REVIEW

Is there any role for prevention strategies for colorectal cancer other than population-based screening?

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Abstract

Colorectal carcinoma is a growing medical problem. Prevention represents the most effective approach for reducing the incidence and mortality. Population-based screening with subsequent colonoscopic polypectomy is the most common strategy. There are, however, other approaches increasing the portfolio of available measures. These include the special care of groups with an increased risk for CRC based on family or medical history and various chemopreventive strategies. Family history is a simple method to identify a person with increased risk of CRC. There are two groups of familial CRC: monogenetic hereditary syndromes such as FAP and HNPCC and hereditary predispositions with sporadic CRC. Recent advances in genetic tests and tailored surveillance strategies are able to decrease the morbidity and mortality in these groups. Therefore a wider recognition of family history as risk indicator of CRC should be encouraged. Chemoprevention is a very promising concept for both primary and secondary prevention of CRC. Although definite evidence is difficult to provide a number of studies suggest a role for nutritional interventions and/or chemoprevention with plant phytosterols, fiber, selenium, calcium, probiotics or COX2 inhibitors as putative chemopreventive strategies. ***(Tab. 4, Ref. 70.)***

Key words: colorectal carcinoma, FAP, HNPCC, familial CRC, prevention, chemoprevention.

Colorectal carcinoma (CRC) represents one of the most difficult health problems in most industrialized countries because of a rapidly increasing incidence and a slowly improving prognosis of this disease. Worldwide, there are more than 876 000 new cases diagnosed per year and 525 000 patients die. In Slovakia, CRC represents the most frequent malignancy with more than 2600 new cases and an incidence of 58.7 cases per 100 000 inhabitants.

CRC is burdened with a high morbidity and mortality and thus enormous effort has been invested into the development of effective prevention strategies. Population based screening and colonoscopic polypectomy of adenomatous colorectal polyps are the mainstream of colorectal prevention and have been very successful in numerous clinical studies (1, 2). However there are several difficulties with population-based programs. First the awareness of CRC and subsequent willingness to participate in screening among the population is rather low. The sensitivity of the program is variable depending on the screening method used. There is a cost/benefit ratio issue and a high recurrence of adenomatous polyps requires repeated colonoscopic controls (3).

Thus, a reasonable question is how to improve the prevention of colorectal carcinoma and what other strategies might enlarge the portfolio of preventive measures for CRC.

In this article we would like to consider and underscore two important approaches for prevention of CRC i.e. identification and management of high-risk groups and chemopreventive strategies.

High-risk group identification and managment

One of strategies for prevention of colorectal carcinoma is the identification and subsequent special evaluation and surveillance of people at risk. Persons at risk for CRC can be easily

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Tab. 1. Overview of genetic predispositions to CRC.

Category	Prevalence (per 100 000 inhabitants)	Clinical characteristics	Genes involved	Relative risk of CRC	Life-time risk of CRC (%)	Risk of other than CRC malignancies
HEREDITARY SYNDROMES						
Polyposis syndromes						
FAP (18)	5-10	Intestinal adenomatous polyposis, common polyps in upper GIT, extraintestinal manifestations such as CHRPE, desmoids and fibromas	APC	30	90-100	Duodenum, thyroid, hepatoblastoma
AFAP (64)	<1	As FAP but onset in older age, fewer polyps and often right sided.	APC	30	90-100	As FAP
Gardner's sy. (65)	<1	FAP and fibromas, epidermoid cysts, osteomas and dental anomalies	APC	30	90-100	As FAP
Turcot's sy. (66)	<1	FAP and meduloblastoma	APC	30	90-100	As FAP
	<1	HNPCC and glioblastoma or astrocytoma	As HNPCC	25	70-90	As HNPCC
Non-polyposis syndromes						
HNPCC (67)	25-50	CRC in young age in many family members, often right sided not precede by polyposis	hMSH2,3 ,6; hMLH1, PMS1,2	25	70-90	Endometrium, small intestine, stomach, ureter and renal pelvis
Muir-Torre sy. (68)	<1	HNPCC and sebaceous adenomas	hMSH2	25	70-90	As HNPCC
Hamartomatosis syndromes						
Peutz-Jeghers sy. (33)	<1	Gastric and intestinal hamartomatosis polyposis, characteristic perioral and bucal hyperpigmentations	LKB1	10-25	60-90	Stomach, small intestine, pancreas
Juvenile polyposis (69)	1	Intestinal hamartomatosis with characteristic histology	SMAD4	3-20	10-70	Stomach, duodenum, pancreas
PTEN sy. (35)	<1	Intestinal hamartomatosis and various malformations such as macrocephaly, trichilemomas, multinodular goiter etc	PTEN	n.a	Not increased	Breast, thyroid gland, endometrium
HEREDITARY PREDISPOSITIONS (10)						
FDR with CRC	10 000**	Sporadic CRC with familial accumulation outside the hereditary syndromes, low penetrance genes considered.	No single genetic mutation known yet.	2-3	6-12	Not reported
FDR with CRC diagnosed before 45	100***			3-6	10-30	
Two FDR with CRC	100***			3-6	8-30	
SDR with CRC	n.a.			1-2	5-7	
FDR with CRA	n.a.			1,5-2,5	5-12	
GENERAL POPULATION		CRC is malignancy with the highest incidence nowadays		1	3-5	

