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Long-term Psychosocial and Behavioral Adjustment in Individuals Receiving Genetic Test Results in Lynch Syndrome

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Abstract

A cross-sectional study of 155 participants who underwent genetic testing for Lynch Syndrome (LS) examined long-term psychosocial and behavioral outcomes. Participants completed standardized measures of perceived risk, psychosocial functioning, knowledge, and a questionnaire of screening activities. Participants were on average 47.3 years and had undergone testing a mean of 5.5 years prior. Eighty four (54%) tested positive for a LS mutation and 71 (46%) negative. For unaffected carriers, perceived lifetime risk of colorectal cancer was 68%, and surprisingly, 40% among those testing negative. Most individuals demonstrated normative levels of psychosocial functioning. However, 25% of those testing negative had moderate depressive symptoms, as measured by the Center for Epidemiologic Studies for Depression Scale, and 31% elevated state anxiety on the State-Trait Anxiety Inventory. Being female and a stronger escape – avoidant coping style were predictive of depressive symptoms. For state anxiety, similar patterns were observed. Quality of life and social support were significantly associated with lower anxiety. Carriers maintained higher knowledge compared to those testing negative, and were more engaged

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in screening. In summary, most individuals adapt to genetic test results over the long term and continue to engage in screening. A subgroup, including some non-carriers, may require added psychosocial support.

Keywords

Lynch syndrome; colorectal cancer; empirical study; genetic testing; long-term follow-up; psychological adjustment; screening and knowledge

Introduction

Hereditary colorectal cancer accounts for 1 - 3% of all colorectal cancers (CRC) [1, 2]. Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer (HNPCC), is an autosomal dominant disorder characterized by an early age of onset of CRC and is associated with an increased risk for other types of cancers, including endometrial and ovarian cancer among others [3, 4]. LS is caused by a mutation in one of the mismatch repair genes: MLH1, MSH2, MSH6 or PMS2 [1]. LS gene mutation carriers are estimated to have an up to 80% lifetime risk of developing CRC and are advised to follow high-risk screening and surveillance guidelines, including colonoscopy every 1-2 years, as well as screening for endometrial cancer [3]. Individuals from LS positive families who do not carry the disease-predisposing mutation are considered to have the same CRC risk as the general population, and are advised to follow population-based CRC screening guidelines.

The majority of studies examining impacts of genetic testing have reported on the short-term psychological and behavioral impact following testing for hereditary CRC [5-10]. High risk mutation carriers may experience increased distress during the immediate post disclosure period (one to three months) that decreases to baseline or pre-test levels by 6 months to 1 year [11], and are within normative ranges [14-16]. A study following patients up to 3 years found no elevations in distress at 3 years [17]. A significant predictor of adjustment to a genetic test result is baseline distress, regardless of mutation status [5].

Genetic counseling involves education about a person's risk. In one previous study, most respondents correctly recalled whether or not they inherited the mutation predisposing them to cancer. However, those testing negatively had a significantly greater accuracy or understanding of their CRC risk, compared to the mutation positive group at both 1 month and 1 year follow-up [18]. A significant proportion of the mutation positive group underestimated their cancer risk at 1 month, with the proportion of under-estimators increasing at 1 year follow-up. The most significant predictor for misunderstanding cancer risk in the mutation positive group at 1 year was lower pre-test perception of risk [18].

It is important to teach and communicate on screening recommendations in addition to genetic risks. A report from the Netherlands following carriers for a mean of 3.5 years found that colonoscopy screening increased significantly from 31% to 88%, and gynecologic screening from 17% to 69% [11]. However, more than one-half of the respondents reported unpleasant colonoscopy experience. There continues to be further need for studies on longer term follow-up among individuals undergoing genetic testing for LS. It is also important to

identify those individuals who may require added follow-up, so that psychosocial and genetic counseling programs can focus their limited resources more efficiently.

Objectives

The objective of this study was to examine the longer-term psychosocial and behavioral impact on individuals undergoing genetic testing for LS in two Canadian familial CRC registries.

Methods

The subjects for this study were accrued through the Ontario Familial Colon Cancer Registry (OFCCR) [19] and the Newfoundland Familial Colon Cancer Registry (NFCCR). CRC cases in the provinces of Ontario and Newfoundland were identified through the provincial Cancer Registries and invited to participate in the Hereditary CRC Registry, as described previously [21].

For the current psychosocial component, individuals from LS mutation positive families who had received a positive or negative test result for one of the LS gene mutations, 2 or more years prior to the time of the study (January 2004 – June 2005), were invited to participate. Additional inclusion criteria were age 18 years or over and having the ability to understand English.

