Improving the management of colorectal neoplasms in clinical practice

Leicher, L.W.

part 1
MANAGEMENT OF HEREDITARY COLORECTAL CANCER

CHAPTER 2

Identification of familial colorectal cancer and hereditary colorectal cancer syndromes through the Dutch population-screening program: results of a pilot study

Sanne J. H. van Erp*, Laura W. Leicher*, Simone D. Hennink, Zeinab Ghorbanoghli, Simone A. C. Breg, Hans Morreau, Maartje Nielsen, James C. H. Hardwick, Jan A. Roukema, Alexandra M. J. Langers, Wouter H. de Vos tot Nederveen Cappel and Hans F. A. Vasen.

** both authors equally contributed to this manuscript.*

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ABSTRACT

OBJECTIVES

In 2014, a population-screening program using immuno-faecal occult blood testing (I-FOBT) has started in the Netherlands. The aims of the present study were to evaluate the proportion of individuals in the Dutch screening program with a positive I-FOBT that fulfill the criteria for familial colorectal cancer (FCC) and to evaluate the proportion of participants that needs genetic counseling or colonoscopic surveillance.

MATERIAL AND METHODS

This retrospective observational study was performed in two large hospitals. Individuals aged between 55-75 years with a positive I-FOBT that underwent colonoscopy were included. A detailed family history was obtained in all individuals.

RESULTS

A total of 657 individuals with a positive I-FOBT test underwent colonoscopy. One hundred twenty (18.3%) participants were found to have a positive family history for CRC, 20 (3.0%) fulfilled the FCC Criteria, 4 (0.6%) the Bethesda guidelines and 1 (0.2%) participant the Amsterdam Criteria. Multiple adenomas (> 10) were found in 21 (3.2%) participants. No cases of serrated polyposis were identified. Based on these criteria and guidelines, a total of 35 (5.3%) required referral to the clinical geneticist and the relatives of 20 (3.0%) participants should be referred for surveillance colonoscopy.

CONCLUSION

Obtaining a detailed family history at the time of intake of participants with a positive I-FOBT in the Dutch surveillance program increased the identification of participants with familial CRC.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers in the Western world. More than 13,000 patients are annually diagnosed with CRC in the Netherlands and over 5,000 patients die due to this condition.[1] When CRC is detected because of symptoms, about 45% of the patients have a metastatic disease. Worldwide screening programs have been implemented in order to prevent the development of CRC and to diagnose CRC at an early stage that allows curative treatment.[2-4]

In February 2014, a national screening program has started in the Netherlands.[5] Individuals aged between 55 and 75 years are offered colorectal testing using a biennial immuno-faecal occult blood test (I-FOBT) and participants with a positive I-FOBT are referred for colonoscopy.[5-7] Previous studies have suggested that this program will lead to a reduction of CRC by 20-25%.[2,8]

In approximately 10 to 15% of all CRC cases, CRC is caused by a combination of hereditary and environmental factors. In 3 to 5% of all cases CRC is due to a hereditary CRC syndrome including Lynch syndrome or one of the polyposis syndromes.[9,10] The term "familial CRC" (FCC) is used for individuals with a clinically relevant increased risk (relative risk > 3) of CRC which justifies surveillance by colonoscopy.[11-13] These individuals have one first degree relative (FDR) with early onset (< 50 years) CRC or two first degree relatives with CRC diagnosed at any age. The lifetime risk of developing CRC for these individuals varies from 10 to 25%, depending on the number of relatives with CRC and the age at diagnosis.[14]

In the Netherlands, it has been estimated that about 100,000 subjects have familial CRC, but unfortunately, most of these people are still unrecognized.[9] An important way to improve the identification of familial and hereditary CRC during the population screening for CRC is by informing them about the risk factors including hereditary factors for CRC at invitation (by a brochure which is attached to the invitation letter including a referral to the website http://www.bevolkingsonderzoekdarmkanker.nl) and by obtaining an appropriate family history in individuals with a positive test result that are referred for colonoscopy.[15,15]

The aims of the present study were to evaluate the proportion of individuals with a positive I-FOBT that comply with the criteria of familial/hereditary CRC in the Dutch population screening program, and to evaluate the proportion of patients that need further genetic analysis based on their personal and family history and/or endoscopic findings.

