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ORIGINAL REPORT

Colorectal Cancer Risk Perception on the Basis of Genetic Test Results in Individuals at Risk for Lynch Syndrome

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ABSTRACT

Purpose
Lynch syndrome is associated with inherited germline mutations in mismatch repair (MMR) genes. Genetic testing in high-risk individuals may yield indeterminate results if no mutation is found or if a mutation of unclear pathogenic significance is observed. There are limited data regarding how well patients with Lynch syndrome understand the clinical implications of genetic test results. This study examines colorectal cancer (CRC) risk perception in individuals tested for MMR mutations and identifies the factors associated with an appropriate interpretation of their cancer risk.

Patients and Methods
A total of 159 individuals who met the Revised Bethesda Guidelines and had previously undergone genetic testing completed a questionnaire eliciting demographic data, cancer history, genetic test results, and an estimate of their CRC risk. Associations between clinical factors, genetic test results, and CRC risk perception were explored using multivariable analyses.

Results
Of the 100 individuals with a pathogenic mutation (true positive), 90 (90%) correctly estimated their CRC risk as "high" or "very high" compared with other individuals their age. However, only 23 (62%) of 37 individuals with an indeterminate genetic test result correctly estimated their risk. Individuals with a history of Lynch syndrome–associated cancer (odds ratio [OR], 0.1; 95% CI, 0.1 to 0.6) or indeterminate genetic test results (OR, 0.2; 95% CI, 0.1 to 0.6) were significantly less likely to estimate their CRC risk as increased.

Conclusion
Patients at risk for Lynch syndrome with an indeterminate genetic test result may be falsely reassured. It is important that health care providers continue to discuss the implications of uninformative results on lifetime cancer risk.

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INTRODUCTION

Lynch syndrome or hereditary nonpolyposis colorectal cancer (HNPCC) is caused by inherited germline mutations in mismatch repair (MMR) genes and accounts for 2% to 5% of colorectal cancers (CRCs).[1,2] It is characterized by young-onset CRC; synchronous and metachronous tumors; and a predisposition to gynecologic, urinary tract, and extracolonic GI cancers. Individuals with Lynch syndrome have an 80% lifetime risk of CRC if colonoscopy is not performed,[3,4] and women have a 40% to 60% lifetime risk of endometrial cancer. For patients with Lynch syndrome, screening with colonoscopy is recommended every 1 to 2 years, beginning at age 20 to 25 years,[5,6] and annual transvaginal ultrasound and/or endometrial aspirate is recommended for women beginning at age 25 to 35 years.[5,7] Screening with colonoscopy has been shown to be effective in reducing the incidence and mortality of CRC by 65% among individuals at risk for Lynch syndrome.[4,8]

Commercial testing is available for mutations in the MMR genes, and test results can guide screening recommendations. In families with a known pathogenic mutation, it is recommended that individuals who carry the mutation (true positive) undergo intensive cancer screening. In contrast, for individuals who do not carry the family mutation (true negative), screening recommendations are the same as those for the general population. However, pathogenic mutations in *MLH1* and *MSH2* have been identified in only 30% to 64% of families who meet clinical criteria for Lynch syndrome and have undergone testing.[9] Genetic testing may not yield a definitive result because of the lack of an identifiable

mutation in one of the known genes or a mutation of unclear pathogenic significance. In the absence of an identified family mutation, these results are considered indeterminate or uninformative. Patients remain at increased risk for CRC, and intensive cancer screening recommendations are made on the basis of their personal and family cancer history.

There are limited data regarding the perception of lifetime cancer risk among patients who have undergone genetic testing for Lynch syndrome. It was our hypothesis that patients with true-positive genetic test results have an appropriate perception of their elevated cancer risk, but patients with indeterminate results may underestimate their CRC risk. We sought to examine CRC risk perception in individuals tested for MMR gene mutations associated with Lynch syndrome and to identify the factors associated with an appropriate cancer risk perception.

PATIENTS AND METHODS

We conducted a cross sectional questionnaire study among individuals with possible Lynch syndrome on the basis of a personal or family history fulfilling the Revised Bethesda Guidelines.[10] Eligible individuals were identified through cancer genetics clinics (Dana-Farber Cancer Institute and Massachusetts General Hospital, Boston, MA; University of Michigan, Ann Arbor, MI; and University of California San Francisco, San Francisco, CA) or referred by a family member. Potential participants were enrolled at a clinical visit or by mail. Participants who were known to have microsatellite-stable tumors were not enrolled onto the study. Participants who had undergone genetic testing were enrolled at least 3 months after disclosure of their test results.