Individuals received their genetic testing in the following programs: the Familial Gastrointestinal Cancer Registry (FGICR) in Ontario, the Ontario Familial Colorectal Cancer Registry and the Newfoundland Familial Colorectal Cancer Registry. Ethical approval was obtained from the Institutional Review Boards at the University of Toronto in Ontario and at Memorial University in Newfoundland.

Individuals were mailed an invitation letter with information outlining the psychosocial study and a consent form. Within two weeks, a follow-up call was made by the study coordinator to inquire about their interest in the study. For participants who were interested and completed the consent form, a battery of standardized psychosocial questionnaires and screening behaviors were mailed to them and once completed, returned using self-addressed envelopes.

Subjects

Two hundred and twenty-three CRC individuals were invited, and 155 (70%) of them consented to the study and completed the questionnaires.

Genetic Counseling

All individuals previously underwent genetic counseling either in-person (85%) or by telephone (15%). Sessions included a risk assessment based on family history and screening recommendations for the participant and family members. Possible outcomes, risks, benefits and limitations of genetic testing were discussed, including the implications for family members and potential reactions to positive genetic test results.

Measurement and Variable Definitions

The measures selected for the study were guided by a theoretical model of stress and adaptation by Baum et al. (1997) [20] and previously described [21]. The model describes the potential influence of personal variables (i.e. age, social support) and appraisal variables (i.e. perceived risk) in relation to adaptation to the potentially life-threatening information of genetic testing. For the current study, the personal factors of interest included demographics such as age, sex, personal history of CRC, type of genetic test result, marital status, coping style, social support, quality of life and family functioning. Appraisal variables included perceived risk of CRC and CRC knowledge. Our primary outcome variables of interest were psychosocial functioning and screening behaviors.

Personal and Appraisal Factors

Demographic and Medical Information Questionnaire—Demographic and medical information included such items as personal history of cancer, ethnicity, age, sex, education, occupation, age at diagnosis (if applicable), genetic test result (i.e. positive or negative) and time since receipt of their test result.

Colonoscopy Screening—A self-report item asked if at-risk participants had undergone a screening colonoscopy in the past year, with response categories as Yes, No or Unsure.

Coping Style and Social Support—Coping style was measured with the Ways of Coping Questionnaire [22] developed by Lazarus and Folkman (1984) and social support was assessed using the Social Support Questionnaire [23] developed by Sarason and Sarason (1987).

Quality of Life and Family Functioning—The Quality of Life Index [24] developed by Ferrans and Powers (1990) was used and to assess family functioning, the McMaster Family Assessment Device included [25].

Perception of Lifetime Risk for CRC—For individuals “at risk”, perceived lifetime risk of developing CRC was measured using a 10-centimeter Linear Analogue Scale anchored at one end with 0% lifetime risk and 100% risk at the other end. Participants were asked to place a mark ‘X’ on the line indicating their lifetime perceived risk.

Hereditary CRC Knowledge—A 12-item hereditary CRC knowledge quiz (with correct total of 12) was developed and previously tested [9] to assess the level of understanding of hereditary aspects of CRC cancer. A range of topics were included, such as transmission to offspring, relative risks of LS-associated cancers and screening modalities.

Psychosocial Functioning

Depressive Symptoms—The Center for Epidemiologic Studies for Depression Scale (CES-D) is a well-validated 20-item scale that measures frequency and intensity of symptoms of depression during the past week [26]. A cut-off score of 16 or over has been used to identify individuals who may be in need of diagnostic follow-up for clinical depression [27].

State Trait Anxiety—The State subscale of The State-Trait Anxiety Inventory (STAI) [28] was used to assess global anxiety and has been used with genetic populations [8]. Internal consistency estimates for the present sample were good (alpha coefficient =0.85 to 0.95).

Specific Distress Associated With Genetic Testing—The Impact of Event Scale (IES) [29] was used to measure distress specifically associated with the event of genetic testing. It has two sub scales: Intrusion and Avoidance and has been frequently used to assess specific response associated with genetic testing [30]. An intrusion score of 11 or higher and an avoidance score of 13 or more (total score of 25 or more) have been suggested as clinically meaningful levels of distress [31].

