UC Irvine

UC Irvine Electronic Theses and Dissertations

Title

An Assessment of Changes to Risk Perception and Lifestyle after Genetic Counseling and Testing for Hereditary Cancer Risk

Permalink

https://escholarship.org/uc/item/6dt814h0

Author

Shehayeb, Susan Salman

Publication Date

2017

Peer reviewed|Thesis/dissertation

eScholarship.org Powered by the California Digital Library
University of California

UNIVERSITY OF CALIFORNIA, IRVINE

An Assessment of Changes to Risk Perception and Lifestyle after Genetic Counseling and Testing for Hereditary Cancer Risk

THESIS

submitted in partial satisfaction for the requirements for the degree of

MASTER OF SCIENCE

in Genetic Counseling

by

Susan Salman Shehayeb

Thesis Committee:
Associate Professor Jason Zell, DO, MPH, Chair
Associate Clinical Professor Kathryn Singh, MPH, MS
Clinical Instructor Charité Ricker, MS

2017

© 2017 Susan Salman Shehayeb

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGMENTS

I would like to thank the UCI Genetic Counseling Program and all the wonderful Genetic Counselors, Geneticists, and Staff who help run it. Pam, thank you for always fostering our strengths and for always having your door open. To Katie, for always pushing me because you believed in me (and for dealing with my stress-induced phone calls). A special thanks to Dr. Kathy Osann for being willing to answer my random statistics questions during her retirement.

To my thesis committee members, Katie Singh, Dr. Zell, and Charité Ricker, I am so thankful for all your advice, wisdom, and patience! And to Julie Culver, for letting me have my first taste of genetic counseling and for always being a mentor. Thank you to Dr. Gregory Idos and the wonderful team at USC for allowing me to be a part of your research.

To my beautiful classmates: Bea, Bethany, Shayna, Holly, Devin, Emma, and Molly. You are always an inspiration. I can't wait to watch you take on the world!

Most of all thank you to my family. For your love, your kindness, and your support, I am forever grateful.

ABSTRACT OF THE THESIS

An Assessment of Changes to Risk Perception and Lifestyle after Genetic Counseling and Testing for Hereditary Cancer Risk

By

Susan Salman Shehayeb

Master of Science in Genetic Counseling

University of California, Irvine, 2017

Associate Professor Jason Zell, Chair

Lifestyle risk factors are known to increase the risks for certain cancers. However, these factors are often not discussed during hereditary cancer risk counseling. This study explored self-reported improvements to lifestyle risk factors and perception of cancer risk in the setting of hereditary cancer risk counseling. The study involved 2,000 participants undergoing genetic counseling at three California hospitals who completed pre-counseling and post-testing surveys, with questions pertaining to risk perception and changes to modifiable lifestyle risk factors.

Results from this study give insight into lifestyle improvements made in the setting of genetic counseling and testing. Over a third of the study participants indicated that they made a lifestyle improvement. Participants with modifiable lifestyle risk factors were not more likely to make improvements to lifestyle than participants without these lifestyle risk factors; they were also not more likely to perceive they were at higher risk for specific cancers. Participants who tested negative for a mutation did not improve their lifestyle more often than those who tested positive for a mutation.

This study identifies a gap in knowledge of cancer risk in participants with modifiable lifestyle risk factors. It also highlights that mutation carriers are engaging in lifestyle improvements even though the benefit to them is not well understood. Thus, it may be important

for genetic counselors to address lifestyle risk factors during risk counseling. Future studies may focus on understanding the impact and efficacy of lifestyle risk counseling during hereditary cancer counseling.

I. INTRODUCTION

1.1 Overview of Cancer

Cancer is the second leading cause of death in the United States, following only heart disease, with one in three women and one in two men expected to be diagnosed in their lifetimes (Hayat et al, 2007). Cancer is the process by which the cells of an organism grow and divide uncontrollably due to genetic mutations. It is not one homogeneous disease but a conglomeration of similar diseases. In fact, within each cancer there is great cellular and genetic heterogeneity, posing a challenge to antineoplastic therapeutics and management (Gerlinger et al, 2012).

Cancer has been recognized as a disease since ancient times. The first known description of cancer comes from Egypt, approximately 3000 B.C., in which a case of breast cancer was described. When it could be performed, the excision of certain surface tumors was thought to be employed during this time. The origin of the word cancer is credited to Hippocrates, who used the Greek word *karkinos*, from which the word carcinoma is derived (Sudhakar, 2009). Early theories about the etiology of cancer included an excess of one of the four humors and trauma. In the 19th century, the idea that cancer was caused by malignant cells, derived from normal cells, was proposed (Sudhakar, 2009).

1.2 Hereditary Causes of Cancer

Today, it is well established that all cancer is genetic, caused by gene mutations that impact cell growth. Mutations can be gain-of-function mutations in oncogenes, genes which promote cell growth or division. They can also be loss-of-function mutations in tumor suppressor genes, genes which regulate of the processes of cell growth or division. These mutations may be somatic or germline. Somatic mutations are acquired, due to processes such as environmental

exposures and aging, and start in only one cell of the body. Germline mutations are hereditary, passed down through a family from generation to generation or a *de novo* event occurring at conception for the first time in an individual, and found in every cell of the body. Hereditary causes of cancer, such as hereditary breast and ovarian cancer (HBOC) syndrome and Lynch syndrome, account for an estimated 5-10% of all cancer diagnoses (Kulkarni and Carley, 2016). Thus, they are an important target for research; better understanding of these conditions and early identification of carriers will lead to better surveillance and lower rates of morbidity and mortality.

In the 1970s, Alfred Knudson proposed the two hit hypothesis, which helped lay the foundation for understanding the genetic basis of cancer (Knudson, 1971). This hypothesis explained that a gene requires a "hit," or a mutation that causes an allele to lose its function, in both alleles of a gene to begin the process of tumorigenesis. When there is a hereditary mutation, a preexisting "hit", only one acquired "hit" is necessary to cause cancer, making it more likely for cancer to occur in this population. The classic example of the two hit hypothesis is retinoblastoma. The age difference between those affected by hereditary retinoblastoma and those without hereditary causes of retinoblastoma can be explained by a preexisting *RB1* mutation in the hereditary group. Because they only need one more mutation to develop two "hits," those with hereditary retinoblastoma are more likely to develop tumors at an earlier age and at a higher frequency than in the general population (Lohmann and Gallie, 2004). This hypothesis applies to tumor suppressor genes, such as *BRCA1* and *BRCA2*, which are important in regulating cell growth and division (Hodgson, 2008).

Another class of genes which are important in cell regulation are DNA repair genes, which work to correct mutations caused by DNA replication and by environmental exposures.

When a loss-of-function mutation occurs in one of these genes, it increases the likelihood that mutations accrued throughout the genome may not be corrected. If the mutations are in areas important for regulating cell function, there can be a significant increase in the risk of cancer. Changes in such genes can be inherited, such as in the case of mutations in *ATM* and the Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*) (Peltomaki, 2001).

Another important mechanism of carcinogenesis is through mutations in proto-oncogenes. Proto-oncogenes are genes that cause cells to grow and divide. When mutations occur in these genes, the cell to grows and divides uncontrollably. Hereditary cancer syndromes can be caused by inherited mutations in proto-oncogenes, such as in the case of multiple endocrine neoplasia type II caused by mutations in the *RET* gene (Nagy et al, 2004).

Identification of genetic causes of cancer, whether hereditary or sporadic, has become important in the development of targeted therapies. Starting with early discoveries such as the development of a treatment targeted to the bcr-abl transcript in leukemia with the Philadelphia chromosome (Salesse and Verfaillie, 2002) and of the use of treatments targeting Her-2 positive breast cancer (Baselga et al, 1996), personalized treatments based on the genetic profile of the tumor have in many cases proven to be a more successful way to treat cancer than nonspecific treatment. Today, therapies based on the genetic profile of the tumor have become an effective way to treat the unique causes of cancer in many different patients. Treatments such as Crizotinib for ALK-positive non-small cell lung cancer, have allowed for better response rates versus standard chemotherapy (Shaw et al, 2013). Thus the genetic background of cancer in each individual patient has become essential in the identification of the best therapies to use to target the cancer. It is important to note that testing for acquired mutations in a tumor is a distinct entity from testing for germline mutations which cause hereditary forms of cancer. However, a

germline mutation can still be the target of chemotherapy, such as in the case of PARP inhibitors used in the setting of HBOC syndrome (Farmer et al, 2005). Thus, a better understanding of the genetic changes in a tumor, whether constitutional or acquired, may help lead to potential therapeutic targets.

1.3 Lifestyle Factors and Cancer Risk

The first environmental link to cancer was the identification by Percivall Pott in 1775 that exposure to chimney soot led to a higher incidence of squamous cell carcinoma of the scrotum in chimney sweeps (Herr, 2011). Although cancer is a genetic disease, it is now accepted that environmental and lifestyle factors can cause acquired gene mutations, contributing to the possibility that an individual may develop a malignancy.

1.3.1 Lifestyle Factors Contributing to Gastrointestinal Cancers

Multiple lifestyle factors are known to increase the risk of developing gastrointestinal cancers. High consumption of processed meat and lower consumption of vegetables, smoking, sedentary lifestyle, heavy alcohol consumption, and obesity, have been associated with an increased risk for developing colorectal cancer (Tarraga Lopez et al, 2014) and *Helicobacterpylori* infections, heavy alcohol consumption, and high salt diet have been shown to increase the risk of developing gastric cancer (Cheng et al, 2016). Additionally, elevated pancreatic cancer risk has been associated with smoking (Iodice et al, 2008) and heavy alcohol use (Lucenteforte et al, 2012).

1.3.2 Lifestyle Factors Contributing to Gynecological Cancers

Human Papilloma virus (HPV) infection has been shown to be a carcinogen causing increased risk for cervical cancer (Schiffman et al, 2016) (Bravo and Felez-Sanchez, 2015). Long term use of estrogen and tamoxifen both increase risk for endometrial cancer (Braun et al, 2016). Hormone replacement therapy and estrogen use also increase the risk of ovarian cancer (Chuffa et al, 2016). In contrast, the use of specific oral contraceptives has been shown to decrease the risk of endometrial (Zaino et al, 2014) and ovarian cancer (Walker et al, 2015).

1.3.3 Lifestyle Factors Contributing to Breast Cancers

High body mass index (BMI) in postmenopausal women has been shown to be associated with increased risk for developing breast cancer, but may be protective in premenopausal women (White et al, 2012). Tamoxifen exposure has been used to reduce the risk in breast cancer, even in the setting of a *BRCA* mutation (Mallick et al, 2016). Increased estrogen exposure is associated with higher risk for breast cancer (Persson, 2000)

1.3.4 Lifestyle Factors Contributing to Skin Cancers

Sun exposure and exposure to UV light are known to increase the risk for skin cancers including melanoma, basal cell carcinoma, and squamous cell carcinoma (Leiter and Garbe, 2008).

1.4 Hereditary Cancer Genes

Since the identification of genes such as *BRCA1*, *BRCA2*, and the Lynch syndrome genes, genetic testing to determine cancer risk has become an important area within the field of genetic counseling. As hereditary causes of cancer were identified and gene mutations began to be

accurately classified, the ability to test if a hereditary cancer syndrome was the root cause of the cancer history in a family became possible. Today mutations in over 100 genes are now known to be associated with elevated risk for cancer.

1.4.1 Hereditary Causes of Cancer: High Risk

Perhaps the most well-known hereditary cause of cancer is Hereditary Breast and Ovarian Cancer (HBOC) syndrome caused by damaging mutations in the *BRCA1* and *BRCA2* genes. A diagnosis of HBOC confers up to an 80% risk of breast cancer in females and up to a 40% risk of ovarian cancer; risks for pancreatic cancer, prostate cancer, male breast cancer, and melanoma are also increased (Ford et al, 1994) (Ford et al, 1998) (Mavaddat et al, 2013). Based on the National Comprehensive Cancer Network (NCCN) guidelines, women with HBOC can consider a bilateral mastectomy, bilateral salpingo-oophorectomy, as well as screening options such as MRI to prevent or decrease their cancer risk (www.nccn.org, Genetic/Familial High Risk Assessment: Breast and Ovarian, version 2.2017; last accessed 06/02/2017).

Lynch syndrome, also known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC) syndrome, is responsible for approximately 3% of all colorectal cancer (Strafford, 2012). Lynch syndrome also increases the risk for uterine cancer (to approximately 25-60%), ovarian cancer, brain tumors, hepatobiliary tract cancers, small bowel cancer, stomach cancer, skin cancer, and urinary tract cancers, among others (Stoffel et al, 2009) (Watson et al, 2008). Lynch syndrome is most often caused by a defect in *MLH1*, *MSH2*, *MSH6*, or *PMS2*; more rarely, mutations in *EPCAM* can cause Lynch syndrome by inactivating *MSH2*. NCCN guidelines recommend the options of increased colonoscopy screening, hysterectomy, and salpingo-oophorectomy for

lowering cancer risk among people with Lynch syndrome (www.nccn.org, Genetic/Familial High Risk Assessment: Colorectal, version 2.2016; last accessed 06/02/2017).

Familial Adenomatous Polyposis (FAP) and Attenuated Familial Adenomatous Polyposis (AFAP), both due to mutations in the *APC* gene, cause increased polyposis and therefore higher rates of colorectal cancer. FAP can confer up to a 100% risk of colorectal cancer; AFAP increases the risk for colorectal cancer, however not to the degree of FAP (Half et al, 2009). Increased risks for other cancers, such as small bowel and thyroid also exist for individuals with *APC* mutations (Half et al, 2009). An important exception is the cause of the I1307K mutation in *APC*, which is found in approximately 10% of individuals of Ashkenazi Jewish ancestry and leads to a 10% risk for colon cancer, approximately double the general population (Jeter et al, 2006). MAP (*MUTYH*-Associated Polyposis), which is caused by biallelic mutations in the *MUTYH*/*MYH* gene, can have a similar phenotype to AFAP and is an important differential diagnosis in the setting of polyposis.

Other highly penetrant causes of hereditary cancer are mutations in *PTEN* (Cowden syndrome), *TP53* (Li-Fraumeni syndrome), *STK11* (Peutz-Jeghers syndrome), *CDH1* (hereditary diffuse gastric cancer syndrome), *BMPR1A* and *SMAD4* (juvenile polyposis syndrome), *CDK4* (cutaneous malignant melanoma syndrome) and *CDKN2A* (familial atypical multiple mole melanoma syndrome), among others.

