SURVEILLANCE IN HEREDITARY NONPOLYPOSIS COLORECTAL CANCER SYNDROME

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Academic Dissertation

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To my family

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I Renkonen-Sinisalo L. Aarnio M. Mecklin JP. Järvinen HJ. Surveillance improves survival of colorectal cancer in patients with hereditary nonpolyposis colorectal cancer. Cancer Detection and Prevention. 24:137-42, 2000.

II Renkonen-Sinisalo L. Sipponen P. Aarnio M. Julkunen R. Aaltonen LA. Sarna S. Järvinen HJ. Mecklin JP. No support for endoscopic surveillance for gastric cancer in hereditary non-polyposis colorectal cancer. Scandinavian Journal of Gastroenterology. 37:574-7, 2002.

III Renkonen-Sinisalo L. Bützow R. Leminen A. Lehtovirta P. Mecklin JP. Järvinen HJ. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. International Journal of Cancer. 120:821-4, 2007.

IV Renkonen-Sinisalo L. Kivisaari A. Kivisaari L. Sarna S. Järvinen HJ. Utility of computed tomographic colonography in surveillance for hereditary nonpolyposis colorectal cancer syndrome. Familial Cancer 6:135-140, 2007.

2. ABBREVIATIONS

APC	= adenomatous polyposis gene
BRCA	= breast cancer gene
CAH	= complex atypical hyperplasia
CH	= complex hyperplasia
CI	= confidence intervals
CIN	= chromosomal instability
CRC	= colorectal cancer
CTC	= computed tomographic colonography
DCC	= deleted in colorectal cancer gene
DNA	= deoxyribonucleic acid
EC	= endometrial carcinoma
FAP	= familial adenomatous polyposis
FIGO	= International Federation of Gynecology and Obstetrics
HNPCC	= hereditary non polyposis colorectal cancer
ICG-HNPCC	= International Collaborative Group for HNPCC
K-ras	= Harvey sarcoma virus homologue, Kirsten type
MLH1	= mutator L homologue gene
MMR	= mismatch repair
MSH2, MSH6	= mutator S homologue gene
MSI	= microsatellite instability
MSI-H	= MSI-positive, high-grade of microsatellite instability
MSI-L	= low-grade of microsatellite instability
NSAID	= nonsteroidal anti-inflammatory drug
p53	= tumor suppressor gene protein p53
PMS1-2	= human homologue of yeast postmeiotic segregation gene
RER	= replication error
SAH	= simple atypical hyperplasia
SH	= simple hyperplasia
SMAD4	= human homolog of Drosophila Mad 4
TVUS	= transvaginal ultrasound
TATI	= tumor-associated trypsin inhibitor
PAPA	= Papanicolau test
QOL	= quality of life

3. ABSTRACT

Aim: Hereditary nonpolyposis colorectal cancer (HNPCC) is an inherited cancer predisposition syndrome characterized by early onset colorectal cancer (CRC) and several other extra-colonic cancers, most commonly endometrial cancer (EC) and gastric cancer.
Our aim was to evaluate the efficiency and results of the ongoing CRC and EC surveillance programs and to evaluate if detectable premalignant changes in the gastric mucosa of mutation carriers existed, which would help in detecting those at risk of gastric cancer thus justifying gastric surveillance. Another aim was to examine a new radiological method, CT-colonography (CTC), for CRC surveillance among HNPCC mutation carriers.

Patients: The patient material is representative. It consists of 579 family members from 111 Finnish HNPCC families almost all harboring a known mismatch repair (MMR) gene mutation.

Methods: The efficacy of Finnish CRC and EC surveillance programs on HNPCC patients was evaluated by comparing the stage and survival of cancer cases detected with surveillance versus without. The performance of a new technique, CTC, was explored using a same-day colonoscopy as a reference standard. We introduced the use of intrauterine aspiration biopsies for EC surveillance in a HNPCC setting. We performed upper GI endoscopies and took biopsies from mutation carriers and their mutation-negative siblings.

Results: The CRC cases detected by surveillance were at significantly more favorable stages than those in the non-surveilled group. This advantage was reflected in a significantly higher CRC-specific survival in the surveilled group. CRC resulted in two deaths in the surveillance group and 33 deaths in the non-surveilled group. Overall survival was also better in surveilled patients (15% died compared to 38% in the non-surveilled group), but the difference was not significant.
The performance of a new technique, CTC, was explored as an alternative surveillance method in CRC surveillance and found insufficient for polyp detection in this population in which every polyp, no matter the size, should be detected and removed.
The assumed differences were searched for in the gastric mucosa from MMR gene mutation carriers and their mutation-negative siblings. We could not observe any, neither premalignant lesions nor cancers. These results gave no support for gastric surveillance.
The EC surveillance program (TVUS and intra-uterine biopsy every 2-3 years) seemed to be efficient. It yielded 11 asymptomatic cancer cases and 14 others with a premalignant lesion in 503 surveillance visits. The stage distribution of the endometrial cancers in the group under surveillance tended to be more favorable than that of the mutation-positive, symptomatic EC patients of the same families who had no surveillance. Furthermore, none of the surveilled EC patients died of EC compared to six in the non-surveilled patients during the follow up. The improvement was, however, not statistically significant.

Another observation was the good performance of endometrial aspiration biopsies used in this setting for the first time, especially since we detected several asymptomatic premalignant hyperplasias, which may help with targeting prophylactic surgery.

Conclusions: The present surveillance program for CRC proved to be efficient. The CRC cases found by surveillance are of earlier stage, which reflects to a better CRC specific survival. Colonoscopy was confirmed as a better surveillance modality than CTC. The current surveillance program for EC using endometrial aspiration biopsy increased the efficacy of gynecological surveillance. Several asymptomatic endometrial cancers, with favorable stages, were detected in addition to several premalignant hyperplastic lesions. Single upper GI endoscopy as a surveillance method did not detect gastric cancer cases or premalignant changes in gastric mucosa of mutation carriers, giving no support for gastric surveillance.

4. INTRODUCTION

Hereditary nonpolyposis colorectal cancer syndrome (HNPCC) is a dominantly inherited syndrome with high penetrance. HNPCC is characterized by an early age at onset of various cancers, especially colorectal and endometrial cancer. The third most common cancer in HNPCC is gastric cancer and several other tumors belong to the spectrum as well, i.e. ovarian, small bowel, biliary and pancreatic cancer, brain tumors and urinary tract cancers. Germline mutations in mismatch repair genes *MLH1*, *MSH2, MSH6*, and *PMS2* are responsible for the syndrome in most HNPCC families. It is the most common form of hereditary colorectal cancers accounting for 2-5% of the total colorectal cancer (CRC) burden (Lynch et al 2006). HNPCC-related endometrial cancer (EC) accounts for 2% of all endometrial cancer patients (Hampel et al 2006).

A HNPCC family can be identified, or at least suspected, by family history using uniform clinical diagnostic criteria such as Amsterdam I or II, or Bethesda criteria. A tumor block from one of the family members can be further analyzed with microsatellite instability (MSI) testing, which is seen in most HNPCC associated cancers or with immunohistochemical staining for mismatch repair proteins, which if negative, can direct the further mutation search to the probably causative gene. If a pathogenetic germline mutation is identified in a family, all the family members can be tested for it and cancer surveillance can be recommended to true mutation carriers. Mutation-negative family members have no excess risk of cancer and can be omitted from surveillance.

The aim of surveillance is to improve survival through detection of tumors at an early stage or, preferably, in a premalignant state. The lifetime risk of CRC for a HNPCC mutation carrier is around 70 % (Aarnio et al 1999; Vasen et al 2001). Most colorectal carcinomas are thought to develop from adenomas through the adenoma-carcinoma sequence, which offers great opportunity to prevent cancer by surveillance and polypectomies (Winawer et al 1993). The high risk of CRC led to the organizing regular colonic surveillance for HNPCC family members soon after the syndrome was acknowledged. The benefit of screening, reflected in the diminishing CRC rate and improving survival, has been assessed in both observational studies and in one prospective clinical trial (Järvinen et al 2000).

The risk of EC is 42-70% and it exceeds the risk of CRC in female mutation carriers (Aarnio et al 1999; Dunlop et al 1997; Hendriks et al 2004). Surveillance for EC has long been recommended but published studies on EC surveillance were previously lacking in the literature. Only two studies have been published using transvaginal ultrasound as a surveillance modality and both presented with very modest results (Dove-Edwin et al 2002; Rijcken et al 2003).

The risk of other cancers is only moderately increased in HNPCC and no easy or reliable methods are available for early detection. Regular surveillance examinations are justified

only if the prevalence of the disease is high enough, examination methods are efficient and easy for the patient, and a clear benefit in terms of survival or easier treatment exist. When treating HNPCC mutation carriers the threshold for arranging symptom targeted examinations should be very low.

Our aim was to evaluate the ongoing CRC and EC surveillance in HNPCC, especially to determine whether cancer detection by surveillance is prognostically advantageous due to early diagnosis and to assess the effect of intra-uterine biopsies in EC-surveillance. Another aim was to examine possible new surveillance programs. We investigated the grounds for future gastric cancer screening by comparing the gastric biopsies of mutation positive and negative siblings in search for premalignant lesions. We also compared a new surveillance method, computerized tomographic colonoscopy (CTC) with optic colonoscopy.

5. REVIEW OF THE LITERATURE

5.1. COLORECTAL CANCER

5.1.1. Epidemiology

In developed countries cancer is a major public health problem. The incidence of CRC increases with age and is similar in both women and men in the general population. The lifetime risk of developing CRC is 5-6 %. CRC incidence and prevalence are still rising but mortality rates have decreased during the last years. The mean annual number of new CRC cases in Finland is about 2500 (Finnish Cancer Registry 2005).
Some predisposing factors for CRC are family history of CRC, previous adenomatous polyps or CRC, or inflammatory bowel disease. About 75% of all new CRC cases occur in people without these predisposing factors (Winawer et al 1997). Patients with a familial risk, those who have two or more first- or second-degree relatives with CRC, make up approximately 20-25% of all CRC patients. Only 5-10% of the total CRC burden is inherited in an autosomal dominant manner of which familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) are the major forms (Lynch and de la Chapelle 2003).
Age is the most important risk factor for CRC and more than 90% of all cases occur in individuals over age 50. Epidemiological studies show that a long history of smoking, a high consumption of red and processed meat, and a low level of calcium intake increase colorectal cancer risk (Akhter et al 2007; Giovannucci 2001; Larsson and Wolk 2006; Park et al 2007). The association of dietary fiber intake and dietary fat with CRC risk has been inconsistent among epidemiologic studies (Bingham et al 2003; Lin et al 2004; Michels et al 2005; Otani et al 2006). Low physical activity and higher body mass index have been found to be associated with increased risk of CRC (Vainio et al 2002).

5.1.2. Premalignant polyps

5.1.2.1. Adenomas

Benign mucosal masses in the colorectum are defined as polyps and are divided into different categories dependent on their histology. They include adenomas, which are benign neoplasms that by definition display dysplasia (Kim and Lance 1997).
Adenomatous polyps represent the largest and most important group because they are premalignant. The prevalence of adenomas is between 22-36% in the general population (estimate based on autopsy series) and they are evenly distributed in the colon with approximately 1/3 occurring proximal to the splenic flexure, although a shift from distal to proximal location in older age groups occurs (Johannsen et al 1989; Vatn and Stalsberg

1982). An adenoma >1cm in size with villous or tubulovillous histology and multiple occurrences predict increased risk of developing further adenomatous polyps, as well as CRC. Only few adenomas develop into cancer and the transformation is estimated to take about 10 years in an average risk patient (Winawer et al 1997).

5.1.2.1.1. Small and diminutive adenomas

Very small polyps, with a diameter of 5mm or less, are defined as diminutive. In general, diminutive polyps are benign. The size of a newly diagnosed adenomatous polyp correlates to the existence of high-grade dysplasia, the risk of malignancy, and to the risk of developing metachronous adenomas or cancer elsewhere in the colon (O'Brien et al 1990; Winawer et al 1997). A large data collection from a German polyp registry of more than 20 000 polyps, removed endoscopically, showed no invasive carcinoma in a group of 5137 diminutive adenomas (Nusko et al 1997). Church (2004), however, observed 4% of the diminutive adenomas to have unfavorable histology, 2% to have severe dysplasia and 1 ‰ already malignant. It is suggested that less than 1% of small (<1cm) adenomas are malignant compared with larger adenomas with a risk greater than 10% (Muto et al 1975).

5.1.2.1.2. Flat adenomas

Muto et al. (1985) first described flat adenomas twenty years ago. Colorectal polyps can be classified, according to their gross appearance at endoscopy, as protruding or nonprotruding (flat). A flat polyp can either be slightly raised or slightly depressed, height no more than twice that of the adjoining mucosa, and because its limits are indistinct they become clearer and visible only after they have been sprayed with dye (Rubio et al 2002). Flat adenomas are reported to be quite common with incidence ranging between 8-40%. They often display high-grade dysplasia compared with polypoid lesions and a tendency to invasion and lymph node metastasis and are therefore suggested to be more aggressive than polypoid tumors (Speake et al 2007). Contradictory observations of aggressiveness have, however, also been published (O'Brien et al 2004).
Flat-type colorectal cancers have also been described with significant similarities to flat adenomas based on pathological and molecular findings. This may indicate that flat adenomas are precursor lesions to some flat or de novo colorectal cancers (Speake et al 2007). The incidence of multiple flat adenomas is higher in individuals with relatives with CRC (Adachi et al 2000; Watanabe et al 1996).

5.1.2.2. Hyperplastic polyps

Hyperplastic polyps are fairly frequent and the prevalence in autopsy studies in individuals younger than 50 years has been documented as 7–40% (Liljegren et al 2003). The significance of hyperplastic polyps in colorectal carcinogenesis is debatable. It is still not clear if hyperplastic polyps are precursors to adenomas or if they constitute an entity of their own with or without a cancer risk (Huang et al 2001). There is some evidence that a hyperplastic polyp–serrated adenoma–carcinoma pathway exists (Jass et al 2002). Some hyperplastic polyps display molecular features as seen in neoplastic lesions such

as mutations in the *K-ras* oncogenes and microsatellite instability (MSI) (Mäkinen et al 2001; Otori et al 1997). Serrated CRC seems to be a biologically distinct subclass of CRC and is suggested to account more than 6% of all CRCs (Laiho et al 2007; Mäkinen et al 2001). Among HNPCC patients, however, the hyperplastic polyps do not seem to be a significant predictor for future adenomas (Liljegren et al 2003).

5.1.3. From polyp to cancer

5.1.3.1. Adenoma-carcinoma sequence

It is widely accepted that most CRC cases progress from adenomas through an adenoma-carcinoma sequence. The sequence is a stepwise process in which small adenomas are first transformed into large adenomas, then into non-invasive carcinoma and finally, into invasive carcinoma. Considerable indirect evidence from a range of epidemiological, clinical, histopathological, and genetic studies supports this phenomenon. Age distribution curves for adenomas and carcinomas show that the prevalence of both increases with increasing age. The varying prevalence of adenomas in different geographical regions correlates with the CRC incidence in those regions. In clinical studies, the anatomical distribution of adenomas and cancers is similar, both occurring more frequently distal to the splenic flexure (O'Brien et al 1990). Patients with one or more large polyps are found to be at an increased risk of future cancer (Atkin et al 1992). Histopathological studies have demonstrated foci of malignancy within colorectal adenomas in 0.2–8.3% of cases (Cranley et al 1986). Several studies have elucidated the natural history of an adenoma left in situ and observed both transformation of an adenoma to carcinoma as well as regression of an adenoma (Stryker et al 1987). Finally, detecting and removing adenomatous polyps significantly reduces the incidence of CRC (Leslie et al 2002; Winawer et al 1993).
It is estimated that 80-90% of the colorectal carcinomas evolve through this sequence. The majority of adenomas, however, do not turn malignant during a normal life time since the process is very slow in the general population (Winawer et al 1997).

5.1.3.2. Colorectal tumorigenesis

Genetic alterations play a role in the development of all colorectal malignancies. These genetic mutations are somatic in the majority of cases and therefore have no implications for future generations.
The genes involved in genetic alterations may be classified into three types: oncogenes, tumor suppressor genes, and DNA repair genes. In normal situations, oncogenes stimulate appropriate cell growth, but mutation or over expression results in a gain of function and causes cells to continue to grow in the absence of growth signals. Tumor suppressor genes normally inhibit progress through the cell cycle or promote apoptosis, but when their expression is absent (as a result of mutation), a loss of normal inhibitory control occurs. Finally, DNA repair genes are involved in controlling the rate of mutation of other genes. Mutated repair genes are unable to repair errors, causing mutations in

oncogenes and tumor suppressor genes to accumulate at an accelerated rate (Leslie et al 2002).

