives if a first-degree relative is affected) with cancer, type of cancer and age at diagnosis [12]. In order to improve the quality of family history taking, more attention should be given to cancer genetics in the curriculum of medical doctors. Another simple way to collect data on family history is to use a questionnaire including all relevant questions. All new patients may be invited to complete the form at home before they visit the hospital. This allows patients to discuss with other family members if there is any uncertainty about a cancer diagnosis.

Assessment of the family history in programs of CRC screening in the general population is important as it allows identification of high-risk groups but also because these groups need different surveillance schemes with more frequent examinations starting at an earlier age. Usually, individuals at risk for familial CRC are advised to have colonoscopy at 5 or 6 year intervals starting from age 45 years. Lynch syndrome families are recommended to start surveillance from an age of between 20 and 25 years and to continue with intervals of 1–2 years [5, 13].

If we succeed in improving family history taking, we need to know which patient with a specific family history should be referred to a clinical genetic centre for additional genetic counselling. Therefore, proper guidelines should be developed especially for primary care doctors. In Table 4, a simple set for guidelines for referral is proposed.

An interesting approach is the possibility of testing all new CRCs for microsatellite instability or loss of expression of the MMR-genes by histochemical analysis as is currently been recommended in Denmark. In most countries the Bethesda criteria are used to select patients for

Table 3 Identification of high-risk groups for colon cancer (CRC) through case finding

Strategies	Countries (total 14)
Assessment of family history in all patients	13
Quality from variable to poor	13
MSI-analysis[a] of colorectal cancer	
Available	14
Only performed in patients suspected of Lynch syndrome	13
In all new colorectal cancers	1
Guidelines available for application of tests	11
Guidelines for referral to clinical genetics centre	
Specialists	12
General practitioners	6
Patient information pamphlet on CRC with information on hereditary CRC	9
Special attention to cancer genetics in the curriculum of medical doctors	5

[a] Or immunohistochemical analysis of the MMR-proteins

these analyses. Clinical geneticists, and other specialists such as oncologist, surgeons, gastroenterologists, pathologists usually only order these tests when a patient complies with one of the criteria. However, in clinical practice, it appears rather difficult to implement these guidelines partly because they mainly depend on an accurately obtained family history. Moreover, there is evidence that with these criteria a substantial proportion of MMR-mutation carriers are being missed [3].

Based on these considerations, MSI-analysis or immunohistochemical analysis of the MMR-proteins of all new CRCs appears to be an appropriate option. Another reason to perform such test in all new cases of CRC in the future is the fact that loss of MMR-protein expression or MSI may predict the response to chemotherapy [14, 15]. The main question is whether such an approach is cost-effective. In 2005, the results of MSI-analysis in a large series of 1,066 new (unselected) cases of CRC were reported by Hampel et al. [3]. MSI was found in approximately 12% of patients. Further analysis by immunohistochemical analysis of the MMR-proteins, testing for methylation status of the *MLH1* promotor and mutation analysis of all four genes identified 23 index patients with a mutation in one of these genes. Analysis of the family members of these cases, revealed another 53 carriers of a MMR-gene alteration. Therefore, these investigators were able to identify a total number of 76 MMR-mutation carriers with screening of all new CRCs using MSI-analysis. The authors recommended immunohistochemical analysis for screening because most laboratories already apply such tests to classify other cancers. If we calculate using the results from Hampel's study the costs of identification of one mutation carrier using immunohistochemical analysis (four proteins) (estimated costs 200 Euro) and assessment of methylation at the *MLH1* promotor site (estimated costs: 200 Euro), the costs are approximately 3,500 Euro per mutation carrier. However, it is important to bear in mind that, like all laboratory testing, MSI and immunohistochemical analysis of the MMR-proteins should be carried out in expert accredited centres, which participate in external quality assessment schemes. (PHG Foundation *Biomarkers in CRC* meeting report, at http://www.phgfoundation.org/file/2743/). This is especially important for immunohistochemical analysis because of the reported problems with this analysis [16].

Some investigators prefer to perform MSI-testing because a positive test result does not directly indicate that the patient has hereditary CRC. Most patients with MSI-high CRCs will have sporadic CRC, with the MSI high phenotype being caused by hypermethylation of the *MLH1* promotor. In contrast, an immunohistochemical test result that shows, for example, loss of expression of MSH2 and MSH6 may suggest the presence of a germ line *MSH2* mutation. If such a test result is interpreted as such, patients could be told that they are carriers of an MMR-gene defect without proper genetic counselling before the test. It should be clear for all specialists that order such tests, that the application of the tests is only meant to identify individuals at high risk of having a genetic predisposition to CRC. Also informed consent should be obtained from the patients prior to the testing.

