Optimizing detection and management of familial and hereditary colorectal cancer syndromes

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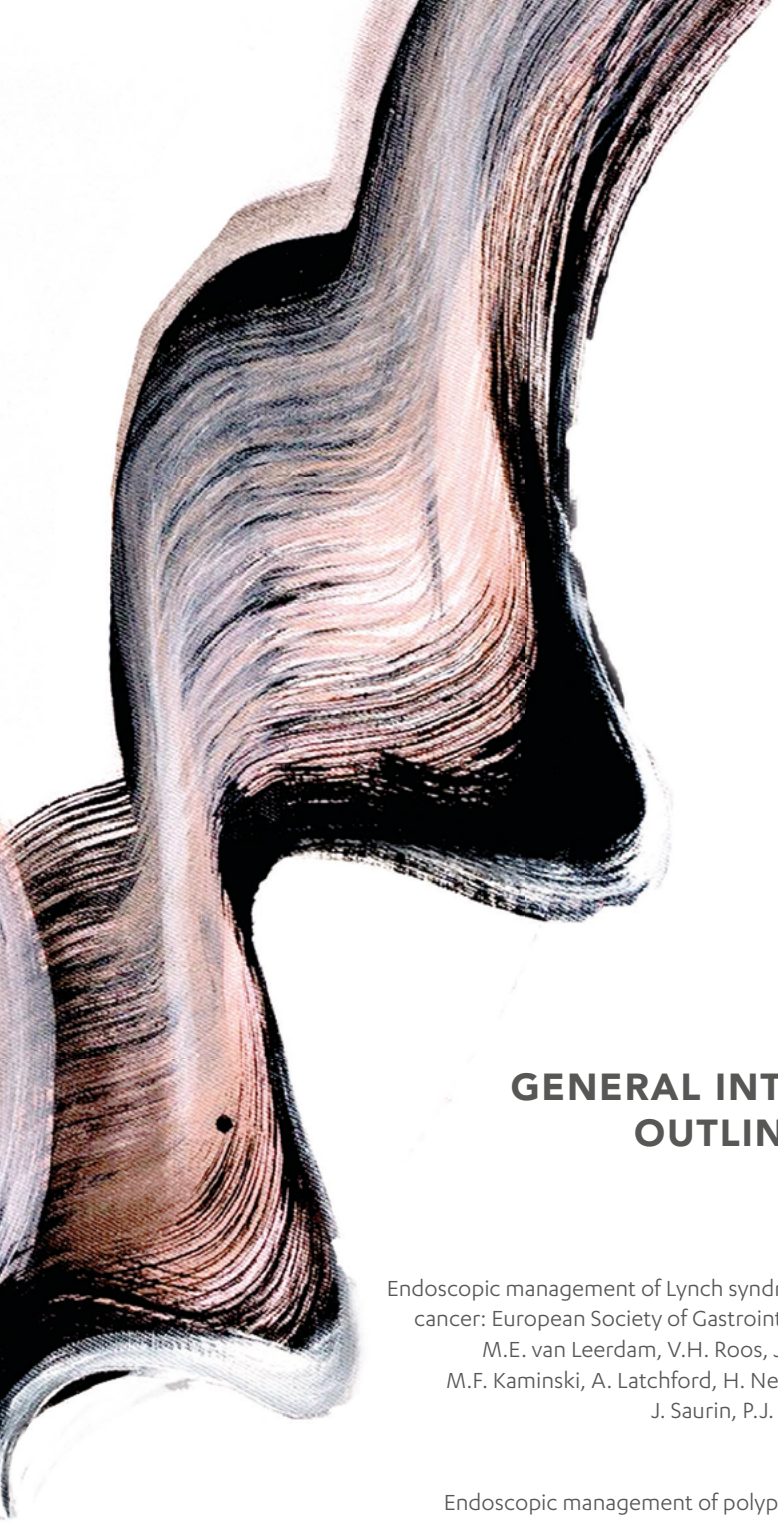

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GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