Of the 462 eligible individuals approached for enrollment, 270 (59%) completed the study questionnaire, 34 (7%) declined to participate, and 158 (34%) were nonresponders. Females and college graduates were more likely to complete the questionnaire. Of the 270 participants who completed study questionnaires, 174 (64%) reported that they had undergone genetic testing for Lynch syndrome more than 3 months prior, and 159 of them provided an estimate of their CRC risk. Data from participants who had not had genetic testing were not included in this analysis. The study was approved by the institutional review boards at all sites.

Measures

The study questionnaire collected demographic data and personal history of colorectal polyps, CRC, and surgery for CRC. Participants provided information about the prevalence of cancers and genetic test results for first- and second-degree relatives. Participants also reported whether they had undergone genetic testing for Lynch syndrome. Test results were verified with medical records, and participants were classified as being true positive (deleterious mutation in *MLH1*, *MSH2*, *or MSH6*), true negative (known mutation in a family member and no mutation found in participant), and indeterminate (mutation of unclear pathogenic significance or no mutation identified in the participant or in a family member).

Participants estimated their CRC risk on a 5-point Likert scale ("very high" through "very low"), comparing their risk of CRC with that of other individuals their age. The following question was used: compared with people your age, what do you think your chances of developing colorectal cancer are? (If you have been diagnosed with colorectal cancer in the past, what do you think are your chances of developing another colorectal cancer?)

For individuals with true-positive or indeterminate genetic test results, their CRC risk perception was considered appropriate if they estimated their risk as being "high" or "very high" compared with that of other individuals their age. For individuals with true-negative results and no personal history of CRC or adenomas, risk perception was considered appropriate if they reported their CRC risk to be "average" compared with that of other individuals their age. For individuals with true-negative genetic test results with a history of CRC or adenomas, risk perception was considered appropriate if they reported their CRC risk as "high" or "very high" compared with that of other individuals their age. Patients who had undergone a total colectomy were excluded from the analysis.

Endometrial cancer risk perception was evaluated for the subset of women at risk who had not undergone prior hysterectomy. Endometrial cancer risk perception was considered appropriate if lifetime risk was reported to be "high" or "very high" in women with true-positive or indeterminate genetic test results and the same as "average" in women with true-negative results.

Statistical Analysis

Proportions of individuals with appropriate cancer risk perception were calculated. Income, age, education, personal history of cancer, and family history of Lynch syndrome cancer in a first-degree relative were analyzed as dichotomous variables. The associations among clinical and demographic factors and CRC risk perception were explored using Fisher's exact test/χ^2. Magnitude of the effect was quantified using odds ratios (ORs).

Multivariable logistic regression analyses were constructed using predictors that were clinically significant and/or predictors with $P < .05$ on univariate analysis. Generalized estimating equations were used to account for potential clustering of results among members of the same family. All P values are two sided, and $P < .05$ was considered significant. Statistical analyses were performed using SAS software (version 9.1, SAS Institute, Cary, NC).

RESULTS

The mean age of the 159 study participants was 46.2 years (range, 18 to 74 years). A total of 100 (63%) individuals were true positive, 22 (14%) were true negative, and 37 (23%) had indeterminate results. Eighty-nine percent (142 of 159) had been evaluated at high-risk or genetics clinics. (Table 1).

Overall, 127 (79.8%) of 159 individuals correctly estimated their risk of CRC (Table 2). Of the 100 individuals with true-positive genetic tests, 90 (90%) appropriately estimated their CRC risk as being "high" or "very high" compared with other individuals their age. In contrast, 23 (62%) of 37 individuals with an indeterminate genetic test result correctly reported that their CRC risk was increased compared with that of other individuals their age.

Of 14 individuals with indeterminate results who underestimated their CRC risk, six estimated their risk as "low" or "very low" compared with "average," and eight estimated their risk to be the same as that of an average individual. All but one of the 14 individuals had a personal history of cancer and nine (64%) of 14 individuals had previously been diagnosed with CRC.

