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Oncology Providers' Opinions on Preventative Recommendations for Patients with BRCA1 or BRCA2 Breast Cancer Mutations

Rebecca L. Crissman
Bethel University

Kathleen Dunsmore
Bethel University

ONCOLOGY PROVIDERS' OPINIONS ON PREVENTATIVE RECOMMENDATIONS FOR PATIENTS WITH BRCA1 OR BRCA2 BREAST CANCER MUTATIONS

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REBECCA CRISSMAN AND KATHLEEN DUNSMORE

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Rebecca Crissman
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GRADUATE RESEARCH APPROVAL:

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DEAN:

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Committee Chair: Dr. Gregory Ekbom

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Committee Member: Dr. Dan Leafblad

ABSTRACT:

BRCA1 and BRCA2 gene mutations have been identified as increasing an individual's risk for developing breast cancer. Genetic testing for these genes has become increasingly more common. However, once genetic testing has established that an individual has either a BRCA1 or BRCA2 mutation, there is no set guideline for preventative measures. The purpose of this study is to gain the opinions of oncology healthcare providers on their recommendation for preventative treatment in women who have been diagnosed with the mutation at varying ages. A web-based survey was emailed to oncology healthcare providers from Minnesota Oncology in Minnesota and Allegheny Health Network of Pennsylvania. The data was analyzed through SPSS and utilized to create an ANOVA comparison of providers' recommendations for preventative services for each of the three hypothetical patient cases. The results display that large variations exist among provider recommendations. Further, a patient can expect to receive more preventative service recommendations and more invasive services as their age increases. Ultimately, this research makes apparent the significant variation among provider recommendations for patients possessing a BRCA1 or BRCA2 mutation. Additionally, this research exposes the obvious need for further investigation regarding preventative services in BRCA mutation carriers and questions the use of BRCA mutation testing until those preventative service guidelines for BRCA mutation carriers are adequately determined.

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Chapter 1: Introduction

Introduction

With the current prevalence of breast cancer rates, one in eight females will develop breast cancer at some point in their life, and one in ten new cancers diagnosed each year are cancers of the female breast (Bray, McCarron, Parkin, 2004). The high prevalence of breast cancer, second only to lung cancer in females, has led to a nationwide movement of accelerated research and preventative measures, and money speaks volumes in this movement. Among government funding and cancer charities, breast cancer wears the crown. In 2007, the top four charities for breast cancer alone had combined revenues of $256 million (Yabroff, Lund, Kepka, Mariotto, 2011). The National Cancer Institute (NCI) allotted $602.7 million for breast cancer research, but only $314.6 million for lung cancer which is the leading cause of cancer deaths in America in 2012 (National Cancer Institute, 2012). That same year, the NCI spent only $105.3 million on pancreatic cancer research, which is just 17.4% of the funds it spent on breast cancer research (National Cancer Institute, 2012). Despite the drastic differences in funds spent between pancreatic and breast cancer research, pancreatic cancer is responsible for nearly the same amount of deaths that breast cancer is responsible for. Additionally, pancreatic cancer usually results in death within a single year from diagnosis (National Cancer Institute, 2012). In the years spanning from 1990 to 2009, direct medical spending on cancer in the United States doubled, and in 2010, breast cancer spending made up 13% of direct medical spending on cancer- nearly $16.5 billion (Yabroff et al 2011). The large expenditures devoted to breast cancer research have

made profound impacts in discoveries, treatments and preventative measures of this disease.