CRC- colorectal carcinoma FAP familial adenomatous polyposis AFAP attenuated familial adenomatous polyposis, HNPCC-human non-polyposis colorectal cancer FDR – first degree relative, SDC second degree relatives, n.a.- not available

* former Bannayan-Ruvalcaba-Riley or Cowden syndrome

** approximately 10% of population reports one FDR with CRC in his family history

*** approximately 1% of population reports two FDR or young relative with CRC in his family history

identified by their medical and family history. An increased CRC risk is known in longstanding colonic inflammatory bowel disease (IBD) of either ulcerative or Crohn's type and depends on the extent and duration of the disease. Patients who underwent curative therapy of CRC and those after polypectomy for colorectal adenoma also carry an increased risk for metachronous CRC. The risk in these groups is well-known and screening for CRC is an integral part of the follow-up of these patients. Risk and recommendations for prevention of CRC in longstanding colonic IBD and in post-colectomy and post-polypectomy patients have been extensively reviewed elsewhere (1,4,5). The aim of this article is to discuss the largest group of persons at risk for CRC i.e. those with family member(s) affected with CRC.

The first observations about the higher accumulation of CRC in certain families started to appear at the turn of 19th and 20th centuries and soon the first familial syndromes such as familial adenomatous polyposis (FAP) (6) or Peutz-Jeghers syndrome were described (7). The first genealogical studies reporting an autosomal dominant type of CRC inheritance without polyposis were published in 1966 by Henry Lynch (8). In the 80s it was already obvious that in families with the Lynch syndrome there was also a higher incidence of other malignancies and during the 90s the concept of human non-polyposis colorectal cancer syndrome was defined. Since the first large clinical study published in 1958 (9), substantial evidence has been published about the familial accumulation of CRC occurrence beyond the frames of hereditary syndromes (10). Rapidly expanding knowledge in the area of CRC heredity has made it a rapidly evolving field.

Hereditary predispositions and syndromes of CRC

Nowadays, it is already generally accepted that heredity is an important etiological factor in the development of CRC. A short overview of our present knowledge of the hereditary syndromes and predispositions to CRC is summarized in table 1. Two distinct categories of inherited predispositions to CRC i.e. hereditary monogenic syndromes and hereditary predispositions are distinguished. The first category comprises the monogenic syndromes consistent with the principles of Mendelian inheritance. Hereditary syndromes of CRC can be classified into three groups: adenomatous polyposes, hamartomatous polyposes and non-polyposis hereditary syndromes. The hereditary syndromes represent approximately 6 % of all CRC cases. The second category includes genetic predispositions to sporadic CRC that are assumed to be of polygenic type. Polygenic predispositions are thought to be responsible for another 15–20 % of CRC cases and the familial occurrence of CRC observed in numerous epidemiological studies that excluded hereditary syndromes is ascribed to them.

