Genetic Counseling in Hereditary Nonpolyposis Colorectal Cancer

By Fred H. Menko, MD, PhD [2], P. Meera Khan, MD, PhD [3], Hans F. A. Vasen, MD, PhD [4], and M. H. Oosterwijk, PhD [5]

Recent identification of gene mutations responsible for hereditary nonpolyposis colorectal cancer (HNPCC) has made possible the presymptomatic diagnosis of at-risk family members. If DNA testing shows that a family member is a gene carrier, that individual's lifetime cancer risk is approximately 90%. If the test is negative, the family member's cancer risk drops to that of the general population.

Introduction

Two main forms of hereditary colorectal cancer can be distinguished: hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP). Both conditions have an autosomal dominant pattern of inheritance. Hereditary nonpolyposis colorectal cancer accounts for approximately 1%-5% of all colorectal cancer cases and FAP accounts for 1% of such cancers [1].

With some exceptions, FAP can be attributed to a germ-line defect in the adenomatous polyposis coli (APC) gene on chromosome 5q [2]. This gene was localized in 1987 and isolated in 1991. As a result, presymptomatic DNA-based diagnosis of FAP has become possible.

Patients with FAP exhibit a characteristic clinical picture of multiple adenomatous polyps in the large bowel. In contrast, patients with HNPCC do not present with pathognomonic signs. Therefore, clinical diagnosis of HNPCC has depended on family studies. Until recently the basic genetic defect of HNPCC was unknown. However, in 1993 a gene for HNPCC was localized on chromosome 2p through linkage analysis of two large HNPCC kindreds [3].

An important additional finding was provided by studies of tumors from HNPCC patients. Most of these tumors have a characteristic pattern of widespread genetic alterations, the so-called microsatellite instability or replication error positive phenotype [4]. This finding directed further studies on the nature of the HNPCC-associated gene on chromosome 2. This gene could then be identified as one normally involved in DNA mismatch repair [5,6]. Thus, HNPCC appears to be due basically to a disturbance of DNA mismatch repair, which leads to genetic instability in somatic cells. Within a year, three additional HNPCC-associated DNA mismatch repair genes were cloned [7,8]. Apparently, HNPCC is a genetically heterogeneous condition, with different genes being involved in different families.

Identification of the gene defects underlying HNPCC introduces the prospect of presymptomatic diagnosis for at-risk family members. Although DNA testing is potentially beneficial for these individuals, it also is associated with various psychosocial consequences. In this article, genetic counseling of HNPCC families will be addressed, with emphasis on presymptomatic DNA-based diagnosis. For the purpose of illustration, clinical information on and mutation assays in two of our HNPCC pedigrees will be presented.

HNPCC: Definition and Diagnosis

As a group, HNPCC patients share certain features: early onset of disease, predominantly proximal tumor localization, a high incidence of multiple primary colorectal cancers, and possible manifestation of other tumor types, notably, endometrial cancer (Table 1). However, as mentioned above, pathognomonic clinical characteristics have not been identified. Therefore, HNPCC can be recognized only by its autosomal dominant inheritance pattern. Penetrance (the percentage of gene carriers who exhibit disease) is approximately 90%; skipped generations seldom occur [1].

In 1990, at the second meeting of the International Collaborative Group on HNPCC in Amsterdam, minimal criteria for the identification of HNPCC kindreds to be included in collaborative studies were proposed. These criteria are generally known as the Amsterdam criteria (Table 2) [9]. Since extracolonic tumors are not included, the diagnosis of HNPCC may be missed if one strictly adheres.
to these criteria for diagnostic purposes [10]. Clinically, HNPCC cannot be identified if the family history is negative. A patient with HNPCC due to a new mutation can be identified only by means of direct mutation studies. In summary, the clinical diagnosis of HNPCC is based on observation of early-onset colorectal cancer and other tumors, notably, endometrial cancer, in successive generations. In large families with many affected individuals, the diagnosis may be straightforward. In small families with only a few affected individuals, the clinical diagnosis of HNPCC must often remain tentative.

**DNA Mismatch Repair Genes and HNPCC**

The DNA in every cell is continuously exposed to injury by various intrinsic and extrinsic factors. Usually, the consequences of damage to the DNA are not severe since the molecule is subject to various control systems that prevent the occurrence of mutations. These systems recognize insults, and subsequent pathways may lead to either repair of the errors or programmed cell death.

DNA repair systems can be separated into two main groups: nucleotide excision repair and mismatch repair. DNA mismatch repair is the repair of base-pair anomalies that occur during DNA replication [11]. The four DNA mismatch repair genes implicated in HNPCC are human homologs of bacterial and yeast DNA mismatch repair genes. The characteristics of these four genes are summarized in Table 3. In most HNPCC families, the condition appears to be due to a germ-line mutation in either the hMSH2 or hMLH1 gene [12].