Given this nationwide effort, research has identified genes that are associated with breast cancer. The findings of a DNA linkage study performed in 1990 identified a gene to be associated with familial breast cancer, breast cancer 1 (BRCA1), to be located on chromosome 17 (Foulkes and Shuen 2013). Follow up research determined that not every apparent genetic breast cancer was directly linked to this gene. Scientists strived to discover other links between genes and breast cancer, and in 1994 found yet another gene known to be associated with breast cancer development and transmission in families. This gene became known as breast cancer 2 (BRCA2), and was found on chromosome 13 (Foulkes and Shuen, 2013). The discovery of BRCA1 and BRCA2 genes laid the foundation for further work showing the occurrences of mutations within these genes resulting in both breast cancer and transmission of cancer within families. It is known that the BRCA1 and BRCA2 mutations are considered autosomal dominant. Autosomal dominant refers to a mutation that is on an autosomal chromosome versus a sex chromosome. This allows the gene to be freely inherited from the maternal or paternal gene line (Kumar, Abbas, Fausto, & Aster, 2010). Inheriting the disease is quite frequent due to its dominant pattern. Dominant inheritance can show phenotypic traits if only one abnormal chromosome is present (Kumar, et al. 2010). Therefore, if only one parent has the mutation, the mutation can be passed on even if the chromosome is matched with a normal allele from the other parent (Korf, 2011).

In addition to the discovery regarding autosomal transmission patterns, it is also now known that BRCA1 and BRCA2 genes are tumor suppressor genes that, in their non-mutated state, are responsible for controlling cell growth and apoptosis. Mutations in these genes are known to lead to rapid, uncontrolled cell growth and proliferation, characteristics that are known to cancers. Mutations refer to permanent changes in the sequence of DNA and can be either inherited from a parent or acquired over the duration of life (Kumar, et al. 2010). Inherited mutations are germ line mutations, and prevail in every cell, because they were present in the initial egg and sperm (Kumar, et al. 2010). . Acquired mutations occur as a result of environmental factors, exposures, or underlying random nucleotide substitutions in the DNA sequence that cause an alteration in the DNA of an individual at some point in time (Kumar, et al. 2010). Unlike inherited mutations, acquired mutations are found in somatic cells, and therefore cannot be passed on to the next generation. Geneticists have found that humans possess two BRCA1 and two BRCA2 genes, located on chromosome #17 and chromosome #13 respectively (Foulkes and Shuen, 2013). A single mutation in copies of BRCA1 or BRCA2 genes results in an increased risk for the development of certain cancers (Foulkes and Shuen, 2013). However, it is widely understood that a single mutation alone will not result in cancer. Consequently, when two copies of the BRCA1 or BRCA2 genes are mutated, the first step in the development of cancer will occur (Foulkes and Shuen, 2013). An individual inheriting a single mutation of the BRCA1 or BRCA2 gene from a parent has a remarkably greater probability of developing cancer because they then only need to further acquire a single mutation during their life in order to possess the two mutations necessary in these genes that will begin the process of cancer development. While two

mutations in the BRCA1 or BRCA2 genes alone are not sufficient to cause cancer in its entirety, these mutations are the first step in the process of tumor development, and contribute significantly to the development of breast cancer (Foulkes and Shuen 2013).

When research revealed that BRCA1 and BRCA2 genes were transmitted in an autosomal dominant pattern within families, and that inheriting these mutations in genes placed individuals at an increased risk for cancer development, genetic testing for the prevalence of BRCA1 and BRCA2 mutations became the answer many patients were looking for (Korf, 2011; Foulkes and Shuen, 2013; Brose, Rebbeck, Calzone, 2002). According to the U.S. Preventive Service Task Force (USPSTF) there is currently no standardized criteria for women being considered for genetic testing for BRCA1 and BRCA2 mutations (U.S Preventive Service Task Force, 2005). However, USPSTF has declared that certain family history patterns indicated a recommendation of a grade B for genetic counseling (U.S Preventive Service Task Force, 2005). Grade B indicates that a healthcare provider should recommend the service to the patient because the service presents fair evidence of a benefit that outweighs the harms to the patient (U.S Preventive Service Task Force, 2005). Family history patterns include, for non-Jewish women, two first-degree relatives with breast cancer. Of these two first-degree relatives with breast cancer one of them must be diagnosed at age 50 or younger (U.S Preventive Service Task Force, 2005). Having three or more first or second-degree relatives diagnosed at any age also results in a grade B recommendation (U.S Preventive Service Task Force, 2005). Having a first-degree relative with bilateral breast cancer or two or more first-degree relatives with ovarian cancer, despite age of diagnosis, also indicates as a grade B recommendation for testing (U.S Preventive Service Task Force, 2005). Finally, having a

male relative with a history of breast cancer or a first or second-degree relative with both breast and ovarian cancer present at any age should prompt genetic testing (U.S Preventive Service Task Force, 2005).

