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Colonoscopy use following mutation detection in Lynch syndrome: Exploring a role for cancer screening in adaptation

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Abstract

Lynch syndrome is the most common inherited form of colorectal cancer. Mutation carriers can reduce the morbidity and mortality associated with colorectal cancer through colonoscopy. Theoretical models suggest that such health related behaviors might also bring psychological benefits. This study assessed whether colonoscopy following mutation detection was associated with levels of depressive symptoms.

Data were obtained from a prospective family cohort study offering genetic services for Lynch syndrome. Participants completed questionnaires prior to the provision of services and 6-months post receipt of mutation results. One hundred thirty four (134) persons were identified to carry a mutation and completed both questionnaires. Main outcome measures were depressive symptoms 6-months post-receipt of test results.

Mutation carriers who did not complete a colonoscopy within the 6 months following receipt of results were 6 times ($p < 0.01$; OR=6.06) more likely to report depressive symptoms at a level of clinical importance compared to those who did undergo colonoscopy.

Facilitating the expeditious use of colonoscopy following mutation detection may benefit newly identified mutation carriers by addressing the objective risks for cancer and moderating underlying emotional distress responses to genetic risk information. Further, depressive symptoms may interfere with behavioral compliance in some patients, suggesting referral to mental health specialists.

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Keywords

Colonoscopy; health behavior; genetic testing; HNPCC / Lynch syndrome

INTRODUCTION

Lynch syndrome (also known as Hereditary Nonpolyposis Colorectal Cancer or HNPCC) is a dominantly inherited cancer susceptibility syndrome predisposing mutation carriers to the early onset of multiple cancers including colorectal, endometrial, stomach, ovarian, small intestine, hepatobiliary system, upper uroepithelial tract, pancreas, and brain. [1] Lynch syndrome (LS), which results from a deleterious mutation in the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6* and *PMS2*, is estimated to account for 1 in 45 cases of colorectal cancer. [2] Individuals carrying a deleterious mutation (carriers) are estimated to have lifetime risks of colorectal cancer as high as 69% in men and 52% in women. [2,3]

Carriers are encouraged to undergo screening for a selected group of LS associated cancers. Recommendations for colon cancer screening include initiating complete endoscopic¹ examination of the colon every 1–2 years beginning as early as 20 years of age. [4,5,6] Colonoscopy has been shown to significantly reduce the mortality and morbidity associated with colorectal cancer in LS. [7,8] Furthermore, behavioral research has shown that the provision of genetic services and unequivocal mutation results improves and appropriately focuses colonoscopy use; carriers increase their use of colonoscopy and non-carriers significantly decrease utilization. [9,10,11,12,13]. Studies reporting on the psychological impact of genetic testing for LS report no long-term adverse effects following the receipt of mutation results in unaffected carriers. [14,15,16,17]

Collectively, the literature suggests an overall benefit to the provision of comprehensive genetic counseling and testing for LS. However, aggregate results based on mean differences have the potential to conceal clinically significant effects on subsets of individuals within cohorts. [18,19] A growing number of studies have reported individual differences in distress responses following the provision of genetic test results even when decreases or no change in distress were found when individuals are considered as a group. [17,19,20,21] Within these studies, mutation carriers are consistently identified as persons more likely to exhibit higher levels of depressive symptoms in the short term. For some, this may be a normal part of adapting to newly acquired health risk information. However, others may be experiencing significant difficulty adapting to their carrier status and may benefit from interventions such as counseling aimed to facilitate psychological adaptation to increased cancer risk. Identifying modifiable factors that might facilitate adaptation among high-risk individuals warrants additional investigation. [22]

The Self-regulation Model of Illness Representations [23] posits that a person's cognitive and emotional images of a health threat generate coping behavior aimed at resolving the objective medical risks and at reducing the emotional distress induced by the threat. In the case of persons newly identified to carry a MMR mutation, completing a colonoscopy soon after the receipt of test results may play two roles: 1) address objective risks for colon cancer and 2) facilitate psychological adaptation to disease risk. The aim of this study was to explore the association between health behavior and psychological wellbeing within the context of an inherited cancer susceptibility syndrome with effective disease prevention options. We hypothesized that those mutation carriers who completed colonoscopy within

¹Colonoscopy is recommended, however, in persons with less than 60 centimeters of colon, flexible sigmoidoscopy provides complete screening of the remaining colon. Hereafter, we will use colonoscopy to represent complete examination of the colon

the 6 months following receipt of genetic test results would be less likely to report clinically significant levels of depressive symptoms than mutation carriers who did not undergo colonoscopy.

