Genetic and clinical aspects of inherited syndromes associated with adenomatous polyposis

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CHAPTER 7

Summary and Discussion

SUMMARY AND DISCUSSION

This thesis aims to improve our understanding of the genetic and clinical aspects of inherited syndromes associated with adenomatous polyposis (APC-associated polyposis, MUTYH associated polyposis, and Constitutional Mismatch Repair Deficiency Syndrome) in order to optimize surveillance and management and to improve life expectancy of these patients.

GENETIC MODIFIERS OF COLONIC PHENOTYPE IN APC- ASSOCIATED POLYPOSIS

APC-associated polyposis is an autosomal dominant cancer predisposition syndrome caused by a germline pathogenic variant in the APC gene. Colonic manifestations of FAP include the development of hundreds to thousands of adenomatous polyps. Correlation between the mutation site in the APC gene and the colonic phenotype of FAP is well-established.[1] However, the phenotypic variability observed in patients with the same APC mutation suggests that beside genotype, other factors modify disease phenotype in APC mutation carriers. The role of modifier genes in disease severity of FAP has been studied and several modifiers have been suggested.[2–5] Yanaru-Fujisawa *et al.* reported the association of Phospholipase A2 Group IIa and fundic gland polyposis in patients with familial adenomatous polyposis.[5] In another study, Crobtree *et al.* suggested that polymorphisms in NAT1 and NAT2 variants may explain the severity of colonic FAP.[6]

In **chapter 2**, we investigated whether Single Nucleotide Polymorphisms (SNPs) that are associated with CRC in the general population might influence colonic phenotype in APC mutation carriers. We genotyped 16 CRC-associated SNPs identified by Genome wide association studies (GWAS) in a cohort of 419 APC mutation carriers and compared allele frequency of these SNPs in patients with less than 100 and more than 100 adenomas. In this study, we identified two CRC-associated SNPs, rs16892766 (8q23.3) and rs3802842 (11q23.1), which show an association with adenoma number in APC mutation carriers. Carriage of the C allele at 8q13.1 (rs16892766) showed a trend of association with ≥100 polyp group. A borderline association was observed in the codominant inheritance

model for rs3802842 and carriers of the risk allele of this SNP were also more frequent in the more severe phenotype group. We then tested the joint association of these two SNPs and both remained borderline significant using dominant mode of inheritance however the interaction of the two SNPs was not significant. Furthermore, we compared the total number of sporadic CRC risk alleles in both groups and the mean number of risk alleles was similar.

CD36 polymorphisms have recently been studied in patients with APC mutation and an association with disease onset was found in these patients.[7,8] In the first study by Holmes *et al*, three SNPs in CD36 (rs1049673, rs1761667 and rs1984112) were tested in 275 FAP patients.[7] In a follow-up study by Corner *et al* on CD36 SNPs in larger cohort of 395 FAP patients, a significant difference in the age of disease onset was seen in patients with APC mutation in the MCR region and homozygous wildtype allele in rs198411 SNP.[8]

Since our study, new CRC-associated SNPs have been identified but their association with the phenotype of FAP has not yet been investigated.[10,11]

In conclusion, it is apparent that SNPs can have a modifying effect on disease phenotype, affecting the age of onset and severity of polyposis. Identifying these modifiers could greatly enhance the personalized management of FAP patients making the search for new modifiers of great importance. In addition, large multicenter studies are necessary to investigate the impact of newly discovered SNPs on the medical treatment of FAP patients.

TUMOR SPECTRUM IN APC MUTATION CARRIERS

Colorectal cancer (CRC) has been the main cause of morbidity and mortality in patients with pathogenic variants in the APC gene, however, colorectal screening and timely preventive colectomy in these patients has led to a substantial reduction in mortality due to CRC.[12–14] Patients with FAP also have increased risk of extracolonic cancers including duodenal cancer, hepatoblastoma, brain, thyroid, and pancreatic cancers. The risk of these cancers varies widely in previous studies.[15–18] Therefore, the value of extra-intestinal screening programs was unknown and there was no consensus regarding the need for additional surveillance recommendations for these cancers. In **chapter 3,** we examined the

tumor spectrum in patients with APC-associated polyposis to understand whether life expectancy of these patients can be further improved by extending of the existing surveillance programs to other organs such as the thyroid, stomach, liver or pancreas.

