Identification and prevention of the Lynch syndrome

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Summary and Discussion

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The studies in this thesis have dealt with the identification of the dominant hereditary disease Lynch syndrome (or Hereditary Nonpolyposis Colorectal Cancer (HNPCC)) and with the surveillance and epidemiological aspects of different high risk groups for developing colorectal cancer (CRC).

LYNCH SYNDROME

Identification of Lynch Syndrome

Identification of families with Lynch syndrome is extremely important because it makes it possible to target effective preventive measures that lead to a substantial reduction in CRC-related mortality. Pre-screening methods to select patients eligible for DNA-analysis are micro satellite instability analysis (MSI); a test to prove involvement of the mismatch repair machinery, and immunohistochemistry (IHC); a test to examine loss of MMR protein expression. IHC can also be used to decide which of the MMR genes is most likely to harbour a mutation and should be analysed first. Most studies reported so far used antibodies against MLH1, MSH2 and MSH6.

In **chapter 2**, we aimed to assess the yield of MSI-analysis in families suspected of Lynch syndrome, to compare the results of IHC and MSI analysis, and to assess the additional value of PMS2 staining. Clinical data and tumors were collected from 725 individuals from 631 HNPCC-like families.

A significant proportion of MSI-H tumors was detected not only in families that complied with the Bethesda criteria (21-49%) but also in families that met other specific criteria (10-26%). We suggested the following revisions to the Bethesda criteria: include late-onset families (three or more cases of CRC diagnosed at age >50 yrs) and raise the age at diagnosis of CRC from 45 to 50 years in the original criteria.

To consider revision and improvement of the Bethesda Guidelines, a HNPCC workshop was held at the National Cancer Institute in Bethesda, MD, in 2002. The results of this meeting and the revised Bethesda guidelines were published in 2004 (see also Introduction).[1]

In addition, (chapter 2) we found that IHC using four antibodies confirmed the results of MSI analysis in 93% of the cases. With IHC, adding PMS2 staining led to the identification of an additional 23% of subjects with an *hMLH1* germ-line mutation.

From this study we recommend the inclusion of PMS2 staining in the panel of antibodies to identify families eligible for mutation analysis.

In **chapter 3**, the diagnostic steps when Lynch syndrome is suspected, analysis of tumour tissue by microsatellite instability analysis and immunohistochemistry, and DNA-analysis are further discussed and practical guidelines are given. Clearly, the rapid detection of new genes involved in cancer, as well as the development of new diagnostic techniques and tools may necessitate modification of our approach to familial colon cancer, as it was developed by the colorectal cancer workgroup at the Leiden University Medical Center. However, the diagnostic scheme presented in chapter 3 allows efficient and effective analysis of families making optimal use of currently available technology.

Adenomas in Lynch Syndrome

In **chapter 4** we studied the role of MMR defects and the development of adenomas in Lynch syndrome families compared with controls from the Dutch HNPCC Registry. In previous reports, autopsy series were used as controls. We showed that carriers of a MMR defect develop adenomas more frequently than controls. The adenomas in the carriers are larger and a significantly higher proportion showed histological features that are associated with a high risk of malignant

degeneration such as a high degree of dysplasia and the presence of more extensive villous architecture.[2] Adenomas and carcinomas in the Lynch syndrome are predominantly located in the proximal colon. Most adenomas in carriers show MSI or absence of immunohistochemical (IHC) staining of one of the MMR proteins. MSI or IHC-analysis may therefore be considered in young patients with large adenomas (≥ 7 mm) and high-grade dysplasia. We concluded that our study indicates that the MMR defect is involved in the early stages of development of adenomas.

Surveillance and Lynch Syndrome

The surveillance guidelines for Lynch syndrome families recommended by the International Collaborative group on HNPCC (InSiGHT) include colonoscopy every two years starting from age 20-25 years.[3] Although Finnish and Dutch studies showed that the risk of developing CRC in mutation carriers under surveillance is decreased dramatically,[4,5] it is still approximately 5-10% over a ten-year period. The question is how improvement of the surveillance protocol can help to prevent the development of CRC.

