Hereditary & familial colorectal cancer
Kallenberg, F.G.J.

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CHAPTER 1

GENERAL INTRODUCTION
Many adults will have a relative, friend, neighbor or colleague affected by colorectal cancer (CRC). This is not surprising, as CRC is among the most commonly diagnosed types of cancer worldwide and in a Western population the lifetime risk of developing CRC is approximately 5%.\(^1\), \(^2\) CRC arises from precursor lesions, mostly adenomatous polyps.\(^3\), \(^4\) Early detection of advanced adenomas and cancer (together referred to as advanced neoplasia) by colonoscopy can reduce both the incidence and mortality of CRC.\(^5\)-\(^7\)

Of all CRC cases, an estimated 15-20% is related to familial or hereditary factors.\(^8\)-\(^10\) The majority of cases with multiple first- and second-degree family members with CRC are classified as Familial CRC (FCC), in whom no underlying genetic cause has been identified so far. Approximately 3-6% of all CRCs have a well-defined inherited genetic predisposition.\(^11\) FCC and hereditary CRC syndromes can be classified as either diseases that are characterized by the presence of only one or several polyps (non-polyposis) and those with multiple colorectal polyps (polyposis) (Table 1).

The diagnosis of FCC is made when there is a relative risk of three or more for developing CRC compared with the general population, without a known genetic mutation.\(^12\) This risk is based on the number and age of first- and second-degree relatives with CRC.

The most prevalent hereditary CRC syndrome is Lynch syndrome (comprising 2-4% of CRC cases).\(^11\), \(^13\) This syndrome is caused by a germline mutation in one of the genes involved in the DNA mismatch repair system. These patients are at a very high risk to develop CRC (25-70% depending on the genotype) and several extra-intestinal malignancies, such as endometrial, gastric, and ovarian cancer, usually at a young age.\(^12\), \(^14\)

The occurrence of tens to thousands of adenomatous polyps may be caused by familial adenomatous polyposis (FAP) and a less profound phenotype is seen in attenuated FAP (AFAP) and \(\text{MUTYH}\)-associated polyposis (MAP). Not as frequent are the more recently discovered syndromes, such as polymerase proofreading associated polyposis (PPAP).\(^15\)

The diagnosis of FAP can be made clinically, by the detection of more than 100 colorectal adenomas, or genetically by the presence of a germline \(\text{APC}\) gene mutation. In contrast, the diagnosis of AFAP, MAP and PPAP are usually only made when a genetic mutation is identified in the \(\text{APC}, \text{MUTYH}\) or \(\text{POLE/POLD1}\) gene, respectively. The remaining group of patients with an attenuated phenotype (10-99 adenomas) in whom no germline mutation is detected, are referred to as patients with Multiple ColoRectal Adenomas without a germline mutation (MCRA).\(^16\) MCRA might have an exogenous origin, but it could potentially also be explained by unclassified or unrecognized mutations in polyposis-associated genes, mutations in unidentified polyposis-associated genes or mosaicism.\(^17\) Until more is known, these patients are clustered together under the definition of MCRA.
Besides the well-known adenomatous polyposis syndromes, also a number of non-adenomatous polyposis syndromes are known. These include hamartomatous polyposis syndromes, caused by a mutation in the \textit{STK11}, \textit{SMAD4}, \textit{BMPRIA} or \textit{PTEN} gene (depending on the syndrome) and, the most common, the serrated polyposis syndrome.\textsuperscript{18} The latter is based on the presence of multiple serrated polyps and defined by the WHO criteria.\textsuperscript{19} In those patients, a genetic cause has not yet been identified and familial occurrence is rare.\textsuperscript{20}

Diagnosing FCC and hereditary CRC syndromes is important for several reasons. Surveillance colonoscopies can reduce CRC incidence and mortality importantly.\textsuperscript{21-23} These patients are also advised to inform their relatives on their risk, who can subsequently consult a clinical geneticist or gastroenterologist for evaluation and surveillance recommendations. In patients with CRC who have a hereditary syndrome, treatment may be adjusted to their increased risk of metachronous CRC.\textsuperscript{12} As patients might also have an increased risk for extra-colonic cancers, surveillance of other organs, such as the endometrium, may also be indicated and preventive hysterectomy is sometimes suggested.\textsuperscript{12, 24}