Enormous effort has been made to explain the links between the hereditary syndromes and colorectal cancer. A great deal of what we know today about colorectal cancer etiology is due to the research of hereditary syndromes and FAP in particular. The basic principle of hereditary syndromes is the following: an affected person inherits one allele of a gene involved in tumor suppressor pathways that is mutated and the second copy that is of wild type. During the life the patient acquires mutation of the wild type allele, a so-called second hit event resulting in the loss of function of the particular protein in the affected cell (loss of heterozygosis). The affected cell proliferates quickly giving rise to adenomatous polyps. Further growth of adenoma and transformation to carcinoma follows after subsequent mutations in other genes regulating cellular growth such as K-ras, DCC, p53, MCC etc (11).

Germline mutations of APC gene have been observed in the majority of FAP patients and 95 % of these mutations lead to the formation of a truncated APC protein with abnormal function. The key part of the APC gene is probably its central region containing a binding domain for ß-catenin (13). The interaction of ß-catenin, APC protein and other factors results in degradation of ß-catenin. Most mutated APC proteins lack a central binding region for ß-catenin and accumulation of ß-catenin occurs. This activates transcription of several target oncogenes, adhesion proteins and metalloproteinases (14).

The genetic basis of hereditary non-polyposis colorectal cancer (HNPCC) lies in germline mutations of mismatch repair genes (MMR). During the DNA replication errors in base pairing occur and result in alteration of the genetic code. The cells therefore have a complex system of proteins that recognize the change, cleave the misreplicated sequence and replace it with a correct one. This DNA repair system is called a mismatch repair system. After a second hit event a dysfunction of the MMR system develops and the mutational activity in affected cells increases approximately thousand fold. Mutations in 8 human MMR genes resulting in HNPCC have been described so far (15). For an updated list see the ICG HNPCC web page *http://www.nfdht.nl*. Most of mutations associated with HNPCC are located in genes hMSH2 (50 %) and hMLH1 (30 %). Persons with a defective MMR system are susceptible to a change in size of so-called microsatellite areas; a fact that is used in genetic testing for HNPCC. Microsatellites are DNA regions with simple repetitive sequences, especially of An and CAn type in a length of up to 40 base pairs. These sequences are often located in the non-coding areas of the genome and their function remains unclear. It is possible to compare several microsatellite areas in the tumor and in the healthy tissue of a CRC patient. If variability in length is present the condition is referred to as microsatellite instability. Several studies have indicated an association between microsatellite instability and mutation of genes important for cell division and growth such as the gene for TGF-ß receptor type II and the BAX gene, which is an important promoter of apoptosis.

Little is known about the precise genetic mechanisms of hereditary predispositions to CRC outside the frame work of hereditary syndromes although there is a substantially larger group of persons at risk. Probably, low penetrance genes and their various polymorphisms may be involved. The I1307K APC polymorphism observed in about 6 % of Ashkenazi Jews might serve as an example (16). Carriers of mutant allele have about doubled life time risk of CRC compared to the non carriers. Although the exact nature of this relationship is not clear and it is not known

whether the mutant genotype has a decreased functionality of APC protein, carriers would be predisposed to a slightly pro-proliferative behavior of their cells, thus favoring pathological clonal expansion. This model could explain the low-penetrance character of this and many other still to be discovered genetic polymorphisms responsible for polygenic predispositions for CRC.

Clinical picture, diagnosis and treatment of hereditary syndromes and predispositions

In the case of hereditary predispositions to sporadic „familial" CRC, the diagnosis and management of the disease does not differ from common clinical practice except for the genetic testing and screening recommendations discussed below. However the clinical picture, diagnosis and therapy of colorectal carcinoma in a person with inherited risk are principally different in the case of hereditary syndromes such as FAP and HNPCC.