In 1990 Fearon and Vogelstein identified genes and loci involved in the carcinogenesis of CRC and presented a model of successive genetic events in the progression of a benign polyp to cancer. In their model, mutations in the adenomatous polyposis coli (*APC*) gene occur early during the development of polyps, mutations of *K-ras* arise during the early adenomatous stage, and mutations of *p53* and deletions on chromosome 18q occur concurrently with the malignant transformation (Fearon and Vogelstein 1990). This pathway is characterized by allelic losses on chromosome 5q (*APC*), 17p (*p53*), and 18q (*DCC/SMAD4*) and is called the "chromosomal instability (CIN) pathway". Of colorectal cancers 75-85% show gains or losses of gross chromosome material as a result of mitotic recombination or aberrant mitotic segregation of chromosomes and are believed to evolve as a consequence of this pathway (Kinzler and Vogelstein 1996; Soreide et al 2006). One of the most famous examples of the CIN pathway is the model of tumorigenesis in FAP, in which multiple small adenomas develop as a result of two hits in the *APC* gene, followed by mutations of *K-ras*, and subsequently mutations of *p53* and deletions on chromosome 18q.

The second, alternative pathway is referred to as the microsatellite instability (MSI) pathway. In this pattern, the genomic instability occurs at the nucleotide level. Microsatellites are a type of DNA that consists of streches of simple sequences, a repeat unit size usually between one and five base pairs. The length of these microsatellites is highly variable from person to person and each individual has microsatellites of a set length. Numerous microsatellites have been mapped throughout the human genome and they are particularly prone to errors during DNA replication. Mismatch repair (MMR) proteins usually repair such errors, but in the absence of competent MMR function (as in HNPCC) microsatellite errors accumulate (Wheeler et al 2000). Microsatellite instability is defined as a change of any length due to either insertion or deletion of repeating units in a microsatellite within a tumor when compared to normal tissue (Boland et al 1998). In 1993 instability of microsatellites at the somatic level was first reported in CRC in particularly, HNPCC (Aaltonen et al 1993; Ionov et al 1993; Peltomäki et al 1993; Thibodeau et al 1993). More recently, colorectal tumors showing MSI have been further classified into those exhibiting high (≥ 2/5 distinctively selected markers exhibit MSI) and low (only 1/5 markers exhibit MSI) levels of instability, referred to as MSI-H and MSI-L. If none of the markers show MSI the tumor belongs to a group called "microsatellite stable" (Boland et al 1998). When a cell is MMR deficient it is not only microsatellites that are at risk of replication error, but also base substitution mutations frequently occur. Thus, MSI can be interpreted as a marker for a state of hypermutability (Leslie et al 2002). Loss of mismatch repair can arise via two distinct routes. These are either MSI-H occurring in HNPCC individuals in which germ line mutations are found in major MMR genes or through a process of MLH1 promotor hypermethylation without mutation, the latter accounting for 10-15% of sporadic cancers.

MSI-H tumors occur more frequently in the proximal colon. In histopathological analysis, they often exhibit poor differentiation, mucinous component, and lymphocyte infiltration (Jass et al 1998). CRC patients with MSI-H tumors seem to have a significant survival advantage compared with microsatellite stable tumors (Choi et al 2002).

5.1.4. Prevention of cancer

5.1.4.1. Polypectomy

Several prospective and retrospective studies have shown that removal of adenomatous polyps is associated with a reduction in the incidence of CRC (Atkin et al 1992; Citarda et al 2001; Winawer et al 1993). The strongest evidence was presented by a prospective colonoscopy study, the National US Polyp Study, which showed a lower than expected incidence of CRC and thus a protective effect at 5.9 years of follow up. (Winawer et al 1993) The effect of polypectomy on CRC rate has also been observed in HNPCC kindreds as the CRC rate was reduced by 62% with surveillance and polypectomies (Järvinen et al 2000).

5.1.4.2. Chemoprevention

Chemoprevention in context with gastrointestinal cancer aims to intervene in the carcinogenetic process and prevent cancer before it occurs. Many of the agents studied have first shown promising results in observational, experimental, or animal studies. The only reliable way to estimate effect of chemoprevention however, is randomized clinical trials. Several agents have been tested, and CRC is the best-studied neoplasia since the outcome in the form of an adenoma is easily detected and the patients with sporadic adenomas are routinely followed with endoscopy (Grau et al 2006).
Clinical trials on antioxidants failed to confirm any positive effect. Epidemiologic studies and clinical trials on dietary fiber have been conflicting. Most trials showed no difference in adenoma recurrence. Clinical studies on ursodeoxycholic acid have also shown contradictory results. Calcium supplementation (with high serum vitamin D levels) has shown a clear risk reduction in adenoma recurrence on every methodological level (Grau et al 2003). The protective effect of aspirin and other non-steroidal anti-inflammatory, NSAID, drugs was first noticed in animal models, followed by encouraging epidemiological studies. Since then several clinical studies have been published showing a protective effect. Sulindac led to polyp regression and prevention in patients with FAP (Giardiello et al 1993). The Aspirin Polyp Prevention Study reported a 17% reduction in adenomas and a 47% risk reduction for large adenomas with low doses aspirin, 81mg. Larger, adult dose (325mg) did not have any effect on adenomas (Baron et al 2003). A large international ongoing collaborative study is designed to test the effect of aspirin with fiber in HNPCC, results are pending.

5.2. HEREDITARY NONPOLYPOSIS COLORECTAL CANCER

HNPCC is characterized by early age at onset of CRC, excess of synchronous and metachronous CRCs, a predilection to the proximal colon, accelerated carcinogenesis, and an excess risk for extracolonic cancers (including endometrium, ovary, stomach, hepatobiliary tract, small bowel, pancreas, brain, transitional cell carcinoma of the ureter and renal pelvis.) In addition, Muir–Torre syndrome is a variant of HNPCC with sebaceous tumors and keratoacanthomas and Turcot's syndrome with glioblastomas and colorectal tumors (Lynch et al 2006).

5.2.1. History and epidemiology of HNPCC

Pathologist Aldred Warthin was first to publish a report of a “cancer family” in 1913. Warthin’s report was based on his seamstress’s family (“Family G”) with excess cancer cases at young age. In 1966, Dr. Henry Lynch published the findings of two large families that had a large number of individuals with multiple different primary cancers transmitted through several generations (Lynch et al 1966). This work led to the updating of Warthin’s old work and in 1971 Lynch published “Cancer Family G revisited”. He demonstrated an autosomal dominant pattern of inheritance and proposed criteria for the Cancer Family Syndrome, which since then has also been called Lynch Syndrome and Hereditary nonpolyposis colon cancer syndrome (HNPCC) (Lynch and Krush 1971). In 1966, Peltokallio was the first to describe families with clustering cancer in Finland (Peltokallio and Peltokallio 1966). In the early 1980s, many clinical reports of cancer family syndrome from several countries, including Finland, were published in the medical literature. In 1989 the International Collaborative Group of Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC) was founded to facilitate collaborative scientific work all around the world.
HNPCC is the most common form of hereditary colorectal cancer. The estimates of its frequency based on clinical criteria have varied widely, but since the era of molecular genetics they have been corrected and HNPCC is estimated to account for 2-5 % of the whole CRC burden (Aaltonen et al 1998; Lynch et al 2006; Samowitz et al 2001).

5.2.2. Diagnostic criteria of HNPCC

Until 1990 uniform criteria and description of HNPCC were lacking. The diagnosis of HNPCC had to be based on clinical data and family history in the absence of a specific biomarker. The clinical diagnostic and selection criteria (the “Amsterdam Criteria”) were determined in 1990 by the ICG-HNPCC to provide an uniform basis for collaborative studies (Vasen et al 1991). These criteria included the following: 1) At least three relatives should have histologically verified colorectal cancer and one of them should be a first degree relative to the other two. 2) At least two successive generations should be affected. 3) In one of the relatives CRC should be diagnosed under 50 years of age. 4) In

addition, different polyposis syndromes have to be excluded. These criteria have been criticized for neglecting extra colonic tumors and also small families may not fulfill them. The less strict “Bethesda Guidelines” were developed 1997 (and revised in 2004) as the basis for molecular screening of putative HNPCC. They differ from the previous Amsterdam I criteria by including synchronous or metachronous CRC or HNPCC-associated extracolonic cancer, adenomas detected before age 40 and CRC with typical HNPCC histology. The aim was to select those individuals that would most likely benefit from MSI testing rather than identifying HNPCC families (Rodriguez-Bigas et al 1997b; Umar et al 2004).
The Bethesda guidelines were impractical in clinical work and so new, simplified diagnostic criteria “Amsterdam Criteria II”, which take into account endometrial, small bowel, ureteral, and renal pelvis cancers, were proposed in 1999 by ICG-HNPCC (Vasen et al 1999).

5.2.3. Molecular genetics of HNPCC

The autosomal dominant mode of inheritance in HNPCC was known for more than 20 years before the knowledge of its molecular genetic background evolved. The observation of MSI in human colorectal tumors, and HNPCC in particular (described in the chapter tumorigenesis), was crucial to further observations of linking HNPCC and MMR deficiency. The main function of the DNA mismatch repair system is to correct mismatches generated during DNA replication and thus maintain genomic stability. MMR deficiency results in a mutator phenotype and MSI.
In 1993, two large kindreds revealed close linkage to microsatellite markers on chromosome 2p (Peltomäki et al 1993). The gene for MSH2 was subsequently identified in this region and shown to have germline mutations in HNPCC patients (Fishel et al 1993; Leach et al 1993). In the same year, a second HNPCC locus was linked to chromosome 3p in two other kindreds and soon *MLH1* was identified (Bronner et al 1994; Lindblom et al 1993; Papadopoulos et al 1994).
In 1995, the DNA sequence of the MSH6 protein was determined and the genes for MSH2 and MSH6 turned out to be located very near each other, most likely on 2p21. The first reports of human germline mutations in *MSH6* causing HNPCC appeared in 1997 (Miyaki et al 1997). Two additional homologues of the mutL gene (*PMS1* on chromosome 2q and *PMS2* on chromosome 7q) have been cloned and mutations found in a small number of HNPCC kindreds (Nicolaides et al 1994). Some support shows that *MLH3* gene may play a causative role in atypical HNPCC (Liu et al 2003).
MLH1 is the most important susceptibility gene for HNPCC. Approximately 250 different germline mutations in *MLH1* have been identified and they account for 50% of all HNPCC related mutations. *MSH2* is the second most frequently mutated gene. Roughly 200 different germline mutations have been detected and their share of the total amount is around 40%. Germline mutations in *MSH6* have been detected in clinically atypical, as well as typical, families and their share of all HNPCC mutations is 10%. *PMS2* seems to be of minor importance in the syndrome, lower penetrance and atypical phenotype are typical. Presently no convincing evidence that germline mutations of *PMS1* would cause predisposition to HNPCC exists (Peltomäki and Vasen 2004; Peltomäki 2005).

5.2.4. Identification of HNPCC

Even the broader clinical criteria are considered too limited leading to missed cases. In clinical work, when screening for an individual who may carry a MMR mutation, the assessment usually starts with evaluating family history and combining it with molecular tumor characteristics such as MSI, if a tumor block is available. Families which fulfill the stringent clinical criteria but the mutation is not found and families with a known mutation but which do not fulfill the criteria, however, do exist. This is often the case in *MSH6* families which may present with atypical phenotype (Buttin et al 2004; Plaschke et al 2004). Notably, among the families that fulfill strict Amsterdam I criteria several have no evidence of a MMR gene mutation (Lindor et al 2005). These families are referred to as having “familial colorectal cancer” or “familial colorectal cancer type X” and they have an increased risk of CRC compared to the general population but a lower risk than seen in those with HNPCC and germline MMR gene mutation (Lindor et al 2006).
According to recent European guidelines the sensitivity of MSI-analysis is slightly better than of immunohistochemistry (IHC) -analysis when detecting possible MMR mutations in colorectal tumor. IHC-analysis using four antibodies (MLH1, MSH2, MSH6, and PMS2) against the MMR proteins holds the advantage for directing mutation analysis towards the underlying gene defect. Thus, MSI or IHC can be used as the first step but IHC is preferable when examining a family with a high probability for harboring a MMR mutation (Vasen et al 2007).

After the MMR gene mutation is identified in a family all the at-risk members should undergo thorough genetic counseling which clarifies the natural history of the syndrome, the cancer risks, and possible benefits or limitations of organized surveillance. After counseling the individual may decide whether or not to continue onto predictive testing. With mutation testing the true mutation carriers can be identified and the surveillance efforts can be targeted to them. The mutation-negative family members do not have an excess cancer risk compared with general population and thus do not need further surveillance (Mecklin and Järvinen 2005). The first reports on the acceptance of genetic testing were not encouraging, only 43% of the high-risk family members chose to receive the test result and the rest declined to participate (Lerman et al 1999). In a Finnish study, 75% of the family members at risk took the genetic test after the first counseling session. Unemployment was the only significant sociodemographic factor predicting refusal or declining of the test (Aktan-Collan et al 2000). Difficulties in reaching the family members at risk have been one of the most common reasons for the low rate of genetic testing (Ponz de Leon et al 2004).

5.2.5. Colorectal cancer in HNPCC

5.2.5.1. Incidence and clinical features

HNPCC mutation carriers have a very high risk of developing colorectal cancer during their lifetime, for males the risk for CRC is the largest. CRC in HNPCC is more often located in the proximal colon (60-70% compared with 30% in general population) and mutation carriers are predisposed to multiple synchronous and metachronous CRCs (Lynch et al 1988; Mecklin and Järvinen 1986; Mecklin and Järvinen 1991; Vasen et al 1990).

HNPCC-related CRCs often show poor differentiation with an excess of mucoid and signet-ring cells, have tumor infiltrating lymphocytes, Crohn's like peritumoral lymphosytic reaction, and medullary growth pattern (Jass et al 1994b; Mecklin et al 1986). In the general population, poor differentiation is associated with poorer CRC prognosis which, however, seems not to be the case in HNPCC related CRC.

Precise risk estimates for HNPCC-related cancers are not available. The estimates tend to differ depending on mutation, sex, and ascertainment status (Lindor et al 2006). Some evidence shows that the 4 most common mutations in the MMR-genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) are associated with different risks for cancer but because of differences in prevalence the risk data is usually presented in joint form. Mutations in *MLH1* and *MSH2* account for nearly 90% of families with identified mutations (Peltomäki and Vasen 2004). In MMR-gene mutation carriers the estimated risk for CRC is 70% by the age of 70 (range 27-82%) (Aarnio et al 1995; Aarnio et al 1999; Dunlop et al 1997; Hendriks et al 2004; Quehenberger et al 2005; Vasen et al 1996; Vasen et al 2001). Colorectal tumors in HNPCC (*MSH2* or *MLH1* mutation carriers) occur approximately 20 years earlier (mean 40-45 years) than in general population. Cancer risk of CRC for male and female mutation carriers is also different and it has been confirmed in all studies. In a Finnish study the standardized incidence ratio for CRC was higher in men (83) than in women (48). The male-to-female ratio was 1.7 (Aarnio et al 1999). The cumulative lifetime risk of CRC in female *MSH6* mutation carriers is significantly lower than in carriers of a mutation in *MLH1* or *MSH2*. In male *MSH6* carriers the risk of CRC was also lower than in *MLH1* and *MSH2* carriers, but the difference was not statistically significant. The mean age at diagnosis was higher (51-57 years) among *MSH6* carriers in both sexes (Hendriks et al 2004; Wagner et al 2001). The phenotypic consequences of *PMS2* mutations appear to be highly variable, often with childhood onset of atypical tumors. CRC is though to be the most common cancer in *PMS2* families, often with a little later onset (Hendriks et al 2006).