METHODS

The data were collected through a protocol approved and monitored by the Institutional Review Boards at the National Human Genome Research Institute (Protocol #95-HG-0165) at the National Institutes of Health (NIH) and the National Naval Medical Center (NNMC. 1995.0045), located in Bethesda, Maryland, (USA). All participants gave their written consent prior to participation. The study was conducted between 1995 and 2006.

Study Population

Individuals with a LS-associated cancer, demonstrating clinical (early age of cancer onset, multiple primary tumors, family history of cancer consistent with the Amsterdam criteria) and pathological (microsatellite instability of tumor tissue) criteria were recruited from oncologists and cancer genetics specialists throughout the United States, and from the cancer clinics within the National Institutes of Health and National Naval Medical Center. Individuals meeting criteria and consenting to participate (109 index cases) received genetics education, counseling and the option of molecular testing for Lynch syndrome (sequencing of *MSH2*, *MLH1* and in some cases *MSH6* genes). One hundred and five (105) chose to undergo genetic testing and forty-five (45) were found to carry a deleterious mutation. Four additional families were referred to the study after the identification of a deleterious mutation in an index case for a total of 49 families. Participation was extended to family members at risk to inherit the identified mutation resulting in the recruitment of 270 family members. Two hundred and fifty six (256) chose to undergo genetic testing and receive the results. Genetic testing in family members was focused on detecting the presence / absence of the family mutation (mutation specific testing). Only individuals identified as mutation carriers and completing the study questionnaires at baseline and 6 months post receipt of genetic test results were considered within the current report resulting in 134 carriers from 47 families.

Procedures

Following the identification of a deleterious MMR mutation in an index case [26], first-degree relatives (FDRs) at 50% risk of inheriting the mutation were invited to participate in a prospective study offering genetic counseling and the option of genetic testing for LS. Those persons consenting to participate completed a paper and pencil questionnaire prior to the in-person provision of genetic services. The questionnaire included assessment of demographic information, cancer history, depressive symptoms and cancer screening practices prior to the provision of genetic services. A comprehensive cancer family history was obtained on all participants and medical records were pursued on persons reporting a history of cancer for confirmation. Participants received comprehensive and standardized genetic education, client-centered counseling and the offer of genetic testing (GCT). The sessions were conducted by a genetic counselor, certified by the American Board of Genetic Counseling, or an advanced practice nurse with training in genetics.

Genetic testing was offered without cost. Those choosing to undergo testing had a blood sample collected and processed in a CLIA (Clinical Laboratory Improvement Amendment) approved laboratory. Results were disclosed in person, within 1–2 months of sample collection on average. Participants' mutation status was categorized as "carrier" or "non-carrier" based upon the CLIA result. Verbal and written cancer screening recommendations following published guidelines [5] were provided in all sessions. In addition,

recommendations in printed format were mailed to participants. Persons choosing genetic testing and receiving mutation carrier results were encouraged to invite their FDRs, at 50% risk to inherit the mutation, to participate, representing a cascade sampling approach to recruitment.

Six (6) months following the provision of mutation results, data on depressive symptoms and cancer screening practices were collected by telephone interview.