In **chapter 5** we discussed whether more intensive surveillance protocols in several subgroups will lead to a further reduction of the CRC incidence in Lynch Syndrome. We found that more frequent (annual in stead of bi-annual) colonoscopic screening of family members aged between 40 and 60 years will not significantly lead to detection of CRC at an earlier stage. In addition, the results indicated that re-examination of patients one year in stead of two years after the removal of an adenoma was not more effective. The probability that children (second degree relatives) develop CRC before the development of a Lynch syndrome-related cancer in their parents is very low (<2%).

In conclusion, based on the results of this observational study, we recommend to perform colonoscopy every two years in carriers of an MMR mutation or first degree relatives of Lynch syndrome families from age 20 until age 80 years.

In **chapter 6**, we evaluate the effect of surveillance on the cancer mortality because of CRC and endometrial cancer (EC) in Lynch Syndrome. We also compare mortality owing to all cancers (except CRC/EC) with mortality in the general population. The most frequent causes of cancer-related death in the total cohort (n = 2788) were CRC, EC, brain tumor, lung cancer and cancer of the stomach. A significant decrease (70%) in standardized mortality ratio (SMR) due to CRC was observed in the period 1990-2004 compared to the period 1960-1975 and was most outspoken for those adhering to a colonoscopic surveillance program. The SMR for EC showed no decreasing trend over time. Over all periods the SMR was significantly increased for cancer of the small bowel, brain, kidney, ovarium, pancreas and stomach. Long-term studies are needed to show that the intensive surveillance program will lead to a further decrease of CRC mortality. National cancer registers, like the Netherlands foundation for the detection of hereditary tumors[6], have proved their usefulness to resolve several clinical questions. The aims of the Netherlands foundation for the detection of hereditary tumors are: (1) to improve surveillance in families with hereditary tumors; (2) to guarantee the continuity of periodic examination; and (3) to advise general physicians and specialists concerning screening methods. This center records personal and medical data of patients as well as personal data and screening results of all first-degree relatives. Long-term studies underline once again the clinical importance of these national registers.

POSITIVE FAMILY HISTORY, NON-LYNCH SYNDROME

In **chapter 7** we prospectively evaluated the incidence of neoplasia during endoscopic surveillance in dominant families at risk of colorectal cancer with and without Lynch syndrome. We found that non-Lynch syndrome families (without MSI / MMR-deficiency) when compared to Lynch syndrome families (with MSI / MMR-deficiency) are actually at equal risk of developing high risk adenomas, but at significantly lower risk of developing (interval) cancers. Individuals from non-Lynch families are at an increased risk of developing multiple adenomas.

At-risk individuals from non-Lynch syndrome families require targeted colonoscopic surveillance. Non-Lynch syndrome families did not develop interval cancers when surveillance was carried out every 5 years (3 yearly if adenomas are seen), suggesting that these intervals are appropriate.

Empirical observations have shown conclusively that a family history of CRC is indicative of an increased personal risk of the disease. Irrespective of whether this increased risk is genetic in origin or due to shared environment in the family, the prevalence of a family history of CRC in the general population is of considerable clinical and public health importance. Such information not only contributes to an understanding of the causes of familial disease, but can also inform strategic implementation of preventive measures for population subgroups deemed to be at increased risk.

Chapter 8 investigates the frequency of a positive family history of CRC among a population-based Dutch cohort of subjects between age 45 and 70 years old. This study demonstrated that the proportion of subjects in the general population with an increased risk for developing CRC based on their reported family history is substantial. Of all subjects in this age group, 11.2% had at least one first degree relative (FDR) with CRC, 2.3% of the respondents had two or more FDRs with CRC or had one FDR with CRC diagnosed before the age of 50 yrs, and 0.3% of the subjects had three or more FDRs with CRC.

