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Explanations of risk in families without identified mutations for hereditary nonpolyposis colorectal cancer

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Abstract

Purpose—Genetic testing for hereditary forms of cancer does not always identify a causative mutation. Little is known about personal or family response to these indeterminate results when a hereditary form of cancer is suspected. This study explored thoughts about and responses to risk for hereditary non-polyposis colorectal cancer (HNPCC) when a family member has received indeterminate genetic test results.

Design—In this qualitative study, data were gathered from index cases who received indeterminate genetic test results through a longitudinal study offering genetic counseling and testing for HNPCC. First-degree relatives of these indeterminate index cases were also invited to participate in the qualitative interview.

Methods—Semi-structured telephone interviews were conducted with index cases and their at-risk first-degree relatives. Data were analyzed using the within- and across-case method.

Findings—The across-case analysis led to the development of the Awareness and Surveillance Trajectory, which describes individual interpretations of and responses to risk, based on personal and family history. Explanations of risk addressed the meaning of cancer in the family and provided context for individual interpretations. They were identified using within-case analysis and organized into a typology: innate, exceptional, idiosyncratic, and undeveloped explanations.

Conclusions—Members of families without identified HNPCC mutations vary in their explanations for, interpretations of, and responses to indeterminate genetic test results.

Clinical Relevance—Explanations of family risk and interpretations of individual risk offer health care providers valuable information. In combination with the Awareness and Surveillance Trajectory, assessment of these beliefs can facilitate development of individualized recommendations and strategies for possible preventive actions.

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Clinical Resources

National Cancer Institute: <http://www.cancer.gov/cancertopics/prevention-genetics-causes/genetics>

National Society of Genetic Counselors: <http://www.nsgc.org/providers/>

Conditions affecting multiple family members across generations are often said to “run in families” (Richards, 1996; Skirton & Eiser, 2003), and are experienced within the context of the family history of disease (McDaniel, Rolland, Feetham, & Miller, 2006a). Clinical practitioners, guided by the biomedical model, typically presume that these diseases are linked to inherited genetic mutations. However, at-risk individuals may have different thoughts about what causes the conditions in their families (Richards, 1996); even those who recognize certain health conditions as heritable may not use genetics-centered language to describe their risk. Lay beliefs can affect communication about risk and participation in risk-reducing behaviors (Feetham, Thomson, & Hinshaw, 2005; McDaniel, et al., 2006a; McDaniel, Rolland, Feetham, & Miller, 2006b). Assessing these beliefs could facilitate education, health promotion (Feetham, et al., 2005), and collaboration with health care providers (McDaniel, et al., 2006b).

Families at risk for hereditary forms of cancer provide one context for examining beliefs about disease. Hereditary non-polyposis colorectal cancer (HNPCC) is an inherited cancer predisposition syndrome that increases risks for numerous cancers, the most prominent of which are colorectal (CRC) and endometrial cancers (Barrow, et al., 2009). At-risk individuals are identified through the *Amsterdam criteria*, which focus on clinical presentation and family history (Vasen & Boland, 2005), or assessment of molecular tumor characteristics, such as *Microsatellite Instability (MSI)*. MSI is a classic pathological characteristic of HNPCC-associated colorectal tumors; its presence warrants testing for HNPCC mutations. Currently, four genes are known to be associated with HNPCC. Testing for a mutation is typically completed in an index case, an individual within the family who has had CRC and meets the Amsterdam criteria or whose tumor demonstrates MSI. Mutation identification allows targeted genetic testing of at-risk family members to clarify disease risk and guide clinical management (Lindor, et al., 2006). An associated mutation is identified in 50–80% of index cases meeting HNPCC criteria; however, 20–50% receive indeterminate genetic test results, in which no change in DNA sequence is detected (EGAPP Working Group, 2009; Vasen & Boland, 2005). This precludes targeted genetic testing of other family members. Genetic advances will likely identify additional HNPCC candidate genes; more extensive testing may eventually pinpoint a genetic cause for the cancers in these families. Until then, family members of index cases who received indeterminate genetic test results must remain vigilant in cancer screening.

Individuals at risk for developing the cancers associated with HNPCC are encouraged to participate in intensive screening protocols (Lindor, et al., 2006). This includes: individuals known to carry an HNPCC-associated mutation; biological family members of mutation-positive index cases who choose not to have genetic testing; and members of families meeting clinical and pathological criteria for HNPCC in which no causative mutation has been identified. Beginning in young adulthood, colonoscopy every 1–2 years facilitates early identification of CRC, or prevents CRC through identification and removal of colorectal polyps. Colonoscopy use reduces the incidence of CRC and improves survival (Jarvinen, et al., 2000). This study focused on CRC and not the other cancers for which HNPCC increases risk due to established screening recommendations (Lindor, et al., 2006) with clear benefits for CRC detection and survival (Jarvinen, et al., 2000).