METHODS

Study population and study design

This retrospective observational study was performed at the department of Gastro-

enterology and Hepatology of the Leiden University Medical Center (LUMC) in Leiden and the Isala Clinics in Zwolle, the Netherlands. All participants aged between 55-75 years with a positive I-FOBT and who underwent a colonoscopy between February and October 2014 in Leiden and between March 2014 and November 2015 in Zwolle were included. In both centers a detailed family history was obtained before colonoscopy. Participants included in the LUMC were requested to complete a questionnaire about their family history (Figure 1). Based on this questionnaire, the participants had a significant positive family history if the family history fulfills the criteria of familial CRC, Amsterdam Criteria or the Bethesda guidelines (Table 1).[13,17-21] These criteria and guidelines were used to identify individuals that should be referred to the clinical geneticist or should be advised colonoscopic surveillance.[22]

Colonoscopies were performed by experienced endoscopists certified by the population screening program and polyps detected at colonoscopy were removed if possible. The removed polyps were evaluated by pathologists also certified by the population screening program. The study was approved by the institutional medical ethical committee of the LUMC.

Data collection

All information concerning the family history obtained during intake and colonoscopy results from the participants were collected in a database. The following information was extracted from the database and questionnaires: demographical data, personal history (CRC, Lynch syndrome-associated tumors (LS-AT; tumors of the colon, endometrium, stomach, small intestine, urethra, bile ducts, pyelum, pancreas, ovary or brains) or other tumors) and family history for CRC (number of first-degree relatives (FDRs) and/or second-degree relatives (SDRs) with CRC and age at diagnosis).

Statistical methods

Descriptive statistics were used to characterize the study population, family history and familial CRC risk. Primary outcome measures were positive family history for CRC and fulfillment of the criteria for familial CRC, Bethesda guidelines and Amsterdam Criteria. All statistical analyses were performed using SPSS 22.0.

RESULTS

Colonoscopic findings

A total of 657 participants with a positive I-FOBT underwent colonoscopy and familial cancer risk assessment. The mean age of the study population was in 70.8 years

in Leiden and 67.8 years in Zwolle and participants were predominantly male (57.8% and 62.7%). The findings at colonoscopy of both centers are described in Table 2.

Table 2.
Findings at colonoscopy

Findings colonoscopy	Leiden (n = 332)	Zwolle (n = 325)
Male, n (%)	192 (57.8)	204 (62.7)
Age at inclusion (years), mean (range)	70.8 (62-76)	67.8 (60-76)
Cecal intubation, n (%)	325 (97.9)	320 (98.5)
Serrated polyps, n (%)	66 (19.8)	85 (26.2)
Serrated polyposis*	0 (0.0)	0 (0.0)
Adenomas, n (%)	175 (52.7)	254 (78.2)
AAP, n (%)	152 (45.8)	128 (39.4)
Multiple adenomas, n (%)		
Yes:		
2-9	182 (54.8)	165 (50.8)
10-19	15 (4.5)	6 (1.8)
> 20	0 (0.0)	0 (0.0)
Total	197 (59.3)	171 (52.6)
CRC, n (%)	25 (7.5)	24 (7.4)

*5 serrated lesions proximal of the sigmoid of which 2 > 1 cm, or 20 serrated lesions throughout the colon

A total of 49 participants (7.5%) were diagnosed with CRC and 280 (42.6%) had advanced adenomas (AAP). Multiple adenomas (2 or more) were found in 368 (56.0%) participants and more than 10 adenomas were observed in 21 of the 657 cases (3.2%). In 151 participants serrated polyps were found, none of them complied with the criteria for serrated polyposis.

