The Lynch Syndrome: Melding Natural History and Molecular Genetics to Genetic Counseling and Cancer Control

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Hereditary nonpolyposis colorectal cancer (HNPCC), also referred to as Lynch syndromes I and II, is an autosomal, dominantly inherited disorder that accounts for approximately 5% of all colorectal cancers. While colorectal cancer is the most frequently occurring malignancy in HNPCC, other types of cancer occur with increased statistical significance. A better understanding of its natural history, particularly early age of onset and the pattern of multiple primary cancer excess, is essential for the diagnosis and management of HNPCC.

Introduction

Of the estimated 138,200 new cases of colorectal cancer that occurred in the United States in 1995 (70,700 in men and 67,500 in women), 100,000 involved the colon and 38,200 involved the rectum.[1] Estimated deaths in 1995 attributable to colorectal cancer are 47,500 for colon cancer and 7,800 for rectal cancer.[1]

Despite progress in chemotherapy, radiation therapy, and surgery, little change has occurred in the survival of patients with colorectal cancer. This dismal therapeutic situation has stimulated the study of the etiology of colorectal cancer so that an understanding of its causes can be applied to its early detection and prevention. It is in this realm that genetics has become particularly important, given its power to predict cancer risk. Our purpose is to focus attention on the clinical and molecular genetics, cancer phenotype, surveillance, management, and genetic counseling for patients at high risk for hereditary nonpolyposis colorectal cancer of the Lynch syndrome I and II variants.

What Is Hereditary Nonpolyposis Colorectal Cancer?

HNPCC, also referred to as Lynch syndromes I and II, is one of several hereditary colorectal cancer syndromes (Figure). Lynch syndrome I is an autosomal, dominantly inherited predisposition to colorectal cancer with right-sided predominance (70% proximal to the splenic flexure) and an excess of multiple primary colorectal cancer (45% 10 years after incomplete colonic resection as opposed to subtotal colectomy). Lynch syndrome II not only shows all of the features of Lynch syndrome I, but also involves an enormous array of extracolonic colorectal cancers, particularly endometrial carcinoma, followed by carcinoma of the ovary, small bowel, stomach and pancreas, and transitional cell carcinoma of the ureter and renal pelvis.[2,3]

Knowledge of the genetics and natural history, coupled with a detailed family cancer history, is mandatory for diagnosis of HNPCC and, ultimately, genetic counseling. Herefore, the patient's cancer genetic risk status could be evaluated with, at the most, a 50% level of confidence, based on the patient's position in the HNPCC pedigree (those with one or more first-degree relatives with HNPCC syndrome cancer) in accord with the autosomal dominant mode of genetic transmission of the cancer trait. However, discoveries that have led to identification of the germline mutations responsible for HNPCC now enable the theoretical determination of cancer genetic risk during embryogenesis. The penetrance of the deleterious genotype is approximately 85% to 90%.

Frequency of HNPCC

In noting the major controversy relevant to the true frequency of HNPCC, Mecklin et al[4] designed a nonselected, prospective, multicenter study that assessed family background and other risk factors of colorectal cancer over a 12-month period for all new colorectal cancer patients in 10 hospitals in Finland. They found three (0.7%) cases of verified HNPCC and seven (1.7%) cases of suspected HNPCC following the evaluation of families with features indicative of susceptibility to cancer. This study revealed a lower frequency of HNPCC when compared to past investigations in Finland. When seen in context with the disclosure of common ancestral founding mutation (involving hMLH1) in Finnish HNPCC families, the findings indicate possible strong geographic differences in the occurrence of HNPCC.[5]

The lowest known estimate of HNPCC occurrence is 1%, which translates into 1500 new cases of HNPCC annually in the United States. Estimates of HNPCC incidence range as high as 5%, or 7500 new occurrences of HNPCC in the United States each year. Either estimate indicates that HNPCC poses a major public health problem, since each new case would signify a family prone not only to colorectal cancer, but also to a variety of extracolonic cancers.

Molecular Genetics and HNPCC

Molecular genetic studies have identified germline mutations in an increasingly large number of hereditary cancer syndromes (Table). The genetic basis for HNPCC has been proven by genetic linkage between cancer occurrences and chromosome 2p in some families[6] and 3p in others.[7]

Localization of a DNA mismatch repair gene in the critical region of chromosome 2p was documented with the discovery of hMSH2 mutations in this gene in several HNPCC families.[8,9] Subsequently, a second mismatch repair gene was found in the critical region of 3p, and mutations of that gene (hMLH1) were found in the HNPCC families previously linked to chromosome 3p.[10,11] Mutations in these genes appear to account for 90% of all known HNPCC families.[12] hPMS1 and hPMS2 also are mismatch repair genes in HNPCC.[13]

Defective DNA mismatch repair results in a steady accumulation of mutations. The mutation load can be detected as errors in long tandem repeat sequences, which are errors that produce microsatellite instability. A tumor with microsatellite instability is defined as showing replication error (RER) phenotype.

Molecular Genetics and HNPCC

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Colonic Adenomas and HNPCC

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HNPCC implies an absence of colonic adenomas. However, adenomas occur in HNPCC at the same rate as those in the general population. These adenomas are believed to be precursors to cancer of the colon in HNPCC.[14,15] Jass et al.[16,17] suggest that HNPCC adenomas are more likely to progress to adenocarcinoma, and do so more quickly, than those of the general population. The DNA mismatch repair defect in HNPCC may underlie the accelerated progression. Theoretically, the multiple steps necessary for such transition would be acquired more quickly in cells with the mutator phenotype. In a study of genetic instability at the adenoma stage in patients with HNPCC who were evaluated to determine whether acquisition of genetic instability at the adenoma stage would promote malignant transformation relevant to the adenoma-carcinoma progression in HNPCC, Jacoby et al.[18] found that while genetic instability was observed in some loci in these adenomas, "in almost all cases, the proportion of microsatellite loci altered was significantly less (P<0.01) in completely benign adenomas (24%) than in benign areas of adenomas with malignancy (54%). However, in all cases of tumor progression, at least one subclone from the adenoma stage was closely related to the carcinoma." Thus, there was some degree of genetic instability at the benign adenoma stage in HNPCC tumors from most of these patients. Furthermore, adenomas that showed a greater rate of genetic instability were found to be more likely to progress to colorectal carcinoma. These findings provide further documentation that adenomas are precursors to colorectal cancer in HNPCC. In addition, they harbor important implications for the accelerated polyp to colorectal cancer hypothesis in colorectal cancer.[16,17]

While the reasons for this accelerated progression of polyps to colorectal cancer in HNPCC remain enigmatic, it is hypothesized that loss of the wild-type gene in HNPCC usually is necessary to bring about the DNA repair defect, a concept in accord with the belief that HNPCC genes are tumor suppressor genes.[19] Random loss of the wild-type allele would be expected to occur frequently (analogous to loss of the wild-type antigen-presenting cells [APC] gene in polyposis).[20] Yet few neoplasms are seen. It is possible that loss of DNA repair proficiency has little or no effect on the stage of initiation but impacts on subsequent progression.

Adenomas are known to show DNA hypomethylation.[8] It has been suggested that DNA hypomethylation would be a prerequisite for unmasking the DNA repair defect. Two additional observations support this argument: (1) The DNA repair defect occurs in 15% of sporadic carcinomas but is rare in sporadic adenoma,21-23 (2) Adenomas in HNPCC show an anatomical distribution similar to the general population.[17] Thus, it is hypothesized that microadenomas in HNPCC are initiated on a sporadic basis. The mutator phenotype will develop in a small number of these, producing an inexorable stepwise accumulation of mutations leading to adenoma progression and eventually malignant change. For reasons that remain unclear, the effect will be more pronounced in adenomas originating in the proximal colon. The clinical expression of the above will be appreciated in follow-up surveillance through the appearance of small numbers of large adenomas (or early cancers) within one to three years of a negative colonoscopic examination. Additional evidence of the accelerated progression of HNPCC polyps to colorectal cancer comes from an apparent increased frequency of interval cancers in HNPCC.

Interval Cancer

Vasen et aI.[24] followed a cohort of 41 HNPCC families comprised of 394 first-degree relatives who participated in a nationwide colonoscopy surveillance program in which the mean follow-up period was five years. They unexpectedly observed a high rate of advanced colorectal cancers that were diagnosed within two to five years following a negative screening examination. The shortest interval between negative colonic screening examinations and the diagnosis of colorectal cancer in six of these patients was two years.

Our experience with interval cancers has been comparable. For example, a woman with a Lynch syndrome II diagnosis who had manifested endometrial carcinoma at 36 years of age underwent colonoscopy every two years. Eighteen months after a normal colonoscopic evaluation, she was diagnosed with Dukes’ B1 cancer of the transverse colon and underwent a segmental colonic resection. At that point, she insisted on colonoscopies every six months. Five months after her last colonoscopy, she was found to have two primary colon cancers, Dukes’ B1 in the cecum and Dukes’ A in the low rectum.

There are several possible explanations for these interval cancers. (1) Lesions were missed at the time of colonoscopy. (2) The gene accelerates the progression of adenoma to cancer even in very small adenomas. This finding is consistent with the suggestion that adenomas in HNPCC are more likely to show a villous growth pattern with a high degree of dysplasia as opposed to adenomas in a necropsy series, causing them to undergo more rapid malignant transformation.[17] The hypothesized rapid progression of the adenoma-carcinoma sequence in HNPCC, which can take as little as two to three years, contrasts with findings from the National Polyp Study, in which the adenoma-carcinoma sequence in the general population takes approximately eight to 10 years.[25,26] Finally, (3) gene carriers may develop "de novo" cancers.

Improved Colorectal Cancer Prognosis in the Lynch Syndromes

When compared by stage, patients with colorectal cancer in HNPCC families show a better prognosis than patients with colorectal cancer in the general population. Several theoretical possibilities relating to the adenoma-carcinoma progression, if it truly exists. Indolent behavior has been suggested,[27,28] but no prospective, controlled series has confirmed this impression. Interestingly, colorectal cancers in HNPCC have a more aggressive histology as evidenced by increased frequency of poorly differentiated, mucinous, and signet cell histology. Shibata et al.[29] suggest that RER+ cells acquire such an enormous mutational load that their own survival is adversely affected.

Colorectal cancers in HNPCC have a higher frequency of peritumoral lymphocyte response, suggesting a host immunologic protective aspect of this hereditary disorder.[17] Immunologic factors may explain the better prognosis of colorectal cancer in HNPCC. Another possibility is that the rapid progression from adenoma to carcinoma may actually benefit the patient by preserving host immune response. Immunologic studies have shown that tumors influence host immune response by altering host T-cell receptors in mice with colon cancer.[30] The defective T-cell response, however, was seen only in animals with long-standing tumors, implying that rapid tumor growth may allow preservation of immune response. No experimental evidence exists that HNPCC patients have a stronger immune response to colorectal cancer than the general population, but this intriguing hypothesis merits study.

Genetic Counseling and HNPCC

Genetic counseling of HNPCC family members includes education on the natural history, genetics, surveillance, and management recommendations for this disease. Extensive counseling is imperative before they submit to presymptomatic DNA genetic testing. DNA results should be revealed on a one-to-one basis by the physician or genetic counselor with periodic follow-up counseling. We initiate this counseling in the mid to late teens, depending on the patient's maturity. Because of the proximal predominance of colon cancer, we recommend that colonoscopy be initiated at 25 years of age and repeated biennially through 35 years of age and annually thereafter. However, for those who have undergone DNA testing and have been found to have one of the HNPCC germline mutations, colonoscopy is initiated at 20 years of age and repeated annually. We believe that this frequency of colonoscopy (annual) in germline carriers of HNPCC genes is appropriate when considering our hypothesis of accelerated progression of adenoma to carcinoma.

If a patient develops colorectal cancer, subtotal colectomy is recommended due to the vulnerability of the entire colonic mucosa to cancer, as evidenced by the enormous risk for synchronous and metachronous colorectal cancers. Women who present with colorectal cancer and who have completed their families are candidates for prophylactic total abdominal hysterecotomy and bilateral salpingo oophorectomy, which can be performed at the same time as subtotal colectomy. Also, patients with proven evidence of HNPCC germline mutation are given the option of prophylactic subtotal colectomy.

Principles of Genetic Counseling

The following guidelines for genetic counseling were established a quarter of a century ago,[31] but they are equally important today, particularly given the prodigious advances in knowledge about cancer genetics in concert with the ongoing molecular genetics revolution. Hereditary carriers require a specialized form of genetic counseling.[32]

1. Genetic counseling implies that we are dealing with an ego-involved patient who may be apprehensive about his or her risk of cancer, as well as that of family members.
2. Genetic counseling is medically oriented in that the counselor has both an interest in and an obligation to explore the disease status of the patient. Therefore, the...
Genetic Counseling Difficulties and HNPCC

In the past, genetic counseling in HNPCC was imprecise due to the lack of premonitory physical stigmata of the genetic susceptibility of HNPCC to cancer. Diagnoses were based exclusively on the natural history and the pattern of cancer distribution within a given extended HNPCC kindred. An exception was a subset of Lynch syndrome II patients who harbored the phenotypic expression of cutaneous signs of cancer risk relevant to the Muir-Torre syndrome,[33,34] including sebaceous adenomas, sebaceous carcinomas, and multiple keratoacanthomas in concert with multiple visceral cancers.

The risk of first-degree relatives of HNPCC syndrome cancer patients for developing cancer of specific anatomic sites could be assessed at only approximately 50%. Therefore, it was unknown whether family members were at approximately 90% risk for these cancers (based on the gene's penetrance) or whether they had escaped inheriting the deleterious gene and therefore reverted to the general population risk (5%) for colorectal cancer. Fortunately, the genetic predictability for HNPCC has changed as a result of several of the mentioned discoveries of the HNPCC genes.[5-9] This information can now be used for highly definitive genetic risk assessment, particularly when a simple blood test for HNPCC germline mutations becomes clinically available. Specifically, high-risk patients can be advised if they have inherited the deleterious cancer-prone susceptibility gene in a manner similar to that employed for familial adenomatous polyposis (FAP) and its APC mutations.[35] The HNPCC germline carrier patients could then follow vigorous surveillance and management recommendations. The gene-negative patients would avoid these rigorous, expensive, and time-consuming surveillance/management measures and could follow the American Cancer Society's recommendations for the general population.

