Cancer Genetics 233–234 (2019) 43–47

Cancer Genetics

SHORT COMMUNICATION

The benefits of a model of interval comprehensive assessments (MICA) in hereditary cancer Syndromes: Hereditary diffuse gastric cancer (HDGC) as an example

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Abstract

A high percentage of individuals at risk for hereditary cancer syndromes are unaware of their risk. This is especially detrimental in syndromes such as hereditary diffuse gastric cancer due to a *CDH1* germline mutation, for which lifesaving prevention is possible. Surveillance for diffuse gastric cancer in the syndrome is limited, hence the recommendation for prophylactic total gastrectomy for mutation carriers. Genetic counseling and testing is crucial in suspected families but initial contact could be limited, leading to the importance of an interval comprehensive review every 5–8 years to identify and screen additional high-risk individuals.

Our contact with a hereditary diffuse gastric cancer family in Jordan in 2011 led to a number of family members receiving education and genetic counseling. Our model of interval comprehensive assessment (MICA) was constructed and implemented by conducting family information service, video call and emails to the high-risk individuals 7 years after initial contact. Using an updated family pedigree we reached out to an additional thirteen high-risk members in six different countries and provided them with genetic education, counseling, and testing. Six members agreed to *CDH1* testing (46%). Four tested positive (66%) and one member (25%) underwent prophylactic total gastrectomy.

Keywords Hereditary diffuse gastric cancer, Lobular breast cancer, Hereditary cancer, *CDH1*, Genetic counseling, Genetic testing.

Introduction

The estimated number of individuals in the United States who are carriers of a hereditary cancer syndrome mutation but who are unaware of their carrier status is staggering and remains a significant health concern in the early diagnosis, detection, and prevention of cancer in these individuals and their bloodline relatives.

For example, it is estimated that one million individuals in the United States carry Lynch syndrome mutations, with only 50,000 of these (5%) identified and aware of their cancer predisposition, leaving 950,000 unaware and needing to be identified [1]. Similar numbers exist for individuals who are yet to be identified as carriers of a germline mutation predisposing to breast and ovarian cancer, as shown in an analysis by Drohan et al. [2]. It is considered likely that similar statistics are true of other hereditary cancer syndromes, including hereditary diffuse gastric cancer (HDGC), the syndrome involved in this paper.

Received May 4, 2018; received in revised form November 25, 2018; accepted March 20, 2019

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2210-7762/$ - see front matter © 2019 Published by Elsevier Inc.
https://doi.org/10.1016/j.cancergen.2019.03.005

Effectively identifying such individuals is key to providing early cancer diagnosis and preventing cancer in members of hereditary cancer-prone families [2,3]. Once a key individual is identified as a carrier of a hereditary cancer pathogenic germline mutation, then extension of contact to at-risk relatives can increase awareness of the cancer risk in the family and cascade genetic counseling and testing can be offered to all who are at risk [4,5].

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominantly inherited cancer predisposition syndrome which accounts for approximately 1–3% of all gastric cancers [6,7]. Up to 30% of families with HDGC harbor mutations in the *CDH1* gene [6]. Those with a *CDH1* mutation have an 80% cumulative lifetime risk of developing diffuse gastric cancer and women carrying the mutation have a 60% cumulative lifetime risk of developing lobular breast cancer (LBC), an integral component of HDGC.

Most researchers have emphasized the limitations of surveillance for diffuse gastric cancer in HDGC and, therefore, the importance of the option of prophylactic total gastrectomy (PTG) for *CDH1* mutation carriers [6,8–11].

CDH1 gene codes the epithelial cell protein E-cadherin which plays a major role in cell adhesion and tumor suppression. Multiple germline mutations have been described in literature such as point, frameshift, nonsense and missense mutations [12–14]. Not all mutations are clinically significant; some are benign or with uncertain significance and others are considered pathogenic [14]. The identification of a pathogenic CD*H1* mutation in a family creates the foundation for additional testing. After initial contact and testing has been conducted in the family, subsequent contact with the family is vital to identify additional high-risk family members. In a five-to eight-year time span from initial contact, new family members may be identified and those who initially refused testing may change their mind, younger members may reach the age of medical decision, and previous cultural beliefs that might have been a barrier to testing or acceptance of PTG may change. In such high-risk families, implementing an interval comprehensive counselling model can provide potentially lifesaving risk reduction management options for patients with *CDH1* mutations.

Our purpose in this study is to propose such a model of interval comprehensive assessment (MICA) in high-risk individuals harboring hereditary cancer syndromes. We implemented MICA on a Jordanian family, previously identified to harbor HDGC and with a known pathogenic *CDH1* mutation segregating through multiple generations of this family.