Statistical Methods

Descriptive statistics including frequency distributions, means and standard deviations and proportions were calculated. For continuous outcomes, such as psychosocial functioning, parametric and non-parametric independent t tests and correlations were carried out to examine potential differences between age, gender, disease and result status (i.e. affected positive, at-risk positive and negative). Distributions of the psychological measures (IES, STAI, CES-D) were examined, as well as their correlations. Unless otherwise indicated, all significance levels presented in the analyses are two-tailed ($p < 0.05$). The clinical cut-off for depressive symptoms (CESD) was a score of 16, the cut-off for symptoms of State anxiety (STAI) was 36, and the cut-off for the IES were 11 for Intrusion and 13 for Avoidance. A series of stepwise linear regression analyses were conducted in order to examine potential independent predictors of depression and anxiety. Statistical significance was corrected for multiple comparisons when relevant.

Results

Sample Characteristics

There were no significant differences between participants and non-participants on most of the demographic variables, time since receipt of genetic test result or registry source (see Table 1). Current age differed significantly by cancer status and test result, with individuals previously diagnosed with CRC being significantly older than at-risk individuals who tested positive and negative (at-risk mutation positive were the youngest group). Educational level was significantly lower for the mutation negative group, compared to those who tested positive. There were significantly more at-risk mutation positive individuals, and individuals who tested negative in the NFCCR.

Colonoscopy Screening—Self-reported screening in the past year was significantly higher in individuals who tested positive, compared to those who tested negative.

Coping Style and Social Support—A range of coping styles were used by those with both positive and negative test results. Carriers without cancer reported a higher escape avoidance score than carriers with cancer. The group difference was not statistically significant. Perceived social support from family and friends was fairly high, with an

average of 3 family members perceived as being available to provide support. Similarly, satisfaction with social support was high, with an average 5.7 on a 6 point scale.

Family Functioning and Quality of Life—Family functioning, as measured by subscales of the McMaster Family Assessment Device (FAD) were in the normative ranges and below a mean score of 2, indicating no clinical problem areas in family communication, role functioning and general functioning. Health and general functioning, socioeconomic, and family aspects of quality of life, as measured by the QOL were within normal ranges, and did not differ significantly between those with a positive and those with a negative test result.

Perception of Lifetime Risk for CRC—Perceived lifetime percentage risk of developing CRC was significantly higher for those at-risk who tested positive ($67.7\% \pm 20.9$, range 20 – 100) compared to those at risk who tested negative ($40.4\% \pm 26.8$, range 0 – 100) (see Figure 1).

Knowledge of Hereditary CRC—Those with a positive test result scored significantly higher on the hereditary knowledge quiz than those with a negative test result (see Figure 2). The group difference remained statistically significant after controlling for education level. While carriers were significantly more knowledgeable than non-carriers, there were knowledge deficits across groups in areas concerning LS-associated cancer risks and frequencies of transmission of mutations in families.

Psychosocial Functioning

Depression—The mean level of depressive symptoms as measured by the CES-D was $8.34 (\pm 8.71)$, below the clinical cut-off of 16 for all groups. However, for the mutation negative group, 25% of participants scored higher than the clinical cut off point for CESD – demonstrating moderate depressive symptoms, compared to either of the mutation positive groups (10 – 12%). The group difference was not statistically significant (see table 2).

Intrusion and Avoidance—The mean levels of intrusion (5.83 ± 6.9) and avoidance (6.6 ± 8.0) as measured by the IES were not indicative of elevated levels of cancer-related distress, nor different among the three groups. However, there were subgroups of individuals who met the criteria for elevation in distress. For intrusion, 26% of those who tested negative scored above the cut- off, compared to 21% for either the two mutation positive group with, or without a previous cancer. For avoidance, 23% of those who tested negative scored above the cut- off, compared with 18% for both the mutation positive group with a previous cancer or without a previous cancer. There were no statistically significant differences in proportions between groups (see table 2).

The State and Trait Anxiety—The STAI State and Trait anxiety mean scores were within normative ranges. The mutation negative group reporting significantly higher average scores of the STAI State and Trait anxiety than the other two groups. The proportion of the mutation negative group above the STAI Trait anxiety cut off score was 34%, higher than

22% for non-affected mutation positive carriers, and 14% for the affected carriers. There were no statistically significant differences in proportions between groups (see table 2).

Predictors of Anxiety and Depression in the Study Sample

We conducted a series of stepwise linear regression analyses to explore potential predictors of the main psychological dependent variables of depressive symptoms and state anxiety amongst carriers and non-carriers. Based on the preceding analyses, we examined the following independent variables: age, gender, educational level, test result, cancer status, perceived risk, coping style, perceived social support, family functioning, quality of life, and hereditary CRC knowledge.