The incidence of a metachronous CRC has been reported to be 18-40% at 10 years after the treatment of first CRC (Aarnio et al 1995; Fitzgibbons et al 1987). Incidence figures of metachronous CRC are, however, strongly influenced by possible existence of a surveillance program and the surgical method chosen at the time of the first CRC. De vos tot Nederveen Cappel et al performed a retrospective cohort study in patients from 114 Dutch families meeting the Amsterdam criteria, 63 had an identified mutation. The aim of this study was to asses the risk of developing CRC (first cancer or metachronous CRC

after colon resection) within the surveillance program. The cumulative risk of developing a first CRC in 10 years was 10.5% in a group of proven mutation carriers who had had an intact colon in the first surveillance session. The cumulative risk of developing a second, metachronous CRC after partial colon resection in 10 years was 15.7% among the families with a known mutation. Only one out of 29 patients (3.4%) who had undergone a previous subtotal colectomy developed rectal cancer during surveillance (De Vos tot Nederveen Cappel et al 2002). The risk of rectal cancer after total or subtotal colectomy was estimated to be 12% at 12 years according to an earlier, retrospective international study (Rodriguez-Bigas et al 1997a).
The incidence of CRC in HNPCC is prone to decrease because of effective surveillance programs.

5.2.5.2. Adenomas in HNPCC

Adenomas appear in the colon of HNPCC patients regardless of the term “non-polypose” and most probably the colorectal carcinoma arises as a stepwise process through the adenoma-carcinoma sequence as is suspected in the general population. Adenomas in HNPCC are supposed to occur at the same rate (Love and Morrissey 1984; Mecklin and Järvinen 1986; Mecklin et al 1995; Strul et al 2006) or with a moderately increased prevalence than in general population (Lanspa et al 1990). One study exists from the Netherlands in which the adenoma incidence was studied comparing known mutation carriers and their mutation negative siblings. Carriers of a MMR defect developed adenomas significantly more frequently and at younger age than their siblings. At 60 years, only 30% of the true mutation carriers were still free of adenomas, compared to 71% of their mutation negative family members (De Jong et al 2004).
The adenomas are larger and a significantly higher proportion show a high degree of dysplasia and more extensive villous architecture than sporadic adenomas, histological features that make them more prone to malignant conversion (De Jong et al 2004; Jass and Stewart 1992; Jass et al 1994a). A pronounced proximal distribution of adenomas is also seen in HNPCC (Lanspa et al 1990). Most adenomas in HNPCC mutation carriers show MSI or absence of IHC staining of one of the MMR proteins giving the possibility for MSI- or IHC-analysis of large adenomas (De Jong et al 2004). The progression from adenoma to CRC seems to be accelerated in HNPCC (Järvinen et al 1995; Jass 1995; Lindgren et al 2002; Lynch et al 1995; Mecklin et al 1986).

5.2.5.3. Surveillance methods

5.2.5.3.1. Double-contrast barium enema

The double-contrast barium enema (DCBE) is inexpensive and cost-effective as a CRC screening strategy. It examines the entire colon and rectum, but for the visualization of the full colorectum a flexible sigmoidoscopy is recommended to complete the examination. It is insensitive compared with colonoscopy, even in the hands of a skilled radiologist (Rex et al 1997a; Winawer et al 2000). Furthermore, it is uncomfortable and, if positive, requires a second bowel preparation and colonoscopy. Patients also claim to

experience more discomfort with DCBE than with CT colonography (CTC) and would prefer CTC to DCBE as a surveillance modality (Gluecker et al 2003). The rise in diagnostic and therapeutic colonoscopy and CTC has led to a reciprocal decline in DCBE, which has resulted in fewer radiologists who are well trained and expert in DCBE (Rex 2002). The risk of colonic perforation in DCBE is rare, 0,004 % in a retrospective analysis of over 700 000 DCBE examinations (Blakeborough et al 1997).

5.2.5.3.2. Colonoscopy

Colonoscopy was introduced in the early 1970s and since it makes endoscopic polypectomy feasible it is the only technique available that gives the opportunity to diagnose, take biopsies, and remove premalignant lesions during the same session. Colonoscopy allows visualization of the entire colon, experienced endoscopists can survey the entire colon in 92-97% of cases (Nelson et al 2002; Wexner et al 2001). Incomplete colonoscopy requires either a repeat colonoscopy or some other supplemental examination.
Colonoscopy is often regarded as the gold standard for detecting polyps or cancer, but errors in the ability to detect neoplasia are well documented and the overall miss rate is 15-24% but improving with increasing polyp size. Polyps ≥1 cm are rarely missed (Hixson et al 1990; Postic et al 2002; Rex et al 1997b). Conventionel colonoscopy has proven to be more effective in polyp surveillance of general population than DCBE (Norfleet et al 1991; Winawer et al 2000). According to a Canadian population-based study, however, 4% of right-sided colon cancers were missed in usual clinical practice (Bressler et al 2004).
Colonoscopy has some limitations of use, for example the frequent need for sedation, intraprocedural cardiovascular complications(1-2%), potential risk of perforation (0.03-0.8 %), bleeding (0.08-1.6 %), death (0.0001-0.3 %), and the cost of the procedure. The risk of perforation and bleeding are of course greater after polypectomies (Rex et al 1997b; Wexner et al 2001; Winawer et al 1997). HNPCC mutation carriers have described regular surveillance colonoscopies as painful (36%), uncomfortable (39%), and easy (25%) according to a Finnish questionnaire study (Pylvänäinen et al 2006).

5.2.5.3.3. CT colonography

CT colonography was first introduced by Vining in the mid-nineties (Vining 1997). It is a rather new non-invasive imaging technique, which involves full bowel preparation followed by rectal gas insufflation and helical CT scanning of the distended colon. Images are then evaluated using image analysis software. The terms CT colography, CT colonoscopy, CT pneumocolon, virtual colonoscopy, and virtual endoscopy have all been used in literature.

<u>Bowel preparation for CTC</u>
The bowel preparation is important and a well-cleansed and well-distended colon facilitates polyp detection and minimizes false-positive findings. The bowel preparation though is considered troublesome by many patients and often residual fecal material or

fluid are present in the colon. This has lead to the concept of fecal tagging, which can be achieved by ingesting small amounts of barium or iodine with the meals prior to imaging (Lefere et al 2005; Macari and Bini 2005).

Technique and data interpretation in CTC

The images are obtained in both supine and prone positions after distending the colon with room air or carbon dioxide. CTC hardware and software are rapidly evolving areas resulting in better performance and diminishing radiation exposure. These developments are for the most part due to moving from a single-section scanner to multi-detector row CT scanners allowing up to 64 sections to be obtained in a single rotation of the x-ray tube. Multi-detector row scanners allow large volumes of data acquired in a single breath hold. This near-isotropic data allow coronal, sagittal and endoluminal (virtual) images to be obtained and thus, facilitates differentiation (Macari and Bini 2005).
There are two primary techniques for data interpretation, the 2D or 3D approach. Most of the published series are based on 2D interpretation, which has its benefits. The whole colonic mucosa can be visualized in one pass, which is time-efficient and many authors have used 3D and multiplanar reformation only for problem solving. With improving software and 3D workstations the time factor is, however, vanishing and the radiologist can perform a “fly-through” (antegrade and retrograde) in the colon which simulates a true endoscopy (Macari and Bini 2005).

Radiation Dose in CTC

When using imaging examination that uses ionizing radiation for surveillance purposes, exposure is a serious concern. When a multi-detector row scanner and thin collimation are used with two acquisitions the resulting exposure would be great. The radiation dose can, however, be decreased at CT by increasing pitch and collimation or by decreasing the peak voltage or milliampere-seconds level. Substantial reductions in milliampere–seconds values can be achieved without sacrificing polyp detectability because there is very high tissue contrast between insufflated gas and the colonic mucosa (Kalra et al 2004; Macari and Bini 2005).
In a study from Macari et al. (2002) the resultant effective doses for both supine and prone imaging were 5.0 mSv for men and 7.8 mSv for women, which is similar to the dose reported for DBCE and still, the sensitivity of CTC for the detection of 10mm or larger polyps was greater than 90%.

Performance of CTC

The ultimate goal of CTC is the detection of all pathological lesions and the detection of significant lesion would logically lead to colonoscopy and biopsies or polypectomy. The definition of a clinically significant lesion is important from this point of view.
Most gastroenterologists agree that in a general population screening it is crucial not to miss patients with lesions sized more than 10mm in diameter and would be desirable to detect all lesions sized more than 6mm (Cotton et al 2004). There seems to be a majority opinion among authors that diminutive colonic polyps could be regarded as clinically insignificant and therefore ignored on CT colonography (Bond 2001; Dachman and Yoshida 2003; Macari and Bini 2005).

Several single-center studies have reported excellent per-patient sensitivities of more than 90% for detection of large lesions (sized ≥10mm) but confusingly, there are other large studies presenting much lower sensitivities, between 50-60% (Johnson et al 2003; Pickhardt et al 2003; Rockey et al 2005; Yee et al 2001). According to a recent meta-analysis of 24 CTC studies, the average per-patient sensitivity for detecting large polyps was 93% (95%CI: 73% to 98%) and average specificity 97% (95%CI: 95% to 99%), but these test characteristics diminished with the size of the target lesion. The data was too heterogeneous to allow meta-analysis when polyps of all sizes were included, but the sensitivities ranged between 45-97% and specificities between 26-97% among the studies included (Halligan et al 2005).
Limitations, however, exist in these studies which should be taken into account when considering expanding the indications to surveillance or screening purposes. The single-center studies are emphasized in these figures and most of them were initiated by committed radiologists, pioneers in the technique. To be valuable as a screening tool, CTC must perform well in routine practice (Cotton et al 2004; Johnson et al 2003). Additionally, the study populations have mostly been symptomatic patients and it is likely that differences occur in polyp detection rates and a low prevalence of abnormality may diminish sensitivity (Halligan et al 2005; Johnson et al 2003). Two large studies evaluated CTC in an asymptomatic population and only one of them could reasonably claim that subjects truly represented a screening population and again, the results were mixed (Johnson et al 2003; Pickhardt et al 2003). According to a recent meta-analysis CTC is highly sensitive for detection of cancer (Halligan et al 2005).
(The 5 largest studies published so far are presented in Table 9 in the Discussion)

Complications of CTC

Only few studies exist of complication rates of CTC. Pickhardt (2006) recently reported the results of a large questionnaire survey which gathered the complications of 20 medical centers and of more than 21 000 CTC studies. The overall complication rate was 0.02%, colonic perforation rate 0.009%, and the rate for symptomatic perforations 0.005%. No perforations were seen in the patients in whom the colonic distention was achieved with patient-controlled insufflation or a slow automated CO2-delivery compared with staff-controlled manual insufflation.

5.2.5.4. CRC survival

The primary observation of better survival in HNPCC related CRC than in sporadic form was from a small series in the late 1970s (Lynch et al 1978). Sankila et al. (1996) confirmed the finding later. They studied 175 patients with HNPCC related CRC and compared them with more than 14 000 patients from the National Cancer registry who had sporadic CRC. The 5-year relative survival rate for the HNPCC CRC-patients was significantly better, 65% versus 44%, than for the patients with sporadic CRC. Similar observations of better survival in relation to HNPCC have been published by other authors and the phenomenon appears to be independent of stage (Aarnio et al 1998; Watson et al 1998). HNPCC related CRC also seems to have better prognosis than CRC related to patients with Familial Polyposis or Ulcerative Colitis (Aarnio et al 1998), though there are some contradictory results published as well (Bertario et al 1999).

There is an apparent paradoxical correlation between the poor differentiation often seen in the histology of HNPCC related CRC and the favorable prognosis (Mecklin et al 1986). Speculations suggest that the peritumoral lymphoid response and Crohn's-like pattern may be indicative of a host defense mechanism (Graham and Appelman 1990).

5.2.5.5. CRC surveillance

The high risk of developing CRC in HNPCC has led to the concept of organized surveillance. Within families in which a HNPCC mutation has been identified, family members who test negative for the mutation are not at an increased risk of developing CRC and do not need regular surveillance with colonoscopies. When a mutation has not been identified in a family which fulfills the Amsterdam II criteria all family members are possible gene carriers and thus require regular surveillance.
Colonoscopy is at the moment the most used method for HNPCC colorectal surveillance, because it is easily arranged in an out-patient manner and it allows detection and removal of a lesion in its premalignant adenomatous state and thus prevents cancer. The surveillance may also detect CRC in its asymptomatic, early state.
The benefits of colorectal screening in HNPCC have been assessed in several studies (Arrigoni et al 2005; De Vos tot Nederveen Cappel et al 2002; Järvinen et al 1995; Järvinen et al 2000; Lanspa et al 1990; Love and Morrissey 1984; Mecklin and Järvinen 1986; Vasen et al 1989). The first descriptive series of colonoscopy as a screening method in HNPCC were published in the 1980s. They all confirmed similar results of over representation of colorectal tumors, in particularly synchronous and metachronous tumors and more proximal location of both adenomas and carcinomas thus suggesting the adenoma-carcinoma pathway in tumorigenesis (Lanspa et al 1990; Love and Morrissey 1984; Mecklin and Järvinen 1986).
Vasen et al. (1995) studied a series of 388 asymptomatic HNPCC family members within a surveillance program offering colonoscopy in every 2 - 3 years. A control group consisted of 238 family members with symptomatic CRC. Of the actual study group, 8.5% were diagnosed with an adenoma and 2.8% (11) developed CRC during the 5-year follow up. These 11 screened CRC cases were compared with the CRC cases in the control group and they were of earlier stage and their 5-year survival was better than in the control group (87% versus 63%).
A prospective, controlled study comparing colonoscopy surveillance with a 3-year interval and no surveillance at all in the asymptomatic HNPCC family members started in 1984 in Finland. The results of this study have been published in two sets, first in 1995 and the final outcome in 2000 (Järvinen et al 1995; Järvinen et al 2000). The original division between the two groups was made by the family members themselves, they were all offered surveillance but some chose not to attend and some were not traceable. Because of the long follow up some of the patients in original non-surveillance group eventually started surveillance but the results were calculated according to the original status. The CRC rate was reduced by 62% with surveillance. Eight subjects out of 133 (6%) developed CRC during the study period compared to 19/119 (16%) in the control group. The decrease resulted from the removal of adenomas in 19 family members. The stage distribution of the CRC cases was significantly superior in the study group. All CRCs were local compared with 10 local and 9 disseminated cases in the control group. No CRC

related mortality occurred in the surveilled group compared with 9 CRC related deaths in the control group. The difference with the overall death rates was also significant, 10 versus 26 subjects.
A large HNPCC cohort study from the Netherlands showed that the CRC related standardized mortality ratio has significantly decreased (70%) over time measured in 3 successive 15-year periods reflecting the era of surveillance colonoscopies. This observation was confirmed by the finding of a significantly lower standardized mortality ratio among the subjects who were involved in surveillance program compared with the ones who were not (De Jong et al 2006b).
Several studies have shown that the risk of developing CRC before the age of 25 is very low and there are only anecdotal examples of HNPCC patients who have developed CRC before the age of 20 (De Jong et al 2006a). It is generally agreed that surveillance should be initiated at the age of 20-25 years (Burke et al 1997; Mecklin and Järvinen 2005; Vasen et al 1993). Since the cumulative lifetime risk of CRC in female *MSH6* carriers is significantly lower and the mean age at diagnosis is higher, it is suggested that in this distinct group the starting of colonic surveillance could be postponed until the age of 30 (Hendriks et al 2004). Recommendations regarding the upper age of surveillance are few. According to a Dutch study the risk of a 70-75 year old mutation carrier to develop CRC in the next 10 years is still substantial compared to the mean life expectancy, thus favoring continuing colonoscopic examinations till the age of 80, if the patient is otherwise healthy (De Jong et al 2006a). A publication from an European group emphasized the individual assessment on this matter (Vasen et al 2007).
Colonoscopic surveillance in HNPCC is estimated to provide greater quality-adjusted life expectancy compared with all colectomy strategies in the mathematical Markov model (Syngal et al 1998). Two studies on cost-effectiveness have been performed with decision analysis comparing surveillance versus no surveillance with similar results. Endoscopic surveillance starting at the age of 25 is extremely cost-effective (Olsen et al 2007; Vasen et al 1998).

5.2.5.6. Appropriate surveillance interval

The need for regular colorectal surveillance in HNPCC is widely accepted but no conclusive evidence exists on appropriate surveillance interval. No prospective studies are available comparing different intervals. The Finnish trial showed that colonoscopy every 3 years significantly reduced CRC incidence and also mortality, probably because of previous polyp removal (Järvinen et al 2000). Interval cancers (asymptomatic CRC detected in scheduled surveillance colonoscopy), however, still did occur and have also been detected in several other studies raising the doubt of surveillance intervals being too long (Vasen et al 1995; Vasen et al 1995). On the other hand, it has been debated that too frequent surveillance colonoscopies might warrant the compliance and to some extent may adversely impact on resource availability (Brown et al 2003; Johnson et al 2006; Lund et al 2001).
A retrospective cohort study of patients from 114 Dutch families meeting the Amsterdam criteria (63 with an identified mutation) was conducted in 1985-2000. One aim of that study was to compare the stage of the surveillance-detected cancers in relation to surveillance interval between successive colonoscopies (2-3 years versus 1-2 years).

