Communication, encouragement, and cancer screening in families with and without mutations for hereditary nonpolyposis colorectal cancer: A pilot study

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Purpose: Known and suspected mutation carriers for hereditary nonpolyposis colorectal cancer are advised to have colonoscopies every 1 to 2 years to detect colorectal cancer. Little is known about colonoscopy completion in families suspected of having hereditary nonpolyposis colorectal cancer but without identified mutations. **Methods:** This study examined the effect of communication and encouragement on colonoscopy in families with and without known mutations. Twenty-three respondents from 11 families with indeterminate genetic test results were matched with 23 respondents from 11 families with mutation-positive results. Hierarchical modeling examined the effects of relational characteristics on time since last colonoscopy in index cases and their first-degree relatives. **Results:** Nearly one fifth of respondents were not screening appropriately. Time since last screening did not differ according to family mutation status. However, respondents who communicated about risk and received encouragement to screen from a greater proportion of named family members, and those who had a greater proportion of named family members involved in both communication and encouragement were significantly more likely to have a shorter time interval since last colonoscopy. **Conclusion:** Identifying patterns of interaction within at-risk families, regardless of gene mutation status, may be one avenue for promoting screening adherence. ***Genet Med*** **2009:11(10):728–734.**

Key Words: *hereditary nonpolyposis colorectal cancer, cancer screening, communication, encouragement, indeterminate genetic test results*

Hereditary nonpolyposis colorectal cancer (HNPCC) is an inherited cancer susceptibility syndrome predisposing affected individuals to increased risks for colorectal cancer (CRC) as well as endometrial, ovarian, small intestine, and other cancers. Risk for HNPCC is evaluated based on clinical presentation, pathologic criteria, and family history.[1,2] Mutations in mismatch repair (MMR) genes are associated with HNPCC. Individuals carrying a MMR gene mutation have estimated lifetime risks of developing CRC as high as 69% in men and 52% in women.[3–5] Advances in mutation detection have dramatically improved during the last decade, with the identification of mutations within MMR genes associated with HNPCC improving from 50%[6] to estimates as high as 84%.[7] Even with this significant improvement in detecting disease-causing mutations, a proportion of individuals suspected of having HNPCC will receive indeterminate results. Indeterminate results occur when no mutation is present, current technology does not detect the mutation, or a mutation is present in a gene not yet known to be associated with HNPCC.[6] Failure to find a mutation in an index case does not eliminate the possibility of HNPCC nor does it decrease the associated cancer risks.

Colonoscopy screening in individuals at risk for HNPCC prevents CRC and reduces associated deaths. Precancerous polyps associated with HNPCC develop earlier in life and progress more quickly to malignancy.[1] A 15-year-controlled study of colonoscopy screening in persons at risk for HNPCC demonstrated a 62% reduction in CRC rates, more favorable stage presentation of cancer, and a reduction in CRC-associated mortality in the intensive screening group.[8] Under current recommendations, individuals at risk for HNPCC should have a colonoscopy every 1 to 2 years starting between the ages of 20 to 25 years.[1] Recent studies[9–11] examining screening behaviors after genetic testing for HNPCC reported varying rates of adherence to screening guidelines among mutation carriers and noncarriers in families with identified mutations. However, there is limited research investigating CRC screening among index cases with indeterminate genetic test results and their at-risk first-degree relatives (FDRs). Limited data suggest that index cases with indeterminate genetic test results might be less likely to screen for CRC in the year after receiving their genetic test results compared with those with mutation-positive test results.[12]

This study was guided by the framework put forward by Berkman et al.,[13] which focuses on the impact social networks have on health. Relationships can impact health through social and informational influence. The framework builds on the premise that the social networks surrounding individuals are essential to their health and well-being.[14] Previous research found that family support and communication,[15] encouragement to screen and recommendations for screening from family members and health care providers,[16,17] and discussion about CRC with social groups[16] are positively related to CRC screening among individuals at increased risk for CRC. Among families at high risk for CRC, family communication motivates participation in colonoscopy screening.[18] However, although these studies examined the effect of relational factors on CRC screening, they did not include families at risk for HNPCC, whose members need to screen more frequently and at an earlier age for associated cancers, or families at risk for HNPCC but with indeterminate genetic test results. In this study, a family-based approach, focusing on index cases and their FDRs, was used to

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examine the association of communication and encouragement with CRC screening behaviors. Of primary interest was comparing screening between families with indeterminate genetic test results and those with identified mutations and determining whether relational factors affected time since last colonoscopy. The following research questions guided the investigation:

1. What are the CRC screening behaviors of index cases with indeterminate HNPCC genetic test results and their at-risk FDRs, and do these differ from index cases and FDRs in mutation-positive families?
2. What relational factors affect CRC screening in families in which the index case received indeterminate genetic test results, and do these differ from those in mutation-positive families?