FAP is characterized by presence of hundreds to thousands adenomatous polyps in the colon and rectum that unless treated result in inevitable colorectal cancer at a young age. The average age at diagnosis of CRC is 39 years. About 20–30 % of cases is caused by a de-novo mutation and thus lack a positive family history. The polyps mostly appear first with the onset of puberty at an average age of 16 years. Polyposis is usually asymptomatic. Symptoms such as rectal bleeding, change in stool habits, or abdominal pain are usually manifestations of severe polyposis and/or colorectal carcinoma. In case of unknown FAP or de-novo mutations, these symptoms prompt the patient to visit the doctor. Symptoms occur most of the time after the age of 20 years. A distinct variant of FAP is the attenuated FAP (AFAP). It is characterized by fewer polyps (less then 100), later onset of polyposis (approximately 20 years later than in FAP i.e. in 3rd and 4th decade) as well as a later onset of CRC (average age 56) and a more proximal colonic location, mostly in the right colon (17). Patients with FAP can develop several extracolonic manifestations besides colonic polyposis Special lifelong surveillance is required in the case of adenomatous duodenal polyps, desmoids and polyps in the ileal pouch. For an excellent review of the extraintestinal manifestations of FAP and their treatment see King et al. (18)

Sigmoidoscopy is a method of choice for the screening and diagnosis of FAP. The indications for sigmoidoscopy screening are known FAP in the family, ophthalmoscopic findings of congenital hypertrophy of retinal pigment epithelium (CHRPE), multiple fibromas and osteomas as well as a strongly positive family history of CRC (18). If sigmoidoscopy reveals polyposis the colonoscopy should ensue for evaluation of the extent and severity of polyposis. In case of known or suspected AFAP, colonoscopy is the method of choice because very often the polyps are located in the right colon only (17).

Almost every patient with FAP sooner or later develops a colorectal carcinoma. Prophylactic colectomy is thus indicated in all patients with FAP at the age of 17–20 years, possibly even in younger age if the severe carpet type of the polyposis is present. Timing of surgery should be discussed in detail with the patient. The currently recommended technique is total proctocolectomy with ileal pouch-anal anastomosis (IPAA) and mucosectomy up to the dentate line (19). IPAA can be performed also laparoscopically. The quality of life of patients with IPAA is relatively satisfactory, and the main complications is stenoses in the anastomosis region (20). In contrast to IPAA for ulcerative colitis (UC), pouchitis is rare in patients with FAP, which is probably related to the etiology of UC. Colectomy with ileo-rectal anastomosis (IRA) can be an alternative in cases of attenuated phenotype of FAP with no polyps in the rectum.

The burden of colectomy in FAP has prompted research for potential chemopreventive agents that might modify the present treatment strategies (21). The studies with non steroid anti-inflammatory drugs sulindac and celecoxib for prevention of progression of rectal and duodenal polyposis, respectively, have attracted a lot of attention (22,23). Initial promising results, however, have not been confirmed in longer term studies and the place of these agents in the therapy of FAP remains obscure.

HNPCC is the most common form of inherited predisposition for colorectal carcinoma and is responsible for about 5 % (1–10 %) of CRC cases. HNPCC is either a syndrome diagnosed by family history or by means of genetic testing. Before the genetic basis of HNPCC was revealed, the International collaborative group on HNPCC (ICG HNPCC) published clinical criteria named after the meeting place of this group as the Amsterdam criteria (26). The aim of these criteria was to identify high-risk families for HNPCC. The criteria are known also as the 3–2–1 criteria because the diagnosis of Lynch syndrome requires at least 3 affected family members with CRC and that one of them be a first-degree relative of the other two, in at least 2 generations and with at least 1 younger than 50 years. FAP has to be excluded and carcinomas have to be documented and verified. A modified version suitable for smaller families has been described as well. In 1999, the same group revised and extended the criteria (27) now called the Amsterdam II. criteria. These criteria recognize (besides CRC) a so-called HNPCC-associated tumors, i.e. endometrial carcinoma, ileal carcinoma, carcinoma of the renal pelvis and ureter, and require the presence of 3 CRC or HNPCC-associated tumors in a family. Other criteria have remained the same. Meanwhile some experts have sought to broaden the definition of HNPCC-associated tumors to include stomach, ovaries, brain, hepato-biliary tract and sebaceous skin tumors (28). Colorectal carcinoma in HNPCC differs from sporadic CRC in several aspects as shown in Table 2.