Table 3.
Patients with evidence for familial or hereditary CRC syndromes

Patient characteristics	Leiden (n=332)	Zwolle (n=325)	Total (657)
Positive family history for CRC in FDR*, n (%)	67 (20.2)	53 (16.3)	120 (18.3)
Fulfill Criteria for familial CRC, n (%)	10 (3.1)	10 (3.4)	20 (3.0)
1 FDR < 50	3 (0.9)	4 (1.2)	7 (1.1)
2 FDR all ages	6 (1.8)	5 (1.5)	11 (1.7)
2 FDR<70, n (%)	2 (0.6)	2 (0.6)	4 (0.6)
1 FDR<70, 1FDR>70, n (%)	0 (0.0)	1 (0.3)	1 (0.2)
2 FDR>70, n (%)	4 (1.2)	2 (0.6)	6 (0.9)
3 FDR/SDR*	1 (0.3)	1(0.3)	2 (0.3)
Fulfill Amsterdam Criteria**	0 (0.0)	1 (0.3)	1 (0.2)
Fulfill Bethesda Guidelines**	1 (0.3)	3 (0.9)	4 (0.6)
Polyposis Syndrome			
Multiple adenomas (> 10)	15 (4.5)	6 (1.8)	21 (3.2)
Serrated polyposis***	0 (0.0)	0 (0)	0 (0.0)
Personal History			
CRC	2 (0.6)	0 (0)	2 (0.3)
LSAT****	3 (0.9)	1 (0.3)	4 (0.6)

* First degree relative (FDR)/ Second degree relative (SDR)

** For the criteria see table 1

*** Serrated polyposis criteria: 5 serrated lesions proximal of the sigmoid of which 2 > 1 cm, or 20 serrated lesions throughout the colon (rectum not included)

**** LSAT: tumors of the colorectum, endometrium, stomach, liver, kidney, small intestine, urethra, bile ducts, pyelum, pancreas, ovary or brains

Personal and family history of colorectal cancer

In total, 120 of the 657 participants (18.3%) had at least one FDR with CRC. Twenty individuals (3.0%) complied the criteria for familial CRC and 4 (0.6%) fulfilled the Bethesda guidelines. One individual (0.2%) met the Amsterdam criteria. The results of family and personal history are shown in Table 3. No significant correlation was found between a positive family history and having multiple adenomas (> 10) or advanced adenomas.

A total of 35 (5.3%) participants should be referred to the clinical geneticist (Table 4) and the relatives of 20 (3.0%) participants should be referred for surveillance colonoscopy (Table 3) according to the clinical guidelines mentioned before.

Table 4.
Proportion of participants that comply with the criteria for referral to the clinical geneticist

	Leiden (n = 332)	Zwolle (n =325)	Total (n = 657)
Bethesda guidelines, n (%)	1 (0.3)	3 (0.9)	4 (0.6)
Amsterdam criteria, n (%)	0 (0.0)	1 (0.3)	1 (0.2)
Multiple adenomas (> 10) , n (%)	15 (4.6)	6 (1.8)	21 (3.2)
Serrated polyposis, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
1 FDR <50 with CRC, n (%)	3 (0.9)	4 (1.2)	7 (1.1)
3 FDR/SDR with CRC at any age, n (%)	1 (0.3)	1 (0.3)	2 (0.3)
Total, n (%)	20 (6.0)	15 (4.6)	35 (5.3)

DISCUSSION

This study demonstrated that a detailed family history and/or the use of a family history questionnaire at the time of intake of participants with a positive I-FOBT in the Dutch surveillance program led to the identification of familial CRC families in approximately 3% of the cases. Moreover, a substantial proportion of participants were found to have multiple adenomas (> 10) and need further genetic testing for MUTYH and APC-mutations.