Methods

The protocol for this study was approved by the institutional review board of Creighton University. All participants provided written informed consent. Pedigree information and available medical records were collected by our research group. We adhered fully to appropriate privacy concerns related to disclosure of individual results.

Study population

Our initial contact with the family in 2011 included intensive education of as many at-risk family members as possible over a short period of time (three weeks) during a visit by the research team to Jordan [12], wherein we strongly encouraged family members to consider their hereditary risk for HDGC and, if positive for the *CDH1* mutation, to strongly consider undergoing PTG. Cultural and religious challenges were faced, but saliva samples were successfully collected from 23 family members for genetic testing.

Thirteen members tested positive from which one member underwent PTG at that time

Over a span of close to a decade following this contact, the research group has reached out to 42 members of this Jordanian family living in six different countries (United States, Canada, Australia, Sweden, Saudi Arabia and Jordan) on four different continents by providing genetic counseling through secured emails, video calls and traditional face to face family information services.

To the best of our knowledge, *CDH1* genetic testing is not readily available in Jordan.

Testing in 2017 was done through Invitae, a molecular genetics laboratory in San Francisco, California. Genomic DNA obtained from the submitted saliva samples was enriched for targeted regions using a hybridization-based protocol and sequenced using Illumina technology. Sequence analysis and deletion/duplication testing for the known *CDH1* variant c.1137G>*A* was done, this variant is classified as pathogenic in ClincVar [15]. Saliva samples were shipped from family members residing in Canada, Australia, Saudi Arabia and Jordan with a 10- to 21-day turnaround time. Family members were notified of test results by the research group through video calls.

A model of interval comprehensive assessment (MICA)

Our MICA was constructed and implemented within a period of 8 weeks between December 2016 and January 2017 which included conducting a family information service (FIS), video calls and emails to the high-risk individuals identified using an updated family pedigree and through the help of the proband and her nuclear family who had initially approached the research team in 2011. High-risk individuals above the age of 19 were defined as:

1) Siblings and offspring of positive family members;
2) Offspring of parents with unknown genetic status;
3) Family members with unknown genetic status who had refused testing during initial assessment;
4) Family members who reached age of majority to independently consent to genetic testing since the initial contact and meet the above criteria.

An FIS was conducted, emails were sent, and video and phone calls were made to reach out to identified individuals. During the FIS, we invited members who had been previously tested to provide psychological support to their family members, as they were more familiar with the counseling and testing process as well as the impact of cultural and religious beliefs and attitudes. Family members who previously