The Dutch recommendations of colonoscopy interval had changed towards higher frequency in 1996.
There were altogether 35 CRC cases detected within the surveillance program, 21 of which were from the surveillance group with previous intact colon, 13 in the partially resected colon group, and one in the subtotal colectomy group. The previous examination preceding colorectal cancer had not been a complete colonoscopy in 7/35 cases (4 of which developed Dukes C cancer) and additionally, 4/13 CRC cases in the partial colon resection group were detected in the first postoperative colonoscopy giving rise to the doubt that they were in fact synchronous cancers. Altogether 16/35 carcinomas were detected with a shorter surveillance interval (≤ 2 years), the remaining 19 with the program using longer intervals (>2 years). Fifteen out of 16 of the tumors detected with the shorter interval were at local stage compared with 6/19 in the group with longer surveillance intervals. No statistical analyses were conducted (De Vos tot Nederveen Cappel et al 2002).
The reasons for the interval cancers detected even during surveillance with 2-3 year interval are debatable. At least 3 optional explanations to this exist. First, the lesions may be missed in the preceding colonoscopy (Gorski et al 1999). Second, the lesions may develop very fast from a tiny adenoma because of accelerated adenoma-carcinoma sequence. Lastly, the lesions may be fast growing, true “de novo“ carcinomas. Local and national surveillance programs still suggest surveillance intervals with the range from 1 to 3 years. The International Collaborative Group on HNPCC (ICG-HNPCC) has recently recommended a 1-2 year interval (Vasen et al 2007).

5.2.6. Endometrial cancer in HNPCC

5.2.6.1. Incidence and clinical features

HNPCC-related endometrial carcinoma (EC) accounts for at least 1.8 % of all endometrial cancer patients according a recent molecular screening study (Hampel et al 2006). The likelihood of developing EC is higher than of developing CRC in the female HNPCC population. The lifetime risk of EC is 42-60 % based on true mutation carriers harboring *MLH1* or *MSH2* but even higher (71% at 70 years of age) for *MSH6* mutation carriers (Aarnio et al 1999; Dunlop et al 1997; Hendriks et al 2004). The risk seems to be higher for *MSH2* carriers than *MLH1* carriers. (Vasen et al 2001). The cumulative risk of sporadic EC up to age 75 years has been estimated as 1.7% (Amant et al 2005).
EC in HNPCC is characterized by an early age of onset. It is diagnosed approximately 10 years earlier than in the general population, at the mean age of 47 years, regardless of the histology of the tumor (Broaddus et al 2006). Here again, the *MSH6* carriers differ from the others, the mean age at diagnosis is 54 years (Hendriks et al 2004).
Of sporadic EC 80% are of the endometrioid type. Most endometrioid carcinomas are well to moderately differentiated and arise on a background of endometrial hyperplasia. These tumors, also known as type 1 low-grade endometrial carcinomas, have a favorable prognosis. About 10% of endometrial cancers are type 2 (high-grade) lesions. Women with such tumors are at high risk of metastatic disease. These tumors are not estrogen driven, and most are associated with endometrial atrophy. Abnormal uterine bleeding is the most frequent symptom of EC (Amant et al 2005).
Of HNPCC-related EC, 86% are of the endometrioid type but in young age group the HNPCC mutation carriers seem to have more non-endometrioid tumors (14%) than in the sporadic setting (10%). A majority (78%) of HNPCC-related EC cases are detected at an early stage (Broaddus et al 2006).
Van der Bos et al. (2004) from the Netherlands performed a small case-control study to compare HNPCC-related and sporadic endometrioid endometrial carcinomas and they found that the HNPCC-related ones were significantly more often poorly differentiated. Most, but not all, cases of EC in known mutation carriers show MSI-H compared to MSI-H prevalence of 15-30% in sporadic tumors. Most endometrial hyperplasias also present with MSI-H phenotype (De Leeuw et al 2000; Hampel et al 2006).

5.2.6.2. Premalignant lesions

Endometrial hyperplasias are classified according to the World Health Organization (WHO) system published in 1994 (Scully R.E. 1994). The classification divides hyperplasias into simple and complex depending on the glandular architecture (Kurman et al 1985). Both simple and complex hyperplasias are further divided based on the presence of atypia. Atypia usually occurs in endometrium with a complex architecture. All the hyperplasias have an increased risk of developing an endometrioid-type endometrial adenocarcinoma. The risk is lowest in simple and complex hyperplasias (1% and 3%), which are usually self-limiting lesions and can regress. With atypical hyperplasia,

however, there is a considerable risk of transformation into an adenocarcinoma, with complex atypical hyperplasia (CAH) the risk is 25–40% (Kurman et al 1985).

5.2.6.3. Survival and surveillance

Survival of sporadic EC differs greatly according to the FIGO stage. The 5-year survival is around 85% for stage I (95% for low-grade stage IA), 75% for stage II, 45% for stage III, and 25% for stage IV disease (Amant et al 2005).
The survival rate of HNPCC-associated EC is favorable. In a group of 125 women fulfilling the Amsterdam criteria, Vasen et al. (1994) reported that only 12% died of EC. Previous epidemiologic studies have shown that the 5-year survival for women with HNPCC and EC is similar to those with sporadic EC (Boks et al 2002).
Because of the high risk of developing EC in HNPCC, regular surveillance has been suggested. The possible surveillance modalities consist of clinical examination, transvaginal ultrasound (TVUS), papa smear, tumor markers (CA 125, TATI), and intrauterine (aspiration) biopsies. TVUS is easy for the patient and it can accurately assess endometrial thickness. A thin and regular endometrial lining is associated with a very low risk of EC as long as the endometrium is clearly visualized throughout the uterus. The value of TVUS is among postmenopausal women, because in premenopause the “normal” endometrial thickness varies with circulating concentrations of female steroid hormones (Amant et al 2005). Endometrial sampling with Pipelle is a rather sensitive method (81-91%) and specificity is good 98% (Dijkhuizen et al 2000). According to a rather recent estimation endometrial biopsies are the most cost-effective modality when the prevalence of EC is over 15%. TVUS followed by endometrial biopsy if an abnormality is detected is the most cost-effective for populations in which the prevalence of endometrial carcinoma is lower (Dijkhuizen et al 2003).

Two previously published studies of endometrial cancer surveillance in HNPCC exist. The first was a joint study from Netherlands and England in which 269 women from suspected HNPCC families were surveilled with TVUS scans within a 1-2 year interval. A total of 522 TVUS scans detected neither premalignant lesions nor EC. Two cases of interval EC occurred 6 and 24 months after a normal scan (Dove-Edwin et al 2002). The other study evaluated a 10-year experience of TVUS scan as surveillance modality. In all, 42 women entered the program, 17 out of 179 TVUS scans were considered pathological, and the women were referred to endometrial sampling. Three cases of premalignant complex atypical hyperplasia cases were detected. One interval cancer occurred 8 months after a normal scan (Rijcken et al 2003).

5.2.7. Ovarian cancer in HNPCC

5.2.7.1. Incidence and clinical features

Very little is known about HNPCC associated ovarian cancer. The lifetime risk for ovarian cancer in HNPCC ranges between 9-12 % compared to 1.3 % in Finnish general population (Aarnio et al 1995; Aarnio et al 1999). The incidence of ovarian cancer among HNPCC is one third or less of that among women with a BRCA mutation (Offit and Kauff 2006).

The ICG-HNPCC gathered information on 80 HNPCC-related ovarian cancer cases from several countries. The mean age of onset was 43 years, strikingly early compared to the general population (59 years). Most of the tumors (84%) were epithelial but often well or moderately differentiated, 85% were of FIGO stage I or II at diagnosis (30% in the general population). There was a modest excess of endometrioid subtype, which is known to display MSI significantly more often than other subtypes and thus may reflect MMR-deficiency. Synchronous endometrial cancers were reported in 21% of the cases (Watson et al 2001).

5.2.7.2. Survival and surveillance

In sporadic ovarian cancer the 5-year survival rate is 64-89% in FIGO I classes and 13-49% in FIGO III-IV classes. Poor prognosis of ovarian cancer is thought to be due to the fact that the majority of women present with extraovarian, disseminated disease (Rosenthal et al 2006).

Assessed from the retrospective material, the survival rates in stage-corrected HNPCC-related ovarian cancer cases did not differ significantly from the general population. The overall benefit in the HNPCC setting was assumed to reflect earlier stages at diagnosis (Watson et al 2001).

Because of the high risk and poor prognosis, many recommend regular surveillance among HNPCC mutation carriers. There are numerous studies published on ovarian cancer surveillance in high risk *BRCA* mutation carrier groups but there is limited information regarding the risks and benefits of surveillance in populations with a moderate risk. There are no good modalities for early recognition of ovarian cancer. TVUS and CA 125 biomarker are the frequently used methods but they have presented with low positive predictive value in surveillance (Bosse et al 2006). According to a study among women with intermediate risk of ovarian cancer, the surveillance was associated with a substantial rate of abnormal screen results, endometrial sampling, and in women with abnormal ovarian screening findings, a decrease in QOL scores (Kauff et al 2005).

5.2.8. Gastric cancer in HNPCC

5.2.8.1. Incidence and clinical features

The second most common extracolonic malignancy among HNPCC mutation carriers is gastric cancer with a cumulative incidence of 13% by the age of 70 compared to 0.8% in the general population (Aarnio et al 1999). According to a study from Korea, the relative risk of gastric cancer in HNPCC families is 3.2-fold compared to a reference population in a gastric cancer endemic area. The risk is even higher (11.3-fold) in younger age groups (Park et al 2000). The difference in risk may be due to environmental and/or ethnic risk factors.

The HNPCC patients usually have an earlier onset of gastric cancer than the general population (Watson and Lynch 1993). Occurrence of gastric cancer has been suggested to be higher in HNPCC families with mutations of the *MSH2* gene, but a Finnish study of 45 gastric cancer cases showed no differences between families with different mutations (Aarnio et al 1997; Vasen et al 1996).

Aarnio et al. (1997) reported an over-representation (79%) of intestinal type of gastric cancer among putative mutation carriers differing from the usual pattern in Finland (51% intestinal type) (Lauren and Nevalainen 1993).

5.2.8.2. Etiopathogenesis of gastric cancer

An infectious agent, *Helicobacter pylori*, plays a dominant causative role in the etiology of gastric cancer. The bacterial infection is usually acquired in early childhood. The sequence of events from *Helicobacter pylori* infection, non-atrophic gastritis, chronic atrophic gastritis, intestinal metaplasia to dysplasia are considered to be the precursor cascade to the intestinal type of gastric carcinoma. Gland loss in atrophic gastritis is considered the key event in progression to neoplasia (Correa 1992). In the diffuse type of gastric cancer, no clear precursor lesion is known. Diffuse cancer is supposed to arise from the inflamed mucosa such as *Helicobacter pylori* gastritis without intestinal metaplasia. The histopathological status of gastric mucosa can be evaluated according the Sydney System, which grades the severity of inflammation, activity (the degree of polymorphic neutrophil infiltration) atrophy, and intestinal metaplasia on a scale from 0 to 3 from antral and corpus biopsies (Dixon et al 1996).

In a HNPCC setting the intermediate steps from the genetic predisposition to gastric cancer are still unknown. In a Finnish series of HNPCC –related gastric cancer cases the prevalence of *Helicobacter pylori* was only 20% (Aarnio et al 1997).

5.2.8.3. Survival and surveillance

According to a Finnish study the 5-year survival in HNPCC-related gastric cancer is at the same level as in sporadic forms, 15%. Among the cases where radical surgery was possible, the 5-year survival was 48% (Aarnio et al 1997). In Japan, which is a high incidence area, gastric cancer survival has improved with both mass screening (photofluorography as fist line screening) and open access screening (endoscopy)

leading to diagnosis at an earlier stage and thus improved survival. The 5-year survival of early gastric cancer cases has risen to 90% (Whiting et al 2002).
The most used method of surveillance is upper GI endoscopy and biopsies. Other possible strategies include *Helicobacter pylori* assessment and eradication and use of biomarkers such as pepsinogens, gastrin, and *Helicobacter pylori* antibodies. The biomarker surveillance focuses on finding atrophic gastritis as well as cancer (Cao et al 2007). In comparison, a study from England showed that annual surveillance of patients with atrophic gastritis or intestinal metaplasia resulted in diagnosing gastric cancer at an earlier stage and in improving survival (Whiting et al 2002).
There are no studies of gastric cancer surveillance among HNPCC families. Gastric cancer surveillance, with regular upper GI endoscopies, is recommended to families in which gastric cancer clusters (Vasen et al 2007). In a German series, however, only 26% of gastric cancer cases had a family history of gastric cancer, and 98% of the gastric cancers were diagnosed after age 35. They suggested regular upper GI endoscopy in all *MLH1* and *MSH2* mutation carriers starting at 35 (Goecke et al 2006).

5.2.9. Other cancers in HNPCC

Many other malignant neoplasms are also involved in the HNPCC tumor spectrum including carcinoma of urinary tract and kidneys, biliary tract, pancreas, small intestine, and skin. Brain tumors are also seen in excess (Aarnio et al 1995; Aarnio et al 1999; Mecklin and Järvinen 1991; Vasen et al 1990; Vasen et al 1996; Watson and Lynch 1993).

5.2.9.1. Carcinoma of urinary tract

Epithelial tumors of ureter and renal pelvis belong to the HNPCC tumor spectrum. Their cumulative incidence up to 70 years has been estimated to range between 4% (Finnish series) and 12% (Dutch and Norwegian series). In comparison, the cumulative incidence is 0.7 in the Finnish general population (Aarnio et al 1999; Vasen et al 2001). This difference probably reflects the fact that *MLH1* mutation is more prominent in the Finnish series and the risk for uro-epithelial cancers is higher among *MSH2* than *MLH1* mutation carriers (Vasen et al 2001). There is some evidence that the risk is even higher in *MSH6* mutation carriers (Wagner et al 2001).
The possible methods for uroepithelial cancer screening are regular urinanalysis for hematuria or biomarkers, urine cytology, and radiological imaging of upper urinary system. The sensitivity and specificity of urine cytology in screening for transitional cell carcinoma are poor (Keir and Womack 2002). Most of the biomarker studies published are of bladder cancer, which is rare in HNPCC. The markers seem to have higher sensitivity but lower specificity than cytology in detecting bladder cancer (Lokeshwar and Selzer 2006). Uroepithelial tumors may cause filling defects within the collecting system or renal pelvis and excretory urography may help localisation of the tumor. Ultrasound is insensitive for small (<1cm) renal masses and can lead to false-negative diagnosis (Jamis-Dow et al 1996). Based on its availability and accuracy CT is considered the best choice for surveillance imaging. MRI imaging is a suitable substitute without radiation exposure but still not yet widely recommended for screening purposes, because of quality- and cost-issues (Choyke et al 2003).
There are several other hereditary syndromes with a risk for renal cancer. Von Hippel-Lindau disease is the commonest of them and the cumulative risk for (often bilateral) renal carcinoma is almost 70% at the age of 60. In von Hippel-Lindau disease regular renal surveillance is recommended using annual ultrasonography and abdominal CT with 2- 3 year intervals (Singh et al 2001).
The risk of urinary tract cancer in HNPCC is low compared to von Hippel-Lindau disease. It is questionable whether screening for these tumors in all HNPCC families is justified considering the accuracy of the surveillance methods available and the possible adverse effects of them (radiation). Some families may present with a higher risk for uroepithelial cancer and in those cases a targeted surveillance protocol may be considered.
According to a recent study the surveillance for uroepithelial cancers with urine cytology is not effective in HNPCC. Only 0.05% of almost 2000 urine samples yielded an

asymptomatic neoplasia but the rate of false positive results was great (Myrhoj et al 2007).