**Approaches to DNA-Based Diagnosis**

There are two main approaches to presymptomatic DNA-based diagnosis: linkage analysis and direct mutation analysis. In these studies, the genomic DNA is usually isolated from blood samples. In linkage analysis, haplotypes (chromosome regions) that harbor the gene of interest are examined. This method is based on a comparison of haplotypes from affected and unaffected family members. Since different genes are involved in HNPCC, linkage analysis, if feasible, is performed as the first step in identifying the gene locus involved in the family under investigation. Often, linkage studies are of limited value due to small family size or the limited availability of blood samples.

Direct mutation analysis focuses on the individual patient and is not dependent on family studies. Various DNA studies used to investigate HNPCC families are summarized in Table 4. Some mutations, in particular, missense mutations that lead to an amino-acid substitution in the protein product, may not be causally related to the disease. Mutations that result in protein truncation (as a result of base-pair substitutions, deletions, or insertions leading to the generation of stop codons) are expected to be pathogenic. Therefore, new methods for the in vitro detection of protein truncation will probably become increasingly important for diagnostic purposes [13].

**Cancer Risk and Management Options**

Molecular genetics of HNPCC now offers the prospect of presymptomatic DNA-based diagnosis for selected families. If DNA testing reveals that a family member is a gene carrier, his or her (lifetime) cancer risk is approximately 90%. If, on the other hand, the mutation found in affected family members is not detected, the cancer risk for that individual equals that of the general population.

**Screening for Colorectal Adenoma and Cancer**

The mean age at diagnosis of colorectal cancer is 40 to 45 years. Colonoscopic screening is generally started at age 20 to 25 years. Since the biology of HNPCC differs from that of sporadic cancer, the interval between colonoscopies should be tailored to the expected rate of growth of the neoplasms. Recently, the International Collaborative Group on HNPCC recommended a 2-year interval between colonoscopies for proven gene carriers [14].

**Screening for Extracolonic Tumors**

Hereditary nonpolyposis colorectal cancer families may differ in the type of extracolonic tumor exhibited by gene carriers. In particular, there seems to be heterogeneity for cancers of the gynecologic and upper urologic tracts [15]. However, the initial distinction between two subtypes of HNPCC, one with and one without extracolonic tumors (Lynch syndromes I and II, respectively) no longer seems valid. The lifetime risk for endometrial cancer in HNPCC gene carriers may be as high as 30% [16]. Annual gynecologic examination may prove to be advisable for female gene carriers and females at risk for HNPCC. Screening for other extracolonic tumors should be considered only for those families in which these tumor types have been observed and only when screening for the particular tumor type seems feasible.

**Cancer Treatment**
For patients with colon cancer, subtotal colectomy is recommended due to the high risk of a second primary colon cancer. For females with large bowel cancer, hysterectomy at the time of surgery for the colon tumor may be considered.

**Dietary Modification**

Dietary factors are important in the pathogenesis of sporadic colorectal cancer. However, whether these factors also play a role in the expression of HNPCC is unknown. Therefore, dietary advice for HNPCC families is optional.

Since no clear genotype-phenotype correlations have yet been detected for HNPCC, recommendations at present are independent of the gene or mutation identified in the family under investigation.

Management options for HNPCC families are summarized in Table 5.

**Psychosocial Consequences of DNA Testing**

The possible psychosocial sequelae of presymptomatic DNA-based diagnosis are manifold and complex (for a detailed discussion of these consequences, see the Lerman article next month).

Procedures for testing and counseling HNPCC families are based on experience gained previously with other hereditary late-onset disorders, notably, Huntington's disease [17], familial adenomatous polyposis, adult polycystic kidney disease, and hereditary breast and ovarian cancer [18]. The main relevant issues are outline in Table 6.

Presymptomatic DNA-based diagnosis consists of: (1) pretest counseling, (2) blood sampling and (3) post-test counseling. Counseling is provided by both the clinical geneticist and medical psychologist. Generally, both the at-risk family member and his or her partner are invited to counseling sessions.

**Pretest Counseling**

In the pretest phase, the benefits, limitations, and possible adverse effects of testing are discussed. The family member is advised that one cannot predict with certainty what type of cancer a gene carrier may develop at what age. The benefits and limitations of current screening procedures are also discussed.

It should be realized that knowledge of genetic risk among individuals with a positive cancer family history is often limited [19]. The family member is advised that an unfavorable test result may cause psychological distress. Currently, it is difficult to predict beforehand which family member will need psychotherapeutic support. Possible adverse effects on work or insurance are also discussed as part of pretest counseling.

The consequences of testing also pertain to the children. If a family member tests positive, this implies that his or her children now have a 50% risk of inheriting the abnormal gene. As a rule, children are not screened unless there is a medical benefit of diagnosis at a young age [20]. In the case of HNPCC, preventive measures are not recommended before the age of 20 to 25 years. Therefore, DNA testing is generally performed only in individuals who are over 18 years of age.

**Post-Test Counseling**

If, after the informative session, the family member requests DNA testing, a repeat blood sample is drawn and studied. Subsequently, the test result is discussed with the family member.