Two previous pilot studies have been performed to identify familial CRC in individuals that participate in a I-FOBT population screening. The first study performed by Dekker et al. in 2011 in the Netherlands showed that 17% of the participants with a positive I-FOBT in the CRC screening program had a positive family history of CRC. Six percent of the participants had an increased familial CRC risk and approximately 4% had an increased familial CRC risk according to the Bethesda guidelines and/or Amsterdam Criteria. No significant differences were found with respect to colonoscopy results between the participants with an average versus an increased familial CRC risk.[23] The second study, conducted in 2006 in Australia, reported a positive family history for CRC in 19.6% of subjects that participated in a I-FOBT screening program. Fourteen percent had an increased familial CRC risk. Of these participants, 4.2% had a high familial risk sufficient to warrant colonoscopic surveillance.[24] Although both studies showed that a substantial proportion of individuals with a positive I-FOBT result had a positive family history for CRC, detailed information on the family history and the level of CRC risk was lacking. Also, the identification of polyposis syndromes was not addressed.

In the present study, 120 (18.3%) participants were found to have a positive family history for CRC in FDR and 4 (0.6%) had a positive family history for a Lynch syndrome associated tumor. It was found that 3.0% of the participants fulfilled the criteria for familial CRC and 0.6% the Bethesda guidelines. One participant fulfilled the Amsterdam Criteria. Multiple adenomas (> 10) were found in 21 participants (3.2%) and no cases of serrated polyposis were detected. Based on the findings according to the current clinical guidelines, a total of 35 (5.3%) participants should be referred to the clinical geneticist and relatives of 20 (3.0%) participants should be referred for surveillance colonoscopy.

Several studies have indicated that the identification of individuals with familial cancer and Lynch syndrome is suboptimal.[25] A previous Dutch study estimated that 100.000 individuals are at risk for familial or hereditary colorectal cancer but currently only a small proportion of these individuals has been recognized.[9] A nationwide population screening program such as the I-FOBT program in the Netherlands

may not only improve the prognosis of patients with CRC and prevent the development of CRC but also may identify high risk individuals. The program provides full information (website and pamphlets) about the fact that a proportion of patients with CRC is caused by genetic factors. In addition, obtaining a detailed family history in all cases with a positive I-FOBT, will identify many cases with an increased risk of CRC which is demonstrated in this study. Systematic use of a family history questionnaire may further improve the identification.

The presence of multiple adenomas may also indicate an underlying genetic disorder, i.e. polyposis. There is no agreement about the number of adenomas that justifies referral to a clinical geneticist for analysis of mutations in the MUTYH-gene and the APC-gene. Originally, the presence of 10 or more adenomas was a criterion for referral. However, a recent study showed that mutations were rarely detected in patients with 10-20 adenomas (mutation detection rate ~3%) and the mutation detection rate increased in patients with > 20 adenomas.[26]

The prevalence of serrated polyposis is still unknown. In the current study, no cases were identified. It is well known that serrated polyps are difficult to detect.[10] However, in the present study experienced gastroenterologists are certainly be able to identify this syndrome.

Regarding the identification of Lynch syndrome, currently, in many countries universal screening is being implemented. This means that all patients with CRC under the age 70 years (or in some countries all CRC patients independent of the age) are tested for expression of the mismatch repair proteins (MMR-proteins) using immuno-histochemical analysis.[22] This new approach will be helpful to identify all Lynch syndrome cases.

The identification of familial CRC will strongly be improved by case finding during population screening programs. The age distribution of CRC in familial CRC (50-75 years) is almost similar as the patients that are invited for the Dutch population screening program (55-75 years). A recent surveillance study among 550 patients with familial CRC showed that the prevalence of advanced adenomas was two-fold higher than reported in "average risk" individuals.[14] A previous study showed that colonoscopic surveillance led to a reduction of CRC by 80%.[16] Usually, colonoscopic surveillance is recommended in familial CRC with five or six year intervals.[27] However, it is still unknown whether a 10 year interval or two yearly I-FOBT screening is as effective as a 5 year-interval-colonoscopic surveillance.