Lay explanations of hereditary conditions provide insights into an individual’s understanding of the condition and beliefs about risk. The family and social context influence how individuals make sense of their own and others’ risks for inherited conditions (Cox & McKellin, 1999; McAllister, 2003; Skirton & Eiser, 2003). In families with HNPCC mutations, lay models are grounded in personal experiences and interpretations of the family history (McAllister, 2003). Families with indeterminate HNPCC genetic test results provide a unique opportunity to examine interpretations of risk, because widespread genetic

education, counseling, and testing do not typically occur within such families. This study explored thoughts about and response to risk for HNPCC in the context of indeterminate genetic test results.

Methods

This study used a qualitative design with within- and across-case strategies (Ayres, Kavanaugh, & Knafl, 2003). Data for this analysis were gathered following the completion of a longitudinal study on the psychological and behavioral outcomes of genetic education, counseling, and testing for HNPCC (Hadley, et al., 2003; Hadley, et al., 2004), and received ethical approval from the National Human Genome Research Institute. All respondents provided verbal consent, and received gift cards to national retail stores upon completion of study procedures.

Sample and Procedures

This analysis focused on index cases who received indeterminate genetic test results and their first-degree relatives (FDRs). *Index cases* had a personal history of at least one HNPCC-associated cancer, met the Amsterdam criteria (with one exception) (Vasen, Watson, Mecklin, & Lynch, 1999), and were the first in their families to have genetic testing. The excepted index case was adopted; no biological family history was available. Inclusion was based on a history of 2 separate early-onset (<35 yrs) cancers with MSI. *FDRs* were relatives with whom the index case shared, on average, 50% of their genes (e.g., parents, siblings, children). At the time of testing, two genes were known to be associated with HNPCC; however, no change in index cases' DNA sequence was detected.

Eligible index cases participated in the parent protocol, had genetic testing for HNPCC, received indeterminate genetic test results, and spoke and read English. Eligible FDRs were the adult biological siblings or children of index cases, and spoke and read English. Parents were excluded, as many were deceased. Potential participants were identified using modified cascade sampling (Beeson & Doksum, 2001). Index cases were sent informational flyers. Those interested in participating returned a reply form, indicating their willingness to complete a telephone interview and provide study information to FDRs. A study team member (ALE) telephoned interested index cases, described the study, answered questions, confirmed willingness to participate, and scheduled the interview. Index cases were asked to enumerate FDRs to whom they were willing to send information. They were sent packets containing an introductory letter and reply form for distribution to FDRs. One index case did not participate, due to time constraints, but sent packets to his FDRs. A study team member (ALE) telephoned interested FDRs, described the study in more detail, answered questions, confirmed willingness to participate, and scheduled the interview. Ten index cases and 16 FDRs (10 siblings; 6 children) from 11 families were interviewed (Table 1). Three (18.8%) FDRs had a history of cancer and 7 (43.7%) had a history of colorectal polyps. Most participants (88%) were female.

Data Collection

Data were gathered using semi-structured telephone interviews; face-to-face interviews were impractical due to the wide geographic distribution of study respondents. Interview questions were developed to elicit respondents' thoughts about and responses to HNPCC risk information. Among other questions, respondents were asked to describe how they found out about their risk for HNPCC, the impact this information had on them, and their thoughts on the cause of cancer in their family, their own risk for cancer, and others' risks for cancer. Probes were used to encourage further detail. Respondents were encouraged to share relevant information not specifically elicited by interview questions.

Data Management and Analysis

Interviews were recorded using a digital recorder with a telephone adapter (Sony IC ICD-MX20), transcribed verbatim by one author (ALE), and verified through listening to the recordings multiple times. Transcripts were purged of identifying information and uploaded into NVivo7 qualitative analysis software (QSR International, Melbourne, Australia).