\textbf{Table 1.} Familial colorectal cancer and most common hereditary colorectal cancer syndromes subdivided into polyposis and non-polyposis

<table>
<thead>
<tr>
<th>Familial colorectal cancer &amp; Hereditary colorectal cancer syndromes</th>
<th>Involved genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-polyposis</strong></td>
<td></td>
</tr>
<tr>
<td>Familial colorectal cancer (FCC)</td>
<td>-</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>\textit{MLH1, MSH2, MSH6, PMS2, EPCAM}</td>
</tr>
<tr>
<td><strong>Polyposis</strong></td>
<td>Involved genes</td>
</tr>
<tr>
<td>Adenomatous polyposis</td>
<td>\textit{APC}</td>
</tr>
<tr>
<td>Attenuated familial adenomatous polyposis (AFAP)</td>
<td>\textit{APC}</td>
</tr>
<tr>
<td>\textit{MUTYH}-associated polyposis (MAP)</td>
<td>\textit{MUTYH}</td>
</tr>
<tr>
<td>Polymerase proofreading adenomatous polyposis (PPAP)</td>
<td>\textit{POLE, POLD1}</td>
</tr>
<tr>
<td>Multiple colorectal adenomas without a known germline mutation (MCRA)*</td>
<td>-</td>
</tr>
<tr>
<td>Hamartomatous polyposis</td>
<td>\textit{STK11}</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td></td>
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<tr>
<td>Juvenile polyposis</td>
<td>\textit{SMAD4, BMPRIA}</td>
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<tr>
<td>Cowden syndrome</td>
<td>\textit{PTEN}</td>
</tr>
<tr>
<td>Serrated polyposis</td>
<td>\textit{Serrated polyposis syndrome}*</td>
</tr>
</tbody>
</table>
Both non-polyposis Lynch syndrome as well as FCC do not have a specific endoscopic appearance. Consequently taking a detailed assessment of the family history for CRC in all patients presenting with CRC can help to identify the increased risk in these persons. In case of a positive family history, referral criteria for genetic counseling should be applied, such as the Amsterdam II and the revised Bethesda criteria. Thereafter, recommendations about CRC screening and surveillance need to be given.\textsuperscript{12, 24, 25}

However, in daily practice many physicians do not or do not adequately explore family history. This can be attributed in part to insufficient knowledge of the criteria for assessing familial risk and of surveillance strategies.\textsuperscript{26-28} In addition, most patients with CRC and their relatives do not themselves have sufficient knowledge to assess their potentially increased risk for CRC and eligibility for surveillance and genetic referral.\textsuperscript{29, 30} As a consequence, only approximately 15% to 30% of CRC patients and their relatives who would qualify for referral are appropriately referred.\textsuperscript{30, 26, 31, 32} These delays in detecting and managing cancer can lead to unnecessary morbidity and mortality.

Identification barriers are less of an issue in polyposis syndromes. These syndromes are more easily recognized, as the physician is usually alerted by the number or type of polyps. The risk of CRC in these syndromes is well described and, consequently, clear screening and surveillance recommendations for CRC exist.\textsuperscript{12, 24, 25} However, of concern are manifestations outside the colon. The risks of extra-colonic manifestations are increased but less well reported.\textsuperscript{16, 33-37} More knowledge is needed to determine if, how, and when screening and surveillance of extra-colonic manifestations in those syndromes is indicated.

The studies in this thesis investigated methods to improve the identification of patients with FCC and hereditary CRC syndromes and aimed to increase the knowledge on extra-colonic manifestations in patients with adenomatous polyposis syndromes.