The regression model with the best fit included the significant predictors of psychological and spiritual, health and general function aspects of quality of life, and greater hereditary knowledge, as being independently and inversely related to depressive symptoms. In addition, being female and having a stronger escape – avoidant coping style was predictive of higher levels of depressive symptoms and state anxiety. This model explained 28% (Adjusted R^2) of the variance in depression score. For state anxiety, similar patterns were observed. In addition, the family aspects of quality of life and satisfaction with social support were significantly associated with lower anxiety. This model explained 42% of the variance in state anxiety score in the sample (Table 3).

Discussion

Perceived Risk of CRC

Perceived lifetime percentage risk of developing CRC was significantly higher for those at-risk who tested positive compared to those at-risk who tested negative. However, the magnitude of the mean percentage of lifetime risk in the mutation negative group was unexpected, as their objective risk of CRC is that of the general population (6 – 7%). Those testing negative overestimated their risk, suggesting that individuals told that they do not carry a mutation and are at population risk for CRC did not accurately comprehend the information provided. It may also be possible that individuals had difficulty adjusting their personal risk perceptions to that of the population level.

This finding is consistent with previous studies that suggest that risk perceptions for some are not easily modified [44]. Perceptions of risk are often linked to experiences with family history, and while individuals may intellectually understand they do not carry a genetic mutation, they can still feel at increased risk, in part or fully, as a function of the number of family members who had cancer [32], forming an ingrained sense of self that feels vulnerable to cancer [38]. Risk perceptions, while initially modifiable following counseling can be unstable over time, and may return to previous elevations [33, 34].

Psychosocial Outcomes

It is encouraging that most individuals adapted to their genetic test status. Our findings are similar to previous reports of individuals undergoing genetic testing for LS [16, 17, 38]. However, subgroups of those with both positive and negative test results, in this study,

demonstrated genetic-testing related distress, or anxiety and depressive symptoms. These findings are similar to those of others examining populations undergoing genetic testing [16, 35], suggesting that some individuals may become distressed, or continue to exhibit levels of distress present at baseline, that do not remit on their own. There is an emerging body of evidence suggesting that personal variables, such as coping style, social support or prior experience of cancer in the family play a role in adjustment [33, 36, 38]. Consistent predictors of distress are psychosocial functioning during the pre-test period and having a prior history of mental health difficulties [37, 39, 40]. The identification of variables predictive of distress have facilitated the development of screening tools for the genetics context, to help identify those at increased psychological risk [39, 40]. Such tools can assist genetic service providers to target psychosocial care and follow-up. Genetic information can pose psychological burden. For example, individuals are encouraged to disclose important genetic information to family members, including offspring, as well to attend to their own screening requirements and information needs [41, 42]. Providing added psychosocial interventions to standard genetic counseling or strategies to facilitate family communication can reduce psychological burden [43].

Hereditary CRC Knowledge

Individuals testing negative may be less receptive, and less apt to retain or seek out cancer-related risk/hereditary information, and therefore have lower hereditary CRC knowledge than those who testing positive. They are also less likely to be part of an intensive surveillance programs, and therefore, may have less opportunity to engage with the health care services that provide updates or specific information [18]. In contrast, individuals testing positive have greater access to health care professionals, and may have been more motivated to continue to build on their knowledge of hereditary cancers.

Colonoscopy Screening

Self-reports of screening colonoscopy was a positive finding, especially since the mutation carriers are strongly encouraged to engage in regularly screening. There were a number of individuals who tested negative who reported undergoing a colonoscopy in the past year. These findings are consistent with prior reports [45]. We do not have information as to why those individuals were having colonoscopies; most were not over 50 years of age, the age at which it is recommended to begin population- based screening for CRC. We cannot determine whether they had a family history of CRC on the other side of the family that didn't have LS, or whether they may have had bowel symptoms that warranted a colonoscopy.

Limitation

This study is cross-sectional in nature, and therefore, while patterns can be described no conclusions can be made in relation to causal relationships. We also did not have information on pre-test variables that may be associated with the observed post-test levels of functioning.

Summary

In summary, this study contributes to our understanding of the longer-term adjustment and screening behaviors in mutation positive and negative individuals in LS families. Consistent with recently published reports and those on short term adaptation, we found that most mutation positive individuals adapt to their test results and engage in appropriate screening. Our results also support that even over the long term, specific subgroups of individuals, including some participants who receive the news that they do not carry a mutation, have unaddressed needs that should be taken into consideration in planning follow up services.