MATERIALS AND METHODS

Data for this study were gathered through two mechanisms. Data on all index cases and on family members from mutation-positive families were collected as part of an ongoing longitudinal study of genetic education, counseling, and testing for HNPCC, located in the Division of Intramural Research of the National Human Genome Research Institute (NHGRI Protocol #95-HG-0165; National Naval Medical Center Protocol #NNMC.1995.0045). Members of families with indeterminate genetic test results were recruited through an addendum to the original protocol, which received ethical approval from the Institutional Review Board of the National Human Genome Research Institute, NIH, US. All respondents consented to participate.

The parent study has been described in detail.[9,19] Briefly, individuals who met clinical, pathologic, and family history criteria for HNPCC were invited to receive a scripted, face-to-face, genetic education session, as well as client-centered counseling, and the offer of genetic testing for HNPCC. When available, tumor blocks were evaluated for microsatellite instability to provide further evidence of HNPCC. Genetic testing of index cases resulted in either detection of a deleterious mutation (mutation-positive results) or failure to detect a deleterious mutation (indeterminate results); these results were provided to index cases during in-person genetic counseling sessions.

Biological relatives of mutation-positive index cases were recruited to the parent study using cascade sampling. Recruitment started with those at 50% risk to inherit the mutation; those at 25% risk were recruited if the intervening relative had died. Biological relatives of mutation-positive index cases also received scripted, in-person, genetic education information, as well as client-centered genetic counseling. Genetic testing was offered to these individuals. Family members who chose to have genetic testing received test results during an in-person counseling session.

During the provision of genetic test results to all participants in the parent study (index cases and biological relatives of mutation-positive index cases), cancer-screening recommendations were reviewed and written recommendations were provided. Depending on the date of entry into the study, all index cases and mutation-positive family members were instructed to have colonoscopy screening every 1 to 3 or 1 to 2 years, starting at the age of 20 to 25 years.[1,20] Biological relatives of index cases with indeterminate genetic test results were not eligible to participate in genetic counseling, education, or testing through the parent protocol and did not receive screening recommendations from the study team.

Procedure

The goal of this study was to compare colonoscopy screening, and the effect of relational factors on screening, between families with indeterminate and mutation-positive HNPCC genetic test results. The study recruited index cases who had genetic testing and their adult children and siblings (FDRs). Parent study participants (indeterminate and mutation-positive index cases and FDRs of mutation-positive index cases) had all received genetic education, counseling, and testing through the parent study protocol. They were sent a flyer and offered participation in the addendum. Those expressing interest completed a questionnaire and telephone interview. FDRs of index cases with indeterminate genetic test results were recruited using modified cascade sampling.[21] Index cases with indeterminate genetic test results identified FDRs they were willing to contact regarding the study; eligible FDRs were the adult biological children and siblings of index cases. Index cases sent study information to FDRs. Participants received gift cards to nationwide retail stores on completing the study procedures.

Respondent matching

Indeterminate and mutation-positive index cases and FDRs were matched to maximize the power available for the analysis and control for characteristics that might influence screening behaviors (e.g., age at cancer diagnosis of the index case and family history of cancer). The first priority was to match index cases on disease characteristics, whereas the second priority was family characteristics, with FDR relationship to the index case being more important than age. The first step in the matching process was to classify index cases with indeterminate genetic test results according to sex, age, and type of cancer. On the basis of these characteristics, they were matched to mutation-positive index cases, providing matched indeterminate/mutation-positive family pairs. Within each matched family pair, participating FDRs were enumerated, characterized according to relationship to the index case, sex, and age, and matched. Because these characteristics were prioritized, and there were a limited number of participating family members available for the match process, FDRs from mutation-positive families could have positive or negative genetic test results or may not have had genetic testing. The possible effect of mutation-negative status on screening behavior was controlled for in the analyses (see Covariates section, later). All index cases were successfully matched based on sex, 87.5% were matched within a 10-year age range, and 62.5% were matched for type of cancer. One pair of FDRs (6.6%) was not matched on sex, most (73%) were matched based on their relationship to the index case, and nearly half (46.7%) were matched within a 10-year age range.