Variables of Interest

To assess depressive symptoms, we utilized the 20-item Center for Epidemiology Studies – Depression Scale (CES-D) [27] prior to GCT (baseline) and 6 months post receipt of genetic test results (post-disclosure). The CES-D Scale has been widely used in general population samples and in research focused on the provision of genetic testing for LS. [13,17,28] The scale has been shown to correlate with clinical ratings of the severity of depression [27]. Possible scores range from 0–60 with higher scores indicating a greater frequency and/or intensity of depressive symptoms. Published guidelines indicate individuals who score 16 or higher are experiencing clinically significant symptoms of depression. [27] Therefore, we dichotomized CES-D scores as high (CES-D \geq 16) or low (CES-D < 16).

The primary predictor variable of interest was participants' self-reported use of colonoscopy during a 6-month period immediately after the results disclosure.

Covariates

Covariates included in the analyses were identified based on the literature [17]; data on these covariates were collected at baseline. Covariates included age, gender, marital status, personal history of cancer, family history of cancer (number of FDRs with cancer), perceived risk to develop colorectal cancer, colorectal cancer worry, dichotomized CES-D score and colonoscopy use in the year prior to GCT.

Statistical Methods

Hierarchical logistic regressions were fitted to test whether participants who engaged in colonoscopy within 6 months following GCT were less likely to have clinically significant levels of depressive symptoms compared to those who did not undergo colonoscopy during that time. The hierarchical model accounted for clustering of participants within families. All fitted models included covariates, controlled for the number of members within each family as a level 2 covariate, and accounted for over dispersion in the data. Tests of significance were conducted using the Wald statistic based on robust standard errors and a Type I error rate of .05.

RESULTS

Sample Characteristics

Characteristics of the sample are detailed in Table 1. In brief, the sample had a mean age of 41 years, were primarily Caucasian (94%) and health insured (97%). Females represented just over half of the sample (52%). Approximately one half (49%) of the sample had a personal history of cancer and 92% of participants reported having at least one FDR whom had also experienced cancer.

The distribution of clinically significant CES-D scores, stratified by personal history of cancer, is provided in Table 2. At baseline, 22% (29/134) had high CES-D scores (16 or higher) with no difference ($p = 0.90$) between those with a personal history of cancer and those without. At 6 months post disclosure of mutation status, 16% (22/134) had high CES-

D scores with no significant difference ($p=0.33$) detected between those with or without a history of cancer. The change in the number of persons with high CES-D scores between assessments (22% to 16%) represents a noteworthy, but non-significant ($p=0.15$) decrease. No significant association was found between those with high CES-D scores at baseline and those with high CES-D scores at 6 months post receipt of genetic test results. In other words, having a high number of depressive symptoms prior to genetic education, counseling and genetic testing was not associated with having a high number of depressive symptoms following their notification of being a mutation carrier.

Table 3 details use of colonoscopy within the year prior to GCT and 6 months post GCT. Thirty-one percent (31%; 41 of 134) of carriers had undergone colonoscopy within the year prior to GCT with no significant difference ($p = 0.46$) between those with or without a personal history of cancer. In contrast, 52% (70 of 134) underwent colonoscopy within the 6 months following GCT, which represents a significant increase ($p < 0.001$) in colonoscopy use compared to baseline. No significant differences ($p = 0.43$) were noted between those with or without a personal history of cancer in their colonoscopy use 6 months following GCT. Sixty-nine percent (69%; 93 of 134) of carriers reported completion of colonoscopy at least once within the 18 months under study.

Main finding

Table 4 provides odds ratios, confidence intervals and p-values for the hierarchical logistic regression models. Results suggest a significant, negative association between colonoscopy use and depressive symptoms 6 months post-mutation disclosure. More specifically, participants who did not complete a colonoscopy within the 6 months following receipt of mutation carrier results were 6 times ($OR = 6.06$, $p < .01$) more likely to experience clinically significant levels of depressive symptoms than those who had a colonoscopy within the same time period when controlling for covariates.

DISCUSSION

A primary goal of genetic testing in families with Lynch syndrome is to focus cancer-screening resources on family members at increased risk to develop cancer (mismatch repair mutation carriers) and to avoid unnecessary procedures (and associated risks) in family members who are not at increased risk for cancer. Identifying modifiable factors that assist mutation carriers to adapt to their risk for cancer and appropriately utilize available prevention options seems paramount in maximizing the benefits of genetic testing. The findings from this study provide compelling evidence that persons who undergo colonoscopy following the receipt of test results are significantly less likely to experience depressive symptoms at or above a level of clinical concern than mutation carriers who do not undergo colonoscopy screening.