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Figure 1. Perceived percentage lifetime risk of developing CRC (0 – 100%) by carrier status at risk positive versus negative (n = 112)
 $t = 5.3$, $df = 110$, $p < 0.01$

Figure 2. Hereditary CRC knowledge by test result and cancer status
 $t = 3.1$, $df = 110$, $P < 0.01$

Table 1
Demographics and Other Characteristics of Participants & Non-Participants

	Affected Positive (n=32)	At risk Positive (n=52)	Negative (n=71)	
Demographic Variables (continuous)	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	P-value
Age at time of survey (years)	56 (13) 26 – 78	40 (11) 22 – 62	48 (12) 25 – 76	<0.01
Time since disclosure of test result (years)	6 (3) 2 – 13	5 (2) 2 – 9	6 (2) 2 – 9	not significant
Age at time of colon cancer diagnosis	44 (13) 20 – 69	N/A	N/A (one cancer case)	N/A
Demographic Variables (categorical)*	N %	N %	N %	
Gender:				
Male	15 (47%)	19 (37%)	25 (40%)	not significant
Female	16 (52%)	32 (63%)	37 (60%)	
Marital Status:				
Married/ common-law	21 (70%)	41 (82%)	61 (86%)	not significant
Single/ divorced/ separated	9 (30%)	9 (18%)	9 (14%)	
Educational Level:				
High School or less	13 (46%)	19 (37%)	43 (61%)	0.02
College or more	15 (54%)	32 (63%)	27 (39%)	
Ethnic Background:				
Anglo-Saxon	26 (89%)	37 (88%)	58 (95%)	not significant
Other	3 (9%)	5 (12%)	3 (5%)	
Registry source:				
FGICR	14 (44%)	13 (25%)	5 (7%)	0.05
OFCCR	2 (6%)	0	1 (1%)	
NFCCR	16 (50%)	39 (75%)	65 (92%)	
Colonoscopy screening in the previous year	20 (77%)	41 (82%)	21 (34%)	<0.01

Note: not all participants completed every demographic questions – resulting in lower than 155 responses in some of the variables

FGICR = Familial Gastrointestinal Cancer Registry

OFCCR = Ontario Familial Colorectal Cancer Registry

NFCCR = Newfoundland Familial Colorectal Cancer Registry

Table 2
Psychosocial functioning and perceived risk of CRC by test result and cancer status

	Participants (N=155)									
	Affected Positive (N = 32)			At risk Positive (N = 52)			Negative (N = 71)			P value on mean score difference
	Mean (SD)	Range	% > threshold	Mean (SD)	Range	% > threshold	Mean (SD)	Range	% > threshold	
CES – Depression	7.4(9.1)	0-34	10%	7.4(8.8)	0-51	12%	9.5(8.9)	0-28	25%	not significant
IES – Intrusion	5.0(7.0)	0-27	21%	6.0(6.0)	0-21	21%	6.1(7.6)	0-35	26%	not significant
IES – Avoidance	5.6(8.2)	0-30	18%	6.1(6.5)	0-20	18%	7.5(9.0)	0-35	23%	not significant
STAI – State Anxiety	27.1(8.8)	20-51	10%	31.2(9.5)	20-53	26%	33.0(11.0)	20-63	31%	F=3.25, 0.04
STAI- Trait Anxiety	28.8(9.3)	21-60	14%	32.0(9.4)	20-56	22%	34.4(10.3)	20-58	34%	F=3.18, 0.05

Table 3
a: Results of Stepwise Linear Regression Model for CES – Depression (affected carriers verses non affected carriers versus non-carriers)

Model	Standardized coefficient beta	t score	p value
Constant		4.85	0.00
Gender	.18	2.48	0.01
Escape/avoidance coping	.19	2.72	0.01
Psychological/spiritual QOL	-.45	-6.30	0.00
Hereditary knowledge	-.18	-2.49	0.01

$F(7, 147) = 9.7, p < 0.00, \text{Adj } R^2 = 0.28$

Table 3b: Results of Stepwise Linear Regression Model for State Anxiety (affected carriers verses non affected carriers versus non-carriers)

Model	Standardized coefficient beta	t score	p value
Constant		7.18	0.00
Gender	.16	2.59	0.01
Escape/avoidance coping	.17	2.67	0.01
Psychological/spiritual QOL	-.42	-5.36	0.00
Family aspects of QOL	-.17	-2.19	0.03
Satisfaction with social support	-.14	-2.12	0.04

$F(8, 146) = 14.7, p < 0.00, \text{Adj } R^2 = 0.42$