5.2.9.2. Brain tumors

Brain tumors are seen in excess in HNPCC patients. The cumulative incidence of brain tumor was 3.35 at the age of 85 and 3.7 at 70 in Dutch and Finnish studies among HNPCC kindreds. Various histological types and grades occur, especially gliomas, glioblastomas or astrocytomas (Aarnio et al 1999; Lucci-Cordisco et al 2003; Vasen et al 1996).
Since its first description by Turcot et al. in 1959, the association of brain tumors and colorectal carcinomas and adenomas has been refined. The Turcot syndrome can be associated with two different types of germ-line genetic defects. Mutation of the *APC* gene, usually found in FAP, or mutation of a MMR gene (*MLH1*, *MSH2*, *PMS2*) in HNPCC (Hamilton et al 1995).
The risk of a brain tumor appears to be higher in *MSH2* than *MLH1* mutation carriers (Vasen et al 2001). Verified mutation in *PMS2* is a rather rare cause of HNPCC but several of the reported *PMS2* families have presented with central nervous system tumors (Lucci-Cordisco et al 2003).
Organized regular surveillance is not assumed to be beneficial. Heightened clinical suspicion and a more ready referral to neuroradiologic imaging in individuals with HNPCC are recommended, especially if there are several brain tumors in the family (Vasen et al 1996).

5.2.9.3. Carcinoma of pancreas and biliary tract

The prevalence of pancreatic cancer in the general population is 8-12/100 000. More than 90% of pancreatic cancers are ductal adenocarcinomas, which are known for their extremely poor prognosis, the median survival is only 4-6 months. Five-year survival figures of 5-15 % have been published after radical surgery, but according to a population-based analysis the overall 5-year survival was only 0.2% (Carpelan-Holmstrom et al 2005).
The excess risk of pancreatic cancer in HNPCC is poorly documented. Reliable incidence figures do not exist in literature because of only a few documented cases. Six cases of pancreatic cancer were detected out of 1424 high-risk persons from Nebraska showing no significant excess risk of pancreatic cancer when comparing the observed/expected numbers (Watson and Lynch 1993). Six cases of pancreatic cancer were also identified in a Finnish series of 293 putative gene carriers and when they were pooled together with biliary tract cancers (7) and cancers of the Vater papilla (3), a joint cumulative risk of 6.8 % (upto 70 years) and 17.5 %(upto 80 years) was achieved (Aarnio et al 1995). In HNPCC mutation carriers, the cumulative incidence (upto 70 years) for biliary tract cancer is 2% (compared to 0.2% in the Finnish general population) (Aarnio et al 1999).
The efficient screening methods for pancreatic cancer could be high-quality dynamic CT, endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound which all have similar diagnostic accuracy (Wong et al 2001). There are two published studies of cost-

effectiveness in screening for pancreatic cancer among patients with hereditary diseases with excess risk of pancreatic cancer. Theoretical calculations suggest that screening has the potential to be cost-effective in Hereditary pancreatic cancer kindreds (lifelong risk 50%) and among patients with Hereditary pancreatitis aged 50 years or older (53-fold increased risk) (Martin and Ulrich 2000). In another study pancreatic cancer screening in Peutz-Jeghers syndrome would cost over US$ 350 000 per life saved and the screening was recommended only on a research basis. Arguments against screening included unpleasantness of repeated testing, complications, cost, poor sensitivity and specificity, and current lack of evidence of effectiveness (Latchford et al 2006).

5.2.9.4. Carcinoma of small bowel

Small bowel carcinoma is rare in the general population. In a recent population based study from France the mean age at diagnosis was 64 years for men and 70 years for women. Overall annual incidence rate was 1.8 and 1.5 /100 000 for men and women and standardized incidence ratios were 1.2 and 0.8 /100 000 respectively. The tumor histology was heterogeneous, adenocarcinomas as the largest group (40%). The overall 10-year survival rate was 29.6% and adenocarcinoma and sarcoma had the worst prognosis. Stage at diagnosis was a major determinant of survival (Lepage et al 2006). Patients with hereditary CRC syndromes have a significantly increased risk for small bowel cancer. Watson and Lynch (1993) calculated that putative HNPCC mutation carriers have 25-fold risk of small bowel cancer. The estimates of lifetime risk range between 1-4 % in HNPCC and the risk appears to be higher in *MLH1* mutation carriers compared to *MSH2* (Aarnio et al 1995; Vasen et al 1996). According to an analysis from Germany the median age at diagnosis is 39 years in HNPCC mutation carriers. Of HNPCC-related small bowel carcinomas 50% were located in duodenum and 75% were adenocarcinomas. The overall 10-year survival rate was 87%. Almost all of the tumors showed MSI-H (Schulmann et al 2005).
Because of the rarity of small bowel carcinoma there are neither recommendations for nor data of efficacy of surveillance. Half of the small bowel cancers are located in the duodenum and could theoretically be detected in upper GI endoscopy, which may affect the estimates of necessity of regular gastroduodenoscopies in gastric cancer surveillance.

5.2.10. Role of prophylactic surgery in HNPCC

The issue of risk-reducing surgery in HNPCC is rather complex due to several reasons. The patients own mutation status, the underlying germline mutation, the phenotype presented in the kindred, efficacy of surveillance, risk of surgery, and finally the patients will all have an effect on decision making when pursuing a healthier and longer life.

5.2.10.1. Colorectal cancer

The 80% lifetime risk of CRC, 16% risk of metachronous cancer in 10 years after partial resection, and the 3% risk of rectal cancer after subtotal colectomy are figures that advocate considering risk-reducing colorectal surgery (Aarnio et al 1995; De Vos tot Nederveen Cappel et al 2002). Colorectal surveillance in HNPCC, although efficient, cannot guarantee CRC-free life and interval cancers still do occur although the survival is better with surveillance. On the other hand, because of the incomplete penetrance of the mutation, 20% of HNPCC mutation carriers will never develop CRC.
Another aspect to consider is the risk of cancer and mortality due to other tumors of the HNPCC spectrum since protection from CRC may not necessarily lead to prolonged life expectancy (Syngal et al 1998).
If a mutation carrier already has a CRC or a large adenoma, the option of expanding the partial resection to subtotal or total colectomy should be carefully discussed with the patient. The risk of metachronous CRC will be reduced by a larger resection and the further surveillance of the remaining rectum will be easier (Van Dalen et al 2003). There are no trials that would demonstrate improved survival for HNPCC patient after colectomy and ileorectal anastomosis. Some mathematical models, however, have been constructed. Syngal et al. (1998) used a decision analysis model in which they compared various management strategies for mutation carriers and found that prophylactic colectomy at 25 years of age led to the greatest life expectancy, with a gain of 2.1 years with proctocolectomy and 1.8 years with subtotal colectomy compared with surveillance. If surgery was performed at an older age or at identification of an adenomatous polyp or colorectal cancer, the benefits of colectomy decreased. Quality-adjusted life expectancy was better with subtotal colectomy than proctocolectomy, but best with endoscopic surveillance.
Prophylactic surgery without any pre-existing neoplastic lesion is indicated only in those patients for whom colonoscopic surveillance is not technically possible or who refuse to undergo surveillance (Guillem et al 2006).

5.2.10.2. Gynecological cancers

Female carriers of the MMR gene have an elevated risk of EC with a lifetime risk of 42-60% and an ovarian cancer risk of 9%. The risk of EC is highest in *MSH6* carriers (Aarnio et al 1995; Hendriks et al 2004). The survival rate of HNPCC-associated EC is favorable, which is not the case in HNPCC-related ovarian cancer (Vasen et al 1994). The current evidence of efficacy of screening is poor (Dove-Edwin et al 2002; Rijcken et al 2003).

A retrospective study observed benefit of prophylactic hysterectomy and bilateral oophorectomy in HNPCC mutation carriers compared to age-matched HNPCC controls from the same geographical area. Median age at operation was 41 years. None of the HNPCC patients subsequently had neither endometrial nor ovarian cancer compared to 33% and 5% among the controls. The risk for surgical complications was 1.6% (Schmeler et al 2006). Prophylactic surgery reduces, or abolishes, the risk of EC and ovarian cancer, but can be considered major surgery with morbidity and, very seldomly, even mortality (Mäkinen et al 2001). Hysterectomy causes premature menopause if done at a younger age, as may be the case in HNPCC. There is little data of the effect of surveillance or risk-reducing surgery of gynecological cancers in HNPCC and prospective trials are needed (Offit and Kauff 2006). Prophylactic surgery can be considered in mutation carriers of any MMR gene but especially of *MSH6* because of their higher risk for EC. The child bearing option is important in considering the timing of the operation. Prophylactic surgery may also be considered when laparotomy for some other reason is performed (Vasen et al 2007).

5.2.11. General aspects of surveillance

The ethics of a doctor-patient relationship are straightforward when a patient presents with symptoms and seeks help but the situation is different with screening and surveillance. By definition, the subject for screening is asymptomatic and further examinations are pursued by either the physician or health care system. The examinations and further management may be unpleasant, dangerous, may cause worry and influence their quality of life, and, in the case of a false positive finding, may be valueless. One issue to consider is the cost. Most societies have some restrictions on the amount of money that can be spent, and therefore, the cost-effectiveness of surveillance programs should be determined (Parsonnet and Axon 1996).
In the case of HNPCC the patients are at considerable risk of different cancers and the aim of organized surveillance is to detect the tumors in their premalignant state and thus prevent cancer, or at least detect the cancer, in such an early stage that full recovery can be achieved. The main goal is to improve survival.
The general prerequisites for successful screening or surveillance are: Screening protocols should be directed towards those with a relatively high incidence. The condition to be screened should have a natural history with high a death or disability rate. There should be an accepted treatment, which in early stage would reduce death or disability. The screening tool must be efficient, easily applied, and be acceptable to patients. And finally, the costs should be economically balanced (Holland et al 1991; Parsonnet and Axon 1996).
The fundamental requirement for screening is for the true positive to false positive (TP: FP) ratio to be ≥ 1.0, since the proportion of false positives must not exceed that of true positives by any large amount. If the TP:FP ratio is much less than 1.0, then any benefit derived from screening is lost due to excess morbidity, mortality or costs associated with examining and treating a large number of false positives (Wong et al 2001).

5.2.11.1. Compliance with surveillance in HNPCC

Maintaining compliance is essential for good results in any surveillance program. In studies on follow-up colonoscopy after polypectomy in the general population the compliance rate has been 80-85% (Colquhoun et al 2004; Winawer et al 1993). In a prospective HNPCC surveillance study from Finland, the reported compliance was 93% but in a more recent retrospective questionnaire-based study the compliance was significantly better, 98.8% among mutation carriers (Järvinen et al 2000; Pylvänäinen et al 2006). An essential factor affecting the compliance is the awareness of ones own situation and genetic testing is known to improve screening compliance (Wagner et al 2005).

Two recent studies addressed the issue of compliance and clarified the patients opinions of surveillance colonoscopies. Colonoscopies were experienced as painful in 36% or uncomfortable in 39% of the patients in a Finnish study and respectively, 57% of the healthy Dutch patients described them as unpleasant , 32% as fearful, 51% as painful, 16% as shameful, and 14% as hazardous (Pylvänäinen et al 2006; Wagner et al 2005). Many patients find the regular colonoscopies appalling and painful, which is a matter to consider when assessing the colonoscopy intervals. Lund et al. (2001) observed that failure to follow up was greatest in those having an annual examination compared with two- or five-yearly surveillance examinations. Sufficient use of sedatives or analgesics in colonoscopies might also improve compliance.

6. AIMS OF THE STUDY

1) To determine whether CRC detection in HNPCC patients by surveillance is prognostically advantageous because of early diagnosis. To compare the outcome of HNPCC patients whose CRC was found within a surveillance program with the outcomes of symptomatic CRC patients in the same families who had not been subjected to prophylactic screening.

2) To test the hypothesis that the MMR-gene mutations in HNPCC may accelerate the progression of gastritis and development of atrophy and dysplasia or intestinal metaplasia, and thus cause an excess of cancer at a younger age compared to mutation-negative family members. With this hypothesis we could evaluate the effect of gastric surveillance.

3) To describe the results of endometrial cancer screening in the Finnish HNPCC registry. To compare the outcome of HNPCC mutation carriers with EC diagnosed by surveillance with those patients whose EC was detected because of symptoms. To asses the benefit of intra-uterine biopsies in endometrial surveillance.

4) To compare CT-colonography with optic colonoscopy in surveillance setting in HNPCC mutation carriers. To asses the possible benefit of detecting incidental extra-colonic malignancies with this method.

7. PATIENTS AND METHODS

7.1. HNPCC REGISTRY

All the studies in this thesis concern data relating to patients in the Finnish HNPCC registry. The HNPCC registry was established in 1983 and 190 families are now in it. Almost all meet the Amsterdam II criteria and in 144 of them the underlying germline mutation has been detected. Family members from 111 families form the data basis of this thesis. A total of 579 family members participated in the studies of this thesis, 106 participated in two separate studies and 11 were involved in three studies. The mutation testing in Finland started in 1995-1996 and by now over 1814 family members have been tested and 864 of them have been identified as mutation carriers.

7.2. DATA COLLECTION

The patients clinical data and the pathology reports were collected from original patient records from several hospitals around Finland. The Finnish Cancer Registry verified the cancer cases. Survival data were checked at the Population Registration Center of Finland. In Study III, the pathology specimens for premalignant lesions were collected from different hospitals for reviewing. The patient demographics are gathered into Table 1 from all the studies.

Table 1
Patients

	families n	families mut + (%)	patients n	patients mut + (%)	*MLH1* (%)	*MSH2* (%)	*MSH6* (%)	median age years (range)	males (%)
Study 1 (all)	57	86							
Study 1 (study group)	26	88	33	85	97	3	0	46 (28-71)	64
Study 1 (control group)	50	86	104	53	96	4	0	46 (26-77)	58
Study 2 (all)	29	100							
Study 2 (study group)	28	100	73	100	100	0	0	49 (28-71)	36
Study 2 (control group)	13	100	32	0	0	0	0	51 (35-78)	47
Study 3	103	100	385	100	87	8	5		0
Study 4	38	100	78	100	83	12	5	41 (20–70)	49
Altogether	111		579						

7.2.1. Study I

All new CRC cases occurring in known HNPCC families in Finland from 1983 to the end of 1997 were the material for this study. The patients came from 57 different families, 49 families with a known mutation and 8 families which met the Amsterdam criteria. There were 137 CRC patients divided into two groups, dependent on how their CRC had been diagnosed. Thirty-five cases of CRC in 33 patients had been diagnosed via the surveillance program and 115 carcinomas had been found in 104 patients due to symptoms. The non-surveilled group mostly had not been aware of their susceptibility to cancer, nor had they taken part in any screening program. Half of the patients in the surveilled group underwent screening in Helsinki University Central Hospital, and the rest in 8 hospitals scattered all over Finland.

7.2.2. Study II

Seventy-three mutation-positive and their 32 mutation-negative HNPCC family members were willing to take part in this study. Of the control subjects, 18 were first degree relatives to one (or more) mutation-positive study subjects, 6 were second degree relatives, and the rest were other relatives.
A single upper gastrointestinal endoscopy was performed between autumn 1996 and spring 1998. This was conducted in three Finnish hospitals providing HNPCC surveillance endoscopies. Biopsies were taken from antral and corpus areas and were evaluated according to the Sydney System to grade the histopathological features. This grades the severity of inflammation, activity, atrophy, and intestinal metaplasia on a scale from 0 to 3 (Dixon et al 1996). The biopsies were examined by the hospitals own pathologists, and later in a double-blinded manner by a single pathologist specialized in this field.

7.2.3. Study III

This data consisted of all 385 Finnish female mutation carriers tested from 1996 through May 2005. They represented 103 families with 32 different mutations.
Surveillance guidelines for endometrial cancer in HNPCC in Finland recommend ultrasound and intra-uterine sampling biannually or with a three-year interval after age 30-35. Mutation testing has been available in Finland since 1996 and all those tested as mutation carriers have been advised to visit their local hospitals for regular cancer surveillance. Some members of the families fulfilling the Amsterdam criteria began the gynecological surveillance protocol before actual mutation testing.
Out of all the 385 women, the uterus had been removed previously, either for benign or malignant reasons, in 138 cases so there was no need for further surveillance. For other reasons, 72 women withdrew from surveillance. Thus, 175 actually entered the gynecological surveillance program (Figure 1).
Altogether, 503 surveillance visits were arranged and 759 surveillance years passed from the time of enrollment until hysterectomy, death, or the end of the study period (September 2005). The median follow-up time since the first surveillance visit was 3.7

years (range 0-13 years). Fifty-three women had attended only one surveillance visit by the end of this study.
The EC cases detected in the surveillance program were compared to those detected by symptoms. Altogether 83 symptomatic mutation positive EC patients from the same families had been diagnosed and treated between the years 1963 – 2004, their median age was 50 (range 27–85). The treatment of EC patients diagnosed by surveillance took place between 1996 –2004 and their median age was 52 (range 36-71). A single gynecological pathologist re-evaluated the pathology reports of EC cases and the specimens of the premalignant lesions in the surveillance group.

