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Identification and prevention of the Lynch syndrome

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Introduction

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Colorectal cancer (CRC) is one of the most common malignancies in the Western World and is the second most common cause of cancer mortality. In the Netherlands, approximately 9000 new cases are diagnosed each year and about half of them die within 5 years. The lifetime risk of colorectal cancer in the general population is approximately 4%, for men (4-5%) slightly higher compared with women (3-4%). CRC incidence rates in the Netherlands resemble the rates in other Western European countries.

CRC is a multifactorial disease and the etiology is complex. It involves dietary and other environmental risk factors, acting solely or in concert with genetic factors.^{1,2} The role of environmental factors is clearly indicated by its marked variation in prevalence throughout the world. CRC is very common in industrialized countries and rare among rural populations in economically underdeveloped countries.

As with many cancers, a family history of colon cancer has been shown to increase an individual's risk of developing the disease. Approximately 5% of all colorectal cancers occur in the setting of a well described inherited syndrome like Lynch Syndrome (or Hereditary Nonpolyposis Colorectal Cancer (HNPCC)), Familial Adenomatous Polyposis (FAP), and *MUTYH*-associated polyposis.^{3,4}

Family clustering of CRC occurs also with no discernible pattern of inheritance. In around 10-15% of all CRC cases, a positive family history for colorectal cancer is observed and circa 10% of unaffected subjects have a positive family history of CRC.⁵

The biology of CRC provides an excellent opportunity for early detection. Colorectal tumors progress through a series of histopathologic stages, ranging from normal epithelium and single crypt lesions (aberrant crypt foci) to small benign tumors (adenomatous polyps) and malignant cancer (carcinoma), the so-called adenoma-carcinoma sequence.⁶ The development of genetic instability is supposed to be an important event in the multistep

evolution of CRC resulting in genetic alteration in both proto-oncogenes and tumor suppressor genes.^{6,7} *APC* and *KRAS* mutations are generally involved in adenoma formation and growth, while mutations in the *p53* gene and in members of the *TGF-β* pathway are usually associated with malignant transformation.

Survival of CRC is closely related to the clinical and pathological stage of the disease at diagnosis. Evidence from several studies suggests that detection and consecutive removal of precancerous lesions by endoscopic polypectomy reduces the incidence of CRC.

LYNCH SYNDROME

The most common dominantly inherited colorectal cancer syndrome is the Lynch Syndrome.

Clinical characteristics

The syndrome predisposes to cancer,^{5,8} with a lifetime risk of developing any cancer of 85%-90%.⁹ CRC and endometrial cancer are the most frequent carcinomas in Lynch Syndrome, with a cumulative risk of 60%-80% and 30%-50% respectively.^{10,11} Also, significantly increased risks have been reported for cancer of the stomach, small bowel, upper urinary tract (ureter and renal pelvis), ovary, biliary tract, and brain.^{12,13} CRC is often diagnosed at an early age (mean 45 years), can be multiple (with synchronous or metachronous CRC present in 30% of patients), and, in about two-thirds of the cases is located in the proximal part of the colon. Microscopic features frequently observed in colorectal cancer associated with Lynch Syndrome are the presence of peritumoral and tumor infiltrating lymphocytes.

Genetics of Lynch Syndrome

The increased risk for malignancy in Lynch Syndrome is caused by a mutation in one of the DNA mismatch repair (MMR) genes: *hMLH1*, *hMSH2*, *hMSH6*, and *hPMS2*.¹⁴⁻¹⁹ Germline

mutations of *hMLH1* and *hMSH2* account for more than 90% of all known MMR gene mutations in Lynch Syndrome,²⁰ germline mutations of *hMSH6* for 5-10%, whereas mutations of other genes are rare.^{21,22} Mutations in DNA MMR genes result in a failure to repair errors in repetitive sequences that occur during DNA-replication. This failure leads to microsatellite instability (MSI) of the tumor which is the hallmark of Lynch Syndrome.²³⁻²⁷

Most of these microsatellites are noncoding intergenic or intronic sequences. Instability of coding microsatellites often results in frameshift mutations of the corresponding genes, leading to truncated proteins. Numerous coding microsatellites exist in the human genome, some of them in genes that have been proven to be specifically altered in MMR deficient cancer cells, such as *TGF β R2* and *Bax*.²⁸ These genes are called target genes. Accumulation of mutations in such target genes finally may lead to the development of a tumor cell.