We pose two explanations for these results. First, the results may indicate that completing colonoscopy soon after the receipt of test results may play a role in assisting psychological adaptation through behavioral coping processes. The identification of a mutation in the individual through genetic testing clarifies their risk for the colon cancer, but also has the potential to raise (or renew) concerns about whether they currently have colon cancer. Clarifying uncertainty about their cancer status through completion of colonoscopy may help to alleviate associated emotional distress. Second, mutation carriers experiencing higher levels of depressive symptoms following receipt of their test results may not be able to identify or mobilize resources necessary to complete colonoscopy. Further evaluation may be warranted to assess their psychological wellbeing, while facilitating their completion of recommended cancer screening.

We believe these results have important implications for the medical management of individuals identified to carry MMR mutations. Efforts to identify mutation carriers who have not recently undergone colonoscopy with the intent to facilitate screening, may help resolve their uncertainty relative to cancer worry, facilitate emotional adaptation and ultimately, reduce the morbidity and mortality associated with LS cancers. Completing a colonoscopy soon after confirmation of mutation carrier status may be an important step in facilitating adaptation to the threat of cancer. Furthermore, utilizing colonoscopy as a tool to address emotional distress and cope with the threat of colon cancer may extend over the lifetime of the individual as the increased risk for colon cancer persists necessitating periodic colonoscopic evaluation. It seems feasible that carriers may experience cyclic changes in distress / cancer worry relative to their cycle of colonoscopy use; lower following the completion of a colonoscopy with no polyps or cancer detected, but potentially increasing as the interval of time between colonoscopies increases.

Colonoscopy screening post-receipt of mutation carrier results may not necessarily prevent or treat clinically significant levels of depressive symptoms as the varied etiologies for depressive symptoms within this population are complicated and extend beyond cancer-screening. A number of these individuals may need assistance in addressing the psychological barriers that may be preventing colonoscopy use or may be experiencing emotional distress related to the uncertainty of their cancer status. Thus, some may benefit from referral to a psychiatrist, psychologist or professional counselor for assistance in further evaluating their depressive symptoms. For those persons experiencing clinical levels of depression, encouragement to undergo colonoscopy could be considered within a clinical model that includes counseling directed towards treating depressive symptoms.

The results of this study should not be confused with the literature on adherence (compliance) to published cancer screening recommendations for carriers of mismatch repair mutations. In contrast, the aim of this study was to investigate whether health-screening behavior was associated with depressive symptoms, regardless of whether the screening was undertaken prior to the recommended age or outside of the recommended screening intervals for mutation carriers. Certainly, excessive use of cancer screening is not appropriate. However, seeking reassurance that one does not have cancer or facilitating adaptation to newly confirmed mutation status through the uptake of colonoscopy is consistent with the *Self-regulation Model of Illness Representations*, which posits that different cognitive and emotional threats presented to individuals facing disease risk, may influence their interest and uptake of health screening. In this example, the desire to undergo colonoscopy may serve as a coping strategy to moderate underlying emotional distress following the identification of the cancer susceptibility mutation.

Limitations

Depressive symptoms were assessed by the participants' completion of the Center for Epidemiology Studies-Depression (CES-D) scale. While the CES-D has been shown to correlate with clinical ratings of the severity of depression, it is not a psychiatric diagnosis. The dichotomous categorization of the study population into "high" or "low" CES-D scores may under or over-represent the actual occurrence of clinical depression. Therefore, the true incidence of clinical depression within this population is not known.

Other hereditary diseases such as Hereditary Breast and Ovarian Cancer have cancer-screening modalities, which are less effective in detecting the cancers of concern, and therefore may not demonstrate the psychological benefits presented within this study.