Females with HNPCC have a 40–60 % lifetime risk of endometrial carcinoma development (29). However, the prognosis of endometrial carcinoma is relatively favorable, and the overall 5 year survival is about 90% and even in an advanced stages is more than 70 % (30). Persons with HNPCC also have a higher risk of carcinoma of the stomach (lifetime risk of 13 %), ovaries (4 %) and small bowel, urinary tract, kidneys and brain (all less than 4 %) (29).

The therapy of already present malignancy of colon, endometrium and other eventual locations does not principally dif-

Tab. 2. Comparison of HNPCC and sporadic CRC.

	HNPCC	Sporadic CRC
Accumulation of CRC in families	Half of affected family members	Multiple occurence in some families
Etiology	Autosomal dominantly inherited monogenic disease	Multifactorial
Life-time risk of CRC	70-90%	3-5%
Average age of CRC diagnosis (years)	44	64
Right sided location of CRC	70%	10%
Duration of development of sequence normal mucosa – adenoma- carcinoma (years)	1-5	10-20
5 year survival (%)	70%	50%
Synchronous and metachronous CRC	25%	6%
Extraintestinal malignancies	20-50%	low

fer from the therapy of sporadic malignancies. However, based on a known 25 % occurrence of synchronous and metachronous carcinoma in retained colon some authors recommend a more extensive resection i.e. colectomy with ileo-rectal anastomosis. It has been shown that the prognosis of HNPCC colorectal carcinoma is more favorable compared to sporadic forms (31). At moment there are insufficient data to recommend prophylactic colectomy, hysterectomy and oophorectomy as a procedure reducing the risk of particular malignancies (32).

Hamartomatoses are very rare syndromes and for in depth information we refer to reviews (33-35).

Although the discoveries of the genetic background of FAP or HNPCC attracted big attention, the majority of patients with a positive family history of CRC do not meet the definition criteria of genetic syndromes. Familial accumulation of CRC is observed also outside the families with genetic syndromes. Positive family history of one first-degree relative (FDR) i.e. parent, child or sibling reports about 10 % of population. One percent of population reports two or more close relatives with CRC. Large meta-analysis of the risk of CRC in relatives of patients with CRC and colorectal adenoma (CRA) was published recently. All studies included in the meta-analysis have shown an increased risk, including those that excluded monogenic hereditary syndromes. The relative risk of CRC for an index person with a positive family history has been determined as follows: one FDR with CRC RR=2.42 (95 % CI=2.0–2.53), one FDR with colon cancer RR=2.42 (95 % CI=2.20–2.65), one FDR with rectal cancer RR=1.89 (95 % CI=1.62–2.21), parent with CRC RR=2.26 (95 % CI=1.87–2.72), sibling with CRC RR=2.57 (95 % CI=2.19–3.02), more than one FDR with CRC RR=4.25 (95 % CI=3.01–6.08), one FDR with CRC diagnosed before the age of 45 years RR=3.87 (95 % CI=2.40–6.22) and one FDR with colorectal adenoma RR=1.99 (95 % CI=1.55–2.55) (10).

The risk of CRC if family history is positive in second-degree relatives (SDR) i.e. grandparents, aunts and uncles or third-degree relatives i.e. grand-grand parents and cousins is not precisely known. The data from Utah population database indicate relative risk of 1.3–1.5 in second and higher degree relatives (36). Using current mathematical methods it is not possible to calculate the risk in cases of combined positive family history in FDR and SDR.

Genetic counseling and testing for CRC

Family history if properly taken usually gives clues for suspicion of hereditary CRC. Several large studies have shown that the positive family history data on CRC are reliable and have sufficient sensitivity, specificity and positive predictive value for factual reality (37). If the family history is positive for CRC, further data on the number of affected relatives, the age of onset and characteristics of the disease should be obtained.