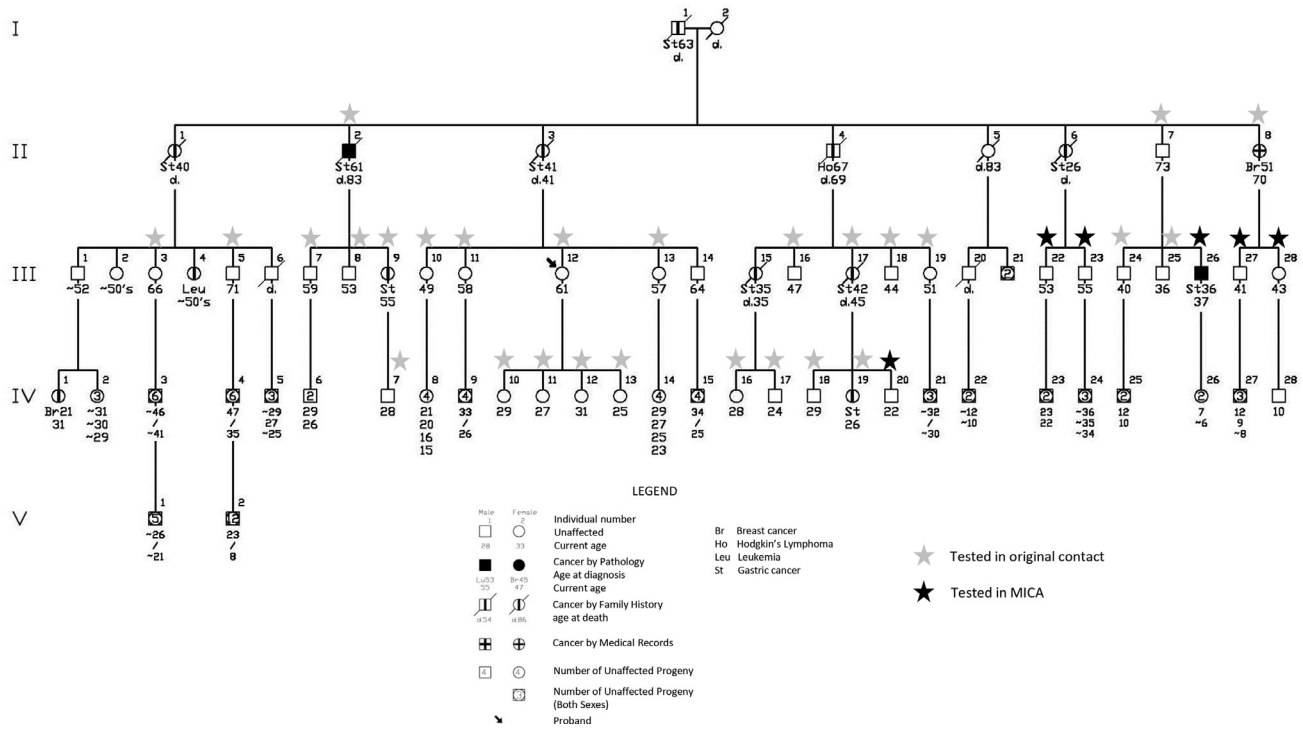

Figure 1 Pedigree of Jordanian hereditary diffuse gastric cancer family showing members involved in initial contact and MICA.

tested positive and had undergone a PTG also attended and shared their experiences related to the decision-making process leading up to the surgery and how they adapted afterwards.

Results

During our MICA, we reached out to 13 high-risk individuals, six (46.1%) of whom were tested (five males and one female). Four (66.7%) tested positive (three males and one female).

Four out of the six members tested (66.7%) had initially refused testing in 2011 and subsequently changed their minds during the MICA; of the remaining two who were tested, one had not known about the increased occurrence of HDGC in the family and the associated risks as he had been living in Australia and not in close contact with the family, and the other family member had been under the legal age of genetic testing at the time of the initial contact. The median age of positive individuals was 43.5 years. One member had undergone an endoscopy which showed signet ring cell carcinoma in the antrum, so he followed our recommendation and underwent a total gastrectomy. However, the other three positive individuals elected to choose surveillance with biannual endoscopy with multiple random biopsies per Cambridge protocol [11]. To date, their biopsies have been negative.

Out of the seven members who declined testing (four males and three females), three were Jordanian residents and refused to attend the FIS. We reached out to the other four by e-mail and phone calls as they lived in the United States and Sweden. The median age of the individuals who declined testing was 47 years.

In our previous study in 2011 [12], 23 members (57.5%) underwent genetic testing; 13 (56.5%) tested positive and

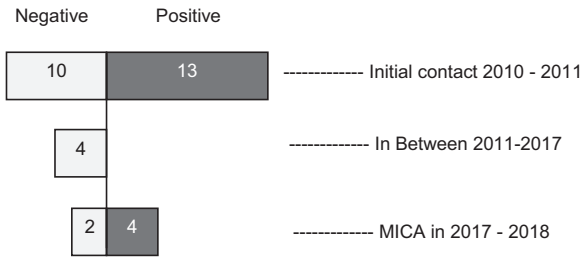

Figure 2 Genetic testing time line.

10 (43.5%) tested negative. Subsequent to our initial contact four family members were tested between 2011–2017, and all tested negative.

In total between the two assessments 33 family members have been tested; 17 tested positive, and 16 tested negative. Eight members underwent a PTG; seven surgeries were done in the United States and one in the United Arab Emirates. Ten members decided to have surveillance through biannual endoscopy or opted to disregard their result as there were no concerning symptoms. (See Figures 1 and 2.) Due to protection of privacy the pedigree is limited in detailed features and does not depict individual genetic results. However, a summary of the testing is provided in aggregate to demonstrate the impact of the initial contact and the MICA.

Discussion

Implementing our model of interval comprehensive assessment (MICA) on a Jordanian family harboring HDGC provided us with an opportunity to expand our knowledge of the family,

involve more members in genetic testing, intensify our concern about the necessity of PTG in *CDH1* mutation positive members, yearly mammograms on *CDH1* mutation positive female members, and bi-annual gastric endoscopy surveillance in members who tested positive but choose to delay or refuse PTG. Also, MICA provided the opportunity to address psychological needs in members who refused testing, members who tested positive and refused PTG, and *CDH1* mutation positive members undergoing PTG. Among those who tested negative, we were able to reassure them that gastric cancer would be very unlikely when compared with their relatives who had positive test results.