Measures

Study variables were derived from surveys assessing self-reported CRC screening behavior and an interview assessing family communication and encouragement to screen. The study used social network analysis[22] to examine the impact of relational factors (e.g., communication and encouragement) on health behaviors. The study focused on family networks, as created by study respondents. At the beginning of the interview, respondents were asked, "When I say 'family', who do you think of?" Individuals listed in response to this question were considered the respondent's family network. Family was defined by the respondent and could include biological as well as nonbiological kin.

Outcome variable

The outcome variable of interest was time since last screening colonoscopy. This was measured using one survey item: "When did you last have a colonoscopy?" Response options included within the past year, between 1 and 2 years ago, between 2 and 3 years ago, >3 years ago, and never had a colonoscopy. Measurement relied on respondents' self-report. Based on recommended cancer screening guidelines, persons at risk for CRC should have screened within the last 3 years, and those with no increased risk for CRC based on genetic test results should have screened according to general population guidelines.

Predictor variables

The predictor variables of interest were family mutation status, communication about cancer risk status, and encouragement to screen for CRC. Family mutation status was defined as mutation-positive versus indeterminate, based on the genetic test results received by the index case in each family, which were confirmed by test report. Communication and encouragement were measured using two interview questions, "With whom in your family have you shared your thoughts about your HNPCC cancer risk status?" and "Who in your family encourages you to screen for CRC?" For both, the proportion of family members named in response to each question was calculated, equivalent to the number of named family members relative to the total number of family members. A variable was also created for network members who were involved in both communication about risk and encouragement to screen. Interaction terms were created to examine the interaction of family mutation status with communication and encouragement.

Covariates

Covariates included age, whether the participant had tested negative for a known family mutation (i.e., was a confirmed noncarrier), and the number of dyads participating from each family. In the absence of other risk factors, individuals from families with identified mutations, who receive mutation-negative test results, are considered to be at population-level risk for CRC. They are not expected to screen as frequently as individuals who have mutation-positive test results or who have not yet had genetic testing but should be screening for CRC according to the general population guidelines (beginning at the age of 50 years). Thus, age and confirmed noncarrier status were included as covariates to account for these respondents. Actual age in years was converted to 50 years and older versus younger than 50 years. An indicator variable was used to denote those participants who tested negative for the known mutation in their families. Carrier status was extracted from study records for individuals who participated in the parent study and was based on pedigree assessment for those who did not. The interaction of age and noncarrier status (older than 50 years × confirmed noncarrier) was also entered into the model.

Data analysis

Hierarchical linear modeling (HLM) techniques were used to examine associations between the predictor variables and the outcome variable of interest. Hierarchical models account for the nested structure of the data.[23,24] Data were obtained from individuals nested within dyads nested within matched family pairs. A three-level model was fitted to account for the matching of participants across families. The first level models the relationship between individual characteristics and the outcome variable; the second level accounted for the matched pairs in these associations; and the third level accounted for matched families. The intraclass coefficient (ICC) was calculated for the unconditional model, yielding an ICC of 0.18. Because the ICC exceeded 0.10, the multilevel model accounting for the matching process was fitted.

HLM 6.06,[25] a software program designed for HLM, was used to fit the models. The outcome variable, time since last colonoscopy, was treated as a continuous variable. Separate bivariate linear regression models were fitted for each predictor variable in an effort to ensure adequate power to detect differences. These models used a random intercept with covariates at Levels 1 and 3; the small sample size prohibited fitting random slope models. Level 1 covariates included age, noncarrier status, and the interaction between age and noncarrier status. The Level 3 covariate was the number of respondent dyads within each family match. A Type I error rate of 0.05 was used for all analyses.