Identification of Lynch Syndrome

The diagnosis of Lynch Syndrome is hampered by the absence of specific diagnostic features. Therefore, in 1990, the international collaborative group on HNPCC (ICG-HNPCC) proposed a set of clinical diagnostic criteria (the Amsterdam criteria) in order to provide a basis for collaborative studies and to provide uniformity in the terminology of Lynch Syndrome.²⁹ Since then, many studies have shown that Lynch Syndrome is also associated with several other extracolonic cancers and this was the reason to propose a new set of criteria (the Amsterdam II criteria) (Table 1).³⁰ Because the Amsterdam criteria have a high specificity

for the diagnoses of Lynch Syndrome, but not a very high sensitivity, in 1996, at an NCI workshop clinical guidelines were proposed for individuals with CRC, suspected for Lynch Syndrome that require further molecular analysis (Bethesda criteria).³¹ In the year 2004, these criteria were revised (Table 2).³²

Due to the heterogeneity of the mutation spectrum of MMR genes, screening is both time-consuming and costly. In addition to family history, MSI analysis and immunohistochemical analysis (IHC) can be used to identify families eligible for mutation analysis of the MMR genes.³³ MSI can be determined by comparing PCR-amplified microsatellite loci from DNA of normal and tumor tissue from the same individual. More than 90% of colorectal cancers in MMR gene mutation carriers show MSI.²¹ However, MSI is not specific to Lynch Syndrome, as it also occurs in 15% of apparently sporadic colorectal and other tumors. It has been recommended that MSI analysis should be performed in all tumors from patients that meet the Bethesda guidelines.³¹

An alternative and relatively inexpensive method to detect possible MMR dysfunction and to identify the MMR gene that is most likely mutated, is the examination of tumor samples for the absence of staining of one of the MMR proteins by immunohistochemical analysis with monoclonal antibodies.

Chapter 2 investigates the yield of MSI-analysis in families suspected for Lynch Syndrome and compares the results of IHC-staining and MSI-analysis.

Chapter 3 shows the diagnostic considerations when an individual with a positive family history for CRC is encountered.

Table 1. Amsterdam II Criteria

- At least three relatives with CRC, cancer of endometrium, small bowel, ureter, or renal pelvis
- One of the three is a first degree relative of the other two
- At least two consecutive generations affected
- Cancer diagnosed at age < 50 years in at least one relative
- Histological confirmation of cancer diagnosis

Table 2. The revised Bethesda Guidelines

Tumors from individuals should be tested for MSI in the following situations:

1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors*, regardless of age.
3. Colorectal cancer with the MSI-H[†] histology[‡] diagnosed in a patient who is less than 60 years of age.
4. Patients with CRC and a first degree relative with an HNPCC associated cancer, with one of the cancers being diagnosed under age 50 years.
5. Patient with CRC and two or more relatives with an HNPCC related tumor, regardless of age.

*Hereditary nonpolyposis colorectal cancers (HNPCC)-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas & keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

[†]MSI-H (microsatellite-high) in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers.

[‡]Presence of tumor infiltrating lymphocytes, Crohn's like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

Adenomas in Lynch Syndrome

Adenomas in patients with Lynch Syndrome show histologic features that are associated with a high risk for malignant degeneration, such as a high degree of dysplasia and the presence of more extensive villous architecture, more often than adenomas in autopsy series. In Lynch Syndrome, the progression from adenoma to carcinoma may take less than three years.^{34,35} Because the change from a minute adenomatous polyp to colorectal cancer takes approximately 10-15 years in the case of sporadic colorectal cancer,³⁶ these findings suggest that the MMR defect is associated with an accelerated adenoma-carcinoma sequence. However, it is not known whether the MMR system is also involved in the initial development of the adenoma. **Chapter 4** provides clinically important information on the development of adenomas in HNPCC.

Surveillance and Lynch Syndrome

Because most CRCs develop from benign adenomatous polyps, this provides an opportunity for detecting and removing them in an early stage.^{34,37} It is widely accepted that

measures to prevent development of colorectal tumors should be targeted on individuals at high risk of this malignancy, such as Lynch Syndrome family members.^{36,38-40}

Surveillance of Lynch Syndrome family members leads to detection of colorectal neoplasm at an earlier stage.⁴¹ Moreover, the results of colonoscopic surveillance in 22 Lynch Syndrome families in Finland demonstrated not only a reduction in incidence of colorectal cancer but also a reduction of overall mortality, largely the result of complete prevention of CRC deaths in the surveillance group.^{42,43} In 1995, the Dutch National Collaborative Group on Lynch Syndrome reported an unexpected high occurrence of cancers detected within two to five years after a negative examination.⁴² This, together with the knowledge of the accelerated adenoma-carcinoma sequence in Lynch Syndrome,^{45,46} was the reason for the International Collaborative Group on Lynch Syndrome to recommend surveillance at an interval of one to two years rather than two to three years.⁴⁷ A recent study reported that Lynch Syndrome patients who are under intensive surveillance developed only local tumors (stage