During the intervening seven years, our team continued to follow the family, with periodic updates from the proband, as more members became interested in testing. Given the time span, we realized that a full comprehensive assessment was needed, which would provide us with another opportunity to counsel, educate, and screen the family at large rather than just individual members. Comparing MICA with the regular individual follow up, MICA was more successful in identifying family members with the *CDH1* mutation as shown above in the results section (Figure 2)

Although PTG was offered to all *CDH1* mutation carriers, only 8 out of 17 (47%) underwent PTG. Hallowell et al. [16] stated that response to a genetic counseling recommendation for PTG would be influenced by a number of potentially competing factors: confirmation of the objective risk by genetic testing and/or receiving a positive biopsy; perceived familial cancer burden and associated perception of risk; expectations for post-surgical life; an increasing inability to tolerate endoscopic procedures as well as patients' concern that a cancer could be missed; and an individual's stage of life, could collectively be compromising issues. In addition to these factors [16], economic situations and family interpretation of the consequences of PTG can be significant issues, as can emotional implications from cultural factors as well as religious issues [12]. Collectively, resolution of these concerns will benefit immensely from a well-orchestrated genetic counseling experience. Indeed, it may require more than one patient contact for effective genetic counseling [17,18] demonstrating the vital need for a MICA to optimize identification of carriers and provide recommended prevention and screening measures.

An advantage in this family was that the proband had gone through screening and a successful PTG that we advised. The proband in this study is a healthcare professional who reached out to our team in 2010 after reading an article written by us that discussed HDGC (17). She was personally concerned knowing that gastric cancer had occurred in three generations of her family and wanted to request more information. The proband was 53 years old at the time of contact. She tested positive for *CDH1* mutation and decided to undergo PTG that we advised at the same age. The proband is a native of Amman, Jordan, she understands existing cultural challenges and barriers that may inhibit at-risk individuals from pursuing the goal of screening and health intervention. Therein, she broke several culture barriers and encouraged recruitment of other family members who were resisting testing. Moreover, the proband was available to relatives for continuous follow-up, responding to questions and concerns whenever necessary. This enabled the proband to be the center of a multidisciplinary team of healthcare providers and gastroenterologist in Jordan, genetic counsellors, oncologists and internists at Creighton University. Having an active proband along with a well-structured genetic counselling model can help overcome existing cultural challenges and barriers that may hamper at-risk individuals from pursuing the goal of genetic testing and appropriate cancer prevention and screening interventions.

Especially in cases where such an active proband or key family member is not available, one option for increasing genetic counseling and screening is the use of patient navigators [19,20]. Braun et al. [21] have shown that genetic navigation programs increased access to cancer care in underserved individuals and that recruiting navigators from the same background can help in removing structural and cultural barriers to genetic services [21].

Gastric cancer has been diagnosed at the age of 16 as mentioned by Fitzgerlad et al. (8) MICA may help with the dilemma of legal age of genetic testing in which a short interval period of 5–8 years, as shown in this study, is needed. In our study at least 25 members (ranging between eight months to 15 years of age) were under the legal age of genetic testing during our first visit, but not all of them were at risk, given that their parents genetic status was unknown. MICA has decreased that number to six members (ranging between six and ten year of age). Our research team will continue to follow this Jordanian family with HDGC and an associated *CDH1* mutation, by working with the proband and family members as well as conducting MICA every 5–8 years in order to continually offer education, gene testing, and psychological support. We believe that MICA is an excellent tool for regular assessment in families harboring hereditary cancer syndromes such as HDGC, familial adenomatous polyposis, Lynch syndrome and ovarian breast cancer syndrome were screening and intervention can impact the disease course outcome.

Conclusion

As far as we know, this is one of the first proposed models in a hereditary cancer syndrome for interval comprehensive assessment which we implemented in a Jordanian family with HDGC. This is of particular importance and, indeed, mandatory, when dealing with potentially lifesaving remedies for patients with mutations associated with a high mortality rate in the absence of a preventive measure such as PTG in HDGC. Our group's reasons for returning to Jordan included the need to connect with family members who were too young to be provided with *CDH1* testing during our original visit, and to re-contact family members who, for whatever reason, had declined testing during our original visit or who were positive for the mutation but declined PTG or elected surveillance over PTG despite being informed of the general inadequacy of surveillance. The latter group would include those who had declined PTG due to cultural or religious issues. Clearly, as a family is developed further, with more at-risk relatives identified, these interval comprehensive assessments should continue, along with compassionate genetic counseling and psychological support. Further studies are needed to apply such a model in different hereditary cancer syndromes to optimize genetic screening utilization for cancer prevention.

Acknowledgment

We wish to thank Tami Richardson-Nelson, B.G.S., for technical assistance.

Funding sources

This publication is supported by revenue from Nebraska's excise tax on cigarettes awarded to Creighton University through the Nebraska Department of Health & Human Services (DHHS). Its contents represent the views of the authors and do not necessarily represent the official views of the State of Nebraska or DHHS.

Funding was also received from the Liz's Legacy fund through Kicks for a Cure.

Dr. Henry Lynch's work is partially funded through the Charles F. and Mary C. Heider Chair in Cancer Research, which he holds at Creighton University.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cancergen.2019.03.005.

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