Problem Statement

Currently, there exists a gap in understanding screening criteria and risk reduction strategies among carriers of BRCA1 and BRCA2 genes in patients and providers alike (Metcalfe, Shappell, Brierley, Bernhardt, McKinnon, Peshkin, 2013). The increased stress regarding awareness of carrying BRCA1 or BRCA2 genes presents a problem for many patients (Patenaude, Tung, Ryan, Ellisen, Hewitt, Schneider, Graber, 2013). Additionally, the large variation in health care provider recommendations that exists drives the desire to address and further discuss the recommendations made by oncology providers.

Purpose

The purpose of this study was to evaluate oncology provider opinions for patient care recommendations for patients who are diagnosed as BRCA1 or BRCA2 carriers (and without active cancer diagnoses) among different ages. The study assessed the healthcare provider practices regarding prevention, screening recommendations, and any procedures for follow-up care of these patients. Therefore, the principle of the research was to provide guidelines for patients who are carriers of BRCA1 or BRCA2 regarding preventative screening or procedures available dependent on their age.

Significance of the Study

The discoveries regarding BRCA1 and BRCA2 mutations mentioned above lacks specific guidelines regarding use of this information for preventive care. After genetic

testing determines deleterious mutations in BRCA1 or BRCA2 genes, many individuals do not know what to do with the results or where to turn. Patients become distressed over the knowledge of such mutations, and healthcare providers are hesitant to make recommendations for preventative measures based on the knowledge of the mutation the patient possesses (Patenaude et al 2013). One study in particular examined the psychological distress of young women ages 18-24 years of age whom were daughters of BRCA1 or BRCA2 mutation carriers (Patenaude et al 2013). In addition to displaying large gaps in knowledge related to information such as screenings and risk-reducing surgeries as preventative measures, the study found that these young women had high stress regarding cancer development (Patenaude et al 2013).

Not only were patients undergoing genetic testing stressed and unsure of what to do regarding knowledge of these mutations but an investigation conducted in 2013 revealed significant variation in recommendations offered to these patients by their healthcare providers (Metcalfe et al 2013). In that study, providers responded to questionnaires regarding recommendations for patients who carry deleterious BRCA1 or BRCA2 genes. The providers then made recommendations for particular patient case studies that they were given. It was found that prophylactic oophorectomy was more often recommended than alternative treatments including tamoxifen or prophylactic mastectomy. However, a large variation in recommendations existed despite the same patient case studies being presented to the health care providers (Metcalfe et al 2013).

Research Question

Overall, the following research question was explored in this study: What role, if any, does age of a patient with the diagnosis as a BRCA1 or BRCA2 mutation carrier state

have on a physician's, physician assistant's or nurse practitioner's recommendations for preventative health practices? This question was explored using the null hypothesis that no difference in the number of preventative services exists between Patient A, Patient B and Patient C. Patient A being age 25, patient B being 45 and patient C being 55 (please refer to appendix A for further detail).

H_o: Patient A= Patient B= Patient C

H_1: Patient A≠ Patient B ≠ Patient C

Chapter 2: Literature Review

Introduction

This chapter will discuss the research that currently exists in the scientific community on Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2) mutations. Furthermore, the chapter will address genetic testing, ethical controversies surrounding genetic testing, preventative screening guidelines, psychological stress related to carrier status, and the prophylactic actions that are available. Finally, this chapter will point out the current gap in knowledge regarding preventative measures once BRCA1 or BRCA2 carrier status is recognized.