Strengths of the study include the cross-sectional design and the full attention that was paid to the family history and the additional use of questionnaires in Leiden to assess the familial CRC risk. In almost all cases, personal and familial

history was fully verified during intake. Another strength of the study is that the colonoscopies were all performed in two hospitals by well-trained gastroenterologists.

In summary, this pilot study provides a detailed overview of the familial CRC risk assessment in the Dutch I-FOBT screening program that started in 2014. The study demonstrates that a proportion of the patients need further genetic testing and surveillance colonoscopies. The preliminary results of the I-FOBT screening are encouraging. Making optimal use of the patient contact arising from the screening program to identify high risk groups will further improve the prognosis of patients with familial CRC and their families.

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Figure 1. Questionnaire to assess the familial CRC risk given at intake

		Type of cancer	Age at diagnosis
Children			
How many children do you have?			
Did they develop cancer?	Yes / No		
If yes, who developed cancer	Child 1		
and what type of cancer?	Child 2		
	Child 3		
Parents			
Did they develop cancer?	Yes / No		
If yes, who developed cancer	Father		
and what type of cancer?	Mother		
Brothers			
How many brothers do you have?			
Did they develop cancer?	Yes / No		
If yes, who developed cancer	Brother 1		
and what type of cancer?	Brother 2		
	Brother 3		
Sisters			
How many sisters do you have?			
Did they develop cancer?	Yes / No		
If yes, who developed cancer	Sister 1		
and what type of cancer?	Sister 2		
	Sister 3		
Family from paternal site			
How many uncles do you have?			
How many aunts do you have?			
Did they develop cancer?	Yes / No		
If yes, who developed cancer	Uncle 1		
and what type of cancer?	Uncle 2		
	Aunt 1		
	Aunt 2		
Did grandfather or grandmother			
develop cancer?	Yes / No		
If yes, who developed cancer	Grandfather		
and what type of cancer?	Grandmother		
Family maternal site			
How many uncles do you have?			
How many aunts do you have?			
Did they develop cancer?	Yes / No		
If yes, who developed cancer	Uncle 1		
and what type?	Uncle 2		
	Aunt 1		
	Aunt 2		
Did grandfather or grandmother			
developed cancer?	Yes / No		
If yes, who developed cancer	Grandfather		
and what type of cancer?	Grandmother		

Table 1.
Criteria for Familial CRC, the Amsterdam Criteria and Bethesda Guidelines
FCC Criteria

- 1 FDR*<50
- 2 FDR all ages
  - 2 FDR<70
  - 2 FDR>70
- 3 FDR/SDR**

Amsterdam Criteria

- 3 patients with CRC (Amsterdam Criteria I) or Lynch Syndrome Associated Tumor*** (LSAT, Amsterdam Criteria II) of which one is a FDR of the other two and,
- 1 of these 3 patients <50 and,
- 2 consecutive generations in the family are affected and,
- Familial adenomatous polyposis must have been excluded

Evidence for Polyposis Syndrome

- Multiple adenomas (> 10)
- Serrated polyposis****

Revised Bethesda Guidelines

- Patient with CRC<50 or,
- Patient with synchronous or metachronous CRC or LSAT or,
- Patient with CRC and 1 FDR with CRC or LSAT with one of the tumors <50 or,
- Patient with CRC and >2FDR/SDR with CRC or LSAT at any age

*First Degree Relative (FDR)

** Second Degree Relative (SDR)

*** LSAT: tumors of the colorectum, endometrium, stomach, small intestine, urethra, bile ducts, pyelum, pancreas, ovary or brains

**** 5 adenomas proximal of the sigmoid of which 2 adenomas > 1 cm, or 20 serrated lesions proximal of the sigmoid