Among the individuals with true-negative results, eight (36%) of 22 incorrectly estimated their CRC risk. Four individuals underestimated their cancer risk as being "low" or "very low" compared with that of other individuals their age. Three individuals from Amsterdam families overestimated their CRC risk as being "very high" despite a negative test for the identified family mutation and no personal history of cancer or polyps.

On univariate analysis (Table 3), there was no significant difference in the accuracy of CRC risk perception by age, sex, income, family cancer history, or by study site. Individuals seen at a high-risk cancer clinic or by a genetic counselor were not more likely to correctly estimate their cancer risk. However, race/ethnicity, education, a personal history of a Lynch syndrome–associated cancer, and indeterminate genetic test results (compared with a positive test result) were associated with accurate CRC risk perception on univariate analysis.

Table 1. Characteristics of Study Population (N = 159)

Characteristic	No. of Patients	%
Age at cancer diagnosis, years		
< 50	92	57.8
≥ 50	66	41.5
Unknown	1	0.6
Sex		
Female	116	73.0
Male	43	27.0
Race/ethnicity*		
White	145	90.7
African American	2	1.3
Hispanic	5	3.1
Native American	2	1.3
Asian American	3	1.9
Other	4	2.5
Education		
< College graduate	47	29.5
≥ College graduate	110	69.2
Unknown	2	1.3
Household income, US$		
< 50,000	30	18.8
≥ 50,000	118	74.2
Unknown	11	6.9
Personal history of cancer		
Yes	93	58.5
No	66	41.5
Personal history of Lynch syndrome cancer		
Yes	88	55.3
No	71	44.7
Prior MSI test performed		
Yes	33	20.8
No	126	79.2
Test results		
True positive	100	62.9
Indeterminate	37	23.2
True negative	22	13.8
First-degree relative with Lynch syndrome cancer		
Yes	141	88.7
No	18	11.3
Ever evaluated at genetics/high-risk clinic		
Yes	142	89.3
No	16	10.1
Unknown	1	0.6
Site of care		
Dana-Farber Cancer Institute	52	32.7
Massachusetts General Hospital	10	6.3
University of California San Francisco	67	42.1
University of Michigan	30	18.9

Abbreviation: MSI, microsatellite instability.
*Individuals reported belonging to more than one racial/ethnic group.

In multivariable logistic regression analysis (Table 3), participants with indeterminate results for a Lynch syndrome mutation (OR, 0.22; 95% CI, 0.1 to 0.6) were significantly less likely to appropriately estimate their CRC risk compared with individuals with true-positive results. Participants with a personal history of Lynch syndrome–associated cancer were also significantly less likely to appropriately estimate their CRC risk (OR, 0.08; 95% CI, 0.1 to 0.6).

To explore whether CRC risk perception had an impact on screening practices, we examined colonoscopy rates in all study participants. Sixty-two percent of individuals with accurate risk perception reported having had a colonoscopy at least every 5 years, compared with 29% of individuals with inaccurate risk perception (OR, 3.94; 95% CI, 1.7 to 9.2). Because individuals with true-positive and indeterminate results are at high risk for Lynch syndrome and require intensive CRC screening, an appropriate screening interval for them was considered to be every 2 years or more often, and every 5 years for individuals with true-negative results who had a history of an adenoma or every 10 years in the absence of a history of an adenoma. We found that patients with accurate CRC risk perception were significantly more likely to have undergone appropriate CRC screening compared with those who had inaccurate risk perception (OR, 2.47; 95% CI, 1.1 to 5.7).

Fifty-three women who had not previously undergone a hysterectomy provided an estimate of their lifetime risk of endometrial cancer. Endometrial cancer risk was reported to be "high" or "very high" compared with "average" by 27 (90%) of 30 women with true-positive results, seven (64%) of 11 with indeterminate results, and zero (0%) of 12 women with true-negative results. Women who accurately estimated their CRC risk were significantly more likely to accurately perceive their endometrial cancer risk (OR, 21.0; 95% CI, 2.2 to 200.3).