It has been found that family members often rationalize their feelings. Individuals who have an unfavorable test result may emphasize the benefits of testing and screening. It may take a trained psychologist to reveal the underlying emotions. Both short-term and prolonged follow-up after DNA testing are needed to determine the full psychological impact of testing. It has been reported that a favorable test result (ie, the family member has not inherited the gene defect) may also be followed by psychological distress. Survivor guilt has been noticed in this context.

Measures should be taken to prevent withdrawal from screening due to fear and denial. Therefore, recognition and discussion of possible barriers to screening are an important aspect of counseling.

Regional or national HNPCC registries have been instituted to ensure surveillance of at-risk family members.

**Two HNPCC Kindreds**

The pedigrees of two of our HNPCC families currently under investigation are depicted in Figures 1a, 1b and 2. The kindreds illustrate the clinical variability of the syndrome. In both cases, the pathogenic mutation has been identified. Presymptomatic DNA-based diagnosis has been completed in Family 1 (kindred NL-13) and has been started in Family 2 (kindred NL-7).

Kindred NL-13 (Figure 1a and 1b) includes an unaffected gene carrier (pedigree number II-1), who appears to be a case of nonpenetrance. Interestingly, the identical twin brother of the index case
(pedigree number III-6) had no colonic neoplasia. Gene carriers in kindred NL-7 (Figure 2) exhibit early-onset colorectal cancer, stomach, or endometrial cancer. Stomach cancer was observed in earlier generations. The ages at diagnosis suggest progressively decreased ages of onset of cancer in successive generations.

**Responsible Mutations**

In both kindreds, the condition is due to an inactivating mutation of the hMSH2 gene. Denaturing gradient-gel electrophoresis (Table 4) revealed alterations in the hMSH2 gene. Subsequent DNA sequencing delineated the nature and site of the gene defect. The mutation in family NL-13 was found to be a base insertion in codon 532 of exon 10, which terminated the translation of the gene three codons downstream. The NL-7 mutation was due to a base deletion in either codon 380 or 381 of exon 7, leading to translation termination at codon 387. These mutations have been described in a separate publication [13].

In kindred NL-13, the mutation was detected in all the investigated patients (pedigree numbers II-5, II-7, II-8, III-5, III-7 and III-37). Similarly, in kindred NL-7, the mutation was demonstrated in all the patients tested (pedigree numbers IV-1, IV-2, IV-6, IV-12, IV-14, and V-2). The information obtained in the research phase offered the possibility of presymptomatic DNA-based diagnosis. This prospect was discussed with family members by the clinical geneticist and medical psychologist.

**Reactions to DNA Testing**

We encountered complex reactions to DNA testing in Family 1. Notably, some family members saw an unfavorable test result in a positive light, and conversely, a favorable test result was sometimes perceived as having negative consequences. The twin brother of the index patient stated that the positive test result increased his feeling of solidarity with his deceased brother. One of his sisters felt that the tragic death of her brother had also had a positive effect on the siblings, since they now could be tested and screened to prevent disease. One family member in whom a colonic polyp had been detected was not reassured by the favorable DNA test result. Also, one of the brothers who tested negative worried that he would no longer be under surveillance.

In summary, it is important that the perception of the test result by the family member be evaluated critically. It is also important to offer follow-up counseling.

**Genetic Counseling in Clinical Practice**

Diagnostic certainty is a prerequisite for genetic counseling. For the diagnosis of HNPCC with its far-reaching consequences for patients and family members, verification of family history and expansion of pedigree data are essential. The responsibility of the genetic counselor extends from the index patient or family member to his or her relatives. The other at-risk family members are generally invited for counseling through the patient or family member known to the geneticist. When a clinical diagnosis has been established, an informative group session may be organized with the family members, followed by individual counseling.

It is important for the clinician to have expert laboratory support. DNA studies may be performed after obtaining informed consent. The DNA studies will usually consist of linkage studies and direct mutation analysis. Close cooperation between the clinical and molecular geneticists is needed for the interpretation of DNA test results.

Clearly, a multidisciplinary approach is required for the management of HNPCC families. In the hospital setting, the team includes a geneticist, surgeon, gastroenterologist, internist, social worker, and psychologist. The team may prefer to organize a specialized cancer family clinic. Lay organizations may be helpful in defining the best policies for HNPCC families. Presymptomatic DNA testing for cancer is now in the investigative phase. It must be emphasized that at present such studies should take place in a controlled research environment [21]. It is hoped that a careful team approach will ensure that the potential benefits of presymptomatic DNA testing far outweigh any potential adverse effects.

**References:**

Genetic Counseling in Hereditary Nonpolyposis Colorectal Cancer
Published on Physicians Practice (http://www.physicianspractice.com)


Source URL: http://www.physicianspractice.com/review-article/genetic-counseling-hereditary-nonpolyposis-colorectal-cancer-0

Links: