Etiology, Natural History, Management, and Molecular Genetics of Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndromes): Genetic Counseling Implications

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Abstract

We estimate that 5–10% of virtually all forms of cancer are due to a primary hereditary etiology. However, a hereditary cancer diagnosis is often missed because the family history of cancer is given short shrift in medical practice. Hereditary nonpolyposis colorectal cancer (HNPCC) certainly fits this estimate, although some studies suggest that a minimum of 2% with a range as high as 10% of the total colorectal cancer burden is due to HNPCC. Mutations in one of the four mismatch repair genes, i.e., hMSH2, hMLH1, hPMS1, and hPMS2, account for about 70% of HNPCC kindreds. Other germ-line mutations are likely to be identified to account for the remainder of HNPCC patients. By far the most common HNPCC mutations involve hMSH2 and hMLH1, with hPMS1 and hPMS2 accounting for only about 3% of such families. Prior to these molecular genetic discoveries, the genetic counselor could only provide the patient with an estimate of a 50% likelihood of manifesting HNPCC based on the counselee having one or more first-degree relatives manifesting syndrome cancers in their direct genetic lineage. Because DNA testing has become available in families with known mutations, we have provided pretest group education in the form of a family information service with intensive education about the natural history, genetic risk, surveillance, and options for management of HNPCC, as well as discussion of the potential for fear, anxiety, apprehension, and insurance or employer discrimination that might impact on this DNA testing. Following informed consent, these relatives were then counseled on a one-to-one basis. Using DNA-based genetic counseling involving hMSH2 or hMLH1, we have provided this service to four extended HNPCC kindreds. Details of this genetic counseling experience on these four kindreds will be discussed.

Introduction

The question as to whether a subset of cancer susceptibility is due to heritable genetic mutations has been answered beyond any doubt during the past decade through molecular genetic studies of family members in large cancer syndrome kindreds. Specific germ-line mutations have been linked to cancer occurrences in such families, making it possible to test for the mutation in as yet unaffected family members. The public health implications are still unclear, because it is not known how much of the total cancer burden is due to heredity. In the case of CRC,2 the annual incidence in the United States is approximately 131,200 (1). Less than 1% of the total CRC burden will manifest rare hereditary disorders predisposing to CRC, such as familial adenomatous polyposis and Peutz-Jeghers syndrome (2, 3). The overwhelming majority of the hereditary CRC cases will be HNPCC, estimated to range from a low of approximately 2% to a high of 10% of the total CRC burden (4–8), or 2,600–13,000 cases annually in the United States. HNPCC cases in which germ-line mutations have been identified will also have high-risk relatives suitable for DNA testing and, consequently, genetic counseling.

What Is HNPCC? HNPCC is an autosomal dominantly inherited disease that causes an increased susceptibility to CRC and other cancers, especially adenocarcinoma of the endometrium, ovary, stomach, small bowel, hepatobiliary tract, and urological tract (4, 9, 10). It is distinguished from certain other CRC-associated syndromes in that it lacks striking stigmata, such as the profuse colonic adenomas seen in familial adenomatous polyposis (4, 9, 11–13).

During the past several years, genetic linkage studies localized genes responsible for HNPCC to chromosome 2p16 (6) and 3p21 (14). Subsequently, germ-line mutations were identified in the hMSH2 MMR gene in HNPCC families, confirming the syndrome’s genetic basis (15). It is currently believed that mutations in two of the human MMR genes, i.e., hMSH2 and hMLH1, account for about 67% of HNPCC kindreds (11). A small proportion, about 3%, are due to mutations in two other MMR genes, hPMS1 and hPMS2. Clearly, other MMR genes are likely to be identified to account for the approximate 30% of HNPCC kindreds that are not due to the presently identified HNPCC germ-line mutations. The inheritance of a single mutated copy of one of these genes leads to a very high risk of...
cancer in HNPCC by impairing the genome guardian function of DNA MMR and thus accelerating tumor progression (16).

Testing for germ-line mutations in these genes may have important implications for cancer control. However, there are limitations. Kinzler and Vogelstein (17) and Liu et al. (11) have pointed out that such tests are insensitive. Tests for mutations will fail to find mutations in a substantial fraction of families who merit testing based on their pedigree findings, and, because these tests are insensitive, we will not be able to infer that a mutation is absent. Furthermore, virtually all reported germ-line MMR mutations have been identified in "classical" HNPCC kindreds. These families were ascertained because of their striking cancer phenotype. Hence, a strong ascertainment bias has been present in studies to date (5, 11, 18–20). It is possible that such families give a misleading picture of the phenotype associated with MMR mutations. However, Dunlop et al. (21) have examined the lifetime cancer risk associated with germ-line MMR gene mutations regardless of family history, and they confirmed that high penetrance is observed even when family history is not used in the selection process.

Our purpose is to provide an update on the natural history and management of HNPCC and to describe our DNA-based genetic counseling experience with 130 high-risk individuals who are members of four extended and classical HNPCC kindreds. Appropriate emphasis will be given to those educational strategies we provide prior to DNA studies (FISs) and at the time of disclosure of the results. Patient attitudes, feelings, perceptions of their cancer risk, confidentiality concerns, and their initial judgments and decisions at the time of disclosure of DNA results will be discussed.

Materials and Methods

This study has been approved by Creighton University’s Institutional Review Board. Signed consent was required for this DNA testing, and our confidentiality policy was fully described. DNA-based genetic counseling was performed on 130 high-risk members from four extended HNPCC kindreds. These families were ascertained because of their striking cancer phenotype. Hence, a strong ascertainment bias has been present in studies to date (5, 11, 18–20). It is possible that such families give a misleading picture of the phenotype associated with MMR mutations. However, Dunlop et al. (21) have examined the lifetime cancer risk associated with germ-line MMR gene mutations regardless of family history, and they confirmed that high penetrance is observed even when family history is not used in the selection process.

The Creighton genetic counseling team provided a FIS to these patients prior to DNA testing and the time of disclosure, and 87% of counseled patients attended a FIS, an open family educational meeting in which multiple family members were informed about the genetics and natural history of cancer occurrences that characterize HNPCC in general and their kindred in particular. They became fully acquainted with available surveillance and management strategies pertinent to HNPCC and the limitations of these strategies. Emphasis was given to the powerful cancer risk implications of these germ-line mutations. They were advised about what might transpire at a future genetic counseling session during which disclosure of their DNA findings would occur. Herein they were told about the potential benefits (targeted cancer screening, options for prophylactic surgery, and removal of doubt of being a germ-line mutation carrier or noncarrier) as well as potential risks (fear, anxiety, apprehension, intrafamily strife, and insurance or employer discrimination). Limitations of this knowledge, inclusive of the uncertainty in cancer risk estimates associated with mutation carriage, were stressed. Their primary physicians were also provided with these DNA test results when the patient requested such and signed an appropriate permission form for its release.

Data were collected through the use of a flow chart, which we designed specifically for this project. It is not standardized, but it served as a structured outline for use during the genetic counseling session. This enabled the genetic counselor to keep systematic notes. Following each session, all of the material discussed was dictated to provide more full coverage of the important queries, psychosocial information, and overall responses of the counselee.

Results

Genetic counseling and test results were offered to 219 family members. It was not actually provided to 89 of these family members. Sixty-seven % of these 89 individuals did not respond to the invitation, 22% have had their counseling postponed, and 10% refused, citing fear of knowing, fear of insurance discrimination, survival guilt, and disinterest. Of the 130 high-risk family members counseled (each had one or more primary or secondary relatives affected with a HNPCC syndrome cancer or were themselves already cancer affected), 36% were positive, and 64% were found to be negative for the respective germ-line (hMSH2 or hMLH1) mutation. Table 1 provides a breakdown of the salient genetic counseling responses that were observed in these sessions. Noteworthy was the finding that most members (75%) from these four families cited concern about the genetic risk status of their children or other close family members as being the primary reason for their being tested. If they were identified as mutation positive, many indicated that they would advise their adult children to undergo DNA testing. (Testing of persons under age 18 was not offered.) Several patients who did not

<table>
<thead>
<tr>
<th>No.</th>
<th>Counclee responses</th>
</tr>
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<tbody>
<tr>
<td>N = 106 (%)</td>
<td>Reason for seeking risk assessment</td>
</tr>
<tr>
<td>N = 45 (%)</td>
<td>Positive mutation test</td>
</tr>
<tr>
<td>N = 80 (%)</td>
<td>Negative mutation test</td>
</tr>
<tr>
<td>Sad/Crying</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Surprised</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Guilty</td>
<td>1 (1)</td>
</tr>
<tr>
<td>None (flat)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Relief</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Relieved</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Happy</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Survival guilt</td>
<td>5 (5)</td>
</tr>
<tr>
<td>None (flat)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Sad/crying</td>
<td>3 (3)</td>
</tr>
<tr>
<td>18 said they were concerned with sharing information with their insurance company</td>
<td></td>
</tr>
</tbody>
</table>

* The total number is variable for items because not all patients were asked each item. Twenty-four persons were not questioned about reasons. Five persons were not questioned about emotional response.
The total number is variable for lactic surgery. Most (57%) genetic result to make more informed decisions about prophy-
be positive for the respective germ-line mutation that they
more informed decisions about procreation. Five % sought their
have children indicated that they were seeking results to make
more informed decisions about prophylactic surgery. Most (57%) believed that if they were found to
be positive for the respective germ-line mutation that they
would increase their screening and would need to be more
health conscious. Sixteen % of those found to be gene positive
were concerned about insurance discrimination. When mutation
positive, some (20%) exhibited sadness, particularly because of
concern of the potential risk of transmission of the deleterious
mutation to their children. Others were concerned about their
personal cancer destiny, particularly the possibility of an unfa-
vorable prognosis that could lead to their early death and may
put their children in jeopardy of not having a biological parent
to care for them.

As shown in Table 2, a sizable proportion of the high-
risk family members had never had a colonoscopy (48%) or
any colon cancer screening test (28%). Only 14% of the
high-risk women had had endometrial screening, namely,
any form of endometrial aspiration or pelvic ultrasound.
Following receipt of a positive mutation test result, 67% of
individuals said they were considering prophylactic colec-
tomy. Several women who were considering having children
indicated they would likely postpone gynecological prophylac-
tic surgery until after their families were complete. Eighty-seven % of those women who were positive for the
germ-line mutation and who were asked were considering
holding their children in jeopardy of not having a biological parent
to care for them.

Subjects considering prophylactic colectomy

<table>
<thead>
<tr>
<th>Practices and attitudes</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colonoscopy</strong></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>60 (48)</td>
</tr>
<tr>
<td>At least once</td>
<td>64 (52)</td>
</tr>
<tr>
<td>Any type colon screening test</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>35 (28)</td>
</tr>
<tr>
<td>At least once</td>
<td>89 (72)</td>
</tr>
<tr>
<td>Endometrial screening</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>51 (86)</td>
</tr>
<tr>
<td>At least once</td>
<td>8 (14)</td>
</tr>
</tbody>
</table>

Subjects intending to follow lifetime surveillance recommendations

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before receiving results</td>
<td>10 of 20 (50)</td>
</tr>
<tr>
<td>After receiving results</td>
<td>12 of 18 (67)</td>
</tr>
</tbody>
</table>

Subjects still opting for testing after receiving results

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before receiving results</td>
<td>7 of 8 (87)</td>
</tr>
<tr>
<td>After receiving results</td>
<td>15 of 24 (62)</td>
</tr>
</tbody>
</table>

Table 2 Colonoscopy practices and attitudes toward prophylactic colectomy in 130 members in four HNPCC families

Discussion

Prior to the discovery of the HNPCC genes, the best risk
assessment of a HNPCC family member was based on cancer
diagnoses in close relatives. If the patient had one or more
first-degree relatives affected with CRC or endometrial carci-
noma, the risk of carrying the cancer-prone genotype would be
50%. Rarely, higher risks could be established. For example, a
patient with a parent and child affected with a HNPCC cancer
would be considered to be an obligate gene carrier. Persons at
very low risk among the blood relatives of affected persons
were also difficult to identify. Factors that obfuscate HNPCC
disease interpretation include incomplete gene penetrance,
late age of cancer onset, early death of key relatives from causes
other than cancer, incomplete medical and pathology document-
ation including outright destruction of medical records and
pathology tissues, lack of participation of family members and/or
family physicians, denial of cancer history due to fear
that such disclosure might compromise insurability or employ-
ment, and incorrect paternity. In families in which the mutation
is known, some of these problems can be resolved by DNA
testing. Experience in DNA-based genetic counseling for
HNPCC has been extremely limited (22). The following anec-
dotes are provided to illustrate some recurring patterns we
observed in counseling these four families.

For one reason or another, family members may have
difficulty incorporating the factual information provided during
a counseling session. Each family member has his or her own
ideas of what is predictive of an individual's cancer risk. Two
elements of this are phenotypic features, such as complexion
and personality traits. Another example is survivability. One
gentleman in a HNPCC family was convinced that he was not
a gene carrier because he survived his colon cancer. He ex-
pressed doubt about his positive DNA test result. Everyone else
that he knew of in his family who had had colon cancer had died
from it, so he thought that his colon cancer was different from
the colon cancer of other family members. After a discussion
about and explanation of the natural history features of HNPCC
and the difference in prognosis of any cancer based on the stage at diagnosis, this gentleman was then able to accept that he was positive for the mutation.

Secrets kept to protect loved ones from being hurt, or to protect parents from experiencing guilt that they might have passed a mutation on to a child, can have the potential for causing much greater pain and anger than the truth. Parents do not want to cause fear and anxiety for their children and some keep putting off telling them about their potential risk for cancer, waiting for a better time. One young woman came to her counseling session with conflicting emotions of grief and intense anger with her mother. Her mother, who had recently died, had not informed her children about the family history and its potential impact on them. This young woman’s intense emotions needed to be vented and acknowledged before she could comprehend the information provided.

Multiple cancer occurrences and deaths at young ages are common for many of the families with HNPCC. A family’s response to the multiple losses can result in disintegration of the family unit or in greater cohesion as family members provide mutual support. Due to their concern that their children may develop cancer, many parents encourage their high-risk adult offspring to undergo DNA testing. These parents express the belief that certainty regarding carrier status will facilitate proper surveillance to detect or prevent cancer occurrences. One individual and his wife accompanied their adult children to obtain their results. After members received their results individually, the nuclear family was seen as a group to discuss their feelings and to review the recommendations and options for management. This family unit showed great support for each other. The family expressed intense relief and happiness for family members who were negative but also expressed concern for family members who were positive. They also stressed to each other that one cannot feel guilty or somehow responsible for one person’s inheriting a mutation and another not inheriting it.

However, some individuals may experience alienation or survivor guilt when faced with the possibility of receiving a negative result to their DNA testing. One woman, after learning of several of her siblings’ positive results, came to the conclusion that she could not receive her results. She said she would never again be able to face her siblings if she received a negative result. Obviously, this woman’s decision not to receive her results was respected; she was also assured that the result would be available to her if she should change her mind.

As a result of the young age of cancer diagnosis in many of these families, some parents are convinced that their minor children should have DNA testing performed, despite the fact that the results would provide no advantage during childhood. After one woman received her positive results, her fears for her own future were quickly displaced by fear and anxiety for her young child. She requested that he be tested. Her concern and anxiety for him and his future well-being were acknowledged prior to explaining the drawbacks of testing before he can make his own informed consent, particularly in the absence of any real advantage to him.

The genetic counseling findings in our four HNPCC families have many similarities to our DNA-based genetic counseling observations in a sample of HBOC families that harbored the BRCA1 germ-line mutation (23, 24). Specifically, in our HNPCC patients, concern about the genetic and health risks for their children was the primary reason for participation in the study for 75% of the family members, which was virtually the same as in the HBOC cohort. Other striking similarities between DNA-based genetic counseling experience in HNPCC and HBOC pertain to concerns about prophylactic surgery. For example, in HNPCC, of those testing positive for the germ-line mutation, 67% indicated that they would seriously consider prophylactic colectomy, and a similar number of HBOC patients who tested positive for the BRCA1 mutation indicated they would consider prophylactic oophorectomy (23). Virtually all of the HNPCC and HBOC patients, regardless of whether they tested positive or negative, indicated that they would participate in the DNA-based genetic counseling research study once again, and serious emotional disturbances were not observed among these patients at this time. Another common theme in our HNPCC and HBOC findings was concern about possible insurance discrimination, expressed by about 20–25% of patients studied with each of these hereditary disorders. Indeed, a few decided not to receive their results because of fear of insurance problems not only for themselves but also for their close relatives should they be identified as the harbinger of a deleterious germ-line mutation.

Genetic Counseling and Strategies. Genetic counseling in an ideal situation should enable the patient to grasp all of the available information about HNPCC that may impact on his or her decisions about such matters as surveillance and management, inclusive of the option of surgical prophylaxis, as well as insurance or employment discrimination. The patient may wonder why colonoscopy is indicated at an early age and why it must be performed more frequently than in patients who lack susceptibility to HNPCC. Clearly, the need for initiating colonoscopy early, and herein we suggest beginning at age 25, is based on the average early age of onset of CRC (age ~44). These facts need to be understood by the patient. However, it is a bit more difficult to explain the reasoning behind the need for an increased frequency of colonoscopy, which we recommend every other year through age 35 and annually thereafter among high-risk and/or germ-line mutation carriers. We explain this in terms of evidence that adenomas in HNPCC undergo accelerated carcinogenesis (16). Colonic adenomas in patients in the general population may take anywhere from 5 to 10 years to evolve into a carcinoma (25). Eddy (26) has estimated that the average time for a 1-cm adenoma to become an invasive carcinoma is 7 years (range, 0–14 years). Clearly, some carcinomas may grow more rapidly than others. In HNPCC, it is believed that an adenoma may evolve to carcinoma at a more rapid pace, requiring perhaps only 2–3 years to complete this malignant transformation process (16). It is suggested that in HNPCC, mutational events are accelerated as a result of defective DNA MMR (16). However, it should also be stressed to patients that data on the efficacy of screening and prevention procedures have not yet been examined in persons who carry HNPCC-associated mutations.

Summary and Conclusions. In conclusion, DNA testing should be restricted to well-verified candidate families and accompanied by genetic counseling. In these circumstances, we have not observed serious short-term negative consequences of testing, and family members express satisfaction with the process. We found that these high-risk family members sought genetic risk assessment not only for their own health but also for that of their children. We also found that patients exhibited a range of emotional responses when told of their gene testing status. These high-risk patients have many concerns about their lifetime cancer destiny and many questions about cancer and cancer prevention, which arise in the counseling process. Addressing these questions appropriately requires a multidisciplinary team of geneticists, primary care physicians, surgeons, gastroenterologists, genetic counselors, and nurses. Whether this information, or the test results, has a long-term effect on
behavior or quality of life or on cancer morbidity and mortality remains to be seen. Finally, we are still in the dark with respect to those parts of the genetic counseling process that are essential in preventing harm and maximizing the usefulness of the information (22), but progress is being made.

Acknowledgments
We acknowledge the invaluable contribution to this research that was provided by Dr. Bert Vogelstein and his colleagues at the Howard Hughes Medical Institute Research Laboratories, the Johns Hopkins Oncology Center and Molecular Genetics Division, Baltimore, Maryland. In addition, we acknowledge the dedication given to the preparation of this article by Trudy G. Shaw.

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