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GENERAL INTRODUCTION

Colorectal cancer (CRC) is a widespread disease: the fourth most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide [1]. In the Netherlands, yearly approximately 14,000 new cases of CRC are identified and approximately 5,000 persons die as a result of CRC [2]. CRC develops from precursor lesions, also known as polyps, namely adenomas and sessile serrated lesions [3-6]. The majority of sporadic CRCs develop from adenomas, through the well-known adenoma-carcinoma pathway [4, 7]. An estimated 5% of all small adenomas will ultimately develop into cancer, taking at least 10 to 15 years in sporadic CRCs [8-11]. Approximately 15% to 30% of all sporadic CRCs develops from sessile serrated lesions via the serrated neoplasia pathway [4, 5]. The 5-year survival rate of CRC varies with the stage at which the cancer is diagnosed, ranging from 95% for Stage I CRC to 11% for Stage IV [2]. The long dwell-time of polyps and the advantages of early detection provide a window of opportunity to detect premalignant polyps and prevent cancer development. Colonoscopy is the best method to detect and also resect adenomas, sessile serrated lesions and potentially early cancers, reducing the incidence of CRC and CRC-related morbidity and mortality [12]. However, colonoscopy is an invasive, costly and scarce resource and should be reserved for patients at increased risk of developing CRC.

Colorectal cancer screening

To detect CRC at an earlier stage in average risk populations, screening programs are being implemented worldwide, using different tests [13]. In the Netherlands, a national CRC screening program was implemented in 2014 and fully rolled out in 2019. Fecal immunochemical testing (FIT) is the screening method of choice and offered biennially to all individuals aged from 55 to 75 years. It is used as a triage test; it selects those individuals that are at an increased risk of having advanced neoplasia (CRC, advanced adenomas, or advanced serrated lesions) and should undergo colonoscopy.

Although FIT has a low burden and participation rates are relatively high compared to other screening modalities [14], its sensitivity (40% to 91%) is not perfect and thus not all individuals with advanced neoplasia are detected in a single round, which is the main reason to repeat it every two years [15, 16]. Besides, specificity (90% to 95%) is also suboptimal, as a result of which a number of FIT-positive screening participants undergo a colonoscopy that does not lead to the detection of advanced neoplasia [17].

To increase detection rates of advanced neoplasia in a FIT-based screening program without substantially increasing the number of negative colonoscopies, several options can be considered: adjusting FIT cut-off levels to rebalance sensitivity and specificity, or combining FIT with other risk factors for advanced neoplasia, such as age, gender, family history, or FIT-results in previous screening rounds.

Familial risk and hereditary risk of colorectal cancer

According to kindred and twin studies, up to 30% of all CRC patients have a familial risk for this type of cancer [18]. In only 3% to 6% of all patients with CRC an actual genetic cause was detected, identifying mutations in the *APC* gene, *MUTYH* gene, the mismatch repair genes (*MLH1*, *MSH2*,

MSH6, *PMS2*, *EPCAM*) and also, less frequently, in some other CRC related genes [18]. The remaining heterogeneous group of individuals, in whom no germline mutation was detected but who carry a significantly increased risk of CRC because of their family history, is referred to as familial colorectal cancer (FCC). For these individuals, the risk of developing CRC depends on the number of family members affected, the degree of family members affected (i.e. first, second or third degree relative), and their age at diagnosis of CRC [19, 20]. In the Netherlands, FCC is defined as having a relative risk of more than 3 [21]. Individuals with FCC are recommended to undergo surveillance colonoscopies instead of participating in the national FIT-based screening program [22].

In patients with hereditary CRC syndromes, a germline mutation is identified. Generally these cancer syndromes are classified as syndromes characterized by the presence of one or few colorectal polyps (non-polyposis) versus those characterized by the presence of multiple colorectal polyps (polyposis). Lynch syndrome is the most common hereditary non-polyposis CRC syndrome, comprising 2% to 4% of all CRC cases. It is caused by a pathogenic variant in one of the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*) resulting in microsatellite instable cancers [23, 24].

As adenomas in patients with Lynch syndrome have an accelerated adenoma-carcinoma pathway with an estimated dwell-time of 35 months instead of 10 to 15 years, these patients are at risk of developing adenomas and CRC at a young age [25]. The cumulative life-time risk of developing CRC varies from 30% to 74% depending on the genotype [26]. To prevent CRC, patients are advised to undergo colonoscopy surveillance every two years.