RESULTS

Sample characteristics

Complete data were obtained from 46 individuals, including respondents from indeterminate families and their matched counterparts from mutation-positive families. Eight of 13 (61.5%) indeterminate index cases completed both the survey and interview. Fifteen of 34 (44%) FDRs of indeterminate index cases completed both the survey and interview. These 23 respondents from indeterminate families were then matched to 23 respondents from mutation-positive families. Eight (53.3%) FDRs from mutation-positive families tested negative for the identified mutations in their families, whereas two (13.3%) have not yet been tested. Overall, data were obtained from 22 families: 11 mutation-positive and 11 indeterminate.

Respondents were primarily women, well educated, employed, older than 50 years, and partnered (Table 1). All identified themselves as white. All index cases and 13 of 15 FDRs of mutation-positive index cases ($n = 29$; 63% of all respondents) participated in the parent study and received genetic education, counseling, and testing. The mean time since receipt of genetic test results, and the final genetic education and counseling session, was 73.28 ± 30.2 months. Average time elapsed for index cases was 81.94 ± 31.05 months and for FDRs, 62.62 ± 26.44 months. All FDRs of indeterminate index cases and two FDRs of mutation-positive index cases ($n = 17$; 37% of all respondents) did not receive genetic education, counseling, and testing through the parent study. Over half of the total sample (53%) had a colonoscopy within the past 2 years. However, 28.2% of the total sample either never had a colonoscopy or had a colonoscopy >3 years ago (Table 2). This includes 26.1% of respondents from families with indeterminate genetic test results, who remain at high risk for HNPCC-associated cancers, and 13% of respondents at risk for HNPCC from mutation-positive families. In total, 19.6% of all respondents who remain at risk for HNPCC last had a colonoscopy >3 years ago.

Enumeration of family members yielded 599 social ties across all respondents. Respondents named, on average, 11.93 ± 6.65 family members to be in their family networks (range, 3–43; Table 1). Of these, half were in the same generation as the participant (50%), one third were younger (33%), and the remainder were older (17%). On average, enumerated network members were 44 years of age (SD = 22 years). Over half (55%) were women and 49% were at risk of HNPCC. Predominantly, biological family (70%) were enumerated; however, nonbiological family (20%, including spouse), social ties,

Table 1 Demographic, social, and clinical data

Variable	Percentage	Mean (SD)
Age (older than 50 yr)	54	
Respondent not at risk	17	
Sex (female)	89	
Previous cancer diagnosis	50	
Nonparticipant in parent study	37	
Partnered	67	
Employed	59	
Highest level of education completed[a]		3.70 (1.03)
Last colonoscopy[b]		2.59 (1.44)
Months since last genetic education/ counseling session		73.28 (30.19)
Number of named individuals in respondent's network		11.93 (6.65)
Proportion network members encouraging CRC screening		0.23 (.26)
Proportion network members talked to about genetic counseling and testing for HNPCC		0.51 (.35)
Proportion network members with whom respondent shared thoughts about risk for HNPCC cancers		0.51 (.36)
Proportion network members involved in communication and encouragement		0.20 (.25)

[a]1 = less than high school, 2 = high school graduate, 3 = vocational school/some college, 4 = college, 5 = graduate school.
[b]1 = within the past year, 2 = in the past 1–2 yr, 3 = in the past 2–3 yr, 4 = >3 yr ago, 5 = never.

such as friends (7%), and health care providers (3%) were also enumerated.

Predictor variables

Family mutation status was not significantly associated with time since last colonoscopy ($P = 0.46$) nor did it moderate the associations among communication, encouragement, and time since last CRC screening. Communicating about risk for HNPCC with a greater proportion of network members was significantly associated with more recent colonoscopies ($P = 0.04$). Similarly, having a larger proportion of network members who encourage CRC screening was associated with more recent colonoscopies ($P < 0.01$) (Table 3). Results also indicated that having a larger proportion of family members involved in both communication and encouragement was associated with more recent colonoscopies ($P < 0.01$).