And finally, the data for this study were collected within the structure of a clinical research investigation offering comprehensive genetic counseling and testing and may not reflect the representative outcomes in a clinical setting.

Concluding comments

Undertaking a medical procedure is most often considered as a cognitively based, problem-focused coping strategy that is initiated to manage disease risk. [24] However, growing arguments and an emerging literature of empirical evidence also exists to support the claim that medical screening may also be undertaken with the intent to be reassured about one's health in the face of disease risk. [23,25] Based upon our findings, anticipatory counseling regarding the impact of screening behavior on adaptation and psychological wellbeing may be beneficial in persons considering genetic testing for LS. Additional studies are warranted to explore the potential pathways that health behavior may play in facilitating psychological wellbeing and adaptation. More specifically, future research might explore the impact of expeditious scheduling of post-test colonoscopy on psychological wellbeing to inform practice guidelines.

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Table 1

Sample Characteristics (Baseline)

Variables of Interest	
Age	Mean: 41 years SD: 13.6 Range: 18 – 83 years
Gender (% Female)	52
Marital Status (% married)	61
Race (% Caucasian)	94
Health Insured (% insured)	97
Personal history of cancer (% with cancer history)	49
Family history of cancer: number of first degree relatives	Mean: 1.9 SD: 1.23 Range: 0–6
Perceived risk for colorectal cancer	Mean: 4.1 SD: 1.09 Range: 1–5
Colorectal cancer worry	Mean: 5.1 SD: 2.05 Range: 3–12

Table 2Frequency of High CES-D scores ($n = 16$)

	Baseline Assessment (Pre-GCT)	6 months post disclosure (Post-GCT)	Comparison of pre- & post-GCT (p-values)
All mutation carriers	22% (29/134)	16% (22/134)	0.15
Mutation carriers with history of cancer (Affected)	23% (15/65)	18% (12/65)	0.41
Mutation carriers with no history of cancer (Unaffected)	20% (14/69) ^a	14% (10/69) ^b	0.32

CES-D = Center for Epidemiology Studies – Depression Scale

GCT = Genetic counseling & testing

^aNo significant difference between affected and unaffected carriers ($p = 0.90$) pre-GCT^bNo significant difference between affected and unaffected carriers ($p = 0.33$) post-GCT

Table 3

Colonoscopy use by mutation carriers pre- & post-GCT

	Baseline Assessment (Pre-GCT)	6 months post disclosure (Post-GCT)	Comparison of pre- & post-GCT colonoscopy use (p-values)
All mutation carriers	31% (41/134)	52% (70/134)	0.001
Mutation carriers with history of cancer (affected)	37% (24/65)	57% (37/65)	0.04
Mutation carriers with no history of cancer (unaffected)	25% (17/69) ^a	48% (33/69) ^b	0.003

GCT = Genetic counseling & testing

^aNo significant difference between affected and unaffected carriers (p = 0.46) pre-GCT^bNo significant difference between affected and unaffected carriers (p=0.43) post-GCT

Table 4

Multilevel Generalized Linear Model for high CES-D Scores (6 months post mutation disclosure)

Covariates	OR	95% CI for OR		p value
Age	0.99	0.95	1.03	.73
Gender (Referent: Male)	1.46	0.42	5.02	.55
Marital Status (Referent: Not Married)	1.77	0.53	5.97	.36
Cancer history (Referent: Not affected)	1.44	0.39	5.33	.59
Family history of cancer: # 1st degree relatives	1.00	0.68	1.46	.99
Perceived risk for colorectal cancer (baseline)	1.04	0.63	1.73	.86
Colorectal cancer worry (baseline)	1.53	1.19	1.97	< .01
High CES-D (≥ 16) at baseline	2.17	0.68	6.94	.19
Screening Variables	OR	95% CI		p value
No colonoscopy use pre-GCT	1.49	0.30	7.48	.63
No Colonoscopy use: 6 months post-disclosure	6.06	2.09	17.59	.001

CES-D = Center for Epidemiology Studies-Depression scale

GCT = Genetic counseling & testing

N = 129 due to missing data on covariates