Undergoing colonoscopy surveillance every 1 to 2 years has been shown to significantly reduce CRC-related incidence and mortality [27]. Despite surveillance, however, studies have reported that the cumulative lifetime CRC risk at 70 years in Lynch patients undergoing colonoscopy surveillance still varies from 0% to 46% [28, 29]. Further research on the causes of the persistent CRC risk and interventions are needed to lower these numbers. Lynch patients are also at increased risk of developing other extra-colonic malignancies, such as endometrial, ovary, gastric, urinary tract, stomach, small bowel, biliary tract, brain, and skin cancers.

Hereditary polyposis syndromes, of which Familial Adenomatous Polyposis is the most common, are relatively rare: they represent <1% of all patients with CRC [18]. Familial adenomatous polyposis (FAP) syndrome is caused by an autosomal dominant mutation in the *APC* gene [30]. The syndrome is characterized by the presence of hundreds to thousands colorectal adenomas. Since these patients have an almost 100% risk of developing CRC at a median age of 35-45 years when left untreated, they require extensive colonoscopy surveillance and a prophylactic colectomy or proctocolectomy [31]. However, the optimal timing and type of prophylactic (procto-)colectomy is highly dependent on a patient's genotype and phenotype, while the personal preferences of the surgeon, patients and their family also play a role [32].

Surgery is not a definitive solution in polyp management, as adenomas reoccur in the ileum and retained rectum and lifelong endoscopy surveillance is therefore warranted [33, 34]. In the past decade, advances in endoscopy have resulted in optimized surveillance strategies and rapidly evolving endoscopic resection techniques, which influence polyposis management. FAP is also associated with extra-colonic manifestations, of which duodenal adenomatosis is the most common one, with a lifetime risk approaching 100% [35-37]. The estimated cumulative risk of developing into duodenal cancer is 4% to 10% and therefore regular gastroduodenoscopy surveillance is indicated [35, 37-39].

Besides desmoids, gastric adenomas are increasingly recognized during gastroduodenoscopy and those lesions may develop into cancer as well, although the frequency at which these lesions occur and cancer develops is still uncertain [40-42].

Patients with an *APC* mutation and a less profuse phenotype (arbitrarily defined as <100 colorectal adenomas) are referred to as having attenuated familial adenomatous polyposis (AFAP). These patients have a lower risk of developing CRC and, if so, at a later onset [43]. Another mutation associated with polyposis syndromes is a biallelic mutation in the *MUTYH* gene, also referred to as MUTYH-associated polyposis (MAP). This polyposis syndrome has a later onset of developing colorectal adenomas and shows a wide phenotypic variation with a reported lifetime CRC risk between 19% to 43% [44-46]. Besides adenomatous polyposis, other polyposis syndromes are also diagnosed, such as Peutz-Jeghers- and Juvenile polyposis syndrome, both characterized by the development of hamartomatous polyps, and serrated polyposis syndrome characterized by the presence of sessile serrated lesions. Other known polyposis-associated genes include *PTEN*, *GREM1*, *POLE/POLD1* and biallelic *NTHL1*.

Early recognition of hereditary and familial CRC syndromes has implications for patients as well as for their family members, as they can be provided with appropriate surveillance strategies. Patients with hereditary polyposis syndromes are usually recognized during endoscopy through the detection of multiple colorectal polyps. Hereditary non-polyposis syndromes, however, are less easily recognized and diagnosed. Previous studies have shown that physicians currently have insufficient knowledge about the referral criteria for genetic testing and surveillance guidelines [47-49]. In addition, the knowledge on heredity is limited in many patients [50]. As a consequence, only 15% to 30% of the FCC and Lynch syndrome patients and their family members are adequately diagnosed and referred for colonoscopy surveillance or genetic counseling; a missed opportunity for prevention [51-54].

To detect patients with Lynch syndrome, standardized tumor testing to detect mismatch repair deficiency (by microsatellite instability or immunohistochemistry) of tissue from all colorectal- and endometrial cancers of patients below 70 years of age is performed since 2016 [21].