BRCA1 and BRCA2 Mutation

Breast cancer is a growing concern especially in the United States. In 2010, 206,966 women were diagnosed with breast cancer and 40,996 women died (*CDC-Breast Cancer Home Page,* 2013). Researchers have found genetic mutations in the BRCA1 and BRCA2 genes that correlate with hereditary breast cancer (Surbone, 2011; Foulkes & Shuen, 2013). Genetic testing is now available for persons with a strong family history of breast cancer to identify the mutation. However, with this advance in technology, no clear recommendations for genetic testing have been developed. Furthermore, no specific guidelines exist for patients or healthcare providers in regards to preventative care for carriers of BRCA1 and BRCA2 mutations.

BRCA1 and BRCA2 genes are considered to be tumor suppressor genes which inhibit tumor growth through many different pathways including DNA damage repair mechanisms and cell cycle checkpoints (Kobayashi, Ohno, Sasaki, & Matsuura, 2013).

The BRCA1 and BRCA2 mutations have been located on chromosome 17 and 13 respectively (Foulkes & Shuen, 2013). Cells maintain DNA function by having several DNA damage repair mechanisms. In non-mutated cells, BRCA1 and BRCA2 are able to recognize damages in DNA (Kobayashi et al., 2013). These include nucleotide base damage, single stranded break, double stranded break, and DNA cross-linking (Kobayashi et al., 2013). Compromised DNA repair mechanisms have been demonstrated in a study where cultured embryonic stem cells revealed that BRCA1 mutation cells had higher sensitivity to oxidative reagents (Deng & Scott, 2000). In the presence of oxidative reagents, DNA damage can occur, leading to genetic instability (Deng & Scott, 2000). When a BRCA1 or BRCA2 mutation is present, the cell loses its' ability to repair the DNA damage (Deng &Scott, 2000). This genetic instability has the capability of causing tumors (Deng & Scott, 2000).

The other pathway that BRCA1 and BRCA2 mutations are closely related to is the cellular cycle checkpoints. This cycle regulates cell transitions from Growth 1 (G1), Growth 2 (G2), Synthesis (S), and Mitosis (M) phases (Deng & Scott, 2000). BRCA1 is associated with many proteins that are involved in the cell cycle checkpoints (Deng & Scott, 2000). Specifically, BRCA1 has been associated with proteins involved in the transition from G2 to M phase (Deng & Scott, 2000). If DNA damage is present, then the BRCA1 gene will recognize this damage and then arrest the cell in the G2 phase in order to repair the DNA (Deng & Scott, 2000). When a BRCA1 or BRCA2 mutation is present, then the cell lacks the ability to be arrested in the G2 phase. When the cell possesses the deficiency of being halted in the G2 phase the damaged DNA will enter the mitotic phase

and replicate (Deng & Scott, 2000). The replication of damaged DNA leads to an even more genetically unstable cell that develops into a tumor (Deng & Scott, 2000).

BRCA1 and BRCA2 mutations have been found to be inheritable mutations that are located in germline cells (Foulkes & Shuen, 2013). Acquired mutations in contrast, are located in somatic cells and cannot be passed on from generation to generation (Foulkes & Shuen, 2013). Autosomal dominant refers to the fact that only one parent needs to be a carrier to pass on the phenotypic trait (Korf, 2011). Even though the mutation has an autosomal dominance pattern, there is often a second mutation that needs to occur in order for cancer to develop (Foulkes & Shuen, 2013). Therefore, if a BRCA1 or BRCA2 mutation is inherited the offspring will have a greater probability of developing cancer because only one additional acquired mutation must occur to enable the formation of cancer (Foulkes & Shuen, 2013). This increased probability is astonishing, approximately 60-80% of persons having the BRCA1 mutation will develop breast cancer within their lifetime (Kobayashi et al., 2013).