In this study on 582 APC mutation carriers, 85 extracolonic malignancies were diagnosed in 74 patients. The most common extracolonic cancers found were duodenal cancer and skin tumors. The frequency of other FAP-associated cancers such as cancer of the thyroid, liver (hepatoblastoma), brain and stomach were low. Among the benign lesions, the most frequent were fundic gland polyps, duodenal and gastric adenomas and desmoid tumors. The most prevalent cause of death was cancer (59%), with 42% of the cancer deaths due to CRC and 21% of the cancer deaths due to duodenal cancer. Other causes of cancer deaths were lung cancer in three patients, pancreatic cancer and cancer of unknown primary in two patients and brain tumor, gastric cancer, non-Hodgkin lymphoma and hepatocellular carcinoma in one patient. One patient died because from thyroid cancer at the age of 78 years. The second and third most common causes of death were cardiovascular disease (12.5% of all deaths) and desmoid tumors (10.7% of all deaths), respectively.

A (recent) systematic review and meta-analysis on the prevalence of thyroid disease in FAP concluded that although benign thyroid disease is common, thyroid cancer is infrequent and only a small subset of patients may benefit from screening ultrasound.[19] This finding is supported by the results of our study where thyroid cancer was documented in 1.5% and only one patient died at age 78 years. More recently, a retrospective study on the morbidity and mortality was conducted among 107 patients with familial adenomatous polyposis (FAP) in Japan. Cancer and/or desmoid tumor was reported in 59 % of patients and CRC was the leading cause of death (46%) followed by desmoid tumor, small intestinal cancer, ovarian cancer, duodenal cancer, and sepsis. However, all patients with gastric or thyroid cancer were alive at the last follow-up.[20] Considering the high incidence of benign thyroid disease, low prevalence of thyroid cancer and rare mortality in FAP patients,[17,18] it seems that thyroid

screening will cause additional burden and anxiety but no survival benefit for these patients.

Upper GI endoscopy starting at the age of 20-25 years is currently recommended for management of duodenal polyps however there are no recommendations regarding screening for intestinal cancers distal to duodenum as high-level evidence is lacking.[21–23] In our cohort, we also did not detect any malignancies of small intestine distal to the duodenum however a recent study on 107 FAP patients in Japan, three small intestinal malignancies were detected and was the cause of death in 2 patients.[20]

Regarding pancreatic cancer in FAP, screening is also not recommended as there is not high-quality evidence and individualized screening maybe appropriate if family history is present.[22,23] Routine hepatoblastoma screening is currently debatable and guidelines suggest that abdominal ultrasound and measurement of α-fetoprotein every 3–6 months during the first 5-10 year of life may be considered especially if family history is present.[22,23] In our study, 4 cases of hepatoblastoma were documented however there no mortality related to this malignancy.

On the basis of our study and data in the literature, we concluded that extending these surveillance programs to extraintestinal cancers will not further improve life expectancy in APC mutation carriers.

BARRETT'S ESOPHAGUS IN APC AND MUTYH ASSOCIATED POLYPOSIS

Barrett's esophagus (BE), characterized by replacement of squamous epithelium by columnar epithelium in distal esophagus, is thought to be responsible for most cases of esophageal adenocarcinoma (EAC). Chronic inflammation due to gastro-esophageal reflux disease (GERD) is the main cause of the BE and EAC. Other than GERD, abdominal obesity and smoking are known risk factors of Barrett's esophagus and associated adenocarcinoma.[24–27]

Genetic factors also play a role in BE and EAC.[28–31] High genetic correlation and polygenic overlap was reported between BE and EAC.[28] In addition, a genome-wide association study has identified three significant susceptibility loci in a combined group of cases with esophageal adenocarcinoma and Barrett's

esophagus.[31] Dai *et al* also reported a susceptibility locus which modifies the association of gastroesophageal reflux with Barrett's esophagus.[30]

MUTYH-associated polyposis caused by germline biallelic MUTYH mutations was first described in 2002.[32] Colonic phenotype of patients with MUTYH-associated polyposis (MAP) mostly resembles AFAP. Various studies reported an increased risk of extraintestinal malignancies including ovarian, bladder, and skin cancers and a trend of increased risk of breast cancer.[33] Benign cutaneous tumors, lipomas, and benign endometrial and breast tumors have also been found in MAP patients.[33]