Based on the findings, we estimate that more than 500.000 subjects in the Netherlands in age group 45 - 70 years, run a risk for developing CRC, which is increased at least 2-3 times. Approximately, 100.000 of these subjects have an increased relative risk of four or more. If all subjects with a positive family history will be identified and encouraged to participate in surveillance protocols, more than ten to fifteen percent of all colorectal cancers (900 - 1400 cases every year in the Netherlands) might be prevented. Colonoscopy is currently the appropriate surveillance method for this high risk group. Studies are needed to elucidate the best surveillance interval for this high risk group.

GENERAL POPULATION

Colorectal cancer is a common and preventable disease. CRC screening for average risk individuals has been shown to be beneficial, resulting in decreased mortality from, and a lower incidence of CRC.

Chapter 9 provides clinically important information on the occurrence and basic characteristics of adenomas identified in a young population not at risk for colorectal cancer. Although the frequency of adenomas in this young population is substantial, advanced pathology was rarely observed. We found a prevalence of adenomas / carcinomas at first colonoscopy of 6.1% and at first sigmoidoscopy of 2.9% in our cohort.

Based on our findings we conclude that the risk of developing adenomas / CRC in young individuals without evidence for genetic predisposition is low in the Netherlands. Surveillance programmes should, therefore, focus on young individuals with a positive

family (or personal) history for adenomas or CRC, or on individuals >50 yr.

FUTURE PERSPECTIVES

Identification

Because cancer and death by cancer is preventable by intensified clinical surveillance[4,7], identifying Lynch Syndrome mutation carriers is clinically important. The hallmark of identification of potential mutation carriers is a thorough review of the family medical history. There is much room for clinical improvement in eliciting and evaluating family history of cancer.[8] All medical doctors should know about the importance of taking a family medical history, as well as knowing how to proceed when a patient proves to have one or more relatives with CRC. It is also necessary to raise the level of awareness regarding familial CRC in the general population, so that those with a substantially increased risk can take advantage of the special services available.

Another challenge for the (near) future if one wants to increase identification of Lynch Syndrome is to perform MSI in every CRC. One side effect is a burden of false positive results. On the other hand, the presence of the MSI-H phenotype (sporadic and hereditary) has also been associated with an improved prognosis[9] and altered responses to various chemotherapies[10], when compared to MSS tumors. Thus, in addition to providing diagnostic information, MSI (and IHC) analyses may have important prognostic and therapeutic implications as well.

Surveillance

Lynch Syndrome

Although the risk of developing CRC in mutation carriers under surveillance is decreased dramatically, it is still approximately 5-10% over a ten-year period.[5] More frequent colonoscopic screening in subgroups of Lynch syndrome mutation carriers will not significantly lead to detection of CRC at an earlier stage.[11] Most likely, this is due to the miss rate of colonoscopy, especially for small and flat lesions.[12-14] Relative to conventional colonoscopy, high-resolution colonoscopy with chromoendoscopy markedly improves the detection of adenomas in patients with HNPCC syndrome and may help to prevent colorectal carcinoma in patients with a very high risk of colorectal cancer.[15] Future studies are needed to investigate further into the yield of chromoendocopy. Also training should be started for all gastroenterologists to introduce this technique on a wide scale.

As a result of intensive surveillance programmes, the mortality rate due to CRC has decreased dramatically (chapter 5). For the next generation, this decrease in mortality will probably continue. Because of the increase in life expectancy of Lynch syndrome mutation carriers, the incidence of other, extra-colonic, tumors will increase. Future studies are needed to evaluate this trend in shift of mortality.

Non-Lynch syndrome

More than 900 cases every year might be prevented if all subjects with a positive family history are identified and encouraged to participate in surveillance protocols. The rate of carcinogenesis in familial colorectal cancer is unknown, and consequently so is the optimal surveillance interval. This is why a national study was started in the Netherlands in 2002; The Familial Colorectal Tumor Surveillance study (FACTS-study).[16] Five-hundred and fifty subjects in age group 45 - 65 years are invited to participate. All participants have a) one first degree relative diagnosed with CRC before the age of 50 years, or b) have two first degree relatives diagnosed with CRC (any age). The subjects are divided at random into two groups: colonoscopy after 3

and 6 years, or colonoscopy after 6 years. We hope the yield of the first colonoscopy will be available in 2007.

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