Genetic testing can be used if diagnosis of hereditary syndrome is suspected. Testing for FAP and the two most common HNPCC genes is available in most developed countries. Results from experiences in Czech republic (38) and Slovakia (39,40) have been recently published. The indication for genetic testing of FAP is colonic polyposis detected on colonoscopy or known FAP in the family. Because of the lack of distinctive clinical symptoms other than age and family history the indication for HNPCC testing is less obvious. The situation is even more complicated by a combination of various genetic tests for HNPCC diagnosis. However most experts recommend starting the testing for microsatellite instability and then if positive proceeding to germline testing. The Bethesda guidelines are widely recognized as the criteria for MSI testing (41). Compared to the Amsterdam criteria these are less strict, but more sensitive and sufficiently specific (42). Genetic testing for MSI should be performed in persons with two synchronous or metachronous HNPCC-associated carcinomas, in persons younger than 45 years with HNPCC-associated carcinoma, in persons younger than 40 years with colorectal adenoma and in persons with CRC whose relatives have had HNPCC-associated carcinoma diagnosed under age 45.

Before starting genetic testing genetic counseling is recommended. The patient should be informed in detail about the risks of particular malignancies, their therapy and prevention strategies. It is also important to know the family's experiences with the disease, awareness about the risk and expectations from participation in a prevention program. The patient should be also informed about the possibilities and limitations of genetic tests

Tab. 3. Postcolectomy surveillance of FAP patients according to King et al.

General examination
Annual evaluation of symptoms Annual examination of thyroid gland Annual liver palpation and ultrasound
Upper endoscopy
Extended upper endoscopy and side-view examination of papilla every 1 to 5 years after colonic polyposis are first detected or probably when patient is no older than 25 years If adenomas are small (<5mm) and papilla appears grossly normal, increase frequency to every 2 years If duodenal adenomas are >5mm and there is adenomatous treansforamtion of papilla (<1 cm, low-grade dysplasia), remove polyps >5mm and repeat upper endoscopy with papilla biopsies annually If large or highly dysplastic duodenal or papillary adenomas are found, endoscopic ultrasonography and aggressive endoscopic or surgical resection must be considered
Pouchoscopy, ileoscopy or proctoscopy
If total proctocolectomy, examine ileal pouch (Kock or J-pouch) or terminal ileum (Brooke ileostomy) every 3-5 years If adenomas found, remove all >5 mm and increase subsequent surveillance frequency If total colectomy, examine rectum every 6 months and remove all adenomas >5 mm
Abdominal CT
Abdominal CT to look for desmoids only in case of new abdominal symptoms

and in particular about the possibility of ambiguous results. Informed consent for genetic testing should ensue.

The strategy of genetic testing is similar in FAP and HNPCC although different testing methods are used. If a mutation of either the APC or MMR gene is not known in the family yet, it is recommended to start testing in an affected family member (43). If the identification of a pathologic mutation in a tested gene is made, all family members at risk can be tested for this mutation. Once the mutation in APC is known, the family member can be diagnosed as "mutation carrier" in case of a positive test or "not mutation carrier" in case of a negative test. If the identification of APC mutation in an affected family member fails the result of genetic testing is "mutation not detected". That does not mean, however, that a mutation is not present. If it is not possible to examine an affected family member genetic testing can be tried in asymptomatic family member(s). This approach is questionable, probably insensitive and negative test results must be strictly interpreted as "mutation not detected".

The above strategy implies that in a considerable number of patients the test result would be ambivalent i.e. mutation was neither detected nor ruled out. It has been shown that patients not informed about this eventuality before the test perceive this outcome as frustrating with a negative impact on compliance (44).

Many genetic tests for the detection of APC mutations are available today. These include protein truncation testing, heteroduplex analysis, sequencing of the full APC gene and linkage analysis. Genetic tests for FAP are performed from routine peripheral blood samples and analyze the DNA from the lymphocytes. Use of a specific method is a question of preference of each particular genetic laboratory and financial coverage by the health care insurance. A combination of multiple genetic tests has about an 85 % sensitivity in mutation identification in a FAP family (38,40).