DISCUSSION

This analysis focused on associations among communication, encouragement, and time since last colonoscopy among index cases with and without known HNPCC mutations and their FDRs. Family mutation status, communication about risk for HNPCC, encouragement to screen for CRC, and having family members who were involved in both communication and encouragement, were significantly associated with time since last colonoscopy. These findings represent one of the first comparisons of screening behavior between indeterminate and mutation-positive families. Although the study sample was relatively small, use of social network analysis and matching indeterminate and mutation-positive families facilitated the examination of the variables of interest.

There was no difference in time since last colonoscopy between respondents from mutation-positive versus indeterminate families. This finding adds to the existing literature on screening[26] by evaluating reported health behaviors instead of screening intentions. For respondents from indeterminate families, heightened awareness of family history might facilitate screening participation.[12] The finding is consistent with the behavioral impact of appropriate genetic education and counseling on HNPCC screening.[27,28] However, it is important to note that not all participants received genetic counseling, suggesting that communication about HNPCC and encouragement of CRC screening within at-risk families could be effective in promoting appropriate colonoscopy use. This contrasts with other findings that index cases with inconclusive genetic test results are less likely to have a colonoscopy in the year after receiving their genetic test results compared with mutation-positive index cases.[12] The screening behaviors presented here represent the long-term behavioral impact of genetic education and counseling, with measurements obtained, on average, 6 years after disclosure of genetic test results. Indeterminate and inconclusive genetic test results have the potential to cause greater emotional distress than true-negative results.[29,30] Some participants, particularly those in families with indeterminate genetic test results, may have taken longer to accept and act on screening recommendations. In addition, differences in sample size and variable measurement could contribute to reported differences.

Respondents who received encouragement to screen for CRC from a larger proportion of family members had more recent colonoscopies. Among at-risk siblings, FDRs of patients with CRC, and individuals at high risk for CRC, encouragement and recommendations to screen from family members and physicians are reported to improve screening.[16–18] Although participants were not asked specifically about health care providers during creation of the family network, 43% included a health care provider in their networks (data not shown). In addition, 3% of named encouragers were health care providers. Further examination of the role of health care providers in encouraging screening among individuals at high risk for CRC is warranted, including an exploration of the roles played by different health care providers (e.g., specialists and primary care providers). As genomics moves out of specialized clinics and into general practice, the role and influence of local health care providers on screening behaviors could increase.[31] In the general population, having a primary health care provider is associated with having a colonoscopy.[32] Under many health insurance plans, referrals from a primary health care provider are necessary to obtain screening examinations such as colonoscopy. This may be of particular importance in families at risk for HNPCC, given the need for early CRC screening. Improved education regarding hereditary cancer syndromes among general practitioners would help mitigate limited knowledge,[33,34] providing an important link among specialty care, general practice, and families. Future studies would benefit from including measures of encouragement to screen that focus on particular network members. This

Table 2 Time since last colonoscopy

	Entire sample ($n = 46$)		Mutation-positive families ($n = 23$)		Indeterminate families ($n = 23$)	
Interval	N (N^a)	Percent	N	Percent	N	Percent
Within the past year	14 (9)	30.4	9	39.1	5	21.7
Between 1–2 yr ago	11 (6)	23.9	4	17.4	7	30.4
Between 2–3 yr ago	8 (4)	17.4	3	13.0	5	21.7
More than 3 yr ago	6 (3)	13.0	4[b]	17.4	2	8.7
Never	7 (0)	15.2	3[c]	13.0	4	17.4

[a]Number with cancer history.
[b]Includes two individuals with identified mutations.
[c]Includes two individuals who have not received genetic testing for the family mutation and 1 individual who is mutation negative, but older than 50 yr.

Table 3 Logistic regression analysis

Variable	Coefficient	SE	Effect size	P
Proportion encouraged	−1.27	0.39	−0.23	<0.01
Proportion shared status	−1.15	0.53	−0.29	0.04
Proportion family members involved in communication and encouragement	−1.44	0.44	−0.25	<0.01

Separate logistic regression models were built for each outcome variable of interest. All analyses control for age (>50), risk status (not at risk), age × risk status, family mutation status, and number of dyads per family match.
Effect sizes were calculated by standardizing the regression coefficients.[39]
Outcome variable: last colonoscopy (1 = within the past year, 2 = in the past 1–2 yr, 3 = in the past 2–3 yr, 4 = more than 3 yr ago, 5 = never).

could help determine whether there is a differential effect of encouragement, depending on whether it is provided by a family member or a health care provider.