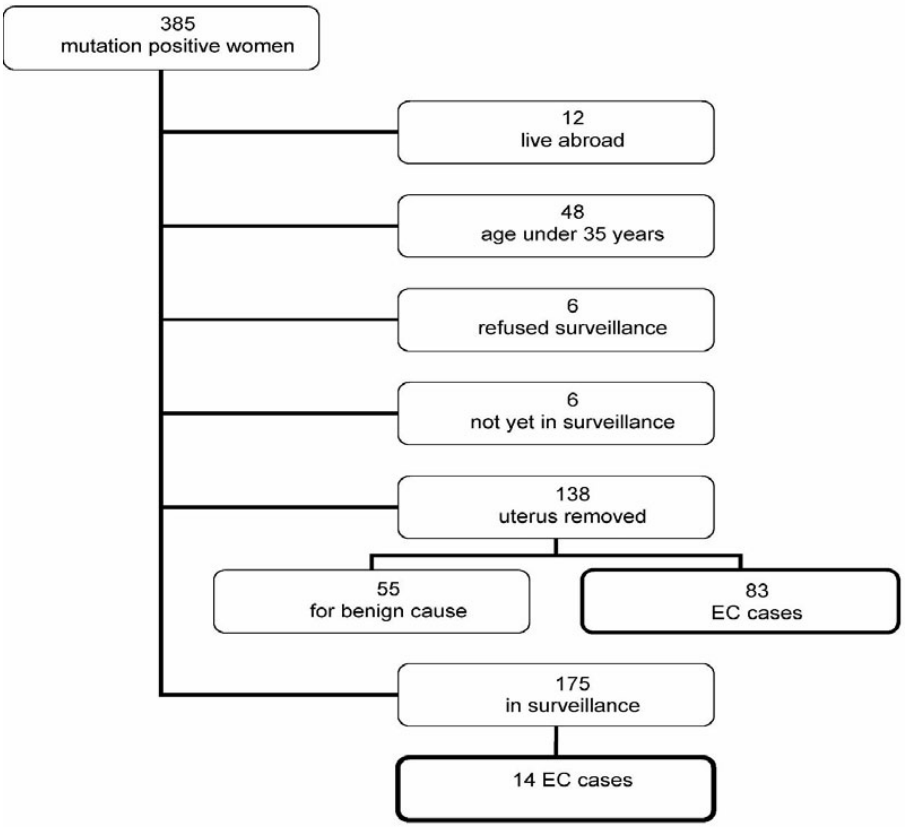

Figure 1 Flow chart of Finnish mutation-positive HNPCC women according to their gynaecologic surveillance and EC status

7.2.4. Study IV

We included all the eligible HNPCC mutation carriers on surveillance in Helsinki University Central Hospital at the time of study enrollment. The data consisted of 78 patients, all tested as HNPCC mutation carriers from 38 different families. The study examinations were conducted between November 2000 and June 2004.
Those subjects who had had previous right-sided colonic resection were excluded because, at the time of study enrollment, the existence of ileocaecal valve was

considered necessary for the technical success in colonic distention. None of the patients had had previous colon cancer. One patient was included with a prior rectal cancer, treated with abdominoperineal resection and a permanent colostomy. Seven of the patients had had gynecological cancer, two a cutaneous malignancy, and one a glioblastoma.

CT Colonography

The enrolled patients went through a CTC just prior to a pre-scheduled surveillance colonoscopy. Patients underwent standard colonic preparation with PhosphoralR (Ferring, Norway). No fecal tagging was used. A rectal tube was inserted for room air administration immediately prior to the CT performed with a 4-row multidetector scanner (Marconi Mx 8000, Philips). A scout scan was taken and intravenous scopolamine was routinely used. Twenty-seven patients (35%) received intravenous iodinated contrast material during CT. If the supine CT images contained fluid or were suboptimal in any way, the images were obtained in prone position as well (58 cases, 76%). Image interpretation was performed using commercially available software (Impax 4.5 Agfa) with a multiplanar 2D reformation. Two radiologists interpreted the images in a blinded manner, unaware of the results of the colonoscopy or of each other. The two observers had previous experience with CTC in >40 and >100 cases.

Colonoscopy

The routine colonoscopy served as a reference standard. Seventy-two examinations (92 %) were performed by one single colonoscopist, the rest by three other colorectal surgeons experienced with this technique. Colonoscopists were blinded to the results of CT colonography. A standard video colonoscope was inserted into the caecum and sequentially withdrawn segment by segment for the detection of polyps. The colonoscopist assessed the size and the location of each polyp visually. All polyps were removed and sent for a histological evaluation.

Analysis

A polyp found in the CT image was considered a match if it was located in the same or the immediately adjacent anatomic segment at colonoscopy and if its size was within the limits of +/- 50% of the endoscopic measurement. A polyp found with CTC but not with colonoscopy was regarded as a false-positive finding.

The colorectum was divided into six segments (caecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum) for quality measurement purposes. The segments were evaluated for colon distension and for overall quality for analysis. The results of the successive surveillance colonoscopies were also evaluated. Sixty-one subjects have already had their following colonoscopy and the cancer cases found in them were retrospectively compared with the earlier CTC findings.

7.3. STATISTICAL ANALYSIS

We performed statistical calculations in studies I, II and III with the SPSS statistical package (SPSS Inc., Chicago, Illinois).

7.3.1. Study I

We tested the difference between tumor stage distributions in the surveilled and non-surveilled groups using the chi-squared test. Survival curves and CRC-specific survival curves were constructed for each group using Kaplan-Meier analysis. The significance of differences between the two groups was tested using the log rank test.

7.3.2. Study II

Cross-tables (Fischer's exact test and McNemar in paired tests) were used with different patient settings to examine the reliability of the sampling, and to exclude a possible underlying bias. Binaric logistic regression analysis was used on the whole material (mutation status as the dependent variable) and age, sex, occurrence of *Helicobacter pylori*, atrophy, inflammation, activity, and intestinal metaplasia (the last five variables transformed into dichotomous form) as independent variables. Each variable was also calculated with stepwise, backwards elimination.

7.3.3. Study III

The difference between the FIGO-stage distribution of EC-cases in the two groups was tested using the chi-squared test. EC related survival curves were constructed using Kaplan-Meier analysis. The significance of differences between the two groups was tested using the log-rank test.

7.3.4. Study IV

The sensitivity and specificity of CTC was calculated in a per-patient manner. The results of the two radiologists were analyzed separately in two settings: discovering all the lesions or the large ones only. Sensitivity, specificity, positive and negative predictive values and their confidence intervals were calculated using CIA 2.1.1 software (Bryant TN, University of Southampton).

7.4. ETHICAL ASPECTS

For studies II and IV a written informed consent was obtained from every patient, as was the case with the patients whose pathology specimens were reviewed in study III. The study protocols were approved by the Ethics Committees of the Helsinki University Central Hospital, (study II, IV) and the Jyväskylä Central Hospital (II). In addition, all subjects of the HNPCC families have given written informed consent to mutation testing and separately, to surveillance in the case of mutation positive result.

8. RESULTS

8.1. STUDY I

Stage

The stage distribution of the 34 carcinomas in the surveilled group was significantly more favorable than that of the 114 tumors in the non-surveilled group ($p<0.001$). Data for one patient were missing in each group. There were five Dukes C cases (15%) in the surveillance group. One of them was a CRC diagnosed during the patients first colonoscopy. Two others had had very long intervals of 96 and 115 months since their previous examination. In the remaining two cases, the intervals since previous examination had only been 15 and 20 months. There were no CRC cases with distant metastasis. In the non-surveilled group, CRC was considered disseminated or inoperable (Dukes D) in 19 cases (17%). Seventeen CRC cases (16%) were of stage Dukes C (Table 2). Clinical details about the 21 interval cancer cases are presented in Table 3. Synchronous CRC occurred in two patients in the surveillance group and in 10 in the non-surveilled group. During this 15-year time period metachronous CRC was observed in 2 and 11 patients in the surveilled and non-surveilled groups, respectively.

Table 2

Stage distribution

	Surveilled group	Non-surveilled group
CRC cases	35	115
Dukes A	17 (50 %)	20 (17%)
Dukes B	12 (35%)	58 (50%)
Dukes C	5 (15%)	17 (16%)
Dukes D	-	19 (17%)
Stage not known	1	1

Chi-squared test 18.05, $p < 0.001$ between the two groups

Table 3

Clinical details about 21 cancer cases detected in 20 patients enrolled in surveillance

(13 CRC cases discovered in first examination excluded)

No	Age (years)	Prev. "clean" examination	Interval (months)	Diagnostic examination	Stage	Site of cancer
1	58	ES.	7	ES.	A	rectum
2	58	B.E.	7	ES.	B	ascending c.
3	48	ES.	12	ES.	A	rectum
4	48	ES.	13	ES.	A	rectum
5	62	ES.	15	ES.	C	transverse c.
6	43	ES. + B.E.	20	ES.	C	ascending c.
7	43	ES.	26	ES.	A	ascending c.
8	38	ES.	32	ES.	B	ascending c.
9	31	ES.	36	ES.	A	sigmoid c.
10	41	ES.	36	ES.	B	sigmoid c.
11	48	ES.	36	ES.	A+A	cecum and rectum
12	35	ES.	37	B.E.	B	cecum
13	55	ES. + B.E.	38	ES.	B	cecum
14	46	B.E. + SS.	39	ES.	B	ascending c.
15	33	B.E.	59	B.E.	B+A	ascending and sigmoid c.
16	41	ES.	60	B.E.	B	transverse c.
17	71	ES.	61	ES.	A	rectum
18	58	ES.	68	ES.	A	transverse c.
19	38	ES.	96	ES.	C	rectum
20	57	B.E.	115	ES.	C	transverse c.
21	64	B.E. + SS.	122	ES.	B+A	transverse c. and rectum.

ES.= full endoscopy, B.E = barium enema, SS.=sigmoidoscopy

Survival

Five out of 33 patients (15%) in the surveilled group had died compared to 40 out of 104 patients (38%) in the non-surveilled group. CRC resulted in two deaths in the surveillance group and 33 deaths in the non-surveilled group. In the two cases of death because of CRC in the surveilled group the tumor stages were A and B. The first was a 71 year-old man with a malignant polyp in the distal rectum who refused laparotomy. He was treated by local excision and the actual lymph node status was therefore not known. He died 16 months later, with multiple metastases. The second case was a 55-year-old woman with previous endometrial cancer. She died with multiple metastases one year after surgery for caecal cancer originally staged as Dukes B. In the non-surveilled group, the tumor

stage distribution of fatal cases at the time of diagnosis was stage B in 12, stage C in 5, and stage D in 15 cases. Stage information was missing in one case.

The cumulative CRC-specific survival was 93% in the surveilled group, significantly higher than the 68% in the non-surveilled group ($p<0.02$) 10 years after surgery.(Fig 2). The overall survival was also initially better in the surveilled group than in the non-surveilled group, but the difference was not significant (Fig 3).

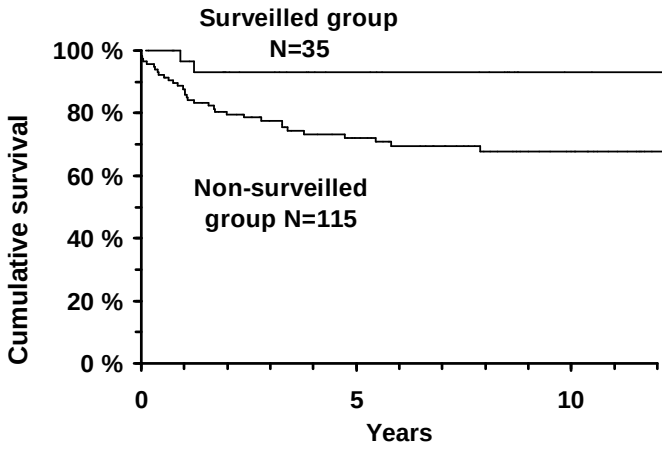

Figure 2

CRC-specific survival

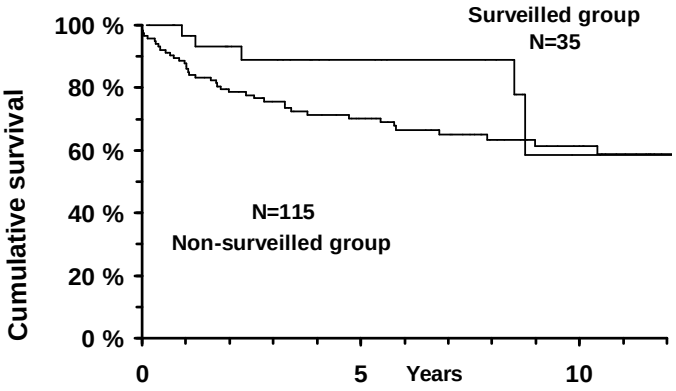

Figure 3

Overall survival

8.2. STUDY II

Tumors and polyps

In 105 upper gastrointestinal endoscopies only one neoplastic lesion was found, duodenal cancer of 2cm in diameter in a 69 year-old, mutation-positive man, whose gastric biopsies were normal. Gastric polyps were found in 6 mutation carriers (8.2%) and in 2 (6.3%) controls, 4 (5.5%) and 1 (3.1%) of which were cystic hamartomatous polyps, the rest were inflammatory polyps.

The patient with duodenal cancer was operated on with local resection and died 2.5 years later of metastatic disease. None of the others developed gastric cancer during a follow-up period of 3 to 4 years according to the Finnish Cancer Registry.

Data check and gastric biopsy findings

For reliability reasons the whole data set was checked by calculating the difference between mutation carriers and mutation negative family members with cross-tables in a four-step fashion using either the whole material (Fischer's exact test), including only the 12 families with their own controls (Fischer's exact test), by pairing the whole material randomly (McNemar test), or lastly by pairing the true siblings (McNemar test). These results were very similar and showed no statistical difference, thus excluding a sampling bias, and enabling us to continue with binaric logistic regression analysis on the whole material.

No statistical difference arose in gastric biopsy findings between these two groups regarding age, sex, occurrence of *Helicobacter pylori* (OR=1.8, CI=0.1–29.8, p=0.7), inflammation (OR=1.2, CI=0.2–8.9, p=0.9), atrophy (OR=2.0, CI=0.3–12.5, p=0.4), activity (OR=0.4, CI=0.0–6.5, p=0.5) or intestinal metaplasia (OR=0.8, CI=0.2–3.9, p=0.8) analysed with binaric logistic regression analysis in fixed model and dichotomous variables. Stepwise, backwards elimination was also used but it did not affect the results.

8.3. STUDY III

Endometrial cancer

One hundred and seventy-five women attended EC surveillance program. Among them 14 cases (8%) of EC (all adenocarcinoma) were discovered. In 11 of these cases the diagnosis of EC was based on the screening examination, 2 others were interval cancers based on symptoms manifesting 3 and 31 months after the surveillance visit. One occult EC was discovered after prophylactic hysterectomy, which was performed (with no prior endometrial sampling) during simultaneous colectomy for CRC. Of the 11 EC cases found by true screening, 9 were detected or suspected by endometrial samples, 8 as EC, and 1 as a complex hyperplasia (CH). Altogether 4 had a suspicious finding in TVUS and 2 had a suspicious PAPA smear. An increased tumor marker value (CA 125) was observed in only one case (Table 4).