1.4.2 Hereditary Causes of Cancer: Moderate Risk

While there is no current consensus regarding the distinction between “high penetrance and “moderate penetrance” genes, the genes discussed in this section are usually considered to have moderate penetrance (Tung et al, 2016). Mutations in these genes generally cause a lower risk of cancer; however, these genes are not as well studied and less is understood about the

exact lifetime cancer risks caused by mutations in these genes (Loveday et al, 2011) (Loveday et al, 2012) (Roberts et al, 2011). Genes considered moderate penetrance genes include *ATM*, *CHEK2*, *PALB2*, *BRIP1*, *RAD51C*, *RAD51D*, *BARD1*, *NBN*, *POLE*, *POLD1*, and *GREM1*. Importantly, NCCN recommends screening and consideration prophylactic surgery for mutations found in some of these genes; thus testing of these genes is worthwhile. For this study, the I1307K mutation in *APC* and monoallelic *MUTYH* mutations are also considered to be of moderate penetrance. Of note, many of these genes can confer other risks, such as Fanconi anemia, in the setting of biallelic mutations (when both alleles have a germline mutation).

1.5 Advances in Hereditary Cancer Testing

A combination of advances has led to an increase in the desire for cancer genetic counseling and testing. Changes in societal views about stigma of genetic disease and preventative surgery have increased individuals' desire to pursue genetic testing. A parallel decrease in the cost of testing due to developments in technology such as next generation sequencing and the availability of panel testing to investigate multiple causes at once, has led to an increase in the diagnosis of hereditary cancer syndromes. Furthermore, legal rulings (such as Association for Molecular Pathology v. Myriad Genetics, Inc.) and social changes, such as the "Angelina Jolie Effect," have led to an increase in the awareness of and demand for genetic testing (Sherkow and Greely, 2015) (Desai and Jena, 2016).

1.6 Lifestyle Factors in the Setting of Hereditary Cancer

The role of most lifestyle changes in lowering or exacerbating cancer risk in the context of a hereditary cancer syndrome is not well understood. Generally, risks due to lifestyle factors are lower than those due to mutations. For example, breast cancer risk due to postmenopausal

obesity is thought to be around 1.2 to 2–fold over the population risk of 10-12 % (White et al, 2012). In contrast, mutation risks for high penetrance genes such as *BRCA1*/2 confer a risk of up to 80%. However, there has been some evidence that lifestyle factors can affect cancer risk in the setting of a hereditary cancer syndrome. Smoking has been shown to modulate colorectal cancer risk in Lynch syndrome (Watson et al, 2014) and, there is some preliminary evidence that physical activity may affect breast cancer risk in *BRCA1*/2 carriers (Pijpe et al, 2010). It is known that some of the risk of cancer in a hereditary cancer syndrome may be modified by other non-genetic factors as well. For example, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with FAP has been shown to decrease the polyp burden by causing adenomas to regress (Matsumoto et al, 2006) and the use of oral contraceptive pills is thought to decrease ovarian cancer risk in HBOC carriers (Rieder et al, 2016).

1.6.1 Role of Genetic Counselors in Lifestyle Risk Counseling

There is currently no consensus regarding the role of genetic counselors in counseling about lifestyle factors as a risk for cancer. Initial research has suggested that genetic counselors generally do not want to counsel about how lifestyle affects cancer risk for various reasons including that they believe that not enough is known or that it is not relevant to a cancer genetic counseling session (Rees et al, 2006). However, some patients have indicated that they want lifestyle factors to be addressed in their cancer genetic counseling sessions (Dickens, 2016). It is possible that patients are already changing their lifestyle with the expectation that it may lower their cancer risks without having medical guidance or discussing their choices with their providers. This study aims to reveal possible alterations to lifestyle factors that patients may be making after undergoing genetic counseling and testing.

1.6.2 Previous Research

Preliminary research has been done into how people who undergo genetic counseling and testing may change their lifestyle to modify risk (Quillin, 2016) (Paalosalo-Harris and Skirton, 2017). However, it is still not well understood exactly how people decide to alter their environmental factors after addressing the possible hereditary causes of cancer in their families.

Quillin investigated the lifestyle risk factors among people who self-reported having genetic testing for HBOC and/or Lynch syndrome and found that those who had genetic testing had the same modifiable risk factors as those who did not (Quillin, 2016). It was unknown whether or not these individuals had genetic counseling and what the results of their testing were.

Research has been conducted on smokers undergoing testing for single nucleotide polymorphisms, common genetic variations between individuals, which may be associated with increased risk for lung cancer (Marcy et al, 2002). Results of studies have shown that smokers found to have *CYP2D6* polymorphisms which increased lung cancer risk were more motivated to attempt to stop smoking after counseling. Testing negative for these polymorphisms provided false reassurance for other smokers. However, lifestyle changes in the setting of hereditary cancer counseling for mutations which increase cancer risks much more significantly than polymorphisms is not well studied.

It is also unknown if the way in which people perceive their cancer risk may correlate with changes to their lifestyle. Previous research has shown that the link between risk perception and lifestyle risk factors is unclear (Paalosalo-Harris and Skirton, 2017). This study aims to investigate if individuals who are undergoing genetic counseling and testing for hereditary cancer syndromes are engaging in improvements to lifestyle and whether this relates to cancer risk perception; furthermore, it aims to elucidate possible relationships between demographic factors and lifestyle improvements. We will also explore if participants with modifiable risk

factors are making lifestyle improvements and how these individuals perceive their risks for cancer.

II. METHODS

This study was reviewed and was not classified as human research by the Institutional Review Board of the University of California, Irvine (UCI). The original research study from which data was taken for this study was reviewed and classified as human research by the Institutional Review Board of the University of Southern California (OS-13-1 Protocol).

2.1 Recruitment

Participants were recruited through the genetics clinics at the University of Southern California (USC) Norris Comprehensive Cancer Center and the Los Angeles County+University of Southern California (LAC+USC) Hospital, Los Angeles, CA and from Stanford Cancer Institute in Stanford, California. If they met study criteria, patients were invited during their clinic appointment to participate in a longitudinal research study assessing reactions to genetic counseling and panel testing for cancer predisposition genes. Patients were then given a study information sheet with a brief overview of the research project as well as contact information for the research team. The potential participants were asked to review the study information sheet and sign a consent form before enrollment in the study.

2.2 Participants

Participants in this study were required to have a family history or personal history which conferred at least a 2.5% risk of having a mutation via a validated cancer risk model (BOADICEA, PREMM, BRCAPro, etc.). Individuals for whom there was a known familial mutation were not eligible for participation in the study unless there was a family or personal history not accounted for by the familial mutation. Participants were required to undergo genetic

counseling and to complete a baseline questionnaire before results disclosure to be enrolled. The surveys were available in both English and Spanish and in written and email form. There were no exclusion criteria based on gender, religious beliefs, or educational attainment. The study had a total sample size of 2,000.

2.3 Protection of Participant Privacy

The privacy of the participants was protected throughout the study. All research data sent to researchers at UCI was sent electronically. No personal identifiers were sent to researchers at the University of California, Irvine. There were no known harms or discomforts associated with the other than blood draw, which would have been done for genetic testing regardless, and the possibility of psychological harm from being asked questions about cancer or from anxiety of testing positive for a mutation.

2.4 Informed Consent

Informed written consent for the original study was obtained using a study information sheet and consent form sheet. The study information sheet includes information regarding the study aims and questionnaire time-points, as well as information about genetic causes of cancer and a list of the genes tested. The consent form explicitly laid out the aims of the study, the potential risks and benefits, the options of how to receive follow-up questionnaires, contact information for human rights research protection offices and the research team, and the rights of the participant, including the right to withdraw from the study at any time point. These documents were approved by the Institutional Review Board of USC. The possible risks associated with the procedures described in this study include risk from blood draw and possible

risk from genetic testing such as anxiety over a positive test result. The consent form also explained that no compensation or direct benefits were anticipated from participation in the study; there was the possible benefit of learning more about cancer genes and how patients react to panel testing, however these are societal benefits and not expected to benefit the individual participants. In some cases, testing was paid for by the study, if access to testing was limited by financial status. Individuals who decided to continue with the study after counseling, reviewing the information sheet, and reading through the consent form were asked to sign the consent form. For individuals who consented to study participation, the standard clinical intake questionnaire served as the baseline study survey.

2.5 Testing

Panel testing was performed through Myriad Genetics (Salt Lake City, Utah). The panel test run for each patient was myRisk. For most participants this included 25 genes (*APC*, *ATM*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *SMAD4*, *STK11*, *TP53*). However, 334 participants (16.7%), beginning with patients in the summer of 2016, were tested for three additional genes (*POLE*, *POLD1*, *GREM1*) due to updates to the myRisk panel.

2.6 Survey

The baseline survey was available as a paper questionnaire and as an online questionnaire before the genetic counseling appointment (Appendix A). During the consenting process participants were asked to indicate if they would prefer to receive future questionnaires via email or mail. Questionnaires were sent at three-month, six-month, one-year, two-year, and three-year

time points, with surveys timed at intervals after genetic testing results were disclosed. For the purposes of this project, only certain questions from the baseline questionnaire and the three-month questionnaire (Appendix B) were analyzed. There was an effective response rate of 64% at the three month questionnaire time point; this included individuals who were still alive between the two time points and had received their three month questionnaire (not all participants had received their three month questionnaire at the time of this study's analysis).

Analyzed questions from the baseline questionnaire consisted of approximately 40 demographic questions, including information assessing age, sex, cancer diagnosis, race/ethnicity, language spoken, cigarette and alcohol use, and height and weight. Additional questions contained Likert scales regarding perceived risk for cancer and perceived risk for cancer as compared to other individuals. Questions analyzed from the three-month questionnaire included the same questions regarding perceived risks for certain cancers as well as a Likert scale regarding changes to lifestyle behaviors since receiving genetic test results. The major themes addressed in the survey included perceived cancer risk, reactions to genetic counseling and testing results, and changes to lifestyle behaviors after genetic testing. All questions were created by the researchers at the participating institutions.

2.7 Data Entry

Data from paper questionnaires were entered by researchers at the participating institutions into a computer database. Specific questions used for this research project were exported to Microsoft Excel after the collection period.

2.8 Survey Scoring and Grouping

Participants were compared based on demographic characteristics including race/ethnicity, sex, age, and educational status. Participants were also compared based on lifestyle factors including body mass index (BMI, less than 18.5 was underweight, 18.5 to 24.9 was normal, of 25 to 29.9 was overweight, and 30 or more was obese), smoking status (non-smoker, past smoker, current smoker), and heavy drinking status (defined as 7 or more drinks per week for females or 14 or more drinks per week for males based on NIH National Institute on Alcohol Abuse and Alcoholism guidelines) Mutation status (positive versus negative or variant of uncertain significance) and mutation type (high penetrance versus moderate penetrance) were also compared. High penetrance was classified as mutations in *APC* (with the exception of I1307K), *BMPR1A*, *BRCA1*, *BRCA2*, *CDH1*, *CDK4*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MUTYH* (biallelic mutations only), *PMS2*, *PTEN*, *SMAD4*, *STK11*, or *TP53* while moderate penetrance was classified as mutations in *ATM*, *BARD1*, *BRIP1*, *CHEK2*, *NBN*, *PALB2*, *RAD51C*, *RAD51D*, *POLE*, *POLD1*, and *GREM1*, as well as *APC* I1307K carriers and *MUTYH* monoallelic carriers. Responses to the Likert scale detailing changes in lifestyle were compared to changes in perceived cancer risk from the baseline questionnaire and the three month questionnaire.

A subset of questions from the baseline questionnaire and three month questionnaire required participants to use a Likert scale to rate their likelihood of developing different cancers on a scale from “no risk” to “very high” (no risk, very low, somewhat low, moderate, somewhat high, very high). “Don’t know” and “not applicable” were also options. Those who answered “very low” or “somewhat low” were combined as low risk. Similarly the “somewhat high” and “very high” groups were combined as “high risk.” A similar question that asked participants to

compare their likelihood of developing certain cancers with the risk of an average person the same age used the same Likert scale as above and was asked on both the baseline questionnaire and the 3-month follow-up questionnaire. These scores were analyzed to determine if participants felt they were higher than average risk when they answered "somewhat high" or "very high" or if they felt they were not when they answered otherwise. The same method was used to determine if participants felt lower than average risk. Those who answered "don't know" or "not applicable" were not included in the associated analyses.

Another Likert scale was used to assess the participants' self-reported changes to lifestyle at three months. The lifestyle activities which were ascertained were "eat a healthy diet," "exercise," "avoid sunburn," "smoking," "drinking alcohol," and "performing self-breast exams." Participants were asked if these activities had decreased, stayed the same, or increased in the previous 6 months. An option for not applicable was also included (1= decreased, 2 = stayed the same, 3 = increased, 0 = not applicable). An increase of a healthy lifestyle factor (eat a healthy diet, exercise, avoid sunburn, and perform self-breast exam) or a decrease of an unhealthy lifestyle factor (smoking and drinking) was given a score of 1. Scores for all the lifestyle factors combined were summed to give a total improvement score. The total improvement score was divided by the total possible improvements each participant could have made based on sex, mastectomy status, smoking status, and drinking status. For some participants the maximum number of factors which could be improved was 3 but for others it was as many as 6. This resulted in a total lifestyle percent improvement score (see examples of calculations in Figure 1). This percent improvement score was categorized as either "any improvement" or "no improvement." Participants who did not respond to any of the lifestyle questions were included in the "no improvement" group. Within the group that made "any

improvement," a "great improvement" was categorized as an improvement of 50% or more of the lifestyle factors the participant was able to improve and a "moderate improvement" was categorized as an improvement of less than 50% of the lifestyle factors.

FIGURE 1: EXAMPLES OF CALCULATION OF TOTAL LIFESTYLE PERCENT IMPROVEMENT SCORE

1. Male smoker and nondrinker who decreased smoking and increased eating a healthy diet
Total factors improved: 2 (smoking, eat a healthy diet)
Total factors able to improve: 4 (smoking, eat a healthy diet, avoid sunburn, exercise)
Total lifestyle percent improvement score: 2/4 x100%= **50%**

2. Female non-smoker and drinker with a history of bilateral mastectomy who decreased drinking
Total factors improved: 1 (drinking)
Total factors able to improve: 4 (drinking, eat a healthy diet, avoid sunburn, exercise)
Total lifestyle percent improvement score: 1/4 x100%= **25%**

3. Female smoker and nondrinker who increased eating a healthy diet, increased exercise, and decreased sun exposure
Total factors improved: 3 (eat a healthy diet, avoid sunburn, exercise)
Total factors able to improve: 5 (smoking, eat a healthy diet, avoid sunburn, exercise, perform self-breast exams)
Total lifestyle percent improvement score: 3/5 x100%= **60%**

Figure 1 shows example calculations of the total lifestyle percent improvement score. Total lifestyle factors improved by a participant were divided by the total possible lifestyle factors that participant was able to improve and multiplied by 100% to calculate the score.

2.9 Survey Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) Version 22 (IBM, Armonk, NY). Chi-square analyses were conducted to compare demographics and lifestyle improvement, modifiable risk factors and lifestyle improvement, modifiable risk factors and cancer risk perception, mutation status and lifestyle improvement, mutation status and cancer risk perception, and lifestyle improvement and cancer risk perception. A p-value of less than 0.05 was considered statistically significant.