A meta-analysis of current literature was conducted in 2000 in an attempt to establish an evidence-based medicine model for patients carrying BRCA1 or BRCA2 mutations (Chen & Parmigiani, 2007). The study collected literature from PubMed and used statistical analysis for the purpose of finding risk predictions regarding the prevalence of developing cancer in carriers of BRCA1 and BRCA2 mutations (Chen & Parmigiani, 2007). The study used DerSimonian and Laird random effects as the modeling approach (Chen & Parmigiani 2007). The results showed that carriers of BRCA1 mutation, by age 70, have a breast cancer risk of 55% and a risk of 47% for BRCA2 mutation carriers (Chen & Parmigiani 2007). Genetic counseling is now

routinely offered to patients who are at high risk for carrying the mutation (Chen & Parmigiani, 2007).

BRCA1 and BRCA2 Genetic Testing Guidelines

According to the U.S. Preventive Service Task Force (USPSTF), currently no standardized criteria for women being considered for genetic testing for BRCA1 and BRCA2 mutations exist. However, USPSTF has declared that certain family history patterns prompt a recommendation of a grade B for genetic counseling. Grade B indicates that a healthcare provider should recommend the service to the patient because the service presents fair evidence that benefits outweighs harms to the patient (U.S Preventive Service Task Force, 2005). The family history patterns include, non-Jewish women and two first-degree relatives with breast cancer (U.S Preventive Service Task Force, 2005). Of these two first-degree relatives with breast cancer, one of them must be diagnosed at age 50 or younger (U.S Preventive Service Task Force, 2005). Having three or more first or second-degree relatives diagnosed at any age also establishes a grade B recommendation. Having a first-degree relative with bilateral breast cancer, or two or more first-degree relatives with ovarian cancer, despite age of diagnosis, also prompts a grade B recommendation (U.S Preventive Service Task Force, 2005). Finally, having a male relative with a history of breast cancer, or a first or second-degree relative with both breast and ovarian cancer present at any age, should indicate genetic testing (U.S Preventive Service Task Force, 2005).

Ethical Controversies with Genetic Testing

With the initiation of genetic testing many ethical concerns have arisen (O'Neill, Luta, Walker, Peshkin, Abraham, & Tercyak, 2010; Samani, Tomaszewski, & Schunkert,

2010; Matloff, Shappell, Brierley, Bernhardt, McKinnon, & Peshkin, 2000). Genetic discrimination, direct-to-consumer genetic testing, pediatric testing for BRCA1 or BRCA2 mutations and physician's liabilities have all been topics of ethical conversation (O'Neill et al., 2010; Samani et al., 2010; Cook-Deegan, DeRienxo, Carbone, Chandrasekharan, Heaney, & Conover, 2010; Surbone, 2001; Wolf, 1995; Matloff et al., 2000). Reviewing the ethical controversies allows providers to have a better understanding of the obstacles patients encounter when choosing to undergo genetic testing for the BRCA1 or BRCA2 deleterious mutations.

Genetic discrimination has been a prevalent topic in conversations surrounding testing for BRCA1 or BRCA2 mutation because discrimination has occurred in the past for diseases that were not related to cancer (Natowicz et al., 1992). Many individuals fear that genetic testing may reveal a BRCA1 or BRCA2 mutation, and that the carrier status will then place them at an increased risk for discrimination by family members, health insurance companies, or even potential employees and future partners (Surbone, 2001; Wolf, 1995). Due to the fear of discrimination, high-risk individuals may refrain from undergoing testing and fail to receive proper preventative interventions that may be needed (Matloff et al., 2000). Other individuals may elect to undergo testing, but out of fear, use false names, pay out of pocket, or request the omission of test results from their medical records to prevent forms of discrimination that may occur (Feero et al., 2008).