Data were analyzed using the within- and across-case method (Ayres, et al., 2003). Across-case comparisons of individual accounts resulted in an Awareness and Surveillance Trajectory. The trajectory organized the ways respondents interpreted their personal risk for HNPCC, actions taken in response, and the points at which respondents revisited their interpretations and actions. In the within-case analysis, themes were identified through multiple readings of each interview. To facilitate recognition of patterns not evident from individual transcripts (Miles & Huberman, 1994), themes of interest were entered into Microsoft Excel^R spreadsheet software (Microsoft Corporation, Seattle, WA). Themes present in every interview included cause of cancer in the family, the respondent's risk for cancer, others' risks for cancer, screening behaviors, and polyps. Clusters of quotes on similar topics were identified and labeled based on the topic(s) identified within each cluster. Responses in three themes (cause of cancer, own risk, others' risks) varied systematically across cases. This variation led to a typology of more general explanations of risk for cancer across family members. These explanations were identified, characterized, and named, consistent with the within- and across-case approach. Subsequent analyses examined associations among explanation types, individual interpretations of risk, descriptions of screening behaviors, and the trajectory. In all direct quotes from participants, ellipses (...) indicate the removal of noncontributory utterances; brackets ([]) indicate clarifications made in quotes shortened for space considerations.

Results

The Awareness & Surveillance Trajectory

The trajectory (Figure 1) began with awareness of a personal or family history of CRC or colorectal polyps, and the individual's consequent interpretation of personal risk. Determination of risk status (at risk vs. not at risk) led to a decision regarding behavioral responses to risk (colonoscopy vs. no colonoscopy). For those respondents deciding to have colonoscopy, detection of polyps or cancer prompted reconsideration of risk and subsequent actions. Decision points in the trajectory (e.g., at risk vs. not at risk) were revisited when respondents encountered new information, or made new interpretations of old information. For example, one FDR believed she was at risk, based on her family history of CRC and polyps, but had decided not to have a colonoscopy, because of her age. However, her mother's strong recommendation that she have a colonoscopy prodded her to revisit this decision, leading the respondent to schedule her first colonoscopy.

Respondent-initiated discussions of colorectal polyps were central to trajectory development. In some cases, detection of polyps in the respondent or a family member prompted reconsideration of risk interpretation. For others, lack of polyps helped bolster beliefs about a lower risk for cancer. For example, one FDR highlighted her lack of polyps: "I think I'm at an increased risk for colon cancer, because...my sister had colon cancer. Although...I have now got three sisters who have premalignant polyps and so I'm the only one that hasn't...I'm kind of hoping I don't have the gene." For another FDR, lack of polyps supported her belief that she was not at risk. However, she stated that her mother was at risk "...because she's had polyps already and she also had ovarian cancer." Finally, another FDR asserted that polyps increased her risk for cancer, while her brothers' lack of polyps mitigated their risk for disease. For these respondents, presence or absence of polyps

provided information about personal risk unavailable to them through other means (e.g., mutation identification).

Explanations of Risk

This study identified four types of explanations of risk: innate, exceptional, idiosyncratic, and undeveloped (Table 2). Explanations of risk were broader than interpretations, addressed cancer risk for self and others, and provided context for interpretations of personal risk.

Innate—Innate explanations focused on genetics and family history. Slight differences in explanations defined two groups within this explanation type: 9 respondents focused only on genetics and family history; the other 3 respondents acknowledged the potential contribution of environmental and lifestyle factors. Genes were highlighted as the probable cause of cancer in their families. One index case said "... [t]here's a lot of differences in us, so when I look at it, I'm like, [the cancer in our family's] gotta be genetic." All thought their personal or family histories of cancer increased their and their biological relatives' risks for HNPCC-associated cancers. One index case described the intersection of lifestyle choices and biology: "The propensity, I would suggest, is probably genetic. I would also suggest that over the years, eating habits or lifestyle habits probably played a role in [causing cancer in my family]". Thus, although all respondents within this group recognized the role of genetics in their risk, some participants felt that environmental or lifestyle factors could increase or decrease this risk.

Exceptional—Two women who viewed their risk as different from that of their family members had exceptional explanations, but each saw herself as exceptional in a different way. One of the women, an index case, was adopted and did not know her biological family's medical history. She believed her cancer was caused by genetics and lifestyle: "...I think it was a spontaneous [genetic] thing that happened. But there are other things...I feel that possibly stress had an impact on [my cancer developing]." Her adoptive family members were not at risk because they were not blood relations. Although the genetic cause of her cancer was linked to her biological family, she did not consider her two biological children to be at increased risk. Her explanation was consistent with her cancer history, but not the potential for future cancers in her family. The other woman, a FDR, believed lifestyle choices caused the index case's CRC: "...in my dad's case, [the cancer] was stress-related...In our family...I don't think there's a whole lot of real healthy avenues for stress, if it sucks, it just sucks and you're just supposed to be able to handle a lot...I think that affects the gut, and your colon." In contrast, her lifestyle choices lowered her risk for cancer: "I don't drink, I don't smoke...I eat very well, and I have a low stress level."