III. RESULTS

3.1 Demographic Features of the Study Population

Of the 2,000 participants, the overwhelming majority of the participants were female (N=1612; 80.6%) and mean age was 51 years old (SD=13.4). Most participants identified as Non-Hispanic Whites (N=803; 40.2%) or Hispanics (N=748; 37.4%), with less frequently represented ancestries including Asian (11.5%), African American or Black (3.9%), Native Hawaiian or Pacific Islander (0.4%), and Alaskan Native or Native American (0.4%), as well as Unknown/Other/More than One Race (6.4%) (Table 1A).

Most participants had either a higher level of education, such as a college degree (21.1%) or graduate (17.8%) degree, or a lower level of education, such as high school (18.6%) or elementary school (11.1%) education, with a smaller proportion of the individuals indicating that they received vocational or trade school (4.0%), junior college (4.5%), or some college (13.3%) education.

Most individuals had a past or current diagnosis of cancer, some with multiple diagnoses, while 26.9% had no history of cancer or only a history of non-melanoma skin cancer. Of those with a diagnosis of cancer, breast cancer diagnoses (N=684; 34.2%) made up the largest category followed by colon cancer diagnoses (N=300; 15.0%). Some of these participants had diagnoses of multiple cancers and may be counted more than once in Table 1. Of the participants, 27.5% of had a history of smoking or were smokers at the time of the study, with 57.1% stating that they were never smokers. Nondrinkers (55.3%) were more common than drinkers (34.0%). Height and weight were used to calculate body mass index (BMI) for participants, with 2.6% of participants classified as underweight (BMI below 18.5), 29.5% as normal (BMI of 18.5-24.9), 23.9% as overweight (BMI of 25-29.9), and 19.9% as obese (BMI of 30 or higher). Of the

participants, most had a negative test result (87.8%), classified as either a completely negative result or any variant of uncertain significance (VUS) which was not likely pathogenic. Of the participants, 12.1% were found to have a mutation that causes cancer susceptibility in either a moderate or high penetrance gene.

TABLE 1A: CHARACTERISTICS OF 2,000 STUDY PARTICIPANTS	**N**	**%**
Age		
29 and younger	100	5.0%
30 to 39	282	14.1%
40 to 49	530	26.5%
50 to 59	502	25.1%
60 to 69	409	20.5%
70 and older	169	8.4%
Unknown	8	0.4%
Gender		
Male	388	19.4%
Female	1612	80.6%
Level of education		
Elementary school	222	11.1%
High school	371	18.6%
Trade/Vocational school	79	4.0%
Junior college	89	4.5%
Some college	265	13.3%
College degree	421	21.1%
Graduate degree	355	17.8%
Race/Ethnicity		
Non-Hispanic, White	803	40.2%
Black or African American	77	3.9%
Hispanic	748	37.4%
Asian	229	11.5%
Native Hawaiian or Pacific Islander	7	0.4%
American Indian or Alaska Native	9	0.4%
Unknown/More than One Race/Other	127	6.4%
Cancer status		
Unaffected or non-melanoma skin cancer	537	26.9%
Breast/breast DCIS	684	34.2%
Colorectal	300	15.0%
Other	428	21.4%
Unknown	51	2.5%
Smoking status		
Non-smoker	1141	57.1%
Smoker (current or past)	550	27.5%
Unknown	309	15.4%
Drinking status		
Nondrinker	1106	55.3%
Heavy Drinker	35	1.8%
Casual Drinker	644	32.2%
Unknown	215	10.7%

TABLE 1A: CHARACTERISTICS OF 2,000 STUDY PARTICIPANTS (CONTINUED)		N	%
BMI			
Underweight		51	2.6%
Normal		590	29.5%
Overweight		478	23.9%
Obese		397	19.9%
Unknown		484	24.1%
Mutation status			
Positive		242	12.1%
	High penetrance mutation	126	6.3%
	Moderate penetrance mutation	116	5.8%
Negative		1757	87.8%
	Variant of Uncertain Significance (VUS)	690	34.5%
	No variant	1067	53.3%
Unknown		1	0.1%

Table 1A describes the demographic features of the 2,000 study participants. Participants were characterized based on age, gender, level of education, race/ethnicity, cancer status, smoking status, drinking status, BMI, and mutation status.

We also performed separate analyses for individuals with no cancer history, as their cancer risk perception may be distinct from individuals who have had a cancer diagnosis. Additionally, individuals with cancer may have been limited in their ability to improve lifestyle due to their treatment. Of those who were unaffected, defined as having no diagnosis of cancer or only a diagnosis of non-melanoma skin cancer, mean age was 47 years old (SD=13.2). Those in the 40-49 age range (27.4%) made up the largest group (Table 1B). Unaffected individuals were still mostly female (83.1%). Nearly half of all unaffected individuals had either a college degree (25.1%) or a graduate degree (24.6%). Non-Hispanic Whites was the most common race/ethnicity category (46.7%), followed by Hispanics (30.2%).

Most unaffected individuals were non-smokers (58.8%) and nearly half were nondrinkers (44.9%). For BMI, 22.9% were overweight and 19.6% were obese. Of the unaffected participants, 10.2% were positive for a mutation, with 4.5% found to have a high penetrance mutation. Most unaffected individuals tested negative (89.8%), with 33.5% found to have a variant of uncertain significance.

TABLE 1B: CHARACTERISTICS OF 537 UNAFFECTED PARTICIPANTS		N	%
Age			
29 and younger		51	9.5%
30 to 39		115	21.4%
40 to 49		147	27.4%
50 to 59		124	23.1%
60 to 69		80	14.9%
70 and older		20	3.7%
Gender			
Male		91	16.9%
Female		446	83.1%
Level of education			
Elementary school		35	6.5%
High school		75	14.0%
Trade/Vocational school		25	4.7%
Junior college		19	3.5%
Some college		73	13.6%
College degree		135	25.1%
Graduate degree		132	24.6%
Unknown		43	8.0%
Race/Ethnicity			
Non-Hispanic, White		251	46.7%
Black or African American		35	6.5%
Hispanic		162	30.2%
Asian		40	7.4%
Race/Ethnicity (Continued)			
Native Hawaiian or Pacific Islander		1	0.2%
American Indian or Alaska Native		3	0.6%
Unknown/More than One Race/Other		45	8.4%
Smoking status			
Non-smoker		316	58.8%
Smoker (current or past)		150	28.0%
Unknown		71	13.2%
Drinking status			
Nondrinker		241	44.9%
Heavy Drinker		14	2.6%
Casual Drinker		228	42.5%
Unknown		54	10.0%
BMI			
Underweight		7	1.2%
Normal		191	35.6%
Overweight		123	22.9%
Obese		105	19.6%
Unknown		111	20.7%
Mutation status			
Positive		55	10.2%
	High penetrance mutation	24	4.5%
	Moderate penetrance mutation	31	5.7%
Negative		482	89.8%
	Variant of Uncertain Significance (VUS)	180	33.5%
	No variant	302	56.3%

Table 1B shows the demographic features of the 537 study participants with no cancer diagnosis.

3.2 Lifestyle Improvements Within Demographic Categories

At the three-month follow-up survey, participants were asked about changes to the following lifestyle factors: smoking, drinking, sun exposure, eating a healthy diet, exercising, and self-breast exams. A total lifestyle percentage improvement score was calculated as described previously. Overall, 36.4% of participants reported making an improvement to their lifestyle. Females we more likely to make lifestyle improvements than males, with 38% of females making improvements versus 29.4% of males (p=0.001). There was no significant difference in race/ethnicity, educational status, or age among those who made improvements (Table 2A). Participants who did not respond to a particular lifestyle question were categorized as "no improvement" for that question.

TABLE 2A: LIFESTYLE IMPROVEMENTS SINCE RECEIVING TEST RESULTS

		N	Any Improvement N (%)	No Improvement N (%)	p-value
Total		2000	728 (36.4%)	1272 (63.6%)	
Sex	Male	388	114 (29.4%)	274 (70.6%)	**0.001**
	Female	1612	613 (38.0%)	999 (62.0%)	
Race/Ethnicity	White, Non-Hispanic	803	288 (35.9%)	515 (64.1%)	0.337
	African American or Black	77	22 (28.6%)	55 (71.3%)	
	Hispanic	748	289 (38.6%)	459 (61.4%)	
	Asian	229	77 (33.6%)	152 (66.4%)	
	Other	143	51 (35.7%)	92 (64.3%)	
Educational status	Elementary School	222	92 (41.5%)	130 (58.6%)	0.241
	High school	371	129 (34.8%)	242 (65.2%)	
	Trade/Vocational school	79	25 (31.6%)	54 (68.4%)	
	Junior college	89	30 (33.7%)	59 (66.3%)	
	Some college	265	97 (36.6%)	168 (63.4%)	
	College degree	421	177 (42.0%)	244 (58.0%)	
	Graduate degree	355	134 (37.7%)	221 (62.3%)	
Age	29 or younger	100	38 (38.0%)	62 (62.0%)	0.077
	30-39	282	92 (32.6%)	190 (67.4%)	
	40-49	530	203 (38.3%)	327 (61.7%)	
	50-59	502	191 (38.0%)	311 (62.0%)	
	60-69	409	156 (38.1%)	253 (61.9%)	
	70 or older	169	46 (27.2%)	123 (72.8%)	

Table 2A shows the percentage of individuals who made any lifestyle improvement by demographic category. Lifestyle improvements were compared on the basis of sex, race/ethnicity, educational status, and age. p-values less than 0.05 are in bold.

Those who made any improvement were further analyzed after being divided into two groups; those who made "great improvements" or those who made moderate improvements." Great improvement was defined as an improvement score of 50% or higher (an improvement over 50% or more of the lifestyle factors which they could improve) and moderate improvement was defined as an improvement score of up to 49% (an improvement over less than 50% of the lifestyle factors which they could improve). When comparing great and moderate improvements, there were significant differences among demographic features (Table 2B). A significant difference in lifestyle improvement was seen based on educational status, with those with 76.7% of individuals with a Junior college education making an improvement and 75.0% of individuals with an Elementary school education making an improvement, compared to 32.1% of individuals with a Graduate degree ($p<0.001$). Hispanic participants were more likely to report making a great improvement than other racial/ethnic groups ($p<0.001$). There was a significant difference seen based on age when comparing those who made great versus moderate improvements. Those who were in the age range of 40-49 followed by those in the age range of 50-59 tended to make larger improvements more often than those in other age ranges ($p=0.033$). For unaffected individuals, there were no significant differences in demographic factors among those who made improvements (Table 2C). There were also no significant differences in demographic factors, except for race/ethnicity, among those who made great or moderate improvements (Table 2D).

TABLE 2B: DEGREE OF LIFESTYLE IMPROVEMENTS MADE SINCE RECEIVING TEST RESULTS

		N	Great Improvement N (%)	Moderate Improvement N (%)	p-value
Total		727	386 (53.1%)	341 (46.9%)	
Sex	Male	114	49 (43.0%)	65 (57.0%)	**0.018**
	Female	613	337 (55.0%)	276 (45.0%)	
Race/Ethnicity	White, Non-Hispanic	288	122 (42.4%)	166 (57.6%)	**<0.001**
	African American or Black	22	8 (36.4%)	14 (63.6%)	
	Hispanic	289	196 (67.8%)	93 (32.2%)	
	Asian	77	37 (48.1%)	40 (51.9%)	
	Other	51	23 (45.1%)	28 (54.9%)	
Educational status	Elementary School	92	69 (75.0%)	23 (25.0%)	**<0.001**
	High school	129	78 (60.5%)	51 (39.5%)	
	Trade/Vocational school	25	17 (68.0%)	8 (32.0%)	
	Junior college	30	23 (76.7%)	7 (23.3%)	
	Some college	97	46 (47.4%)	51 (52.6%)	
	College degree	177	85 (48.0%)	92 (52.0%)	
	Graduate degree	134	43 (32.1%)	91 (67.9%)	
Age	29 or younger	38	15 (39.5%)	23 (60.5%)	**0.033**
	30-39	92	43 (46.7%)	49 (53.3%)	
	40-49	203	119 (58.6%)	84 (41.4%)	
	50-59	191	110 (57.6%)	81 (42.4%)	
	60-69	156	80 (51.3%)	76 (43.7%)	
	70 or older	46	18 (39.7%)	28 (60.9%)	

Table 2B shows the percentage of individuals who made great improvements or moderate improvements by demographic category. Lifestyle improvements were compared on the basis of sex, race/ethnicity, educational status, and age. p-values less than 0.05 are in bold.

TABLE 2C: LIFESTYLE IMPROVEMENTS AMONG UNAFFECTED INDIVIDUALS SINCE RECEIVING TEST RESULTS

		N	Any Improvement N (%)	No Improvement N (%)	p-value
Total		537	186 (34.6%)	351 (65.4%)	
Sex	Male	91	32 (35.2%)	59 (64.8%)	0.908
	Female	446	154 (34.5%)	292 (65.5%)	
Race/Ethnicity	White, Non-Hispanic	251	87 (34.7%)	164 (65.3%)	0.996
	African American or Black	35	11 (31.4%)	24 (68.6%)	
	Hispanic	162	57 (35.2%)	105 (64.8%)	
	Asian	40	14 (35.0%)	26 (65.0%)	
	Other	49	17 (34.7%)	32 (65.3%)	
Educational status	Elementary School	35	14 (40.0%)	21 (60.0%)	0.935
	High school	75	27 (36.0%)	48 (64.0%)	
	Trade/Vocational school	25	8 (32.0%)	17 (68.0%)	
	Junior college	19	6 (31.6%)	13 (68.4%)	
	Some college	73	23 (31.5%)	50 (68.5%)	
	College degree	135	53 (39.3%)	82 (60.7%)	
	Graduate degree	132	48 (36.4%)	84 (63.6%)	
Age	29 or younger	51	25 (49.0%)	26 (51.0%)	0.231
	30-39	115	43 (37.4%)	72 (62.6%)	
	40-49	147	47 (32.0%)	100 (68.0%)	
	50-59	124	41 (33.1%)	83 (66.9%)	
	60-69	80	25 (31.3%)	55 (68.8%)	
	70 or older	20	5 (25.0%)	15 (75.0%)	

Table 2C shows the percentage of unaffected individuals who made any lifestyle improvement by demographic category. Lifestyle improvements were compared on the basis of sex, race/ethnicity, educational status, and age. p-values less than 0.05 are in bold.