Congress passed anti-discrimination legislation known as the Genetic Information Non-discrimination Act (GINA) in 2008 in an attempt to eliminate genetic discrimination (Van Hoyweghen & Horstman, 2008). GINA was first created to ensure that health insurers and employers were not discriminating against individuals based on genetic

testing (Van Hoyweghen & Horstman, 2008). In addition, GINA protects patients with BRCA1 or BRCA2 mutations that predispose individuals to breast and ovarian cancer, as well as genetic profiling of existing cancers (Van Hoyweghen & Horstman, 2008). However, GINA does not cover life insurance, disability or long-term care insurance, does not interfere with recommendations for testing, does not regulate insurance underwriting on current health status, and does not mandate coverage for testing or treatments (Van Hoyweghen & Horstman, 2008).

Direct-to-consumer (DTC) genetic testing is another topic that raises ethical concerns (U.S. National Library of Medicine, 2013). In DTC testing, individuals order a genetic test kit they can utilize at home (U.S. National Library of Medicine, 2013). Once completed, the test is mailed back to the center and results are available within a few weeks, often over the phone or via a webpage (U.S. National Library of Medicine, 2013). This testing raises many concerns because patients may often lack the proper counseling and patient education following the results, and subsequently lack the proper medical follow-up (Cook-Deegan et al., 2010). In addition to the lack of proper counseling that would enable the patient to better understand test results, DTC genetic testing may jeopardize patients' privacy (Cook-Deegan et al., 2010). Although GINA was enacted to prevent genetic discrimination as discussed above, patients found to carry mutations by way of DTC genetic testing may risk ineligibility for life insurance or other agreements as a result of breeches in their genetic confidentiality (Cook-Deegan et al., 2010).

Additionally, DTC genetic testing may identify surrogate genetic markers otherwise known as single-nucleotide polymorphisms (SNPs) rather than diagnostic genetic variants (Samani et al., 2010). SNPs lead to a small increase in the risk of

disease, contributing only to a 1.2-fold increased risk of developing breast cancer (Samani et al., 2010). Identifying unproven genetic markers and conveying information to the patient that they are a carrier might lead to excess expenditure on unneeded preventative measures and procedures (Samani et al., 2010).

The proper age for genetic testing raises added concerns in families and physicians alike (O'Neill et al., 2010). Current guidelines recommend against pediatric genetic testing for BRCA1 or BRCA2 mutations because of the lack of benefit and psychosocial risk associated with testing in this age group (O'Neill et al., 2010). Despite the recommendations against testing adolescents for the BRCA1 or BRCA2 genetic mutations, this issue has long been a concern in families where high-risk familial cancer is prevalent (O'Neill et al., 2010). When families are known to exhibit familial breast cancers and approach physicians regarding genetic testing for their daughters or sons, United States Preventative Task Force (USPTF) recommendations often influence physicians to discourage the testing process (O'Neill et al., 2010). The recommendations were created to protect the adolescent from the psychosocial trauma that may occur as a result of testing or the findings of genetic testing (O'Neill et al., 2010).

A 2010 study assessed the recommendations regarding genetic testing of 161 family and adolescent primary care providers (O'Neill et al., 2010). The providers were given a patient scenario of a healthy 13 year-old female whose mother was either a BRCA 1 or BRCA 2 mutation carrier (O'Neill et al., 2010). Even with the knowledge of USPTF recommendations against genetic testing for BRCA1 or BRCA 2 mutations in adolescents, the results of the test displayed that 31% of providers recommended adolescent genetic testing unconditionally (O'Neill et al., 2010). The results of this study

also revealed that providers were moderately willing to make the recommendation for testing in adolescents, and recommendations for adolescent genetic testing were correlated with physicians who possessed higher clinical practice volumes (O'Neill et al., 2010).

In consideration of genetic testing for individuals a plethora of additional ethical questions arise. These questions include which individuals should have their genome sequenced and who is responsible for prescribing the test (Surbone, 2011). Should an individual be allowed to conduct the test on their own with kits for direct-to-consumer testing? Who is responsible for providing patient education or counseling (Surbone, 2011)? If an individual chooses to elect to have genetic testing completed, debates regarding who should have access to the individual's genetic information is yet another ethical question (Surbone, 2011). Lastly, physicians question the liability they may incur when it comes to treating multiple members of a single family. Physicians and providers strive to ensure optimal care for all patients within the family, while protecting the privacy of members within a family who wish to not share their results of genetic testing (Lucassen & Parker, 2010).

