A Belgian register for Lynch-Syndrome families

Background and rationale

What is Lynch Syndrome?

Colorectal cancer (CRC) is one of the most frequent malignant tumours in the industrialized countries. In Belgium, more than 6500 new cases are diagnosed each year (National Cancer register, 2004). The majority of colorectal cancer patients have sporadic disease and only a minority of colorectal cancers are familial or have a genetic cause.

The two most common forms of hereditary cancers are Familial Adenomatous Polyposis (FAP) and Hereditary Non-polyposis Colorectal Cancer (HNPCC), currently referred to as Lynch Syndrome (LS). While FAP is a rare disorder, accounting for less than 1% of all colorectal cancers, LS is more common, probably representing about 1-3% of all colorectal cancers. Given the cumulative risk of CRC being about 5%, the population incidence of Lynch syndrome is estimated between 1:2000 and 1:660 (de la Chapelle, 2005) potentially resulting in 6000-16000 affected individuals in Belgium.

DNA mismatch repair genes (hMLH1, hMSH2, hMSH6, hPMS1, hPMS2) are involved in LS of which hMLH1 on chromosome 3 and hMSH2 on chromosome 2 are the most common (Lynch & Lynch, 2000). LS is an autosomal dominant inherited disorder characterized by an increased lifetime risk to develop colorectal cancer of which the reports in the literature vary between 30 and 85% (Vasen, 2005). Additionally, there is an increased risk of endometrial cancer between 40-60% (Lu et al., 2005) as well as of other extra-colonic tumours including e.g. cancers of the small bowel, upper urologic tract or ovarian cancer (Watson et al., 2008). The mean age at diagnosis of all cancers related to Lynch syndrome is generally lower than in the general population. Colorectal adenomas are more frequent and the adenoma–carcinoma sequence is accelerated in carriers of a MMR-defect compared to the general population (Vasen, 2005). Although some patients with LS develop carcinoma despite surveillance, the stage distribution of the tumors in CRC cases detected by surveillance is more favourable than in patients with symptomatic colorectal cancer (Bernstein et al., 2003, Järvinen et al., 2000, Renkonen-Sinisalo et al., 2000). There is also evidence that LS-patients with colorectal carcinoma have a better prognosis than sporadic colorectal carcinoma patients and this survival advantage was consistent across stages and significant in the overall stage-stratified analysis in the study of Watson et al. (1998). Therefore it is assumed that the improved survival for LS patients is a biological property of the LS-associated CRC and not the result of screening differences.

Rationale for early detection and prevention

For high-risk individuals, pre-symptomatic detection and treatment of precancerous adenomas or early cancers by screening is important since studies have shown that regular surveillance reduces morbidity and mortality from colorectal cancer. Järvinen et al. (2000) reported that a

3-year interval colonoscopy screening in families with LS reduces the colorectal cancer rate by 62% within a 15-year follow-up period and overall death rate decreased by approximately 65%. Also De Jong et al. (2006) showed a significant reduction in CRC mortality since the introduction of screening in the Netherlands.

International guidelines recommend colonoscopies, usually starting at the age of 25, with a maximum interval of 24 months between each examination. Because colorectal cancer has a premalignant stage of adenomas, the main aim of these colonoscopies is to prevent the development of cancer by means of detecting and removing polyps. Female carriers are also advised to have yearly transvaginal ultrasound. Surveillance for other types of cancer are only indicated in the case of familial occurrence (Vasen et al., 2007).

Genetic counselling and testing can play an important role in increasing compliance with screening recommendations. Cancer genetic counselling and testing can provide the patient and family a more precise risk-assessment and options to decrease risk, including recommendations for cancer screening procedures. Although compliance with screening recommendations in MMR gene mutation carriers after genetic testing is not perfect and delays in undergoing screening can occur, the majority of mutation carriers are adherent (Bleiker et al., 2005, Claes et al., 2005, Hadley et al., 2005, Ponz de Leon et al., 2004, Pylvanainen et al., 2006, Wagner et al., 2005) and the psychological risks of regular screening remain low (Liljegren, 2004). Hadley et al. (2005) reported that the most common reason given for an individual's decision to screen (or not screen) in their study was that the doctor did (or did not) recommend it. Additionally, Bleiker et al. (2005) addressed the feasibility of reminder letters to stimulate long-term compliance. Healthcare professionals' endorsement of screening is therefore important.