DISCUSSION

The results of our multicenter study indicate that cancer risk perception in individuals undergoing genetic evaluation for Lynch syndrome varies significantly with the genetic test result, and that a significant proportion of individuals who are at high risk for CRC underestimate their risk. In our study, 90% of individuals with a true-positive genetic test result correctly recognized their CRC risk as increased; however, 38% with indeterminate test results did not believe their risk of CRC was above average, and 36% of individuals with true-negative results misinterpreted their CRC risk. Individuals previously diagnosed with Lynch syndrome–associated cancer were more likely to underestimate their risk of developing a second CRC. Women with inaccurate CRC risk perception were also less likely to accurately assess their risk of endometrial cancer.

Studies of cancer risk perception in patients undergoing testing for familial cancer syndromes have predominantly included patients at risk for hereditary breast and ovarian cancer,[11-13] and few studies include patients at risk for Lynch syndrome.[14,15] Although to our knowledge, there have been no published studies evaluating CRC risk perception in individuals with indeterminate results for Lynch syndrome, a study of 500 women who underwent testing for *BRCA1/2* genes demonstrated lower perceived cancer risk in women with indeterminate results compared with carriers.[11] These results lend support to our findings that individuals with indeterminate results may be falsely reassured even though their risk of CRC is still above that of an average individual. Family cancer history has been demonstrated to influence risk perception,[16] and in our study, nearly all the individuals with true-negative results who had overestimated their CRC risk had a family cancer history that met the Amsterdam criteria for Lynch syndrome. Indeed similar findings of a pessimistic bias have been

Table 2. Colorectal Cancer Risk Perception by Genetic Test Result

Mutation Status and Risk Perception	Appropriate Risk Perception		Inappropriate Risk Perception		Total Cohort	
	No.	%	No.	%	No.	%
True positive					100	63
High/very high	90	90	0			
Average	0		5	5		
Low/very low	0		5	5		
Indeterminate					37	23
High/very high	23	62	0			
Average	0		8	22		
Low/very low	0		6	16		
True negative					22	14
High/very high	0		4	18		
Average	14	64	0			
Low/very low	0		4	18		
Total cohort	127	80	32	20	159	

NOTE: Responses to question: Compared with people your age, what do you think your chances of developing colorectal cancer are? (If you have been diagnosed with colorectal cancer in the past, what do you think are your chances of developing another colorectal cancer?): very high, high, average, low, very low.

noted in women with true-negative *BRCA* results who have a family history of breast cancer.[17] The underestimation of CRC risk in subjects with a history of Lynch syndrome–associated cancer is more complex. It is possible that these individuals believed that because they had been diagnosed with cancer in the past, their risk of developing a second CRC was lower. It is also possible that the optimistic bias in these motivated subjects may have resulted from the perception that recurrent CRC was preventable with endoscopic screening.

It is important to consider potential limitations of our study. First, our method of estimating cancer risk was complex because patients were asked for a comparative assessment of risk in relation to an average individual. This method of qualitatively estimating cancer risk has been widely used, and individuals were able to make clinically important distinctions about whether they thought their risk was the same as the average individual their age or their risk was higher or lower. In addition, the use of numerical values is inherently more cognitively challenging and may result in misclassification.[18] Nevertheless, there is surely inherent individual variation in how participants interpreted the question that is difficult to control for.[19] Second, paticipants were enrolled through specialized cancer centers and were highly motivated individuals. Our results likely represent an optimistic view of accurate risk perception of genetic test results in general. Third, we broadly defined appropriate CRC screening among patients who underwent genetic testing for Lynch syndrome. Additional studies are needed to systematically evaluate compliance with screening because recommendations vary based on patient history as well as on results of molecular evaluation. Fourth, although the general approach to genetic testing was similar across sites, genetic counseling was not standardized as part of the study. Therefore, variations in how and what information was presented by providers and its integration in

Table 3. Analysis of the Association of Risk Factors With Appropriate Cancer Risk Perception

Characteristic	Univariate Analysis			Multivariable Analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age, < 50 years	1.18	0.5 to 2.6	.67			
Sex, female	0.72	0.3 to 1.7	.47			
White race/ethnicity	3.60	1.1 to 11.3	.02	2.46	0.1 to 0.7	.25
Education, < college	0.40	0.2 to 0.9	.03	0.37	0.1 to 1.1	.07
Income, < $50,000	0.81	0.3 to 2.2	.69			
Indeterminate genetic test result	0.18	0.1 to 0.5	.001	0.22	0.1 to 0.6	.01
Personal history of cancer	0.42	0.2 to 1.0	.05			
Personal history of Lynch syndrome cancer	0.35	0.1 to 0.9	.02	0.08	0.1 to 0.6	.02
First-degree relative with cancer	0.81	0.2 to 2.9	1.00			
First-degree relative with Lynch syndrome cancer	1.10	0.4 to 3.0	.86			
Genetics/high-risk clinic visit	0.93	0.3 to 3.5	1.00			
Site of care	NA		.84			