Table 4

Endometrial carcinoma cases in surveillance group

				Screening method at time of diagnosis					**Carcinomas**		
Patient	Mutation	Surveilled time (months)	Age at operation (years)	Endometrium in TVUS	IU sample	PAPA smear	s-CA 12-5 (kU/l)	s-TATI (nmol/l)	Histopathology	Grade	Stage FIGO
1	*MLH1*,ex12	37	53	normal	EC	normal	*na*	*na*	E	1	3A
2	*MLH1*,ex16	37	51	normal	EC	*na*	*na*	*na*	E	1	1B
3	*MLH1*,ex16	58	54	normal	EC	*na*	*na*	*na*	E	1	1A
4	*MSH2*,ex12	35	52	thick	EC	*na*	normal	normal	E	1	1A
5	*MLH1*,ex16	79	54	normal	EC	*na*	*na*	*na*	E+C		1A
6	*MLH1*,ex16	100	66	thick	atrophy	susp npl	normal	normal	E	2	1B
7	*MLH1*,ex14	19	47	thick	EC	*na*	*na*	*na*	E	2	1A
8	*MSH2*,ex9	52	71	thick	*na*	*na*	*na*	*na*	E	1	1B
9	*MLH1*,ex16	29	50	*na*	EC	susp npl	179	*na*	E+sq	2	2B
10	*MLH1*,ex16	50	42	normal	EC	*na*	*na*	*na*	E	2	1A
11	*MSH6*,ex4	11	53	normal	CH	*na*	*na*	*na*	E	2	1B
12	*MLH1*,ex6	0	36	*na*	*na*	*na*	*na*	*na*	E	1	1B
13[1]	*MLH1*,ex16	31	43						E	1	1A
14 [1,2]	*MLH1*,ex16	31	42						1) E+C	3	1A
									2) E	1	1B

[1]=interval cancer
[2]=two different foci of EC

na=data not available
EC=endometrial carcinoma
CH=complex hyperplasia
susp npl=suspicion of neoplasia

E=endometrioid
C=clear cell
Sq=with squamous differentation

The distribution of tumor stage tended to be more favorable in the group attending surveillance than in the 83 mutation-positive EC patients who had not attended surveillance, but the difference was insignificant (Pearson chi-square 0.67) (Table 5). None of the surveilled EC-patients died of cancer in the mean follow-up time of 5 years (range 1-9 years) compared to six deaths due to EC in the non-surveilled group within the median follow up of 13.7 years (range 0-42). The difference in the survival curves (100% versus 92% at 10 years), however, was not significant (p=0.4, log rank).
Six patients in the surveillance group exhibited elevated CA125 values half of whom were transient, one had EC. Six patients had elevated TATI values, one of whom was discovered to have ovarian cancer on the basis of pain symptoms 5 months later, others showed no sign of neoplasia.

Table 5

Figo stage distribution of EC cases diagnosed by surveillance or with symptoms

	EC cases among surveilled	Symptomatic EC cases
IA	6	27
IB	6	32
IC	0	8
IIA	-	1
IIB	1	1
IIIA	1	4
IIIB	-	-
IIIC	-	7
IVA	-	-
IVB	-	2
unknown	-	1
	= 14	= 83

Endometrial hyperplasia

The surveillance of 175 women with IU-samples also detected endometrial hyperplasia in 14 (8.0%) women (Table 6), 11 of whom underwent a prophylactic hysterectomy and the remaining three, showed normal findings at 6, 16, and 45 months. The total frequency of suspicious IU-samples in 503 surveillance visits was 25 (5.0%), and with EC alone, 11 (2.2%). One additional case of occult CH was discovered in a prophylactic hysterectomy 6 months after a normal surveillance visit, with TVUS only.

Table 6

Premalignant findings in surveillance group

Patient	Mutation	Age at time of diagnosis (years)	TVUS finding	IU-sample	Histopathology of removed uterus
1	*MLH1*,ex16	47	normal	CH, EP	CAH
2	*MLH1*,ex16	48	normal	CAH, EP	no hyperplasia
3	*MLH1*,ex17	47	normal	CAH	CAH
4	*MLH1*,ex16	57	normal	SH	SH
5	*MLH1*,ex17	51	thick	CH	CH
6	*MLH1*,ex17	49	polyp	CH, EP	CH
7	*MLH1*,ex16	37	polyp	CH, EP	SAH
8	*MLH1*,ex13	56	normal	CH, EP	CH
9	*MLH1*,ex17	43	normal	CH	
10	*MLH1*,ex4	47	thick	CH	
11	*MLH1*,ex16	41	thick	CAH, SH	CAH
12	*MLH1*,ex16	49	normal	SH	
13	*MLH1*,ex17	44	normal	CH	no hyperplasia
14	*MLH1*,ex16	56	polyp	CAH	CAH

SH = simple hyperplasia
SAH = simple atypical hyperplasia
EP = endometrial polyp
CH = complex hyperplasia
CAH = complex atypical hyperplasia

Ovarian cancer

Of the 175 women surveilled, ovarian cancer of endometrioid type was detected in 4 (2.3%), none of whom were diagnosed at surveillance, two of these were diagnosed by symptoms 2 and 5 months after normal surveillance visits at the ages of 41 and 45 years (stages III and I). The other had exhibited elevated S-TATI values repeatedly for several years, but all other examinations had given normal results. Two other cases were diagnosed incidentally during an operation for EC or complex hyperplasia at the ages of 42 and 50 years (each of stage I). All are still alive and well today.

Hysterectomies

Fifty-nine (34%) women from the surveillance group underwent a hysterectomy in the follow-up period. Eight patients underwent a hysterectomy because of adenocarcinoma in the IU-sample within surveillance, two patients because of symptomatic interval EC, five patients on suspicion of ovarian mass or tumor, and one woman because of massive bleeding. The remaining 43 patients underwent a prophylactic hysterectomy because of a premalignant lesion found in surveillance, laparotomy for some other reason, or solely for mere prophylaxis.

8.4. STUDY IV

Technical quality

Seventy-eight HNPCC family members were enrolled and 76 (97%) of them underwent complete optical colonoscopy. In two cases the colonoscopy was not completed to the cecum. The bowel cleansing was considered suboptimal in 10 patients (13%).
Of the CTC examinations, 65% presented with optimal distension of the colorectum, 20% with one segment suboptimally distended, and 15% with more than one segment collapsed. We regarded 19% (88/468) of the segments studied as technically suboptimal considering the overall effect of distension or remnants of fluid or feces in both acquisitions. None was excluded.

Colonoscopy findings

We found 37 lesions in 28 subjects giving the prevalence of at least one lesion of any kind, 35.9%. The number of subjects with at least one adenoma or carcinoma was 15. Only 6 lesions above the 6mm size threshold occurred and 5 of them were ≥10mm in diameter with prevalences of 7.7% and 6.4%. Two of these were CRC located on the right side of the colon, each were stage Dukes A. Three large adenomas (≥10mm) in the rectosigmoid area and one medium sized adenoma (6-9mm) in the anal canal were identified. Thirty-one diminutive polyps were scattered around the colorectum, 11 were adenomas, and the rest hyperplastic polyps (Table 7).

Diagnostic accuracy of CTC

The sensitivity for detecting a subject with at least one polyp of any size was 25% and 29% for the readers A and B. Specificity for any lesion was 82% and 76%. For the detection of lesions >10mm the sensitivity was 60% and 100% for readers A and B, and each of them achieved a specificity of 96% for the larger lesions (Table 8). Each reader identified the two cancer cases.
We could not see significant differences between patients receiving or not receiving intravenous contrast medium. No complications occurred after CTC but one perforation occurred after polypectomy of a rectal polyp.
Ten patients (13%) presented with extracolonic findings in CTC, 5 with a liver cyst and one with a hemangioma in the liver. Additionally we found one ovarian cyst, one renal cyst, one appendicolith, and one renal stone. Three subjects presented with lymphadenopathy, one of whom had cancer in the ascending colon, staged later as Dukes A. Others showed no other significant findings.

Table 7

Colonoscopy findings

Site	Histology	Lesion size			
		2-5mm	6-9mm	>10mm	
caecum	adenomatous	3		1*	
	hyperplastic	3			
ascending colon	adenomatous	2		1*	
	hyperplastic	1			
transverse colon	adenomatous				
	hyperplastic	3			
descending colon	adenomatous				
	hyperplastic	2			
sigmoid colon	adenomatous	1		1	
	hyperplastic	3			
rectum	adenomatous	5		2	
	hyperplastic	8			
anal canal	adenomatous		1		
	hyperplastic				
TOTAL	adenomatous	11	1	3+2*	=17
	hyperplastic	20	0	0	=20
		= 31	=1	=5	=37

* = cancer

The results of the successive surveillance colonoscopies

Sixty-one out of 78 patients (78.2%) have already gone through their next surveillance colonoscopy (median interval three years) and three cases of CRC were found. One was a sessile Dukes A carcinoma, the second a carcinoma in a pedunculated adenoma (Dukes A), and the third was Dukes B (T3N0) carcinoma. The sessile Dukes A cancer showed up in a surveillance colonoscopy 26 months after the study examinations. The tumor was 25mm in diameter and located in the transverse colon. One of the radiologists had seen a flat 5mm polyp in the same area, on the study CTC, which was considered a false-positive at the time of analysis. No sign of any tumor appeared in a retrospective analysis of the study CTC images of the other two patients with CRC discovered at 36 months and 45 months post-study.

Table 8
Diagnostic performance of ct colonography (per-patient)

All lesions

	Radiologist 1	Radiologist 2
sensitivity	0,25	0,29
CI(95%)	0,13-0,43	0,15-0,47
specificity	0,82	0,76
CI(95%)	0,69-0,90	0,63-0,86
positive predictive value	0,44	0,40
CI(95%)	0,23-0,67	0,22-0,61
negative predictive value	0,66	0,66
CI(95%)	0,54-0,77	0,53-0,76

> 10mm lesions

	Radiologist 1	Radiologist 2
sensitivity	0,6	1
CI(95%)	0,23-0,88	0,57-1,00
specificity	0,96	0,96
CI(95%)	0,89-0,99	0,89-0,99
positive predictive value	0,50	0,63
CI(95%)	0,19-0,81	0,31-0,86
negative predictive value	0,97	1,00
CI(95%)	0,90-0,99	0,95-1,00

9. DISCUSSION

Different aspects of surveillance in HNPCC were studied in this thesis. The patient material is representative, it consists of 579 family members from 111 Finnish HNPCC families almost all harboring a known MMR-gene mutation. In studies I and III the patient inclusion was derived from the national data and every eligible patient from Finland was included. In studies II and IV the patients consented for radiological and endoscopic examinations and were collected from narrower geographical areas because the study was organized only in few hospitals.

When examining the efficacy of Finnish CRC surveillance in HNPCC patients we found colonoscopic surveillance beneficial. Even if CRC cannot be fully prevented by surveillance and polypectomies, tumors detected are usually of early stage and expectation for survival is significantly better than if there had been no surveillance. We also explored the performance of a new technique, CT-colonography as an alternative surveillance method and found its performance insufficient for polyp detection in this population in which every polyp, no matter the size, should be detected and removed. We searched for assumed differences in the gastric histopathology in MMR mutation carriers and their mutation negative siblings but could not observe any differences, neither premalignant lesions nor cancers. Endometrial cancer surveillance in HNPCC seems effective because of the use of endometrial biopsies in addition to TVUS. Cancers in the surveilled patients tended to be of an earlier stage than in symptomatic cases, and no deaths from EC have yet been observed while under surveillance. Additionally, we detected several premalignant hyperplastic lesions.

9.1. SURVEILLANCE OF THE COLON IN HNPCC (I)

The study of surveillance-detected CRC cases in HNPCC families (Study I) is the largest reported and it covered all the CRC cases found in Finnish HNPCC families during 1983-1997. Despite the retrospective nature of the analysis, some important conclusions can be drawn. First, consistent with earlier observations in smaller series the tumors detected by surveillance were at significantly more favorable stages than those in the non-surveilled group (Järvinen et al 1995; Vasen et al 1995). This advantage in terms of stage was reflected in a significantly higher CRC-specific survival in the surveilled group. Overall survival was also initially better in surveilled patients but the difference was not significant, probably because of the small sample size and short follow-up time in relation to most cases.

The surveilled and non-surveilled groups were formed retrospectively according to the way the cancer was diagnosed, in asymptomatic phase within a surveillance program or because of symptoms. Thus, they are not similar even though patients came from the same 57 HNPCC families, had been diagnosed during the same 15-year period, and showed no intergroup difference in sex or age distribution. Our analysis concentrated only on CRC patients and ignored all the healthy surveilled patients in which

polypectomies had been done, so we took no account of the benefit achieved by removal of adenomas in a number of other at-risk members. On the other hand, many potential biases are involved, such as selection bias, lead time bias, and length bias all tending to falsely favor surveillance (Holland et al 1991). The benefit of surveillance should ideally be evaluated in a large randomized trial involving mutation carriers only. To our knowledge only one good-quality prospective clinical trial, also published in 2000, exists, in which all the family members were offered surveillance but some chose not to attend and some were not traceable and thus formed the control group. In a 15-year follow up the CRC rate was reduced by 62% with surveillance, all the CRC cases in the surveilled group were local and there was no CRC related mortality. The difference in overall mortality was significant (Järvinen et al 2000).

Another important observation was that not all cases of CRC can be prevented by surveillance. There were 14 cancers diagnosed at the very first surveillance visit and an additional 21 interval cancers, occurring after previous “clean” colon examination. A few patients may even have advanced tumors with lymph-node metastases, as happened in five of the patients (15%). These may be regarded as failures of surveillance, given that the prevention of CRC via polypectomy, or at least early detection, are the goals. In three cases, the cause of failure was obvious, surveillance had either been started too late because HNPCC susceptibility in the family had only recently been discovered or the interval between examinations had been too long because of problems with patient compliance or the surveillance organization. In two cases, however, stage C tumors were detected 15 and 20 months after previously negative colonoscopy. Additionally, in three other cases early CRC (stages A, A and B) was discovered within less than a year of previous, "clean" colonoscopy/barium enema.

The observation of (advanced) interval cancers raised a question as to the reasons. Other factors than poor patient compliance or defective surveillance organization must also be considered. It has been suggested that the surveillance interval of three years is too long, in mutation carriers at least, partly because the progression from adenoma to CRC seems to be accelerated in HNPCC (Järvinen et al 1995; Jass 1995; Lynch et al 1995; Vasen et al 1995). On the other hand, the five cases of CRC within 1 to 2 years after a negative colonoscopy that we noted raise the possibility of missed adenoma or early cancer. The overall polyp miss rate in colonoscopy is 15-24% but gets smaller with increasing size of the polyp. Polyps ≥1 cm are rarely missed (Hixson et al 1990; Postic et al 2002; Rex et al 1997b). The miss rate as high as 4% of right-sided colon cancer, however, is documented (Bressler et al 2004). Even frequent colonoscopy may result in some lesions being missed. Frequent colonoscopy increases inconvenience to and anxiety in persons at risk, and gives rise to the danger of iatrogenic complications. The appropriate interval between examinations probably needs to be studied in a randomized trial. Because there is slight uncertainty even despite optimal colonoscopic surveillance, prophylactic colectomy should be seen as one possible option, at least in cases in which colonoscopy is technically difficult or when poor compliance can be expected because of other reasons (Guillem et al 2006).

In general the prognosis in CRC is more favorable in members of the HNPCC families than when it occurs sporadically (Aarnio et al 1998; Sankila et al 1996; Watson et al 1998). It was therefore surprising that the two fatalities from CRC in the surveilled group

in our study were both originally classified as localized (stage A and B). Misclassification may be the explanation for these cases.
Our study shows that colonoscopic surveillance is beneficial in at-risk members of the HNPCC families. Even if CRC cannot be prevented by polypectomies, tumors found during surveillance are usually detected so early that expectation of survival is excellent, and significantly better than if there had been no surveillance.

9.2. UTILITY OF CT-COLONOGRAPHY IN HNPCC (IV)

We examined the utility of CTC for the first time as a surveillance tool in a group of asymptomatic MMR gene mutation carriers. Our material differs from earlier studies on CTC in several aspects. The subjects were all asymptomatic and significantly younger, but on regular surveillance because of their hereditary inclination. The prevalence of abnormalities was 35.9% for any pathological lesion in colonoscopy, among the lowest prevalences yet published (Halligan et al 2005). Furthermore, the great majority of lesions were diminutive polyps. Only 7.7% and 6.4% were above the size thresholds of ≥ 6mm and ≥10 mm, thus the size of the lesions distribution was very different from the previous studies (Sosna et al 2003). To best simulate the average, every day routine we did not exclude technically suboptimal examinations.