TABLE 2D: DEGREE OF LIFESTYLE IMPROVEMENTS AMONG UNAFFECTED INDIVIDUALS MADE SINCE RECEIVING TEST RESULTS					
		N	**Great Improvement N (%)**	**Moderate Improvement N (%)**	**p-value**
Total		186	80 (43.0%)	106 (57.0%)	
Sex	Male	32	13 (40.6%)	19 (59.4%)	0.764
	Female	154	67 (43.5%)	87 (56.5%)	
Race/Ethnicity	White, Non-Hispanic	87	28 (32.2%)	59 (67.8%)	**0.002**
	African American or Black	11	4 (36.4%)	7 (63.6%)	
	Hispanic	57	37 (64.9%)	20 (35.1%)	
	Asian	14	6 (42.9%)	8 (57.1%)	
	Other	17	5 (29.4%)	12 (70.6%)	
Educational status	Elementary School	14	9 (64.3%)	5 (35.7%)	0.071
	High school	27	16 (59.3%)	11 (40.7%)	
	Trade/Vocational school	8	4 (50.0%)	4 (50.0%)	
	Junior college	6	4 (66.7%)	2 (33.3%)	
	Some college	23	9 (39.1%)	14 (60.9%)	
	College degree	53	18 (34.0%)	35 (66.0%)	
	Graduate degree	48	15 (31.3%)	33 (68.8%)	
Age	29 or younger	25	7 (28.0%)	18 (72.0%)	0.355
	30-39	43	15 (34.9%)	28 (65.1%)	
	40-49	47	23 (48.9%)	24 (51.1%)	
	50-59	41	20 (48.8%)	21 (51.2%)	
	60-69	25	12 (48.0%)	13 (52.0%)	
	70 or older	5	3 (60.0%)	2 (40.0%)	

Table 2D shows the percentage of unaffected individuals who made great improvements or moderate improvements by demographic category. Lifestyle improvements were compared on the basis of sex, race/ethnicity, educational status, and age. p-values less than 0.05 are in bold.

We analyzed improvements made in each factor to determine which factor was most likely to be improved (Table 3). For each factor, only participants who were able to make improvements for a specific factor were analyzed. For example, only current smokers were analyzed for the "smoking" category. Diet was the factor that was most likely to be improved, with 45% of all respondents making improvements. Smoking was the factor least likely to be improved, with only 18% of current smokers making improvements.

TABLE 3: IMPROVEMENTS MADE AMONG LIFESTYLE FACTORS

	N	Improvement N (%)	No Improvement N (%)	p-value
Smoking	236	43 (18.2%)	193 (81.8%)	**<0.001**
Avoid Sunburn	1025	320 (31.2%)	705 (68.8%)	
Drinking Alcohol	395	106 (26.8%)	289 (73.2%)	
Eat a Healthy Diet	1085	484 (44.6%)	601 (55.4%)	
Exercise	1064	326 (30.6%)	738 (69.4%)	
Perform Self-Breast Exam	852	290 (34.0%)	562 (66.0%)	

Table3 describes the proportion of participants who made improvements to each lifestyle factor. For each factor, improvements were only calculated among those who could possibly make an improvement for that specific factor (N). p-values less than 0.05 are in bold.

3.3 Lifestyle Improvements Among Individuals with Modifiable Lifestyle Risk Factors

Participants who reported lifestyle risk factors such as smoking and heavy drinking, or who were obese were analyzed to see if they made more changes to their lifestyle, given they had more factors upon which they could improve. Overall, there was no significant difference in lifestyle improvements made when comparing those with these lifestyle risk factors and those without (Table 4A). Nearly 33% of current smokers made improvements compared to 38.2% of those who were past smokers or who never had smoked (p=0.269). Just over half of heavy drinkers, made changes compared to 37.8% of those who did not drink heavily or who were nondrinkers (p=0.100). Almost 43% of individuals who were obese indicated that they made improvements to their lifestyle compared to 37.2% of those who were not obese (p=0.058).

TABLE 4A: LIFESTYLE IMPROVEMENTS MADE AMONG PARTICIPANTS WITH MODIFIABLE RISK FACTORS

		N	Any Improvement N (%)	No Improvement N (%)	p-value
Current smoker	Yes	101	33 (32.7%)	68 (67.3%)	0.269
	No	1698	648 (38.2%)	1050 (61.8%)	
Heavy drinker	Yes	35	18 (51.4%)	17 (48.6%)	0.100
	No	1665	629 (37.8%)	1036 (62.2%)	
Obese	Yes	397	169 (42.6%)	228 (57.4%)	0.058
	No	1119	416 (37.2%)	703 (62.8%)	

Table 4A displays the percentage of participants with and without modifiable lifestyle risk factors who made any lifestyle improvement. Modifiable lifestyle risk factors analyzed were smoking, heavy drinking, and obesity. p-values less than 0.05 are in bold.

TABLE 4B: LIFESTYLE IMPROVEMENTS MADE AMONG UNAFFECTED PARTICIPANTS WITH MODIFIABLE RISK FACTORS

		N	Any Improvement N (%)	No Improvement N (%)	p-value
Current smoker	Yes	37	13 (35.1%)	24 (64.9%)	0.981
	No	450	159 (35.3%)	291 (64.7%)	
Heavy drinker	Yes	14	7 (50.0%)	7 (50.0%)	0.263
	No	443	157 (35.4%)	286 (64.6%)	
Obese	Yes	105	44 (41.9%)	61 (58.1%)	0.195
	No	321	112 (34.9%)	209 (65.1%)	

Table 4B displays the percentage of unaffected participants with and without modifiable lifestyle risk factors who made any lifestyle improvement. Modifiable lifestyle risk factors analyzed were smoking, heavy drinking, and obesity. p-values less than 0.05 are in bold.

3.4 Risk Perception among Individuals with Modifiable Lifestyle Risk Factors

Risk perception was evaluated in individuals who reported having modifiable lifestyle risk factors to elucidate whether they perceived that they were at higher than average risk for specific cancers associated with those risk factors. For example pancreatic cancer risk perception was evaluated among ever smokers. Past or current smokers (ever smokers) were evaluated regarding their perceived risks for pancreatic cancer and colon cancer both at baseline questionnaire, pre-genetic counseling, and three months after their genetic test results were disclosed. People who had a history of the specific cancer were excluded from analysis and those

found to have any mutation were excluded at 3-month analysis. At baseline, 19.9% of ever smokers indicated that they were at higher risk than average for pancreatic cancer compared to 17.2% of never smokers (p=0.324) (Table 5A). Furthermore, 33.6% of ever smokers indicated that they were at higher risk for colon cancer versus 28.1% of never smokers (p=0.095). Similarly, among respondents, ever smokers were not significantly more likely to report higher than average risk for pancreatic and colon cancer than never smokers after genetic counseling (Table 5B). Unaffected individuals with a smoking history were not more likely to feel they were at higher than average risk for these cancers at baseline (Table 5C); however, at three months, responding participants did report a significantly higher risk to develop colon cancer (Table 5D).

TABLE 5A: CANCER RISK PERCEPTION BY SMOKING STATUS- AT BASELINE

		N	Higher Than Average Risk N (%)	Not Higher Than Average Risk N (%)	p-value
Risk to develop colon cancer	Ever Smoker	286	96 (33.6%)	190 (66.4%)	0.095
	Never Smoker	595	167 (28.1%)	428 (71.9%)	
Risk to develop pancreatic cancer	Ever Smoker	301	60 (19.9%)	241 (80.1%)	0.324
	Never Smoker	586	101 (17.2%)	485 (82.8%)	

Table 5A describes the perceived risk of smokers, past or current, and non-smokers for developing colon and pancreatic cancer as compared to the average person their age at baseline questionnaire before counseling. p-values less than 0.05 are in bold.

TABLE 5B: CANCER RISK PERCEPTION BY SMOKING STATUS- AT FOLLOW-UP

		N	Higher Than Average Risk N (%)	Not Higher Than Average Risk N (%)	p-value
Risk to develop colon cancer	Ever Smoker	184	55 (29.9%)	129 (70.1%)	0.092
	Never Smoker	341	79 (23.2%)	262 (76.8%)	
Risk to develop pancreatic cancer	Ever Smoker	185	37 (20.0%)	148 (80.0%)	0.060
	Never Smoker	349	48 (13.8%)	301 (86.2%)	

Table 5B describes the perceived risk of smokers, past or current, and non-smokers for developing colon and pancreatic cancer as compared to the average person their age at follow up questionnaire three months after receiving their genetic testing results. p-values less than 0.05 are in bold.

TABLE 5C: CANCER RISK PERCEPTION BY SMOKING STATUS AMONG UNAFFECTED INDIVIDUALS- AT BASELINE

		N	Higher Than Average Risk N (%)	Not Higher Than Average Risk N (%)	p-value
Risk to develop colon cancer	Ever Smoker	98	40 (40.8%)	58 (59.2%)	0.106
	Never Smoker	210	66 (31.4%)	144 (68.6%)	
Risk to develop pancreatic cancer	Ever Smoker	91	19 (20.9%)	72 (79.1%)	0.799
	Never Smoker	189	37 (19.6%)	152 (80.4%)	

Table 5C describes the perceived risk of smokers, past or current, and non-smokers with no history of cancer for developing colon and pancreatic cancer as compared to the average person their age at baseline questionnaire before counseling. p-values less than 0.05 are in bold.

TABLE 5D: CANCER RISK PERCEPTION BY SMOKING STATUS AMONG UNAFFECTED INDIVIDUALS- AT FOLLOW-UP

		N	Higher Than Average Risk N (%)	Not Higher Than Average Risk N (%)	p-value
Risk to develop colon cancer	Ever Smoker	70	27 (38.6%)	43 (61.4%)	**0.032**
	Never Smoker	125	30 (24.0%)	95 (76.0%)	
Risk to develop pancreatic cancer	Ever Smoker	61	8 (13.1%)	53 (86.9%)	0.841
	Never Smoker	116	14 (12.1%)	102 (87.9%)	

Table 5D describes the perceived risk of smokers, past or current, and non-smokers with no history of cancer for developing colon and pancreatic cancer as compared to the average person their age at follow up questionnaire three months after receiving their genetic testing results. p-values less than 0.05 are in bold.

Comparing participants who drink heavily to those who drink casually or do not drink, there was no significant difference in the proportion who reported they were at higher than average risk for stomach cancer (p=0.641), colon cancer (p=0.636), or pancreatic cancer (p=0.492) at baseline (Table 6A). Among those who responded three months after counseling, there was no significant difference between the proportion of "heavy drinkers" and "not heavy drinkers" who felt higher than average risk for stomach (p=0.755), colon (p=0.957), or pancreatic cancer (p=0.753) (Table 6B). This was no different for unaffected participants (Table 6C and Table 6D).

TABLE 6A: CANCER RISK PERCEPTION BY DRINKING STATUS- AT BASELINE

		N	Higher Than Average Risk N (%)	Not Higher Than Average Risk N (%)	p-value
Risk to develop colon cancer	Heavy Drinker	24	8 (33.3%)	16 (66.7%)	0.636
	Not a Heavy Drinker	924	267 (28.9%)	657 (71.1%)	
Risk to develop pancreatic cancer	Heavy Drinker	26	6 (23.1%)	20 (76.9%)	0.492
	Not a Heavy Drinker	931	166 (17.8%)	765 (82.2%)	
Risk to develop stomach cancer	Heavy Drinker	26	6 (23.1%)	20 (76.9%)	0.641
	Not a Heavy Drinker	1010	196 (19.4%)	814 (80.6%)	

Table 6A describes the perceived risk of heavy drinkers and participants who are not heavy drinkers for developing colon, pancreatic, and stomach cancer as compared to the average person their age at baseline questionnaire before counseling. p-values less than 0.05 are in bold.

TABLE 6B: CANCER RISK PERCEPTION BY DRINKING STATUS- AT FOLLOW-UP

		N	Higher Than Average Risk N (%)	Not Higher Than Average Risk N (%)	p-value
Risk to develop colon cancer	Heavy Drinker	20	5 (25.0%)	15 (75.0%)	0.957
	Not a Heavy Drinker	556	142 (25.5%)	414 (74.5%)	
Risk to develop pancreatic cancer	Heavy Drinker	19	2 (10.5%)	17 (89.5%)	0.753
	Not a Heavy Drinker	574	95 (16.6%)	479 (83.4%)	
Risk to develop stomach cancer	Heavy Drinker	18	2 (11.1%)	16 (88.9%)	0.755
	Not a Heavy Drinker	607	111 (18.3%)	496 (81.7%)	

Table 6B describes the perceived risk of heavy drinkers and participants who are not heavy drinkers for developing colon, pancreatic, and stomach cancer as compared to the average person their age at follow up questionnaire three months after receiving their genetic testing results. p-values less than 0.05 are in bold.

TABLE 6C: CANCER RISK PERCEPTION BY DRINKING STATUS AMONG UNAFFECTED INDIVIDUALS- AT BASELINE

		N	Higher Than Average Risk N (%)	Not Higher Than Average Risk N (%)	p-value
Risk to develop colon cancer	Heavy Drinker	12	4 (33.3%)	8 (66.7%)	1.000
	Not a Heavy Drinker	292	100 (34.2%)	192 (65.8%)	
Risk to develop pancreatic cancer	Heavy Drinker	12	3 (25.0%)	9 (75.0%)	0.704
	Not a Heavy Drinker	263	49 (18.6%)	214 (81.4%)	
Risk to develop stomach cancer	Heavy Drinker	11	1 (9.1%)	10 (90.9%)	0.471
	Not a Heavy Drinker	277	58 (20.9%)	219 (79.1%)	

Table 6C describes the perceived risk among the unaffected participants of heavy drinkers and participants who are not heavy drinkers for developing colon, pancreatic, and stomach cancer as compared to the average person their age at baseline questionnaire before counseling. p-values less than 0.05 are in bold.

TABLE 6D: CANCER RISK PERCEPTION BY DRINKING STATUS AMONG UNAFFECTED INDIVIDUALS- AT FOLLOW-UP

		N	Higher Than Average Risk N (%)	Not Higher Than Average Risk N (%)	p-value
Risk to develop colon cancer	Heavy Drinker	9	4 (44.4%)	5 (55.6%)	0.272
	Not a Heavy Drinker	183	50 (27.3%)	133 (72.7%)	
Risk to develop pancreatic cancer	Heavy Drinker	7	1 (14.3%)	6 (85.7%)	1.000
	Not a Heavy Drinker	169	21 (12.4%)	148 (87.6%)	
Risk to develop stomach cancer	Heavy Drinker	6	1 (16.7%)	5 (83.3%)	1.000
	Not a Heavy Drinker	173	25 (14.5%)	148 (85.5%)	

Table 6D describes the perceived risk among the unaffected participants of heavy drinkers and participants who are not heavy drinkers for developing colon, pancreatic, and stomach cancer as compared to the average person their age at follow up questionnaire three months after receiving their genetic testing results. p-values less than 0.05 are in bold.