The role of a cancer registry

Healthcare professionals' endorsement of health screening is important but it also depends on physicians' knowledge of current guidelines. Furthermore, genetic testing for MMR gene mutations may increase compliance with colon cancer screening recommendations but this implies that MMR gene mutation testing should be offered to individuals who have a high probability of having a risk conferring alteration based on their personal and family history of disease. To avoid confusion, explicit and common guidelines are needed for patient identification, treatment and follow-up. Primary care physicians and specialists can play an important role in the identification and management of LS and therefore their awareness of guidelines for genetic counselling and testing is important and needs to be supported.

Also patients and at-risk family members need information about all details of the disease that allows them to become fully involved in discussions and decision-making related to genetic testing, surveillance protocols and in some cases even risk-reducing surgery.

Lastly, hereditary cancer syndromes represent an area of rapid development and hereditary tumors are uncommon. Therefore, patients are better served if strategies are based on the results of collaborative multi-centre studies. This also has the advantage of standardization of

data collection over the whole country and the avoidance of unnecessary duplication of efforts to collect data.

A coordinating register of families with Lynch syndrome can play a very important role here. Careful education and counselling about all details of the disease are essential to promote maximal compliance with the recommended surveillance protocol strategies. Furthermore, experience has shown that long-term surveillance of high-risk families cannot be adequately guaranteed by individual specialists since the continuity of screening has been found to be interrupted by e.g. departure of the coordinating physician, completion of short-term research programs. In several countries, these problems have inspired specialists to establish national and regional registries that monitor the continuity of the surveillance program by periodic assessment of the screening results. The registries also ensure that the same screening protocol is offered to the various branches of large families that are followed-up by different specialists. The success of family-based registry-assisted surveillance is best illustrated by the decrease in the incidence of colorectal cancer in screening-detected cases of LS compared with that in symptomatic cases as discussed earlier. Hereditary cancer registries also have a role in the assessment of the results of long-term surveillance. This is important, as the value of most suggested protocols is as yet unknown (Vasen et al., 2000).
Lynch Syndrome registers have been established in many countries and are largely aimed at identifying and registering Lynch syndrome families, at maintaining databases of patient information, at contributing to research, at coordinating screening procedures, and at providing education and support for families (Bernstein et al., 2003, Lips, 1998, Myrhøj et al., 1994, Madlensky et al., 1995, Ponz de Leon et al., 1999, Pylvanainen et al., 2006, Rodriguez-Bigas, 1996, Vasen et al., 1989).

A Belgian Lynch-syndrome register

In 1993, the Belgian Polyposis Project was created by physicians, from the different university hospitals in Belgium, who represented all medical disciplines related to Familial Adenomatous Polyposis (FAP). A scientific non-profit organization, FAPA (Familial Adenomatous Polyposis Association), was founded for this project which currently receives financial support from the Foundation against Cancer. FAPA manages a register aimed at including all Belgian FAP-patients anonymously. For registration, a written consent has to be obtained from each patient. On a daily basis, FAPA co-workers collect their medical data related to FAP in the different centres where they are or have been treated after consent has been obtained. Additionally, FAPA aims at providing information about polyposis to patients and relatives, at supporting physicians to trace families and to guarantee regular screening and follow-up for their patients, and at stimulating informal contacts between patients creating an opportunity to exchange experiences and to enhance social support.

Based on the experiences with the Belgian Polyposis Project, FAPA wants to expand its activities by creating a register for Lynch Syndrome families with two primary functions:
1) to increase the understanding of LS by creating and maintaining a research resource for fundamental, clinical and epidemiological scientific research (by gathering information on patients and their family members who have either had a LS associated cancer or, because of family history, are at high risk of developing LS) and consequently to improve research capabilities by centralizing data
2) to serve as an educational resource for participants, their physicians and other health care providers.

A preliminary outline of potential initiatives

1) FAPA as a Belgian reference & information centre for Lynch syndrome

- Development of patient brochure about LS
- Development of website for patients and professionals about LS (including professionals' guidelines for diagnosis, screening and follow-up)
- Collection and provision of documentation about LS (books, articles) available at the FAPA office with list of references published on website
- Organization of information day about LS for professionals, patients and relatives
- Information days as a potential means for the set-up and support of activities of a patient organization
- Distribution of newsletter for patients and professionals providing information about the activities of FAPA and news in the field of hereditary CRC and more specific LS.

2) Lynch syndrome register

- Discussion of approach towards LS register because of differences with FAP syndrome (e.g. clinical diagnosis; 50% mutation detection rate; sporadic occurrence of colorectal cancer)
- Development of network of professionals involved in LS
- Development of Belgian register-database (based on FAP experience and experience of the STOET in the Netherlands)
- Development of informed consent form and procedure to ensure privacy based on FAP experience
- Data collection and organization of follow-up based on FAP experience

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