I and II).⁴⁸ Although the Finnish and Dutch studies showed that the risk of developing CRC in mutation carriers under surveillance is decreased dramatically, it is still approximately 5-10% over a ten years period. The question is how improvement of the surveillance protocol can help to prevent the development of CRC. In **chapter 5** we discuss if more intensive surveillance protocols in several subgroups may lead to a further reduction of the CRC incidence in Lynch Syndrome.

In **chapter 6**, we evaluate the effect of surveillance on the cancer mortality in Lynch Syndrome.

POSITIVE FAMILY HISTORY, NON-LYNCH SYNDROME

In families with clustering of CRC (fulfilling the Amsterdam and / or Bethesda criteria), in which the results of the IHC / MSI-analysis of the colorectal tumor(s) are negative, we are not dealing with the Lynch syndrome. The genetic basis of non-Lynch syndrome colorectal cancer predispositions remains unclear. Familial clustering of colorectal cancer is common. This group is likely to be genetically diverse and includes families in which clustering occurs by chance. The actual risk of developing colorectal cancer varies widely. The relative risk associated with a family history of CRC depends on the number of affected relatives and the age at diagnosis.⁴⁹⁻⁵² Subjects with one FDR with CRC diagnosed at age > 50 yrs, have a relative risk (RR) of developing CRC of 2-3.⁵³ Subjects with two (or more) first degree relatives (FDR) with CRC diagnosed at any age, or with one FDR with CRC, diagnosed before the age of 50 yrs have a relative risk of 4 to 6 for developing CRC.^{49,54-56}

Surveillance

CRC in 3 or more relatives, dominant pattern pedigree

Few studies have addressed the colorectal cancer risk in individuals with a family history of colorectal cancer suggestive of a dominant predisposition to colorectal cancer but without molecular evidence of Lynch syndrome. Results from one study show that families who fulfill AC-I criteria but who have no evidence of a DNA MMR defect do not share the same cancer incidence as families with Lynch syndrome (i.e., hereditary MMR deficiency).⁵⁷

We have carried out a prospective study of the outcome of colonoscopic surveillance in at-risk individuals with a family history of colorectal cancer and compared the results in families with and without Lynch syndrome. This is addressed in **chapter 7**.

CRC in 1 or 2 relatives

Most experts also advise colonoscopic surveillance for subjects with a moderately increased risk of developing CRC ($RR \geq 4$). In The Netherlands, a surveillance program is advised for all these subjects from age 45 years (two (or more) first degree relatives (FDR) with CRC diagnosed at any age, or one FDR with CRC, diagnosed before the age of 50 yrs). It is unknown how many subjects fulfil these criteria. We have carried out a study to investigate this number of subjects in age group 45-70 years, within a random cohort among the Dutch population. This study is addressed in **chapter 8**.

GENERAL POPULATION

The vast majority of cases of colorectal cancer occur in individuals with an average risk. There are good reasons to consider the implementation of population-based screening for CRC. Early detection of CRC itself dramatically improves the prognosis. The choices available for CRC screening are FOBT, flexible sigmoidoscopy

every 5 yr, or colonoscopy every 10 yr.^{58,59} CT colonography offers another option but the value of the test has not been firmly established and screening intervals have not been determined.

Research from other countries have shown that screening by testing for small invisible (occult) traces of blood in faeces (faecal occult blood test, FOBT) results in a clear reduction in CRC mortality.⁶⁰ The international community seems to have accepted the value of FOBT in preventing CRC mortality.⁶¹⁻⁶³

Whether or not to introduce population-based screening requires a careful weighing up of both the expected health benefits of screening as well as possible negative effects such as the physical and psychological burden for those being screened, possible over-diagnosis, complications of the screening procedures and disruption of regular health care. In **chapter 9** we evaluate the yield of endoscopic screening in an asymptomatic young population not genetically predisposed to the development of colorectal cancer. This chapter emphasizes the difference in adenoma occurrence at young age in comparison with the high risk groups.

Finally in **chapter 10** the results of the various studies presented in this thesis are summarized, discussed and related to the recent findings published in the literature.

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