When queried at baseline, nearly a third (32.5%) of obese participants and 28.2% of non-obese participants felt that they were at higher than average risk for colon cancer (p=0.246)

(Table 7A). Three months after counseling, 29.1% of obese participants who responded felt at higher than average risk compared to 24.1% of non-obese participants (p=0.292) (Table 7B). Obesity was also assessed as a risk factor for women who were postmenopausal, which was estimated as women 51 years and older. Obese postmenopausal women (58.2%) were more likely to feel that they were at higher than average risk for breast cancer more often than non-obese postmenopausal women (43.6%) (p=0.044). However, among those who responded after counseling there was no significant difference in the proportion of post-menopausal women who felt they were at higher than average risk for breast cancer based on obesity status (p=0.063). Parallel trends were seen among the unaffected group at baseline (Table 7C) and 3 months (Table 7D).

TABLE 7A: CANCER RISK PERCEPTION BY OBESITY STATUS- AT BASELINE

		N	Higher Than Average Risk N (%)	Not Higher Than Average Risk N (%)	p-value
Risk to develop colon cancer	Obese	200	65 (32.5%)	135 (67.5%)	0.246
	Not	596	168 (28.2%)	428 (71.8%)	
Risk to develop breast cancer	Obese	67	39 (58.2%)	28 (41.8%)	**0.044**
	Not	165	72 (43.6%)	93 (56.4%)	

Table 7A describes the perceived risk of obese and non-obese participants for developing colon cancer as compared to the average person their age and the perceived risk of postmenopausal obese and postmenopausal non-obese female participants for developing breast cancer as compared to the average person their age at baseline questionnaire before counseling. p-values less than 0.05 are in bold.

TABLE 7B: CANCER RISK PERCEPTION BY OBESITY STATUS- AT FOLLOW-UP

		N	Higher Than Average Risk N (%)	Not Higher Than Average Risk N (%)	p-value
Risk to develop colon cancer	Obese	110	32 (29.1%)	78 (70.9%)	0.292
	Not	365	88 (24.1%)	277 (75.9%)	
Risk to develop breast cancer	Obese	34	17 (50.0%)	17 (50.0%)	0.063
	Not	85	27 (31.8%)	58 (68.2%)	

Table 7B describes the perceived risk of obese and non-obese participants for developing colon cancer as compared to the average person their age and the perceived risk of postmenopausal obese and postmenopausal non-obese female participants for developing breast cancer as compared to the average person their age at follow up questionnaire three months after receiving their genetic testing results. p-values less than 0.05 are in bold.

TABLE 7C: CANCER RISK PERCEPTION BY OBESITY STATUS AMONG UNAFFECTED INDIVIDUALS- AT BASELINE

		N	Higher Than Average Risk N (%)	Not Higher Than Average Risk N (%)	p-value
Risk to develop colon cancer	Obese	66	18 (27.3%)	48 (72.7%)	0.259
	Not	210	73 (34.8%)	137 (65.2%)	
Risk to develop breast cancer	Obese	32	18 (56.3%)	14 (43.8%)	0.789
	Not	73	39 (53.4%)	34 (46.6%)	

Table 7C describes the perceived risk of obese and non-obese unaffected participants for developing colon cancer as compared to the average person their age and the perceived risk of postmenopausal obese and postmenopausal non-obese unaffected female participants for developing breast cancer as compared to the average person their age at baseline questionnaire before counseling. p-values less than 0.05 are in bold.

TABLE 7D: CANCER RISK PERCEPTION BY OBESITY STATUS AMONG UNAFFECTED INDIVIDUALS- AT FOLLOW-UP

		N	Higher Than Average Risk N (%)	Not Higher Than Average Risk N (%)	p-value
Risk to develop colon cancer	Obese	38	13 (34.2%)	25 (65.8%)	0.430
	Not	148	41 (27.7%)	107 (72.3%)	
Risk to develop breast cancer	Obese	15	7 (46.7%)	8 (53.3%)	0.247
	Not	40	12 (30.0%)	28 (70.0%)	

Table 7D describes the perceived risk of obese and non-obese unaffected participants for developing colon cancer as compared to the average person their age and the perceived risk of postmenopausal obese and postmenopausal non-obese unaffected female participants for developing breast cancer as compared to the average person their age at follow up questionnaire three months after receiving their genetic testing results. p-values less than 0.05 are in bold.

3.5 Lifestyle Improvement and Genetic Test Results

The reported lifestyle improvements of participants were analyzed to see if they were more or less likely to make improvements to lifestyle based on the presence or absence of a mutation. Those who had a mutation did not significantly differ from those who did not have a mutation in terms of who ended up making lifestyle improvements (Table 8A). The proportion of those who made improvements were nearly identical for those who were mutation positive and mutation negative (36.8% versus 36.3%, respectively) (p=0.888). However, of those who made a lifestyle improvement, those with a mutation tended to make a great improvement to lifestyle more often than those without a mutation (p=0.047) (Table 8B). For the unaffected group, no significant difference was seen in terms of improvements to lifestyle (Table 8C) or level of improvement (Table 8D).

TABLE 8A: IMPROVEMENTS TO LIFESTYLE BY MUTATION STATUS

	N	Any Improvement N (%)	No Improvement N (%)	p-value
Positive	242	89 (36.8%)	153 (63.2%)	0.888
Negative	1757	638 (36.3%)	1119 (63.7%)	

Table 8A displays the percentage of individuals who tested positive or negative for a mutation who made any lifestyle improvement. Negative includes individuals found to have a VUS. p-values less than 0.05 are in bold.

TABLE 8B: LEVEL OF IMPROVEMENT TO LIFESTYLE BY MUTATION STATUS

	N	Great Improvement N (%)	Moderate Improvement N (%)	p-value
Positive	89	56 (62.9%)	33 (37.1%)	**0.047**
Negative	638	330 (51.7%)	308 (48.3%)	

Table 8B displays the percentage of individuals who tested positive or negative for a mutation who made a great or moderate lifestyle improvement. Negative includes individuals found to have a VUS. p-values less than 0.05 are in bold.

TABLE 8C: IMPROVEMENTS TO LIFESTYLE AMONG UNAFFECTED INDIVIDUALS BY MUTATION STATUS

	N	Any Improvement N (%)	No Improvement N (%)	p-value
Positive	55	24 (43.6%)	31 (56.4%)	0.139
Negative	482	162 (33.6%)	320 (66.4%)	

Table 8C displays the percentage of unaffected individuals who tested positive or negative for a mutation who made any lifestyle improvement. Negative includes individuals found to have a VUS. p-values less than 0.05 are in bold.

TABLE 8D: LEVEL OF IMPROVEMENT TO LIFESTYLE AMONG UNAFFECTED INDIVIDUALS BY MUTATION STATUS

	N	Great Improvement N (%)	Moderate Improvement N (%)	p-value
Positive	24	13 (54.2%)	11 (45.8%)	0.237
Negative	162	67 (41.4%)	95 (58.6%)	

Table 8D displays the percentage of unaffected individuals who tested positive or negative for a mutation who made a great or moderate lifestyle improvement. Negative includes individuals found to have a VUS. p-values less than 0.05 are in bold.

When stratifying based on type of mutation (high versus moderate penetrance), there was no significant difference in those who made lifestyle improvements. An improvement was made in 35.3% those with a moderate penetrance mutation, as compared to 38.1% of those with a high penetrance mutation (p=0.658) (Table 9A). Of those who had a mutation and made an improvement to lifestyle, there was no significant difference in which group made a great versus moderate improvement based on mutation type (p=0.429) (Table 9B). When analyzing the unaffected group, a significant difference was seen between the types of mutations, with high penetrance mutation carriers more likely to make any improvement (Table 9C). Furthermore, no difference was seen between the high and moderate penetrance groups when analyzing the level of improvement made (Table 9D).

TABLE 9A: IMPROVEMENTS TO LIFESTYLE BY MUTATION TYPE

	N	Any Improvement N (%)	No Improvement N (%)	p-value
High penetrance	126	48 (38.1%)	78 (61.9%)	0.658
Moderate penetrance	116	41 (35.3%)	75 (64.7%)	

Table 9A displays the percentage of individuals who tested positive for a high penetrance mutation or a moderate penetrance mutation who made any lifestyle improvement. p-values less than 0.05 are in bold.

TABLE 9B: LEVEL OF IMPROVEMENT TO LIFESTYLE BY MUTATION TYPE

	N	Great Improvement N (%)	Moderate Improvement N (%)	p-value
High penetrance	48	32 (66.7%)	16 (33.3%)	0.429
Moderate penetrance	41	24 (58.5%)	17 (41.5%)	

Table 9B displays the percentage of individuals who tested positive for a high penetrance mutation or a moderate penetrance mutation who made a great or moderate improvement to lifestyle. p-values less than 0.05 are in bold.

TABLE 9C: IMPROVEMENTS TO LIFESTYLE AMONG UNAFFECTED INDIVIDUALS BY MUTATION TYPE

	N	Any Improvement N (%)	No Improvement N (%)	p-value
High penetrance	24	15 (62.5%)	9 (37.5%)	**0.013**
Moderate penetrance	31	9 (29.0%)	22 (71.0%)	

Table 9C displays the percentage of unaffected individuals who tested positive for a high penetrance mutation or a moderate penetrance mutation who made any lifestyle improvement. p-values less than 0.05 are in bold.

TABLE 9D: LEVEL OF IMPROVEMENT TO LIFESTYLE AMONG UNAFFECTED INDIVIDUALS BY MUTATION TYPE

	N	Great Improvement N (%)	Moderate Improvement N (%)	p-value
High penetrance	15	9 (60.0%)	6 (40.0%)	0.675
Moderate penetrance	9	4 (58.5%)	5 (55.6%)	

Table 9D displays the percentage of unaffected individuals who tested positive for a high penetrance mutation or a moderate penetrance mutation who made a great or moderate improvement to lifestyle. p-values less than 0.05 are in bold.

3.6 Risk Perception and Mutation Type

Individuals with mutations in high and moderate penetrance mutations were also compared in terms of perceived risk for specific cancers. Female carriers of *PALB2*, *ATM*, *NBN*, *CHEK2*, and *BARD1* were characterized as moderate penetrance mutation carriers at risk for breast cancer. Females with *BRCA1*, *BRCA2*, *CDH1*, and *TP53* mutations were characterized as high penetrance mutation carriers at risk for breast cancer. No carriers of mutations in other genes that increased the risk for breast cancer were identified during the course of the study. Of the 37 moderate penetrance mutation carriers at risk for breast cancer, 13 (35.1%) responded to questions regarding their risk for breast cancer 3 months after results disclosure. Of these women, 7.7% felt they had no risk, another 7.7% felt they were at low risk, 15.4% felt they were at moderate risk, and 69.2% felt they were at high risk. Of the high penetrance mutation carriers at risk for breast cancer, 23 (31.1%) responded to risk perception questions about breast cancer three months after they received their results. None felt that they had no risk, 17.4% felt that they were at low risk, 30.4% felt that they were at moderate risk, and 52.2% felt they were at high risk (Figure 2A).

Carriers of mutations that increased risk for colon cancer were also compared based on high and moderate penetrance mutation status. *CHEK2* carriers, monoallelic *MUTYH* carriers

and *APC* I1307K carriers were considered to be moderate penetrance mutation carriers. Mutations in *PMS2*, *MSH2*, *MSH6*, *MLH1*, *EPCAM*, *TP53*, *MUTYH* (if biallelic), and *APC* were considered high penetrance mutations. Of those with moderate penetrance mutations, 35 (48.6%) people answered questions regarding risk perception. Among this group, 8.6% felt that they had no risk for colon cancer, while 28.6%, 31.4%, and 31.4% felt at low, moderate, and high risk, respectively. Of those with a high penetrance mutation, 20 (40.0%) answered questions regarding risk perception. Five percent felt they had no risk, 20.0% felt that they were low risk, 25.0% felt that they were moderate risk, and 50.0% felt that they were high risk for developing colon cancer (Figure 2B). Statistical differences between the two groups were not analyzed due to small sample size (Figure 2A and Figure 2B). Similarly, comparisons between high and moderate penetrance mutation carriers were not conducted for only unaffected individuals due to small sample size.

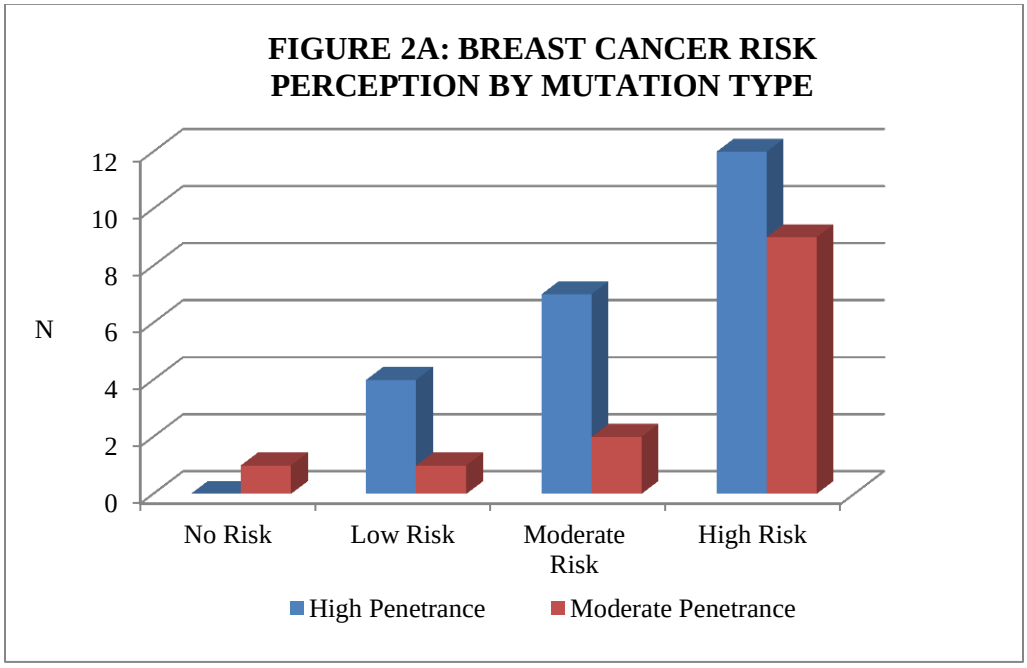

Figure 2A describes the perceived risk for developing breast cancer among female moderate penetrance mutation carriers (red bars) and female high penetrance mutation carriers (blue bars) whose mutations put them at risk for breast cancer.