OUTLINE OF THIS THESIS

Part I Identification of familial- and hereditary colorectal cancer syndromes

The first part on this thesis focuses on identification of individuals with a hereditary or familial CRC syndrome. By adding a family history questionnaire to the existing Dutch FIT-based CRC screening program, we aimed to improve the identification of individuals with a positive CRC family history, thereby increasing the sensitivity of the screening program itself. In the trial reported in **Chapter 2**, we compared the incremental yield in detecting advanced neoplasia of the combined strategy (an online validated family history questionnaire on CRC and other Lynch associated tumors plus FIT) with FIT-only screening [55, 56]. Both individuals with a positive FIT and those with a positive family history (potentially FCC or Lynch), confirmed at genetic counseling, were referred for colonoscopy. Since this strategy for identifying individuals with a hereditary or familial CRC syndrome in an average risk population was totally new, we also conducted a qualitative study on invitees' considerations about this approach, which is presented in **Chapter 3**.

Part II Familial risk of colorectal cancer

The risk of developing CRC for individuals with a familial CRC risk depends on the number of family members affected, the degree of family members affected, and the age at diagnosis of CRC [19, 20]. Knowing the risk of developing CRC in asymptomatic individuals with a family history of CRC would help to develop appropriate surveillance strategies. In the study described in **Chapter 4** we systematically reviewed the available literature, aiming to provide evidence-based estimates of the relative risk, compared with the general population.

Part III Characteristics, management and treatment in familial adenomatous polyposis syndrome

The third part of this thesis focuses on various challenging topics in the management of patients with FAP. To further explore the relevance of gastric adenomas in patients with FAP, we combined the data of two European polyposis registries and assessed the prevalence and characteristics of gastric adenomas, the results of which are summarized in **Chapter 5** [40-42]. We also explored the experience in management of these lesions. In the case-series reported in **Chapter 6**, the challenge of detecting gastric adenomas in between large numbers of fundic gland polyps is discussed.

Duodenal adenomas are the most common extracolonic manifestation in patients with FAP with a life-time risk of almost 100% [35, 57, 58]. Following CRC, duodenal cancers are the second cause of death in patients with FAP, with an estimated 4 to 10% cumulative risk [35, 37-39, 59]. For patients with severe duodenal polyposis, prophylactic duodenal surgery is considered. However, this prophylactic operation has a significant morbidity and mortality and is not a definitive solution as, over time, new adenomas will appear in the "neo-duodenum" [60-62]. With endoscopic techniques evolving over the past decade, timely prophylactic endoscopic interventions, with presumably lower morbidity and mortality rates, might bear promise in preventing duodenal surgery and cancers. **Chapter 7** describes the safety and effectiveness of prophylactic duodenal polypectomies and papillectomies in patients with FAP.

To prevent CRC, all patients with FAP undergo colorectal surgery at a certain point in time. However, a prophylactic colectomy or even proctocolectomy is not a definitive solution as adenomas reappear in the retained rectum and also ileoanal pouch, and also cancers were described [33]. Several risk factors for the development of adenomas have been studied, one of which is fecal stasis. To further explore this factor, we studied whether the restoration of intestinal continuity, which may affect the degree of fecal stasis, comparing the proctocolectomy with ileo-anal pouch reconstruction with the proctocolectomy with end ileostomy, resulted in a different adenoma phenotype (**Chapter 8**).

Ideally, there would be no need for surgery in patients with FAP. Chemopreventive agents could be helpful by preventing adenomas from originating or growing. In the study reported in **Chapter 9** we evaluated the safety and effect of 6 months of Sirolimus (mTORC1 inhibitor) on the progression on intestinal adenomas following (procto)colectomy.

PART IV Surveillance in Lynch syndrome

Previous studies have shown that intensive colonoscopy surveillance in patients with Lynch syndrome significantly lowered the risk of developing CRC, but this risk was not nil [28, 29]. We questioned whether this could be the result of suboptimal colonoscopy quality. In the study described in **Chapter 10** we evaluated whether the well-known quality indicators of colonoscopy (such as cecal intubation rate, adequate bowel preparation, type of endoscope, time-interval between endoscopies and use of chromoendoscopy) were associated with adenoma detection rates and post-colonoscopy CRCs in patients with Lynch syndrome.

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