Respondents who communicated with a higher proportion of family members about risk for HNPCC had more recent colonoscopies. Individuals at high risk for CRC highlighted the motivating influence of family communication about CRC on completion of CRC screening.[18] Among FDRs of patients with sporadic CRC, discussion of CRC with social groups is associated with CRC screening.[16] Open family communication styles may facilitate the sharing of genetic risk information[35]; in turn, family members who learn of their own risk may be more inclined to participate in recommended screening. Having a larger proportion of family members involved in both communication and encouragement was also significantly associated with time since last colonoscopy, prompting speculation about family interactions. The current data were cross-sectional in nature, limiting our ability to ascertain the social mechanisms that promote CRC screening in at-risk families. Learning about the respondent's risk for disease may prompt family to offer encouragement for screening. Alternatively, individuals who encourage CRC screening may be viewed as network members who would be willing to hear and talk about being at risk for cancer. Prospective longitudinal studies would help disentangle these processes, providing necessary information for developing interventions that promote adherence to screening recommendations in at-risk families.

Although health care providers can directly influence patients' actions, they should also recognize the potentially important influence of family members on cancer screening. Tapping into everyday family interactions, in contrast to large-scale public health education campaigns,[36] may be another way to educate individuals at risk for HNPCC about cancer screening and improve compliance with screening recommendations. The benefits of a family-based intervention lie in the continued support and encouragement that family members can offer to at-risk individuals; interactions among family members are generally more frequent than those with health care professionals. Additional study of how social relationships influence individual behaviors[36,37] would aid in the development of interventions based on the informal social network. In this study, actions initiated by both the at-risk individual (communication) and social network members (encouragement) influenced the time since last colonoscopy. These findings might reflect the general communication pattern within the family and its potential effects on cancer screening.[38] After replication and verification of these findings, another potential area of health care provider intervention may include encouraging family communication about disease risk and cancer screening and providing support to individuals at risk for hereditary forms of cancer during these processes.

Several limitations of this study should be considered when interpreting results. The sample size for the study was relatively small, with 46 respondents. This restricted the number of analyses conducted and the inclusion of individual-level covariates (e.g., age, income, and education). Additional differences between groups may not have been apparent because of the small sample size. Because of this, respondents were matched and the number of analyses was limited. Larger-scale studies should be undertaken to better understand possible differences between mutation-positive and indeterminate families. Although respondent matching provided additional power for analysis, exact matches were not possible for all members of all families. Because of limitations of the family match process, individuals who tested negative for known family mutations were included in the analysis. Including only those who remain at high risk for HNPCC-associated cancers would provide an improved comparison for families with indeterminate genetic test results. Finally, broad response categories for the outcome variable limited the amount of detail gleaned from the data. This allowed comparison to data gathered in the parent study; however, measuring time since last colonoscopy in a more precise manner

might have resulted in greater insight into participants' screening behaviors.

Although many respondents in this study are meeting recommendations for colonoscopy screening, 26.1% of individuals from families with indeterminate test results, who remain at risk for HNPCC, are not, having had their most recent colonoscopy >3 years ago, or never having had one (Table 2). In addition, 13% of individuals from mutation-positive families are not screening appropriately. Respondents have more recent colonoscopies when risk is discussed and screening is encouraged. Although these findings have clear implications for clinical care of individuals at risk for HNPCC, replicated and expanded analysis of the association among family communication, family encouragement, and cancer screening would be valuable. Although the findings are limited by the relatively small sample size, use of a research-based population, and lack of ethnic diversity, these results suggest that health care providers should explore and encourage family communication about HNPCC risk to promote appropriate colonoscopy screening in individuals at risk for HNPCC.

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APPENDIX. STUDY QUESTIONS

Creating the family network
When I say "family," who do you think of?
Outcome variable

"When did you last have a colonoscopy?"

Response options: (1) within the past year, (2) between 1 and 2 years ago, (3) between 2 and 3 years ago, (4) more than 3 years ago, (5) never had a colonoscopy.

Predictor variables

Communication: With whom in your family have you shared your thoughts about your HNPCC cancer risk status?

Encouragement: Who in your family encourages you to screen for colorectal cancer?