In conclusion, the results of the present study may be used to improve the identification of individuals with a high risk of developing CRC. In Table 5, our recommendations are summarized. If we can implement these strategies in the

Table 4 Set of guidelines for referral to clinical genetics centre

Features of the family
3 first-degree relative with CRC[a]
2 first-degree relatives with CRC < age 50 years
Patient' features
Multiple CRC or combination colorectal cancer and endometrium cancer
CRC < 35 years

[a] *CRC* colorectal cancer

Table 5 Recommendations from the European Expert Group to improve the identification of hereditary and familial colorectal cancer (CRC)

General population
Special campaigns should be organised to improve the awareness of hereditary CRC in the general population; these initiatives may include programs on television, distribution of information on Lynch syndrome through newspapers, magazines and Internet
The family history should be assessed in all current and future CRC screening programs
Case finding
The curriculum of medical doctors should include cancer genetics with particular reference to proper assessment of the family history
A family history should be assessed in all patients visiting their general practitioner or hospital
Assessment of family history should include questions about the size of the family, the number of relatives with cancer, the type of cancer, and age at diagnosis
Guidelines for referral to clinical genetic centres should be available for general practitioners as well as for medical specialists
Patient information pamphlets about CRC should include information on familial and hereditary CRC, and recommendations for surveillance
Testing of CRC for MSI or immunohistochemical analysis of MMR-proteins should be considered in all new CRCs independent of age at diagnosis with appropriate counselling

near future, we could reach the ultimate goal of identifying all Lynch syndrome families in Western Europe in the upcoming years.

References

1. Mecklin JP (1987) Frequency of hereditary colorectal carcinoma. Gastroenterology 93(5):1021–1025
2. Ponz de Leon M, Sassatelli R, Sacchetti C, Zanghieri G, Scalmati A, Roncucci L (1989) Familial aggregation of tumors in the three-year experience of a population-based colorectal cancer registry. Cancer Res 49(15):4344–4348
3. Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P et al (2005) Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 352(18):1851–1860
4. Lynch HT, de la Chapelle A (2003) Hereditary colorectal cancer. N Engl J Med 348(10):919–932
5. Vasen HF, Moslein G, Alonso A, Bernstein I, Bertario L, Blanco I et al (2007) Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet 44(6):353–362
6. de Jong AE, Vasen HF (2006) The frequency of a positive family history for colorectal cancer: a population-based study in the Netherlands. Neth J Med 64(10):367–370
7. Jarvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomaki P et al (2000) Controlled 15-year trial on screening for colorectal cancer in families with hereditary non-polyposis colorectal cancer. Gastroenterology 118(5):829–834
8. de Jong AE, Hendriks YM, Kleibeuker JH, de Boer SY, Cats A, Griffioen G et al (2006) Decrease in mortality in Lynch syndrome families because of surveillance. Gastroenterology 130(3):665–671
9. Regula J, Rupinski M, Kraszewska E, Polkowski M, Pachlewski J, Orlowska J et al (2006) Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med 355(18):1863–1872
10. Vasen HF, Moslein G, Alonso A, Aretz S, Bernstein I, Bertario L et al (2008) Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 57(5):704–713
11. Umar A, Boland CR, Terdiman JP, Syngal S, de la CA, Ruschoff J et al (2004) Revised Bethesda Guidelines for hereditary non-polyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 96(4):261–268
12. van Dijk DA, Oostindier MJ, Kloosterman-Boele WM, Krijnen P, Vasen HF (2007) Family history is neglected in the work-up of patients with colorectal cancer: a quality assessment using cancer registry data. Fam Cancer 6(1):131–134
13. Lindor NM, Petersen GM, Hadley DW, Kinney AY, Miesfeldt S, Lu KH et al (2006) Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA 296(12):1507–1517
14. Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM et al (2003) Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med 349(3):247–257
15. de Vos tot Nederveen Cappel WH, Meulenbeld HJ, Kleibeuker JH, Nagengast FM, Menko FH, Griffioen G et al (2004) Survival after adjuvant 5-FU treatment for stage III colon cancer in hereditary nonpolyposis colorectal cancer. Int J Cancer 109(3):468–471
16. Overbeek LI, Ligtenberg MJ, Willems RW, Hermens RP, Blokx WA, Dubois SV et al (2008) Interpretation of immunohistochemistry for mismatch repair proteins is only reliable in a specialized setting. Am J Surg Pathol 32(8):1246–1251