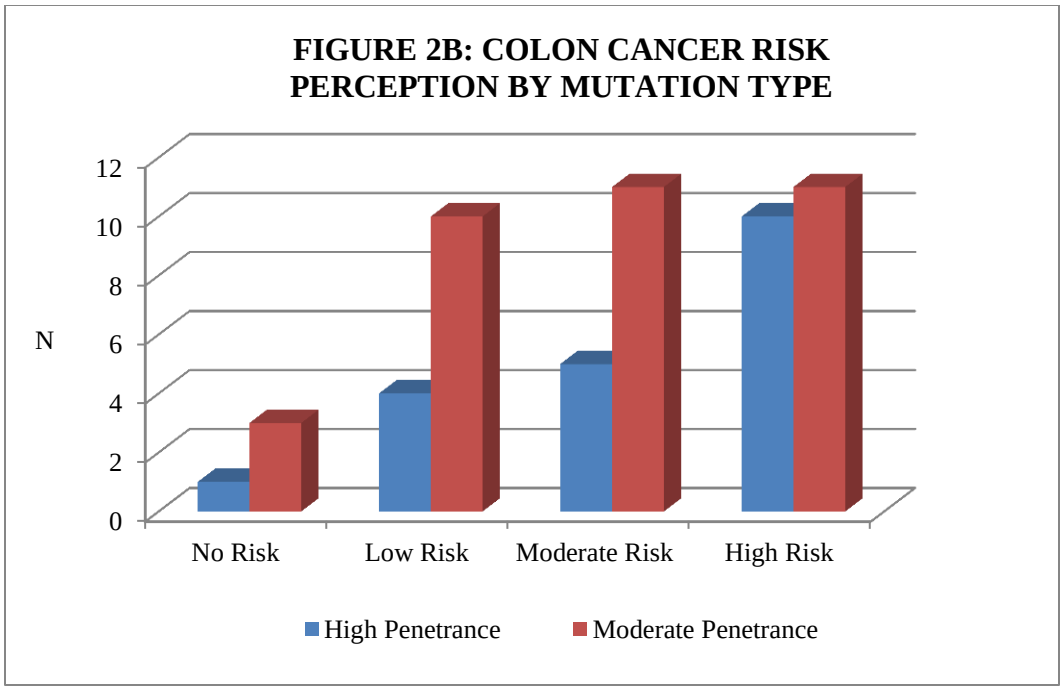

Figure 2B describes the perceived risk for developing colon cancer among moderate penetrance mutation carriers (red bars) and high penetrance mutation carriers (blue bars) whose mutations put them at risk for colon cancer.

3.7 Lifestyle Improvements and Perceived Cancer Risk

Differences in risk perception at 3-month follow-up time point were compared among respondents who made lifestyle improvements. Individuals with a cancer diagnosis were excluded from the analysis for the question pertaining to perception of risk of the cancer they had. For example, participants with breast cancer were excluded from the analysis regarding breast cancer risk perception. In addition, respondents who had a bilateral mastectomy or were male were not included for breast cancer risk questions.

Those who made lifestyle improvements did not tend to feel at lower than average risk for breast, colon, or stomach cancer. However, among those who perceived lower than average risk for pancreatic cancer, 71.9% made an improvement to lifestyle whereas only 62.4% of those who did not perceive lower than average risk made an improvement to lifestyle (p=0.018)

(Figure 3A). Within the group making lifestyle improvements, a higher proportion of those who made a great improvement responded that they were at lower than average risk for colon, pancreatic, and stomach cancer than did those who made a moderate improvement. Those who made a great improvement and those who made a moderate improvement to lifestyle did not tend to be different in risk perception for breast cancer (p=0.329) (Figure 3B). Overall, this pattern of perceived risk was different when only the unaffected group was examined. Within unaffected individuals, no significant difference was seen in risk perception on the basis of any improvements made (Figure 3C) or for level of improvements made (Figure 3D).

FIGURE 3A: LIFESTYLE IMPROVEMENTS COMPARED TO PERCEIVED CANCER RISKS AT 3 MONTHS

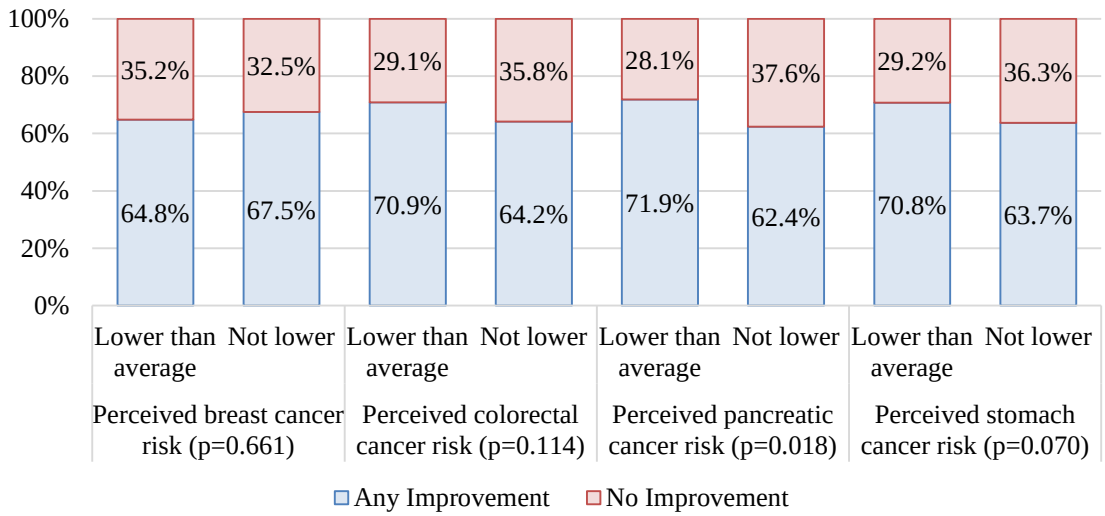

Figure 3A shows the perceived risk (as compared to the average risk for their age) for breast, colorectal, pancreatic, and stomach cancer among participants who made lifestyle improvements. Perceived risk was categorized as not lower than average if participants felt they were about as likely as or more likely than the average person their age to develop the specified cancer. Blue bars represent those who made any improvement in lifestyle and red bars indicate those who made no improvement in lifestyle.

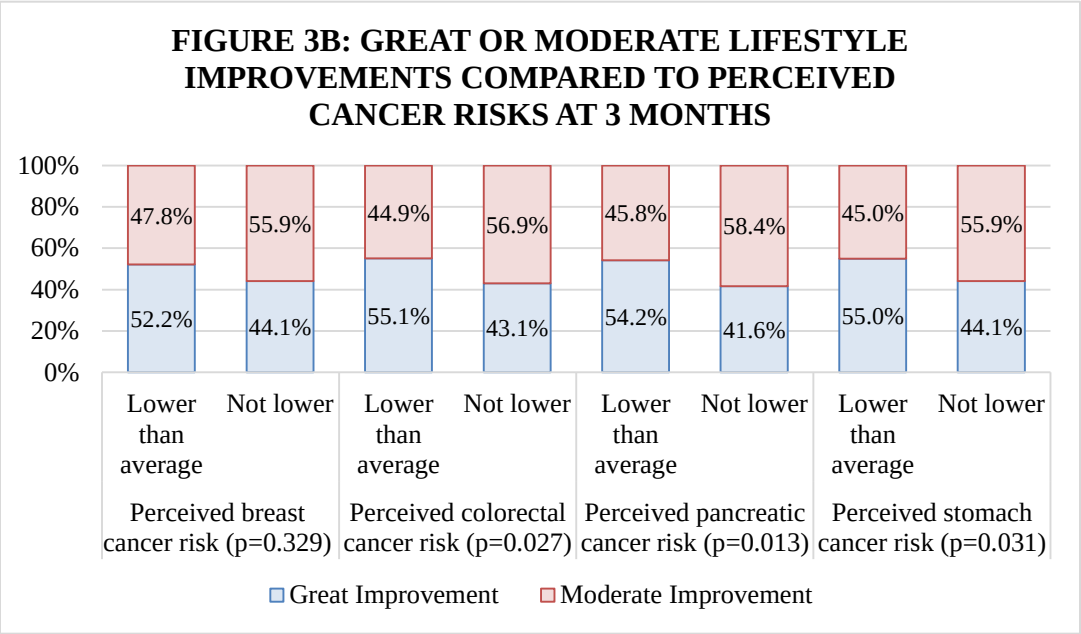

Figure 3B shows the perceived risk (as compared to the average risk for their age) for breast, colorectal, pancreatic, and stomach cancer among participants who made great or moderate lifestyle improvements. Perceived risk was categorized as not lower than average if participants felt they were about as likely or as more likely than the average person their age to develop the specified cancer. Blue bars represent those who made any improvement in lifestyle and red bars indicate those who made no improvement in lifestyle.

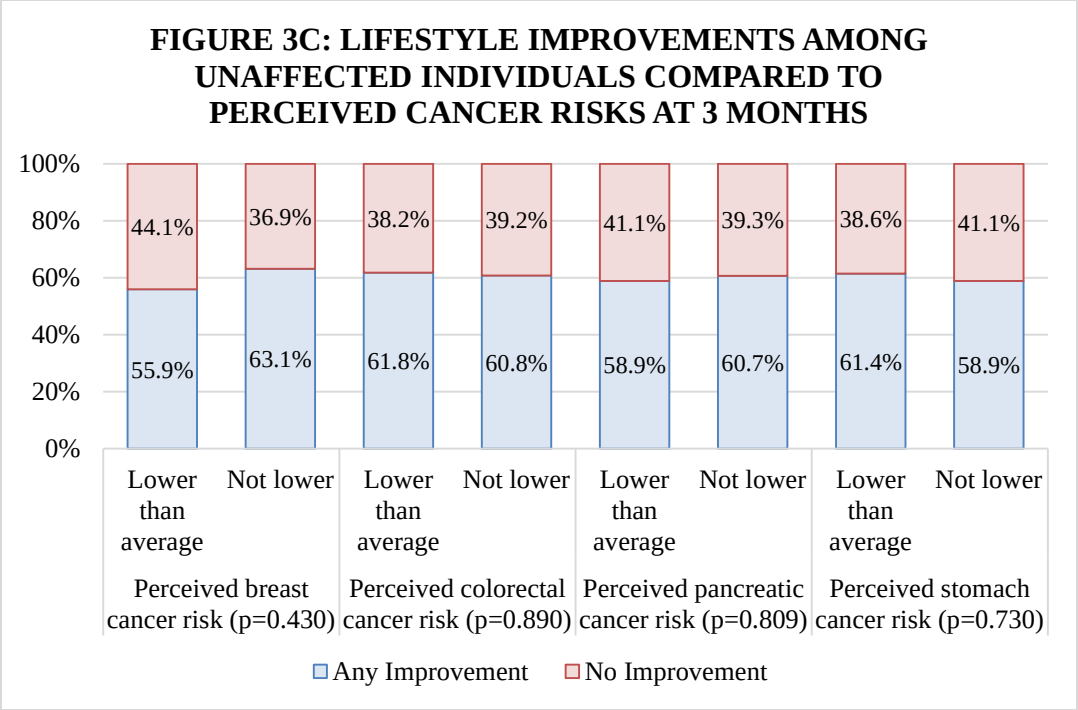

Figure 3C shows the perceived risk (as compared to the average risk for their age) for breast, colorectal, pancreatic, and stomach cancer among unaffected participants who made lifestyle improvements. Perceived risk was categorized as not lower than average if participants felt they were about as likely as or more likely than the average person their age to develop the specified cancer. Blue bars represent those who made any improvement in lifestyle and red bars indicate those who made no improvement in lifestyle.

FIGURE 3D: GREAT OR MODERATE LIFESTYLE IMPROVEMENTS AMONG UNAFFECTED INDIVIDUALS COMPARED TO PERCEIVED CANCER RISKS AT 3 MONTHS

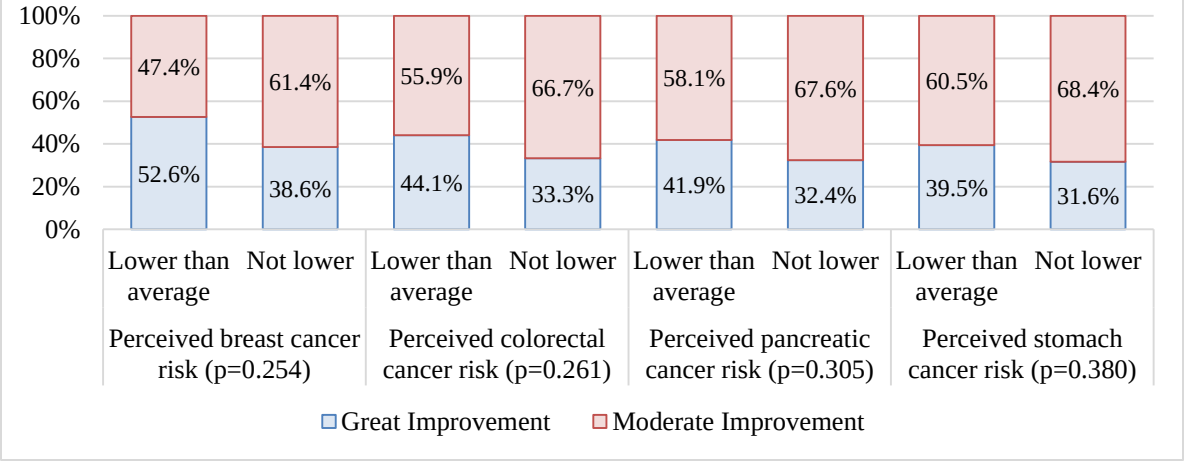

Figure 3D shows the perceived risk for (as compared to the average risk for their age) breast, colorectal, pancreatic, and stomach cancer among unaffected participants who made great or moderate lifestyle improvements. Perceived risk was categorized as now lower than average person if participants felt they were about as likely as or more likely than the average person their age to develop the specified cancer. Blue bars represent those who made any improvement in lifestyle and red bars indicate those who made no improvement in lifestyle.

IV. DISCUSSION

It is well established that environmental and lifestyle factors play a role in cancer risk. However, their contribution in high risk populations or in the setting of a known hereditary cancer syndrome is not well understood. Some patients undergoing hereditary cancer risk assessment have shown interest in learning more about lifestyle factors related to cancer risk. There is a lack of clinical consensus about how to integrate non-genetic risk information into genetic counseling sessions. There is limited research in the area. Our study aimed to understand whether or not individuals would make improvements to their lifestyle after learning more about their risks for cancer and undergoing cancer genetic counseling and testing.

The purpose of this study was to explore improvements made to lifestyle factors important to cancer risk as well as possible relationships to perceived cancer risk in a higher risk population undergoing genetic counseling and testing for hereditary cancer syndromes. Importantly, most participants in this study were not counseled regarding lifestyle risk factors. Thus, this study aimed to elucidate the patterns of lifestyle improvements and risk perception in the absence of lifestyle risk counseling. We report demographic differences between responders who made improvements versus those who did not. Diet was the individual lifestyle factor most likely to improve among all responders. Individuals with modifiable risk factors were not more likely to make lifestyle improvements and were also not more likely to perceive a higher than average risk for specific cancers. Those who had negative genetic testing were not more likely to make improvements to lifestyle than those who had mutations identified.