The per-patient sensitivity to detect at least one lesion, regardless of size, was 25% or 29% in our series, which reflects the great proportion of diminutive polyps and the low overall prevalence of lesions. The analyzing software was not dedicated and we did not use fecal tagging, which may have effected the detection of polyps. Another reason for the poor detection rate may have been the effect of collimation, which is associated with improved detection of diminutive polyps (Macari et al 2002; Taylor et al 2002). Sensitivity was of course improved if we included large lesions only and the interobserver variation (60% and 100%) is explained by chance and the small number of large lesions. The overall sensitivity was at the same level as in some previous studies but worse compared with some others. Our results are presented in table 9 along with the five largest studies so far published. CRC is usually well detected by CTC, as was the case in our study, the two cancer cases were diagnosed in the CTC by each radiologist.
The specificity of our study was as low as 76% and 82% when all lesions were included, which is at the average level especially when the distribution in lesion sizes is noticed. When we included only the large lesions the specificity rose up to 96%.
Fifty patients presented without any findings in colonoscopy, but only 38 and 41 of these were interpreted as normal in CTC by the two radiologists marking the amount of false positive findings.
We did not detect extra-colonic malignancies with CTC in our series. An earlier detection of asymptomatic tumors, e.g. in the small bowel, the kidneys, uroepithelial or gynecological organs, or in the bile ducts might benefit HNPCC patients.
Some caution should be taken with our results. The number of the subjects included was limited and the prevalence of adenomas was low, eventually leading to a low rate of significant findings. Colonoscopy served as a gold standard, which by itself has

limitations in polyp detection rate (Hixson et al 1990; Rex et al 1997b). It was impossible to evaluate if some of the lesions found in the CTC and assessed as false-positive were actually true-positive, but missed by the colonoscopist. Three subjects presented with cancer in surveillance colonoscopies at 26, 36, and 45 months afterwards. One of these had a 5mm polyp in the same area on the CTC, regarded as a false-positive but may have actually been a true–positive finding.

Ionizing radiation in CTC, especially if used regularly poses a problem. Our aim was to lower the radiation dose without losing the sensitivity to detect polyps, but the low-dose protocols are not yet widely used (Rex et al 2006). The resultant effective doses caused by a dual-positioned CTC examination (with a low-dose multi-row detector) is 5.0 mSv for men and 7.8 mSv for women, similar to the dose reported for the DCBE (Macari et al 2002). The surveillance colonoscopies are recommended to be repeated every 1 to 3 years in HNPCC, leading to unbearable radiation doses if they were replaced entirely by CTC examinations.

The size of an adenoma is the most important issue in determining the risk of malignancy, but still 4% of the diminutive adenomas have unfavourable histology (Church 2004). The performance of CTC for diminutive (≤ 5mm) polyps is quite poor, based on the literature, and ongoing debate of their clinical importance in screening the general population continues as most of them are not adenomas (Macari et al 2004). No such thing as a “clinically irrelevant polyp” exists in HNPCC surveillance, however. On the contrary, the aim is to remove all polyps regardless of size. The CTC performance in detecting small polyps in our study was unsatisfactory for this particular patient population. Additionally, the rate of false positive findings was worryingly high since, in normal routine, they would lead to colonoscopy and repeated unnecessary examinations.

Two recent studies assessing the compliance to colonoscopy surveillance among HNPCC mutation carriers observed rather negative experiences, 36-51% of the patients found colonoscopies painful and 39-57% as uncomfortable (Pylvanainen et al 2006; Wagner et al 2005). CTC may be more acceptable for the subjects and especially so if a fecal tagging system evolves and makes it possible to drop the cathartic bowel preparation in the future (Gluecker et al 2003; Iannaccone et al 2004). Even then the use of CTC should be limited to occasional examinations to minimize radiation. On the other hand, if a virtual colonoscopy using MRI technique develops, and achieves excellent performance, it could become a promising option in screening and surveillance settings in the future.

Our main result was that colonoscopy was confirmed to presently be the best modality for CRC surveillance in HNPCC. Endoscopy is superior to radiological examinations in enabling polypectomy during the same session and even small polyp detection was clearly better. We do not recommend CTC as a regular surveillance method in HNPCC, but it is a good alternative if the colonoscopy can not be completed or the subject has other problems preventing regular colonoscopy. Additionally, CTC has the potential benefit of discovering significant extracolonic findings, possibly other malignancies.

Table 9

CT-colonography studies

						Per-patient sensitivity (%)					Per-patient specificity (%)				
Author	**year**	**no of patients**	**prevalence of abnormality**	**diminutive lesions (%)**	**patients with symptoms**	**1-5mm**	**6-9mm**	**overall**	**≥6mm**	**≥10mm**	**1-5mm**	**6-9mm**	**overall**	**≥6mm**	**≥10mm**
Yee	2001	300	61	57	100 %	82	93	90	*nr*	100	*nr*	*nr*	72	*nr*	99
Rockey	2005	614	*nr*	81	88 %	45	55	*nr*	51	59	*nr*	*nr*	*nr*	89	96
Cotton	2004	600	51	79	87 %	13	30	*nr*	39	55	90	93	*nr*	90,5	96
Johnson	2003	703	*nr*	*nr*	0 %	*nr*	65	*nr*	*nr*	64	*nr*	86	*nr*	*nr*	95
Pickhardt	2003	1233	50	74	0 %	*nr*	*nr*	*nr*	89	94	*nr*	*nr*	*nr*	80	96
Renkonen-S	2007	78	36	84	0 %	*nr*	*nr*	25 and 29	*nr*	60 and 100	*nr*	*nr*	82 and 76	*nr*	96 each

nr = not reported

9.3. SURVEILLANCE OF GASTRIC CANCER IN HNPCC (II)

Gastric cancer, usually of the intestinal type, belongs to HNPCC tumor spectrum and is the second most common extracolonic cancer (Aarnio et al 1997). The standardised incidence ratio in Finnish mutation carriers (mainly with a mutation in the *MLH1* gene) compared with the general population is 6.9 (Aarnio et al 1999). The intermediate steps from predisposition to gastric cancer in HNPCC are still unknown, but the proposed sequence of events starting from *Helicobacter pylori* infection, proceeding to superficial gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and finally intestinal cancer may present in this context as well (Correa 1992). The *Helicobacter pylori* infection which works as the trigger in this sequence is, however, rare among Finnish HNPCC patients (Aarnio et al 1997). The survival in gastric cancer is quite poor unless it is detected at an early stage. Some evidence shows that a targeted surveillance of patients with atrophic gastritis or intestinal metaplasia resulted in diagnosing gastric cancer in earlier stage and in improved survival (Whiting et al 2002).
We searched for some difference in gastric histopathology between mutation carriers and their mutation-negative family members that would clarify the steps of gastric carcinogenesis in HNPCC or give tools for prevention and early detection. The control group was gathered from the mutation-negative siblings to minimize environmental effect on the cancer risk. There were, however, no differences between these two groups. In addition, there were no cases of premalignant dysplasia or early cancer in either group warranting further surveillance or prophylactic treatment to prevent cancer. Furthermore, in the one case of duodenal adenocarcinoma detected, the tumor was advanced and the patient died of metastatic disease within 3 years following local surgery. Thus, no benefit was demonstrable in gastroscopic surveillance for *MLH1*-positive HNPCC subjects.

Our study has some limitations. Our series was of relatively limited size and it included one endoscopy session only. A longer follow-up with repeated examinations might have yielded more findings. Uneven sampling of patients from different families may have had an effect on the outcome. Additionally, there remains a possibility that certain mutation types or mutations in other MMR-genes than *MLH1* may have a different gastric cancer risk, as has been debated (Aarnio et al 1997; Vasen et al 1996). The patients in this study and the Finnish HNPCC material differ from some other countries due to an excess of mutations in *MLH1* gene. It remains to be shown whether the endoscopic findings are different in geographic areas with endemic high risk for gastric cancer, or in families with mutations in the *MSH2* or *MSH6* genes. *Helicobacter pylori* infection may imply a significant risk for HNPCC mutation carriers. The prevalence of *Helicobacter pylori* was about 26% in mutation-positive individuals in this study and eradication was undertaken in all cases detected.

Gastric cancer surveillance with regular upper GI endoscopies is, at the moment, recommended only to families in which gastric cancer clusters but there are other opinions as well suggesting regular endoscopies to every mutation carrier regardless of the family history (Goecke et al 2006; Vasen et al 2007). Systematic, regular gastric cancer

surveillance in HNPCC can be justified only if earlier diagnosis and better prognosis can be achieved with them. Further randomized studies are needed to asses the need for surveillance.

9.4. SURVEILLANCE FOR ENDOMETRIAL CANCER IN HNPCC (III)

Recommendations for EC surveillance in HNPCC date back over twenty years. Although the risk of EC is high it has rather good prognosis and it usually presents early with bleeding as the typical symptom. Only two studies are published of endometrial cancer surveillance with rather modest results, both using TVUS as the primary surveillance method (Dove-Edwin et al 2002; Rijcken et al 2003). Our present surveillance program of 175 mutation-positive women at risk for EC yielded 11 asymptomatic cancer cases and 14 others with a premalignant lesion in 503 surveillance visits. The frequency of significant findings was 14.3% of persons surveilled, or 5.0% of screening visits within the median surveillance period of 3.7 years. The stage distribution of the EC tumors in the group under surveillance tended to be more favorable than that of the mutation-positive symptomatic EC patients of the same families who had no surveillance. Furthermore, none of the surveilled EC patients died of EC compared to six in the non-surveilled group. No statistical significant difference, however, aroused in stage distribution or in survival, between the two groups. Thus, the most important advantage of the surveillance may lie in the frequent detection of premalignant lesions, which enables prophylactic hysterectomy in due time and potentially reduces EC incidence.

TVUS proved relatively insensitive in our series supporting the two previous reports on surveillance for EC using TVUS. Adenocarcinoma was diagnosed by IU-sample in several patients with a normal endometrium in TVUS. Dove-Edwin et al. found no asymptomatic EC in a group of 269 women belonging to HNPCC families, neither did Rijcken et al. in a series of 41 mutation-positive women (Dove-Edwin et al 2002; Rijcken et al 2003). This latter study, however, revealed suspicious TVUS findings in 17 of the 179 examinations, which led to endometrial sampling, and the discovery of premalignant CAH in three cases. The combination of endometrial biopsy and TVUS in our series resulted in more than twice as many malignant or premalignant findings as in the series of Rijcken et al. in terms of patient years at risk. This suggests that endometrial biopsies increase the efficacy of endometrial screening. The comparison of these 3 studies on EC surveillance is presented in Table 10.

Interpretation of the clinical significance of hyperplasias may be difficult. Endometrial hyperplasia precedes the development of adenocarcinoma but it may disappear spontaneously as well. Hyperplasia may be simple or complex and all types carry the malignant potential to some degree. The occurrence of atypia represents the greatest risk for progression. With CAH, the risk is 25–40% (Kurman et al 1985; Montgomery et al 2004; Terakawa et al 1997). There were altogether 14 cases with endometrial hyperplasia in the present IU samples, 4 had CAH, 8 had CH, and 2 had SH. Eleven of the 14 patients underwent a prophylactic hysterectomy and no EC was found in the removed endometrium. Hysterectomy for premalignant lesions in these 11 cases very likely prevented the development of cancer, at least for some.

It is hard to prove benefit in survival with EC surveillance because the prognosis can be very good even in symptomatic cases. In a study of 50 Dutch women with EC from HNPCC families the five-year survival rate was 88%, and in this present series of 83 symptomatic non-surveilled women, it was 92%. This baseline figure reflecting the survival without surveillance is assumed to be overoptimistic because it is based solely on mutation-positive members of the families, and thus several historical cases who had died of EC before genetic testing was possible were excluded causing selection bias. No deaths occurred among the surveilled persons in our series. It must also be noted that the size of the group in surveillance is still too small and the follow-up period too short for final evaluation of prognostic advantage.

The Finnish HNPCC registry does not recommend the use of tumor markers in screening for endometrial or ovarian cancer because the determination for screening purposes may cause more harm and unnecessary worry than benefit, and it is discouraged as a surveillance modality (Kauff et al 2005). TVUS and CA 125 biomarker have also presented with low positive predictive value in surveillance for ovarian cancer, which is in accordance with our results (Bosse et al 2006). Markers were, however, obtained in 144 screening visits (28%), mostly CA 125 and TATI. Only one EC patient exhibited an elevated CA 125 level while five other patients exhibited such elevated levels for no clear reason. Such was also the case with TATI in five other cases. One woman repeatedly showed an elevated S-TATI value with no other pathological findings. Eventually she was diagnosed with symptomatic ovarian cancer. Prophylactic ovarectomy may remain the only effective option to reduce mortality due to ovarian cancer, but it may be hard to accept by persons at risk.

The proportion of prophylactic hysterectomies (25%) in the surveillance group was high in our series. Fourteen women of the altogether 43 cases with prophylactic hysterectomy showed a premalignant lesion in the prior surveillance samples, which led to the operation. Prophylactic surgery certainly reduces, or abolishes, the risk of EC (Schmeler et al 2006) , but nevertheless also causes morbidity and, very seldom, even mortality (Mäkinen et al 2001). Therefore, surveillance using endometrial sampling may present as a less invasive but still effective alternative to prophylactic surgery in the prevention or early detection of EC in mutation carriers of MMR-genes.

In conclusion, EC surveillance in HNPCC seems more effective with the use of endometrial biopsies in addition to TVUS alone. Tumors in the surveilled patients tended to be of an earlier stage than in symptomatic cases, and no deaths from EC have yet been observed while under surveillance. A longer follow-up period and a larger group of surveilled patients are, however, necessary to demonstrate a definite survival benefit. There is potential gain in the possibility to detect premalignant lesions and treat cancer in its early stages without adjuvant external radiotherapy.

Table 10

The outcome of surveillance for endometrial cancer in Lynch syndrome families

	UK/ The Netherlands Dove-Edwin et al 2002	The Netherlands Rijken et al 2003	Finland Renkonen-Sinisalo et al 2006
No of subjects	269	41	175
Mutation carriers (%)	not mentioned	27 %	100 %
Patient years at surveillance	826	197	759
Protocol	TVUS	TVUS	TVUS & aspiration biopsy
Number of TVUS scans	522	179	476
Frequency of TVUS	1-2 years	1 year	2-3 years
Number of aspiration biopsies	-	17	382
Premalignant lesions	-	all not mentioned	14
- CAH		3	5
- other hyperplasias		not mentioned	9
Screen-detected cancer	0	0	12*
Interval cancers	2	1	2
Figo I	2	1	12
Figo II	-	-	1
Figo III	-	-	1

* one occult cancer detected at surgery included

9.5. FUTURE ASPECTS

Many aspects of surveillance are still unsolved and questions arising from these series remain to be answered and require further studies.

One of the most important issues yet to be determined is the most appropriate time interval for surveillance colonoscopies considering the efficacy, compliance, and cost-benefit issues. To be reliable the study should be conducted as a clinical trial and preferably in a randomized manner. There is still room for further development of surveillance modalities, for example MRI-colonography holds intriguing possibilities if it proves to be efficient in polyp detection. With EC surveillance we still lack the final proof of its effect on survival. So, prospective trials to asses the benefits of both surveillance and prophylactic surgery are needed. The gastric cancer in HNPCC poses questions because of the recent claims that it demands organized surveillance. At the moment, there are no studies of gastric surveillance programs, not even observational. A randomized controlled trial should be undertaken.

10. CONCLUSIONS

1) The colorectal cancers detected by surveillance were at significantly more favorable stages than those in the non-surveilled group. This advantage in terms of stage was reflected in a significantly higher CRC-specific survival in the surveilled group. Overall survival was also initially better in surveilled patients but the difference was not significant. Our study shows that colonoscopic surveillance is beneficial in at-risk members of the HNPCC families.

2) None of the assumed differences in the prevalence of gastritis, atrophy, or metaplasia in the gastric biopsies could be detected in mutation carriers and their mutation-negative siblings. In addition, there were no cases of premalignant dysplasia or early cancer in either group. One case of advanced duodenal cancer was detected. Thus, no benefit was achieved with this single gastroscopy surveillance for *MLH1*-positive HNPCC subjects.

3) The current EC surveillance program using TVUS and intra-uterine biopsy every 2-3 years proved to increase efficacy. Several asymptomatic endometrial cancers with favorable stages were detected in addition to several premalignant hyperplastic lesions. The outcome of the asymptomatic cancer cases tended to be more favorable and none of them have died of EC compared to six in the control group, although the difference was not significant. EC surveillance seems justified among the mutation positive patients.

4) CT-colonography was less sensitive than colonoscopy in detecting polyps of all sizes and the rate of false positive findings was too high for routine surveillance in a HNPCC setting. We did not find any extra-colonic malignancies in this series. Colonoscopy was confirmed to be best surveillance modality for the time being and CTC should be only used as an alternative choice.

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