When suspecting HNPCC, the direct sequencing of hMLH1 and hMSH2 genes is possible but is complicated and expensive because these genes are large and even a single nucleotide mutation can be located. Therefore direct testing is preceded by more sensitive but nonspecific genetic tests such as microsatellite instability test or immunohistochemical staining for their proteins. Examination of the change of length of microsatellite areas in the tumor tissue using a genetic method is called microsatellite instability (MSI) testing. MSI is observed in more than 90 % of HNPCC associated colorectal carcinomas but only in 12–16 % of sporadic cases. MSI testing (46) is performed from formaldehyde-fixed colorectal tumor biopsies and then compared to healthy mucosa biopsies or DNA from peripheral blood lymphocytes. Five defined loci are examined. A positive test means finding instability in more than 1 locus (MSI-High). Negative test is either finding only one instable locus i.e. low microsatellite instability (MSI-L) or finding none referred to as microsatellite stability (MSS). The positive predictive value of MSI-H for the detection of a mutation in MMR is about 30 %. Before proceeding to germline testing, immunohistochemistry for either hMSH2 or hMLH1 proteins can direct the germline testing to a missing protein's gene thus saving time and resources (47).

Recommendations for screening of high risk individuals with positive family history

Guidelines for screening of asymptomatic family members at risk of FAP originate from the experience of Mayo clinic's experts and have been recently been included in the American gastroenterological association (AGA) guidelines (1). A patient at risk should undergo genetic testing following all specifics and requirements mentioned above. If it is not possible to perform genetic testing or the patient refuses or the results of genetic testing are ambiguous i.e. "mutation not identified" it is recommended to continue with the surveillance as if the family member at risk is a mutation carrier.

Tab. 4. Recommendations of ICG HNPCC for surveillance of patients from suspected or diagnosed HNPCC families.

	METHOD	START OF EXAMINATIONS (YEAR)	FOLLOW UPINTERVALS (YEARS)
Colon	Colonoscopy	20-25	1-2
Endometrium	• Gynecologic examination • Transvaginal ultrasound • Ca-125	30-35	1-2
Stomach*	Gastroduodenoscopy	30-35	1-2
Urinary tract*	• Ultrasound • urine biochemistry	30-35	1-2

* - surveillance is recommended if such malignancies are known in the family

In children with risk of FAP or those who tested positive for APC mutation, it is recommended to perform annual sigmoidoscopic screening starting at the age of 10 years, every two years between 26–35 years and every three years after the age of 35 years. If rectal polyps are found it is recommended to perform colonoscopy and start with gastroscopy screening.

Because of extracolonic manifestations of FAP as well as the risk of carcinoma in the ileal pouch or retained rectum, life-long surveillance of patients is necessary. Recommendations for patients after curative colectomy are summarized in Table 3.

Several guidelines have been published for the clinical surveillance of family members from HNPCC families (32,48). In 1996 ICG HNPCC issued its recommendations for the clinical follow-up of patients with HNPCC, which are summarized in Table 4 (48). The first controlled studies that aimed at investigating the clinical effectiveness of HNPCC surveillance have shown promising results. Vasen et al have shown that screening colonoscopies with 1–2 year intervals resulted in 7–9 year prolongation of expected life duration in HNPCC patients (49). Another recently published 15-year follow-up study has shown a 65 % decrease in total mortality with 3-year interval preventive colonoscopies (50).

Recommendations for screening of CRC in persons with positive family history of CRC are derived from the recommendations for general population and the level of relative risk of CRC patient relatives compared to the general population. The cumulative incidence of CRC in persons with positive family history in the age of 40 years was the same as incidence in the age of 50 years in general population. This shift in risk was observed in every age. Therefore the guidelines recommend staring screening for CRC 10 years earlier than the general population i.e. at the age of 40 using the same method as for the general population i.e. either fecal occult blood testing, sigmoidoscopy, barium enema or colonoscopy depending on the national strategies.

There are however two subgroups with significantly higher risk. The recommendation for those whose FDR was diagnosed with CRC before the age of 45 is to start screening 10 years earlier than the youngest age in which CRC was diagnosed in that family, perform colonoscopy as a method of choice and shorten the intervals to 5 years. The second group with higher risk includes those who report more than one FDR with CRC. The relative risk then exceeds 5 compared to general population. The recommendations for this group advise starting 10 years earlier than the first CRC diagnosed, perform colonoscopies and shorten the intervals to 3–5 years.