Unaffected individuals were analyzed separately for most analyses to identify trends in those with no cancer diagnosis. Affected individuals were not analyzed separately because those with an active diagnosis and those with a past diagnosis of cancer could not be separated (based

on the dataset made available to UCI-based researchers), and we were concerned that analyzing these two groups together could potentially introduce bias because those with an active malignancy may be less able to implement any lifestyle improvements. Generally, demographic features of unaffected individuals tended to be similar to those of the entire study population. However, a higher proportion of the unaffected group was Non-Hispanic White and educated.

We aimed to understand whether or not people with modifiable risk factors felt increased risks for specific cancers compared to the average person's risk. We also hoped to evaluate if participants with increased lifestyle risk factors would be more likely to improve than those without these risk factors. We wanted to study if people who tested negative for a hereditary cancer predisposition would make greater improvements to lifestyle because they did not have a major identifiable genetic risk and therefore more of their personal or shared familial risk may be due to lifestyle factors. Other hypotheses included that people with moderate penetrance mutations would make more lifestyle changes than those with high penetrance mutations because the former group's cancer risks are not completely defined by their mutations; people with high penetrance mutations would feel at higher risk for cancer than those with moderate penetrance mutations; and those who made improvements to lifestyle would feel that they were at lower risk for cancer at follow up than those who did not.

Overall, we found that more than a third of participants made improvements to their lifestyles. Women were significantly more likely to make improvements than men. However, other demographic factors did not tend to be important in terms of who made lifestyle improvements. These differences were not seen when only analyzing unaffected participants; in this group we were unable to identify any statistically significant predictors of lifestyle improvement except in the case of race/ethnicity. In the unaffected group, we found a

statistically significant difference between the race/ethnicities for those who made great improvements versus moderate improvements, with Hispanics making great improvements more often than others.

We found that, generally, respondents with known modifiable lifestyle risk factors were not more likely to make improvements to lifestyle than those without these risk factors, and those with modifiable lifestyle risk factors did not feel that they were at higher than average risk for certain cancers based on these risk factors. For example obese individuals were not more likely to perceive they were at higher than average risk for colon cancer, even though obesity is a risk factor for colon cancer. In contrast to our hypothesis, respondents who did not have mutations identified were not more likely to make improvements to lifestyle than those with mutations. Among respondents who reported having made improvements, a larger proportion of individuals with mutations had made great improvements than those without identified mutations; this difference was not seen in the unaffected group. Among those with mutations, moderate penetrance mutations and high penetrance mutations did not have different impacts on lifestyle improvements or risk perception in the overall group. Within the unaffected group, responders with high penetrance mutations were more likely to make any lifestyle improvement than those with moderate penetrance mutations. As hypothesized, participants who made lifestyle improvements tended to perceive a lower than average risk for colon, stomach, and pancreatic cancer more often than those who did not make improvements. However, there was no significant difference in breast cancer risk perception between those who made improvements and those who did not and there was no difference in risk perception among unaffected individuals who made improvements or did not.

4.1 Demographic Factors and Lifestyle Improvements

As our first goal, we explored which participants were most likely to make improvements to lifestyle. The only demographic factor which was related lifestyle improvement was sex, with females making lifestyle improvements more often than men. Those who made improvements did not tend to differ significantly based on race/ethnicity, age, or educational level. Interestingly, however, when focusing only on the group that made lifestyle improvements, significant differences were seen based on race/ethnicity, age, and educational level and degree of improvement made. Of the different age categories those who were in the age group of 40-49, followed by the age group of 50-59, reported making great improvements most often. In regards to race/ethnicity, the group that most often reported having made a great improvement was individuals of Hispanic ancestry, with Blacks/African Americans having the lowest reporting of making great improvements. Participants with a lower education status were more likely to make great improvements than those who had a higher education status. Of note, participants who were Hispanic were significantly more likely to be of a lower education status so it is possible that only one of these factors, not both, is associated with being more likely to make great improvements to lifestyle. Furthermore, Hispanics were more likely to be obese than participants of other race/ethnicities. Therefore, it is possible that Hispanic participants had more opportunity to make great lifestyle changes.

When analyzing lifestyle improvements in the unaffected group, no significant differences were seen among the different demographic categories for those who made any improvement as compared to those who did not. The only significant difference within the unaffected group was seen when comparing those who made great improvements with those who

made moderate improvements by race/ethnicity, with Hispanics making great improvements more often than those of different racial/ethnic groups.

4.2 Lifestyle Improvements and Perceived Risk in Individuals with Modifiable Lifestyle Risk Factors

Although smokers, drinkers, and those who were obese were probably more likely to be unhealthier overall and thus have more modifiable risk factors, they did not tend to make lifestyle improvements more often than those who did not have these modifiable factors. When analyzing only individuals who were unaffected, there was still no statistically significant difference in lifestyle improvement between those with and without modifiable risk factors. It is possible that they did not make improvements because some of these behaviors may be addictive. Furthermore, genetic counseling is not a behavior modification intervention.

We also studied improvement in each lifestyle factor separately in order to identify which factors were most often improved. Only those who were able to report improvement in a lifestyle factor were analyzed for each factor. The most frequently improved factor was diet, and the least frequent was smoking, neither of which is particularly surprising. Diet is perhaps a more easily modifiable factor as small improvements can be made by most individuals, especially short term. Furthermore, smoking is perhaps the most difficult factor to improve because it is addictive.

Past and current smokers were evaluated to see if they perceived that they were at higher than average risk for pancreatic cancer and for colon cancer. They did not perceive they were at higher than average risk for these cancers. Similarly, heavy drinkers did not perceive they were at higher than average risk for stomach and pancreatic cancers. Those who were obese did not report that they were at higher than average risk for colon cancer than those who were not obese.

However, obese postmenopausal women did indicate they were at higher than average risk for breast cancer on the baseline questionnaire before receiving genetic counseling. This perceived higher risk could have occurred due to differences in other factors, such as family history. Interestingly, this difference was not seen at the 3-month questionnaire, which could be due to a sense of reassurance from negative test results, but this was not examined specifically among women who tested negative.

Except in the case of smokers and perceived colon cancer risk at follow up at 3 months, unaffected participants with modifiable risk factors were not more likely to feel that they were at higher risk for pancreatic, colon, stomach, or breast cancer. This is unsurprising given that lifestyle risks were not a focus of the genetic counseling session. In general, people who had lifestyle risk factors that put them at higher risk for certain cancers do not perceive that they are at higher than average risk for those cancers. Furthermore, the proportion of those with modifiable risk factors who recognized they were at higher than average risk dropped after counseling for all the risk factor-perceived risk comparisons except smokers and pancreatic cancer risk, which was stable. Thus those who have these modifiable risk factors may feel falsely reassured regarding their risks for certain cancers because they tested negative for a hereditary predisposition to cancer, even though it may now be more likely that the cancers in these individuals or in their families are at least partially due to shared lifestyle risk factors.

There has been no consensus about whether genetic counseling is the appropriate forum for discussing lifestyle risk factors with patients (Rees et al, 2006). Individuals presenting for genetic counseling are coming in to understand the risks for cancer in their family. Although counselors may not feel completely comfortable discussing lifestyle factors, it may still be important to provide a full risk assessment. Some counselors feel uncomfortable discussing

lifestyle risks because the importance of these risk factors has not been well-studied in high risk populations. However, counselors educate even when there is not much understood about a condition, such as with conditions that are very rare. Thus, a lack of understanding should not completely dissuade genetic counselors from addressing lifestyle risk factors.

Other genetic counselors feel that they should not discuss lifestyle factors in genetic counseling sessions because it is outside their scope and another provider may be able to give more information (Rees et al, 2006). However, counselors also give some education about lifestyle factors in other scenarios such as diet factors in metabolic conditions, even though a dietician would be a better resource. Even in cancer risk counseling sessions, genetic counselors may talk about non-genetic risk factors such as hormones although it would be more within the scope of an oncologist or a primary care physician.

Furthermore, people undergoing hereditary cancer risk counseling may feel empowered if they understand that at least some of their risk may be modifiable. Because counselors are trained to be educators they are able to help people better understand their risks. Although individuals with lifestyle risk factors did not improve their lifestyles more often than those without these factors, it is possible that some may be motivated to do so if they understood their lifestyle-related cancer risks more clearly. For example, evidence suggests that behavioral counseling can lead to decreased sun exposure and indoor tanning use and increased sun protection such as use of sunscreen which may help decrease skin cancer risks (Lin et al, 2011). Even if these individuals do not decide to change their lifestyles they will at least be making a more educated decision. Moreover, they can be more vigilant about symptoms associated with these cancers and thus, hopefully, present to medical attention at an earlier stage should they develop one of these cancers. Therefore, although genetic counselors may not be entirely

comfortable with discussing lifestyle risk factors with patients due to feelings about inadequate information or incorrect scope, it may be beneficial for patients if they at least start the conversation about these factors. Thus, dependent on the patient and the situation, counselors should be prepared to have a limited conversation regarding lifestyle risk factors. More education on these risk factors may be needed in order to empower genetic counselors to do so.

4.3 Lifestyle Improvements and Mutation Status

We originally hypothesized that those who were found to have mutations would be less likely to make improvements to lifestyle because most of their cancer risk would be accounted for by genetic factors. However, those with mutations were just as likely as those without to make lifestyle improvements; this held true for the unaffected population as well. Furthermore, within the group that made improvements to lifestyle, those who had mutations tended to make greater improvements to their lifestyle more often than those who did not have a mutation. It is possible that because they are at higher risk for cancer, individuals with mutations are trying to assert control over their situation by lowering their risk as much as they possibly can. Although they might not be drastically decreasing their risks for cancer, mutation carriers who improve their lifestyle may benefit from feeling more control. Furthermore, improving their health may help reduce their risk for other medical conditions which may in turn allow them to have better treatment outcomes for cancers they may develop.

We also hypothesized that participant with moderate penetrance mutations would make lifestyle improvements more often than those with high penetrance mutations because less of their risk is attributable to purely genetic factors. However, there was no significant difference in lifestyle improvement based on the level of cancer risk associated with the mutation participants

were found to carry. Furthermore, within the group that improved, there was no significant difference between those who had a moderate penetrance mutation or a high penetrance mutation. Interestingly, within the unaffected group, those with high penetrance mutation were more likely to make an improvement than those with moderate penetrance mutations. This emphasizes an area where genetic counselors may be able to intervene with more education about moderate penetrance risks; because those with moderate penetrance mutations likely have more to gain in modifying lifestyle factors than do those with high penetrance mutations, this may be an important group to educate regarding lifestyle modifications.

4.4 Perceived Cancer Risk and Mutation Type

Participants with high penetrance mutations generally are at higher risk for cancer than those with moderate penetrance mutations. Cancer risks from high and moderate penetrance mutations are most understood for breast and colon cancer. Thus only mutations that increased risk for breast cancer or colorectal cancer in individuals with no history of these specific cancers were evaluated. Analyses were not statistically significant for these groups, likely due to low power because of small sample sizes. However, the distributions of perceived risk were unexpected. For the breast cancer group, none of the high penetrance mutation carriers felt that they had no risk for breast cancer; this was not seen among the moderate penetrance mutation carriers, where 7.7% of these individuals believed they had no risk for breast cancer. A higher proportion (17.7%) of the high penetrance mutation carriers felt that they were at low risk for breast cancer as compared to only 7.7% of the moderate penetrance mutation carriers.

Interestingly, 30.4% of the high penetrance mutation carriers felt at moderate risk for breast cancer compared to only 15.4% of the moderate penetrance group, while 69.2 % of the

moderate risk carriers felt that they were at high risk for breast cancer compared to 52.2% of high risk carriers. The differences in perceived risk between individuals with a high penetrance mutation and individuals with a moderate penetrance mutation with risk for breast cancer were not analyzed for statistical significance due to small sample size. While this distribution could have been due to chance because of small sample size, it is possible that high penetrance mutation carriers feel at slightly lower risk because they are more likely to have clear guidelines for early detection and prevention such as screening and risk-reducing mastectomy, as well as better access to and coverage of these options. Furthermore, because these risks are not tied to specific numbers, it is possible that their significance was different for each participant. For the case of colorectal cancer, the distribution was more consistent with our hypothesis, with 50% of the high penetrance mutation carriers feeling that they were at high risk for colorectal cancer compared to only 31.4% of moderate penetrance mutation carriers. A slightly higher proportion of moderate penetrance mutation carriers felt a moderate risk for colorectal cancer than those with high penetrance mutations. However, differences between high and moderate penetrance mutation carriers were not statistically significant ($p=0.643$). Of note, a larger proportion of both the moderate and high penetrance mutation carriers with risk for colon cancer believed they were at “no risk” or “low risk” for colon cancer than the moderate or high penetrance mutation carriers who had a higher risk for breast cancer did regarding their breast cancer risk. Importantly, risk perception is complex and variable between different individuals. Thus, it is difficult to determine why participants perceived their risks to be high or low.

4.5 Possible Relationships between Risk Perception and Lifestyle Improvements

To understand how lifestyle improvement related to cancer risk perception, we evaluated whether or not those who made improvements to lifestyle also perceived a lower than average risk for certain cancers at the 3-month follow-up survey. Pancreatic cancer was the only cancer for which those respondents who felt they were lower than average risk were more likely to have made an improvement to lifestyle. Interestingly, there were more differences in perceived risk when stratifying based on level of improvement. Within the group that made any improvement to lifestyle, those that made a great improvement tended to feel that their risk for colon, stomach and pancreatic cancer was lower than average more often than those who made a moderate improvement. Those who made a great lifestyle improvement did not perceive a lower risk for breast cancer more often than those who made a moderate improvement.

Of note, breast cancer is the only cancer of those ascertained for which perceived risk did not seem to be lower than average based on lifestyle improvement. This pattern of higher perceived risk for breast cancer could be due to family history. It is possible that participants consider breast cancer risk to be mostly related to family history of breast cancer and not to lifestyle factors in the absence of a mutation. This could be due to the way that breast cancer risk is often calculated when no mutation is found, based on empiric risk models which focus most on family history.

When analyzing only unaffected individuals, there was no significant difference seen when comparing lifestyle improvements and perceived risk for specific cancers at the three-month follow up time point. Unaffected individuals may not relate their cancer risks to lifestyle factors because their future cancer risk may be more abstract than that of a person who has had cancer. Given that individuals with and without cancer have different experiences, it is difficult

to compare the reason behind the difference in perceived risk between a group that includes only unaffected individuals and a group that includes individuals with cancer diagnoses.

4.6 Limitations

This study has several limitations that should be acknowledged. Firstly, data regarding lifestyle improvements was self-reported. Participants who made lifestyle improvements may have been more likely to have responded to the three-month survey. Furthermore, although participants were asked if they improved their lifestyle after genetic counseling and testing, it is possible that improvements made may have been due to other factors and not due to their counseling experience and test results. Although participants indicated whether or not they improved their lifestyles, the amount that they improved for each lifestyle factor could not be quantified. Lifestyle factor improvement was thus measured in terms of the number of factors they improved not in terms of how much they improved each factor. Therefore, it is possible that an individual who made minor lifestyle improvements is still healthier overall than someone who made greater improvements to lifestyle but was much unhealthier initially. Some participants might not have improved their lifestyle because they already were living a very healthy lifestyle.