**O u t l i n e  o f  t h i s  t h e s i s**

**Part I Identification of familial colorectal cancer and hereditary colorectal cancer syndromes**

The first part of this thesis focuses on identifying persons with a hereditary CRC syndrome and FCC. A complete family history collection combined with an adequate application of referral criteria for genetic counseling and surveillance colonoscopies in all patients presenting with CRC is crucial. In **Chapter 2**, we describe the validation of an online patient-administered questionnaire on the family history of cancer, which could facilitate the identification of persons with a hereditary CRC syndrome or FCC. The questionnaire was created in such a manner
that completed questionnaires could be easily held against the nationwide referral criteria for genetic counseling in case of suspected Lynch syndrome and the criteria for surveillance colonoscopies in case of FCC, the two most commonly missed syndromes.\textsuperscript{10, 26-32}

After validation, the questionnaire was implemented at the multidisciplinary clinic for CRC patients in five hospitals, to help identify CRC patients at risk of a hereditary CRC syndrome or FCC. For this purpose, the questionnaire was combined with an automated risk assessment, to be used by health care providers, thereby avoiding the need for a manual comparison against referral criteria. This prospective, multicenter trial with a stepped-wedge design is described in Chapter 3.

Data on family history of CRC may also be of use in screening a general population for CRC. The fecal immunochemical test (FIT), a test that is used for CRC screening in many European countries, has a high participation rate but suboptimal sensitivity for detecting advanced neoplasia.\textsuperscript{38} To increase the performance of FIT-based screening, FIT could be combined with other risk factors, such as family history of CRC.\textsuperscript{39} In Chapter 4, we report on an evaluation of the performance of a hypothetical, combined CRC screening strategy, in which colonoscopy is offered to those with a positive FIT as well as to those with one or more first-degree relatives with CRC. We evaluated the incremental yield of this combined strategy relative to FIT-only screening, in terms of number of cases with advanced neoplasia detected in screening participants, in a post-hoc analysis of data collected previously in a colonoscopy screening trial.

\textbf{Part II Etiology, characteristics and surveillance in adenomatous polyposis syndromes}

In the second part of this thesis we zoom in on the subgroup of patients with an adenomatous polyposis syndrome. As mentioned above, a germline mutation cannot be identified in all patients with adenomatous polyposis.\textsuperscript{40} It is questionable whether these patients have a true hereditary CRC syndrome and therefore other causes should be explored. One of these potential non-hereditary causes is described in Chapter 5. We report a case series of three patients with intestinal polyposis, which might be a late effect of abdominal irradiation that they received for varying cancers.

A wide range of manifestations outside the colon can be identified in adenomatous polyposis syndromes, including duodenal adenomas. Prevalence data and management recommendations for duodenal adenomas in patients with FAP are well known, but only limited data on duodenal polyposis in patients with MCRA and MAP are available.\textsuperscript{16, 33, 35} This makes the development of evidence-based recommendations on upper gastrointestinal screening and surveillance for these patients challenging. We report on the frequency and features of duodenal adenomas in patients with MCRA in Chapter 6, and for patients with MAP in Chapter 7. Our findings can be the basis for development of strategies for upper gastrointestinal surveillance in these patients.
How should we identify these upper gastrointestinal lesions in polyposis patients? Most guidelines recommend to perform a gastroduodenoscopy with a forward-viewing lens. Yet, due to the tangential location of the ampulla of Vater, an additional side-viewing endoscopy is generally advised to visualize this high-risk location. This extra endoscopic procedure is time-consuming, burdensome for the patient and not all endoscopists are qualified to perform this procedure. To avoid the need for this additional investigation, we prospectively evaluated the efficacy of a cap-assisted forward-viewing endoscopy to visualize the duodenum and the ampulla of Vater in patients with FAP. The findings are reported in Chapter 8.

Based on limited data, FAP patients might also have an increased risk for adrenal lesions. However, the exact prevalence and clinical course of these lesions is unknown and neither do we know their prevalence in AFAP and MAP. As a result, current guidelines do not provide screening and surveillance recommendations. In Chapter 9 we report on the frequency, characteristics and clinical course of adrenal lesions in patients with FAP, AFAP and MAP.

In the final Chapter 10 we summarize our findings and discuss future perspectives for the identification of patients with an increased risk of hereditary CRC or FCC. We also provide screening and surveillance recommendations for patients with adenomatous polyposis syndromes.

REFERENCES

32. Wood ME, Kadlubek P, Pham TH, et al. Quality of cancer family history and referral for genetic counseling and testing among oncology practices: a pilot test of quality measures as part of the American Society of Clinical Oncology