Chemoprevention

Besides genetic changes in familial adenomatous polyposis and HNPCC up to 80 % of colorectal cancers are induced by exogenous factors. Colorectal adenomas polypectomy is considered to be a preventive measure. One needs to take into consideration that adenomas smaller than 1 cm rarely transform to cancer and only 25 % of colorectal adenomas are larger than 1 cm.

Chemoprevention offers more promise in prevention. A lot of substances with chemopreventive activity and nutritional and life style interventions are described. Plant derived substances – phytophenols (carotenoids, flavonoids, phytosterols, phytoestrogens) have antioxidant activity which contributes to anti-mitotic and anticarcinogenic effects. Fibers (fruit, vegetables, grains, nuts and especially wheat bran) are mixtures of polysaccharide and non-polysaccharide polymers originating from plants. In a majority of epidemiologic studies the preventive role of these substances was verified (51-56). Besides the transit time acceleration of the gut content they change the pH of the stool. The polysaccharides are split by colonic bacterial enzymes and short chain fatty acids (acetic, propionic and butyric) are formed. Butyrate reduces mutant p53 suppressor gene expression. They also lower the pH and inhibit enzymes changing cholesterol to carcinogenic biliary acids – deoxycholic and litocholic.

Cox2-gene overexpression is found during neoplastic development and can be explained through prostaglandin stimulation. Inhibition of Cox-2-enzyme is mainly achieved by non-steroidal anti-inflammatory drugs, which inhibit prostaglandin production and induce apoptosis (57). Similar selective inhibitory activity and an apoptosis-inducing effect has been demonstrated for the green tea polyphenol (58). A reduction of cancer incidence by 50 % has been described after selenium supplementation (59). The preventive effect of calcium is derived from precipitation of cytolytic substances such as bile acids and fatty acids, which stimulate proliferation of the colorectal epithelium (60). Survival

tables after calcium carbonicum supplementation demonstrated the chemopreventive property of calcium (61).

Total exclusion of carcinogens in the environment is impossible and therefore chemoprevention, nutritional habits and life style are the center of our attention. Epidemiological studies are sometimes more useful than experimental results with single chemical substance because they better reflect the real situation and involve interaction between some nutritional ingredients. There are differences between eating red or white meat, cooked or broiled meat,and with or without vegetables.

As discussed above hereditary risk may range from slightly elevated (e.g. in relatives of CRC patients diagnosed over 60) to almost certain CRC in FAP. Can the fate of colorectal cancer in persons at risk be changed by means of control of other risk factors (e.g. chemoprevention, lifestyle, diet or smoking)? The answer is probably no in the case of hereditary syndromes and probably yes in the case of hereditary predispositions. An interesting study looked at the interaction of the external risk factors and familial risk (62). The relative risk in a group of persons with positive family history and low risk dietary habits was not significantly increased compared to the general population (RR=1.2 95 % CI=0.7–2.1). On the other hand, persons with positive family history and high risk dietary habits had a much higher risk (RR=5.5 95 % CI=3.5–8.7). The conclusion of the authors has been that a healthy diet is able to eliminate the genetic risk as far as hereditary predispositions to CRC are concerned.

Taking a family history is a simple method to identify a person with a higher risk of CRC. There is no doubt that tailored screening and follow-up with a correct diagnosis helps to prevent morbidity and mortality from CRC through identification of its early stages and proper management. This approach is already widely recognized and should be implemented in clinical practice (1).

In this respect there are two very important issues to be supported wherever possible. The first one is a wider recognition of family history as a risk indicator of CRC with the possibility of hereditary syndromes among generalist and specialist. Another issue is the highly specialized management of hereditary syndromes of CRC. This is probably best done by concentrating the knowledge and experience in regional or national registers of such families. Registers provide follow-up of patients and families at risk, offer professional consulting, provide uniform medical care and surveillance of affected families and also perform research in the area of hereditary forms of CRC (63). If not done yet, such a register should be established by a regional health care authority.

Despite the lack of definite evidence, there are very suggestive data for CRC prevention by means of diet and/or chemoprevention (i.e. decrease in consumption of red meat, fat and refined sugar and increase in consumption of fresh fruits and vegetables) (51-56). Dietary measures might even overcome (but can also increase) the risk of CRC in familial CRC (62).

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