While cancer history was known for participants, individuals undergoing treatment could not be differentiated from those in remission. Thus, it is possible that individuals with cancer were undergoing active treatment and were not able to make improvements to lifestyle due to their disease and/or treatment. Similarly, participants only had the option of choosing drinker or nondrinker in regards to alcohol drinking status. It is possible that some participants who usually drink alcohol identified as a nondrinker because they were not drinking during their treatment for cancer.

Individuals who did not respond to a lifestyle question were coded as having made no improvement for that question, which may have introduced bias into the study. Furthermore, demographic characteristics of responders to the three-month survey (64% of all participants) were not analyzed separately and thus the demographic features of responders to the three-month survey may be different than those of the overall study population.

Furthermore, using the data available to our sub-study, there was no method of quantifying participants' risk due to a family history of cancer. It is possible that perceived risk for certain cancers may be influenced by family history for some individuals, but this was not assessed. Participants may have perceived that they were at higher risk for certain cancers in the case of an extensive family history, especially if that result was uninformative for the cancers in their family. In addition, risk perception is likely impacted by factors other than those included in this study and may be distinct in someone with cancer as compared to someone with no history of cancer.

4.7 Future Studies

While this study identified some patterns of lifestyle improvement and risk perception, it is still unknown how much improvement to lifestyle was made by each participant, what motivated people to make lifestyle improvements, and exactly how much of a role lifestyle improvement plays in risk perception for certain cancers. Future studies are needed to understand these concepts. Furthermore, although high risk groups have been shown to not fully understand their elevated risk for certain cancers, it is unknown if education about these risks would motivate individuals to improve their lifestyle. Research is also needed to study the feasibility and effectiveness of genetic counseling as a setting for these interventions.

Another important area for future studies is that of risk perception among mutation carriers. Those with high and moderate risk mutations still identified as being low risk or having no risk for certain cancers, even after learning about mutations which increased their risk for cancer to at least a moderate degree. While it is difficult to speculate about these responses due to the small sample size and the complexity of risk perception, it would be important to explore why some participants identify as having low or no risk.

4.8 Conclusions

This study provided insight into short-term lifestyle improvements made by patients in the setting of hereditary cancer counseling. Concepts regarding risk perceptions for certain groups and how perceived risk related to lifestyle improvements were also explored. We helped define populations for whom interventions to lifestyle could be made and for whom lifestyle risk counseling and further genetic counseling could improve knowledge about their risks for certain cancers.

Overall, over a third of participants made an improvement to their lifestyles, with improvement in diet being the most commonly reported improvement. Only gender was associated with making improvements to lifestyle, with females reporting improvements more often than males. However, among those who did improve, other demographic factors were significant. People with high risk lifestyle factors did not report improving their lifestyle more often than those who did not have these factors, even though they likely live an overall unhealthier lifestyle. These people also are not more likely to perceive they are at an elevated risk for certain cancers than those who do not have these risk factors. Thus, counseling regarding elevated cancer risks due to these risk factors may be important in motivating these individuals

to make lifestyle improvements. Lifestyle improvements did not occur more commonly in those who had negative test results than those who were found to have a mutation. In fact, amongst individuals that made improvements, a greater proportion of those with mutations made great lifestyle improvements than those without a mutation. There was no significant difference in lifestyle improvements based on the penetrance category of the mutation. Future research will be important to identify the motivation behind lifestyle improvements in high risk populations as well as the efficacy of lifestyle risk counseling in a hereditary counseling setting.

REFERENCES

Baselga J, Tripathy D, Mendelsohn J, et al. Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. J Clin Oncol. 1996;14(3):737-44.

Braun MM, Overbeek-Wager EA, Grumbo RJ. Diagnosis and Management of Endometrial Cancer. Am Fam Physician. 2016;93(6):468-74.

Bravo IG, Félez-Sánchez M. Papillomaviruses: Viral evolution, cancer and evolutionary medicine. Evol Med Public Health. 2015;2015(1):32-51.

Cheng XJ, Lin JC, Tu SP. Etiology and Prevention of Gastric Cancer. Gastrointest Tumors. 2016;3(1):25-36.

Chuffa LG, Lupi-Júnior LA, Costa AB, Amorim JP, Seiva FR. The role of sex hormones and steroid receptors on female reproductive cancers. Steroids. 2017;118:93-108.

Desai S, Jena AB. Do celebrity endorsements matter? Observational study of BRCA gene testing and mastectomy rates after Angelina Jolie's New York Times editorial. BMJ. 2016;355:i6357.

Dickens V. The Importance of Discussing Lifestyle Risk Factors in Cancer Genetic Counseling. Poster presented at: NSGC; September 29, 2016; Seattle, Washington.

Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434(7035):917-21.

Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet. 1994;343(8899):692-5.

Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet. 1998;62(3):676-89.

Half E, Bercovich D, Rozen P. Familial adenomatous polyposis. Orphanet J Rare Dis. 2009;4:22.

Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist. 2007;12(1):20-37.

Herr HW. Percivall Pott, the environment and cancer. BJU Int. 2011;108(4):479-81.

Hodgson S. Mechanisms of inherited cancer susceptibility. J Zhejiang Univ Sci B. 2008;9(1):1-4.

Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. Langenbecks Arch Surg. 2008;393(4):535-45.

Jeter JM, Kohlmann W, Gruber SB. Genetics of colorectal cancer. Oncology (Williston Park, NY). 2006;20(3):269-76.

Knudson AG. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA. 1971;68(4):820-3.

Kohlmann W, Gruber SB. Lynch Syndrome. 2004 Feb 5 [Updated 2014 May 22]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1211/

Kulkarni A, Carley H. Advances in the recognition and management of hereditary cancer. Br Med Bull. 2016;120(1):123-138.

Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer--the role of sunlight. Adv Exp Med Biol. 2008;624:89-103.

Lin JS, Eder M, Weinmann S. Behavioral counseling to prevent skin cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;154(3):190-201

Lohmann DR, Gallie BL. Retinoblastoma: revisiting the model prototype of inherited cancer. Am J Med Genet C Semin Med Genet. 2004;129C(1):23-8.

Loveday C, Turnbull C, Ramsay E, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat Genet. 2011;43(9):879-82.

Loveday C, Turnbull C, Ruark E, et al. Germline RAD51C mutations confer susceptibility to ovarian cancer. Nat Genet. 2012;44(5):475-6.

Lucenteforte E, La vecchia C, Silverman D, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol. 2012;23(2):374-82.

Mallick S, Benson R, Julka PK. Breast cancer prevention with anti-estrogens: review of the current evidence and future directions. Breast Cancer. 2016;23(2):170-7.

Marcy TW, Stefanek M, Thompson KM. Genetic testing for lung cancer risk: if physicians can do it, should they?. J Gen Intern Med. 2002;17(12):946-51.

Matsumoto T, Nakamura S, Esaki M, Yao T, Iida M. Effect of the non-steroidal anti-inflammatory drug sulindac on colorectal adenomas of uncolectomized familial adenomatous polyposis. J Gastroenterol Hepatol. 2006;21(1 Pt 2):251-7.

Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst. 2013;105(11):812-22.

Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. Oncogene. 2004;23(38):6445-70.

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian (Version 2.2017) http://www.nccn.org/professionals/physicians_gls/pdf/genetics_screening.pdf. Accessed June 2, 2017.

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (Version 2.2016) http://www.nccn.org/professionals/physicians_gls/pdf/genetics_colon.pdf. Accessed June 2, 2017.

Paalosalo-Harris K, Skirton H. Mixed method systematic review: the relationship between breast cancer risk perception and health-protective behaviour in women with family history of breast cancer. J Adv Nurs. 2017;73(4):760-774.

Peltomäki P. Deficient DNA mismatch repair: a common etiologic factor for colon cancer. Hum Mol Genet. 2001;10(7):735-40.

Persson I. Estrogens in the causation of breast, endometrial and ovarian cancers - evidence and hypotheses from epidemiological findings. J Steroid Biochem Mol Biol. 2000;74(5):357-64.

Pijpe A, Manders P, Brohet RM, et al. Physical activity and the risk of breast cancer in BRCA1/2 mutation carriers. Breast Cancer Res Treat. 2010;120(1):235-44.

Quillin JM. Lifestyle Risk Factors Among People Who Have Had Cancer Genetic Testing. J Genet Couns. 2016;25(5):957-64.

Rees G, Young MA, Gaff C, Martin PR. A qualitative study of health professionals' views regarding provision of information about health-protective behaviors during genetic consultation for breast cancer. J Genet Couns. 2006;15(2):95-104.

Rieder V, Salama M, Glöckner L, et al. Effect of lifestyle and reproductive factors on the onset of breast cancer in female BRCA 1 and 2 mutation carriers. Mol Genet Genomic Med. 2016;4(2):172-7.

Roberts NJ, Jiao Y, Yu J, et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov. 2012;2(1):41-6.

Salesse S, Verfaillie CM. BCR/ABL: from molecular mechanisms of leukemia induction to treatment of chronic myelogenous leukemia. Oncogene. 2002;21(56):8547-59.

Schiffman M, Doorbar J, Wentzensen N, et al. Carcinogenic human papillomavirus infection. Nat Rev Dis Primers. 2016;2:16086.

Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013;368(25):2385-94.

Sherkow JS, Greely HT. The History of Patenting Genetic Material. Annu Rev Genet. 2015;49:161-82.

Stoffel E, Mukherjee B, Raymond VM, et al. Calculation of risk of colorectal and endometrial cancer among patients with Lynch syndrome. Gastroenterology. 2009;137(5):1621-7.

Strafford JC. Genetic testing for lynch syndrome, an inherited cancer of the bowel, endometrium, and ovary. Rev Obstet Gynecol. 2012;5(1):42-9

Sudhakar A. History of Cancer, Ancient and Modern Treatment Methods. J Cancer Sci Ther. 2009;1(2):1-4.

Tárraga López PJ, Albero JS, Rodríguez-Montes JA. Primary and secondary prevention of colorectal cancer. Clin Med Insights Gastroenterol. 2014;7:33-46.

Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol. 2016;13(9):581-8.

Walker JL, Powell CB, Chen LM, et al. Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. Cancer. 2015;121(13):2108-20.

Watson P, Ashwathnarayan R, Lynch HT, Roy HK. Tobacco use and increased colorectal cancer risk in patients with hereditary nonpolyposis colorectal cancer (Lynch syndrome). Arch Intern Med. 2004;164(22):2429-31.

White KK, Park SY, Kolonel LN, Henderson BE, Wilkens LR. Body size and breast cancer risk: the Multiethnic Cohort. Int J Cancer. 2012;131(5):E705-16.

Zaino RJ, Brady WE, Todd W, et al. Histologic effects of medroxyprogesterone acetate on endometrioid endometrial adenocarcinoma: a Gynecologic Oncology Group study. Int J Gynecol Pathol. 2014;33(6):543-53.

APPENDIX A: QUESTIONS FROM BASELINE SURVEY

Age: _____
Gender: ☐ Male ☐ Female

What is the highest level of education you completed?
☐ Elementary school ☐ High school ☐ Trade/Vocational school ☐ Junior college ☐ Some college
☐ College degree ☐ Graduate degree

Ethnic Background: ☐ Not Hispanic or Latino ☐ Hispanic or Latino ☐ Unknown

Race (check all that apply): ☐ American Indian/Alaska Native ☐ Asian
☐ Native Hawaiian or Pacific Islander ☐ Black or African American ☐ White ☐ Other_____

Cancer History:
Have you been diagnosed with cancer? ☐ Yes ☐ No
Type of cancer: _____ Age: _____

Cancer History, continued:
Second type of cancer: _____ Age: _____
Other cancers:
_____

What is your current height: _____ Current weight: _____

Exposures:
Do you drink alcohol? ☐ Yes ☐ No Number of drinks/week_____

Do you currently use tobacco? ☐ Yes ☐ No If **Yes**, how many years used? _____
☐ Cigarettes: amount /day _____
☐ Cigars: amount /day _____
☐ Chew tobacco/snuff: amount /day_____

Have you used tobacco in the past, but have quit? ☐ Yes ☐ No If **Yes**, at what age did you quit? _____

If **Yes**, how many years did you use tobacco? _____
☐ Cigarettes: amount /day _____
☐ Cigars: amount /day _____
☐ Chew tobacco/snuff: amount /day _____

OB/Gyn History (Females):

Have you had a hysterectomy (uterus removed): ☐ Yes ☐ No If **Yes**, at what age? _____

Have you had one or both ovaries removed? ☐ No ☐ One ovary ☐ Both ovaries If **Yes**, at what age? _____

Risk Perceptions:

How likely do you think it is that you will develop the following cancers in the future?

	No risk	Very low	Somewhat Low	Moderate	Somewhat High	Very High	Don't Know	Not Applicable
Colon cancer								
Stomach cancer								
Pancreatic cancer								
For **Females**: Breast cancer								
Ovarian cancer								
Uterine cancer								
For **Males**: Prostate cancer								
Male breast cancer								

Compared to the average person of your age, are you (less likely, about as likely, more likely) to develop the following cancers?

	Less Likely	About as Likely	More Likely	Don't Know	Not Applicable
Colon cancer					
Stomach cancer					
Pancreatic cancer					
For **Females**: Breast cancer					
Ovarian cancer					
Uterine cancer					
For **Males**: Prostate cancer					
Male breast cancer					

APPENDIX B: QUESTIONS FROM 3-MONTH FOLLOW-UP SURVEY

I. Risk Perceptions

We are exploring how receiving genetic test results affects a person's view of cancer risk. Take your time and answer each question as best as you can. You may not remember all the information from your results disclosure session. There are no right or wrong answers. We are just interested in how you are feeling now.

How likely do you think it is that you will develop the following cancers?

	No Risk	Very Low	Somewhat Low	Moderate	Somewhat High	Very High	Don't Know	Not Applicable
Colon cancer								
Stomach cancer								
Pancreatic cancer								
Breast cancer								
Ovarian cancer								
Uterine cancer								
Prostate cancer								

Compared to the average person of your age, are you (less likely, about as likely, more likely) to develop the following cancers?

	Less Likely	About as Likely	More Likely	Don't Know	Not Applicable
Colon cancer					
Stomach cancer					
Pancreatic cancer					
Breast cancer					
Ovarian cancer					
Uterine cancer					
Prostate cancer					

II. Reactions to Results

Now we want to ask you about *changes* in your behavior **in the last 6 months**. Since you received your test results, have you changed the frequency with which you performed the following behaviors?

	Decreased	**Remained the same**	**Increased**	**N/A**
Eat a healthy diet	1	2	3	0
Exercise	1	2	3	0
Avoid sunburn	1	2	3	0
Smoking	1	2	3	0
Drinking alcohol	1	2	3	0
Perform self-breast examinations	1	2	3	0