Establishing the optimal time to initiate gene testing and to provide DNA risk information will be important concerns. When is it appropriate to initiate genetic counseling? Is it prudent to test a child or young adult for gene carriage status? Some argue that children and adolescents cannot make informed decisions about the implications of this status of gene-mutation carrier. Since HNPCC cancers rarely occur in the teenage years, it would seem prudent to provide genetic counseling at an age of maturity, when it will be more meaningful to the patient and when screening is being considered.

These questions have no clear-cut answers, and more research is required. Given the range of differences in maturity among young individuals, this information may be received and interpreted with marked variability. Some may find it extremely beneficial psychologically, while others may find it emotionally devastating. For example, an otherwise normal adolescence may be significantly disrupted by the fact that he or she is a gene carrier with the strong likelihood of eventually manifesting cancer. This knowledge could compromise interpersonal relationships, as well as plans for education, career, and marriage. However, in many circumstances, this disorder can be amenable to appropriate management and treatment. This optimism contrasts strikingly with hereditary disorders such as Huntington's disease, for which medical treatment is unavailable but where genetic counseling experience is accruing.[36-38]

Another consideration is whether members of HNPCC families want to know their genetic cancer-risk status. The anxiety associated with coping with uncertainty must be considered: is it psychologically more advantageous to know whether one is a gene carrier or to remain unaware of the status? These issues require psychological research.

Once the HNPCC syndrome diagnosis has been established, cancer surveillance and management recommendations within the context of genetic counseling should be extended to all available primary and secondary relatives of the proband. Unfortunately, this is not a common practice in the usual clinical practice setting. For example, 59% of patients with the easily recognizable FAP, where proctosigmoidoscopy could lead to the prevention of colorectal cancer through prophylactic colectomy, are not identified early and consequently die of metastatic colorectal cancer.[39] Early identification will be more difficult in HNPCC, where reliable premonitory physical signs of cancer risk are lacking. The message relevant to hereditary colorectal cancer among members of FAP families is not being adequately addressed. The solution lies in the development of a simple blood test for HMSH2, hMLH1, hMSM1, and hPM2.

Much of the negligence in providing genetic counseling to high-risk family members relates to shortcomings in the medical education of physicians. Physicians often are concerned with the medical problems of only their immediate patients; hence, appropriate cancer control measures for high-risk relatives of their patients are not initiated. Also, physicians are reluctant to contact high-risk collateral relatives because it could be misconstrued by the medical community. In some medical circles, this type of solicitation is discouraging and may unjustifiably be interpreted as tantamount to attempts at economic gain on the part of the physician.

Other barriers to effective genetic counseling and cancer control that may impact heavily on compliance with recommended screening procedures include fear and denial by the patient, as well as socioeconomic and educational problems. Health insurance carriers may not reimburse for screening procedures, and high-risk patients might forego surveillance. Based on the past experiences of relatives, patients may fear that their insurance coverage could be cancelled or future policies denied as a result of their increased cancer risk. Others may fear that their own cancer risk will translate into similar discrimination problems for their siblings and children. Hence, to keep this information from their insurance providers, patients may not request coverage for surveillance or management.

How can these problems be resolved? Physicians, insurance actuaries, and medical directors of insurance companies must appreciate the needs of these patients with high genetic risk, including those of HNPCC germline carriers. Research demonstrating the cost:benefit ratio of decreased morbidity and mortality through early cancer diagnosis and cancer prevention - should it be adequately demonstrated - would be useful to third-party carriers.

Conclusions

Genetic counseling, with its ensuing benefit in cancer control, is an emerging resource that portends a hopeful future for those at high risk for the onset of cancer and particularly HNPCC. However, several questions are yet to be answered and many issues are yet to be resolved - ethical, financial, legal, psychological, and social - in a rational and scientific fashion. We must acknowledge the implications associated with confidentiality, stigmatization, and psychosocial effects that often accompany genetic counseling and be prepared to effectively manage these psychodynamic factors.

Support for this effort was provided by grant #1297E from the Council for Tobacco Research, Inc, grant #EDT-84 from the American Cancer Society, and the Nebraska Cancer and Smoking-Related Disease Grant LB959. Appreciation is expressed to Suzanne Nord for technical assistance and to Gabriel Mulcahy, MD, Associate Professor, Chief, Laboratory Medicine, New Jersey Medical School, who helped in the preparation of the table.

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