Idiosyncratic—Idiosyncratic explanations carefully linked reasons for risk to individual characteristics of family members. One FDR identified genetics as the cause of cancer in her family: "I definitely think [cancer in my family is] related to a gene...Especially when you look at all of our lifestyles being somewhat different..." However, explanations based on individual characteristics were offered for others' risks: "...it happens to all the females in the family. So for [my female cousin], we always joke and say we've got the [same] genes...As far as my two brothers, it's...their diets and their lifestyles. They're both heavysset guys, meat and potato, drinking, smoking guys." While multiple family members could be at risk for disease, the reasons for their risk varied.

Undeveloped—Undeveloped explanations did not have coherent explanations of risk. One index case "really [has] no idea to tell you the truth" what causes her family's cancer. Her own risk was based on environmental factors: "I think the chemo weakened my body

systems. And I'm a smoker, and I worry about that." She cited multiple reasons for others' risks: "...if there is a weakness that's born into the body, it could be carried forward... [Or] ...saccharine came out when I was a kid...later on they found that there could be a cancer causing agent in saccharine." Undeveloped explanations did not preclude individual interpretations of risk. However, they do not provide a coherent context for these interpretations. Although respondents with undeveloped explanations may have appropriate responses to risk, their reasons for these responses were poorly articulated.

Interpretations of personal risk and explanations of risk for cancer in the family provided information on how respondents evaluated risk for cancer in the context of indeterminate HNPCC genetic test results. In some cases, interpretations and explanations were not logically linked. Interpretations of personal risk occurred in response to personal experiences and family history, and may be revised, as described in the trajectory. Explanations of risk were broader and applied to the family as a whole; they provided context for respondents' interpretations of their own risk and consequent risk behaviors.

Discussion

Respondents' individual accounts led to development of the Awareness and Surveillance Trajectory. Awareness and interpretation of risk arise from a personal or family history of HNPCC-associated cancers, similar to families at risk for hereditary breast and ovarian cancer (HBOC) (Hamilton et al, 2008; Werner-Lin, 2007). As Hamilton and colleagues state, "...a life trajectory is a multi-dimensional description of the processes of knowing one's risk" (2008; p. 4).

The trajectory can facilitate understanding of how experiential knowledge affects risk interpretations. Experiential knowledge arises from living with, experiencing, or knowing hereditary cancer (d'Agincourt-Canning, 2005). Experiential knowledge of HNPCC-associated cancers affected risk interpretations and movement through the trajectory. Lack of experiential knowledge (e.g., an unknown history) might provide insight into interpretations that do not demonstrate clear links to personal or family history. Future studies could examine the influence of extensive vs. minimal family history on interpretations of risk, and the applicability of these findings beyond families at risk for rare cancer syndromes.

Individual interpretations of risk were consistently associated with screening behaviors, suggesting that they are translated into preventive action. Helping at-risk individuals link their risk interpretations, family experiences, and cancer screening behaviors could facilitate participation in cancer screening. Knowing what individuals think about their own personal risk for cancer, particularly in families without identified HNPCC mutations, could be essential to understanding their current cancer screening practices and intervening to ensure appropriate screening intervals.

Explanations of risk provide the context within which individuals interpret and reinterpret beliefs about their personal risk for cancer and associated screening strategies, as seen in the Awareness and Surveillance Trajectory. As shown in the trajectory, respondents' interpretations of their personal risk of developing cancer were consistent with their actions (i.e. surveillance strategies). Assessment of interpretation of personal or family history of disease could help clinicians understand why at-risk individuals respond in different ways to heightened risk for disease. It is essential that individuals at risk for conditions such as HNPCC have access to health care providers who can assess their interpretations of risk and current screening behaviors, then strategize to facilitate cancer screening.

Explanations of risk are important for families without known mutations for HNPCC. Mutation identification enables testing of at-risk family members and clarification of risk status, and sharing mutation information may prompt appropriate screening by at-risk family members (Hadley, et al., 2004; Pentz, et al., 2005). Families without known mutations cannot rely on mutation-focused discussion to emphasize increased risk for disease, but could use risk explanations to inform and educate others about HNPCC and their health screening decisions. This analysis improves our understanding of the perspective of at-risk individuals in families without identified HNPCC mutations. These results may also be relevant for families meeting Amsterdam criteria in which genetic testing is not available or pursued, or families without a significant history of cancer in which genetic testing is pursued (EGAPP Working Group, 2009).