Abbreviations: OR, odds ratio; NA, not applicable.

the follow-up care of patients would inevitably have existed. Our goal was not to study the effect of a standardized genetic counseling intervention on risk perception, but to focus on the specific outcome of risk perception based on test results. Our findings indicate that hereditary CRC risk counseling may need to include syndrome-specific experts as well as guidance from behavioral scientists to ensure the most effective communication. As genetic testing becomes more prevalent, attention will need to be paid to the content of risk information as well as how it is delivered. Variability in extent and type of counseling as well as individual psychosocial variables may constitute critical factors for patients' understanding of their test results.

Our results also have important downstream implications. Studies have suggested that genetic test results may influence uptake of screening, prophylactic surgery, and the dissemination of risk information to relatives.[20-24] Indeed in our study, individuals with inaccurate CRC risk perception were less likely to have appropriate CRC screening, and women were also more likely to inaccurately assess their risk of endometrial cancer. Thus, it is important to explore the reasons for inappropriate risk perception. Individuals' perception of their cancer risk may be affected by their understanding and retention of genetic test results, variation in communication of risk by their health care providers, and a host of other factors including their personal and family history of cancer. Interpretation of genetic test results can be complicated, and the concept of an indeterminate result is often confusing even for physicians ordering these tests. A study by Giardiello et al in individuals with familial adenomatous polyposis that evaluated the use of commercial *APC* gene testing found that in 31.6% of cases, physicians may have misinterpreted test results because of an indeterminate finding.[25]

What can be done to improve cancer risk perception? Guidelines recommend pre- and post-test counseling and discussion of the implications of genetic predisposition testing.[26] Although the genetic counseling process was not standardized as part of the study, all patients who undergo genetic testing at our institutions are seen by a certified or board-eligible genetic counselor, and the majority of patients also meet with either an oncologist or gastroenterologist with training in genetics at the same visit. Although patients are frequently referred by primary care providers, testing is initiated in the high-risk clinic after pretest counseling. Patients are requested to return for post-test counseling regardless of their result, and in only a few cases are results disclosed via telephone. In those rare circumstances, patients are invited to return for another in-person visit. In our study, 89% of individuals reported being seen by a genetic counselor or in a high-risk clinic. Despite these ideal circumstances under which testing and counseling were performed, 20% of individuals inappropriately estimated their cancer risk. With an increase in direct-to-consumer marketing of genetic testing, there is an even higher risk of the misinterpretation of genetic test results.

Our findings underscore the complexity in risk communication. Studies are needed to systematically evaluate both patient- and physician-related factors responsible for inappropriate perception of risk in order to develop effective interventions. Physician and patient education are necessary so that indeterminate genetic test results do not provide false reassurance. The use of standardized educational material that outlines the implications of test results and recommendations for management may minimize variability in information provided to patients, facilitate knowledge retention, and provide specific screening recommendations for individuals who remain at high risk.

In addition, particularly for indeterminate test results, there needs to be longitudinal follow-up and reinforcement of the meaning of the test results. These patients may benefit from additional genetic counseling and from reinforcement from the primary care physician who observes the patient on a long-term basis after the genetic counseling and testing encounter is completed. The benefits of reinforcement would not be limited to individuals with true-positive and indeterminate results, but would also be available to individuals with true-negative results.

Our study was limited to patients at risk for a highly penetrant inherited cancer syndrome, for which interpretation of true-positive and true-negative results is relatively straightforward in terms of cancer risk and screening recommendations. As additional moderate- and low-susceptibility genes are identified, the implications of even a positive result are likely to be complex and may depend on a variety of factors, including the relationship with other genes, environment, and behaviors. Understanding how patients interpret such information and developing strategies to enhance communication of benefits and limitations of genetic testing is an area worthy of continued study.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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