Gatalica *et al.* reported a high frequency (16%) of Barrett's esophagus (BE) in patients with adenomatous polyposis coli (APC)-associated polyposis (FAP) in a small group of 36 patients.[34] Therefore, to better understand disease phenotype, we examined the prevalence of BE and EAC in patients with MUTYH mutations and also a large cohort with germline APC mutations in **chapter 4.**

We studied the prevalence of BE in 72 patients with MAP and 407 patients with FAP and available upper GI endoscopy and/or pathology reports. We demonstrated that the prevalence of BE in MAP patients was 9.7% which is > 5 times higher than reported in the general population. However, in contrast with the previous study, no increased frequency of BE was found in the FAP patients. Another observation of this study was that in two MAP patients, there appeared to be an accelerated progression from low-grade dysplasia into high-grade dysplasia and EAC, respectively.

In conclusion, this study demonstrates that the prevalence of BE is much higher in patients with MAP compared to the general population. The impaired MUTYH protein function that plays a role in the repair of DNA damage caused by oxidative stress such as GERD may explain the high frequency of BE in MAP. In contrast, the prevalence of BE is not increased in FAP patients.

Based on the results of our study we recommend to pay attention to the presence of BE in patients with MAP when upper GI-endoscopy is performed. If the observed acceleration of high-grade dysplasia and EAC development is confirmed in more studies, intensive follow-up should be considered in patients with BE.

SURVEILLANCE PROTOCOL AND OUTCOME IN CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY SYNDROME

Constitutional mismatch repair deficiency (CMMRD) is an autosomal recessive hereditary cancer syndrome caused by biallelic MMR mutations. Although CMMRD is a rare condition, many more patients are currently being diagnosed due to the recent advancements in high throughput sequencing. The clinical presentation of CMMRD is variable, ranging from benign polyps and multiple café au lait maculae to a wide spectrum of malignancies beginning in childhood including brain, hematological or gastrointestinal.

Durno *et al.* and Sjursen *et al*. reported on the outcome of surveillance of three CMMRD patients over a period of 10 and 26 years respectively.[35,36] In this follow-up period, many malignant tumors such as CRC were diagnosed and treated. In addition, multiple premalignant tumors including high-grade and low-grade adenomatous polyps were detected and removed.

Until recently, no formal guidelines were available for the management of CMMRD patients. Therefore, the newly established European Consortium “Care for CMMRD” (C4CMMRD) decided to develop diagnostic criteria for CMMRD as well as guidelines for management and surveillance.

The WHO has defined a set of criteria that should be met before implementation of screening programs.[37] These criteria can also be applied to surveillance of individuals with a hereditary cancer syndrome. In **chapter 5**, we reviewed the literature and collected clinical data on the tumor spectrum of nearly all CMMRD patients published in the literature, i.e., 146 CMMRD patients from 91 families.[38] The most common cancers in these patients were CRC, brain tumors, hematological malignancies and small bowel cancers, respectively. We also examined the age distribution of the above-mentioned cancers. Using all information on the tumor spectrum, natural course and the age distribution of the malignancies, we evaluated whether surveillance of the various cancers associated with CMMRD complied with the WHO-criteria. Based on our study and discussions among the members of the European Consortium “Care for C4CMMRD", a surveillance protocol was proposed.[38]

The European Consortium, C4CMMRD, also decided to establish a European Registry of CMMRD patients in order to collect clinical data prospectively and allow clinical studies. One of these studies was to evaluate the effectiveness of the C4CMMRD surveillance protocol.

In **chapter 6** we describe the results of surveillance in 22 patients over a period of four years. Despite this short follow-up, the program detected eight malignant tumors including three brain tumors, three upper gastrointestinal cancers and two colorectal cancers. Most of these tumors could successfully be treated. In addition, seven patients developed a symptomatic malignancy, including two brain tumors, one small bowel cancer and four hematological malignancies. At the end of follow-up, 16 out of 22 (73%) patients who participated in the surveillance program are still alive. We compared our results with previous studies of the International Replication Repair Deficiency Consortium.[39–41] In particular, we evaluated the stage of the detected cancers in relation to the surveillance interval and also the age distribution of diagnosis of the cancers and discussed how the surveillance program can be improved.

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