Individual and family experiences with cancer, and the context provided by these experiences, are important for understanding how people respond to risk (d'Agincourt-Canning, 2005). Respondents discussed risk for cancer in the context of their personal and family histories of disease. Interpretations by respondents with innate explanations resulted in elevated assessments of personal risk. "Family history" served as a proxy for genetics or heredity, similar to how blood or 'bad blood' were proxies for heredity in families at risk for HBOC (Kenen, Arden-Jones, & Eeles, 2003). While genetics has different lay definitions (Skirton & Eiser, 2003), family history is a concrete representation of risk (Bottorff, Ratner, Johnson, Lovato, & Joab, 1998; Hamilton & Bowers, 2007). Families with indeterminate genetic test results may focus on what is known: many family members have had cancer. Other studies demonstrated a focus on family history among families with known mutations (Cox & McKellin, 1999; d'Agincourt-Canning, 2005; Hamilton & Bowers, 2007; McAllister, 2003). Studies simultaneously exploring these conceptualizations in families with and without identified mutations would be valuable.

Limitations

Findings may be limited by the relatively small sample size, the focus on a rare genetic condition, and the exclusion of mutation-positive families. Future studies including larger, more diverse samples could help determine whether these findings are more broadly applicable.

HNPCC affects men and women equally, but respondents in this study were overwhelmingly female. This may reflect patterns of family communication, or the possible role of women as kin-keepers (Koehly, et al., 2003). Future research should endeavor to recruit an equal number of males and females, to ensure that these findings reflect the entire experience of being at risk for HNPCC in a family with indeterminate genetic test results.

Clinical Implications

Learning more about clients' interpretations and explanations of risk would improve understanding of beliefs about family conditions and associated health behaviors (Skirton & Eiser, 2003). Explanations provide insight into overall family health literacy and understanding of the condition in the family. In contrast, individual interpretations drive screening behaviors. Understanding how individual clients interpret their risk in the context of family history of disease, and what actions they take in response, can provide valuable tools for clarifying information about the hereditary condition and appropriate actions to minimize risk. For example, clients whose language focuses on family history may benefit from the use of similar terms in a counseling session. Following genetic counseling and/or testing, explanations could guide the development of family-focused interventions, which may be particularly useful in families without identified mutations. Explanations of risk may also be important in families that do not meet syndrome-specific criteria, but that have

significant family histories of particular health conditions. Clarifying risk status in the absence of an identified mutation is an important component of care for families without identified mutations.

Conclusions

Genetic mutations are often assumed to cause conditions that run in families, such as HNPCC. However, at-risk individuals in families without identified genetic mutations demonstrate a broad range of interpretations of personal risk, responses to interpretations, and explanations of the cancer in their families. Understanding how individuals make sense of their family histories in the absence of identified genetic mutations can facilitate appropriate guidance. These findings add to the limited literature on families without identified HNPCC mutations, and could facilitate examination of interpretation of risk information in families at risk for other conditions.

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Figure 1.
Awareness & Surveillance Trajectory

Table 1

Respondent Characteristics

Characteristic	Index cases (n=10)	Children (n=6)	Siblings (n=10)
Age	55.3 ± 8.3 (45–69)	27.83 ± 7.3 (20–41)	54.8 ± 5.3 (44–62)
Gender (Male)	n=2 (20%)		n=1 (10%)
CRC	n=7 (70%)		n=1 (10%)
Ovarian cancer	n=2 (20%)		
Other cancers*	n=4 (40%)		n=3 (30%)
Polyps	n=4 (40%)	n=1 (16.7%)	n=6 (60%)

* Some respondents were diagnosed with more than one form of cancer.

Table 2

Defining Characteristics of Explanation Types

Explanation *	Defining Characteristic	Respondents
Innate	Genetics/family history + lifestyle/environmental factors	5 index cases 4 siblings 1 index case 2 siblings
Exceptional	Not like the rest of my family members	1 index case 1 child
Idiosyncratic	Careful consideration of individual characteristics when assigning risk	1 index case 2 siblings 4 children
Undeveloped	No cohesive explanation of risk	1 index case 2 siblings 1 child

* Explanation types evolved from the patterns of responses to three themes: the cause of cancer in the family; thoughts about one's own risks for cancer; and thoughts about others' risks for cancer.