Despite the many ethical controversies that exist surrounding genetic discrimination, direct-to-consumer genetic testing and pediatric testing, many individuals will still choose to undergo genetic testing to determine if they possess the BRCA1 or BRCA 2 mutations. The challenges these patients endure are obvious in the examination and understanding of the testing process and the controversies surrounding genetic testing. The arduous process of genetic testing proves to be an ethical risk for many

individuals. Therefore, preventative guidelines should be developed to benefit the BRCA1 or BRCA2 patients' overall well-being.

Preventative Screening Guidelines for General Population

Guidelines for routine breast cancer prevention can be controversial for the average female who is not at risk for breast cancer. According to the American Cancer Society, women greater than 40 years of age should be receiving yearly mammograms along with a clinical breast exam every three years starting at age 20 (American Cancer Society guidelines for early protection of cancer, 2013). However, the USPSTF recommends against routine mammogram screening in women ages 40-49 (US Preventative Task Force, 2009). They instead recommend biennial screening mammography for women ages 50-74 (US Preventative Task Force, 2009). They believe evidence is insufficient for routine mammography for women under the age of 50 and over the age of 74 (US Preventative Task Force, 2009). USPSTF also concluded that self-breast examinations showed no clinical benefit (US Preventative Task Force, 2009). Many women may find what appear to be lumps but are actually normal breast tissue and this can cause unnecessary stress and panic in the patient.

Preventative screening methods have been used in clinical practice on a regular basis and have been shown to reduce the mortality rate in breast cancer (US Preventative Task Force, 2009). Since in 2002 the recommendation for routine mammography screening has shown to be 77-95% sensitive and 94-97% specific (US Preventative Task Force, 2009). The sensitivity and specificity of mammography for detecting breast cancer has helped lower the mortality rate in breast cancer. A study done in 2009 found that early detection through mammograms have reduced the mortality rate for women

with breast cancer by 15% (Nelson, Tyne, Naik, Boughatsos, Chan, & Humphery, 2009). There is concern that with the use of mammograms there is also a risk of radiation exposure. Despite that concern, one study revealed that women receiving routine mammograms had low radiation exposure (Nelson et al, 2009). Another main concern has been the psychological impacts the test has on women (Nelson et al, 2009). The major psychological impact of anxiety has not been shown to affect the future of preventative care (Nelson et al, 2009).

Preventative Guidelines for Carriers of BRCA1 or BRCA2 Mutation

Preventative measures have shown to reduce the mortality rate in women with breast cancer. However, no specific guidelines for women who carry BRCA1 or BRCA2 mutation have been established. Thus far, clinicians have used their own clinical judgment in how follow women with the mutation. According to the National Cancer Institute, many prophylactic techniques can be used as a form of preventative care. Some of these protective factors include estrogen hormone therapy, mastectomy, oophorectomy, aromatase inhibitors, and fenretinide (National Cancer Institute, 2013). Furthermore, patients should consider behavioral ways of reducing risk by maintaining a healthy weight, exercising, reducing alcohol intake and tobacco use, and decreasing radiation exposure (Breast Cancer Prevention, 2013).

Psychological Stress Related to Breast Cancer and BRCA1 or BRCA2 Mutation

When receiving a diagnosis of cancer from a medical provider, oftentimes individuals after face immediate stress and panic regarding the unknown course that the disease will have in their body as well as their prognosis. After the initial diagnosis, patients can find peace in knowing disease progression and the steps they can take to

reduce or halt progression. Oftentimes, this same stress and panic ensue when a patient finds out they possess the BRCA1 or BRCA2 mutation that places them at an increased risk of developing breast cancer (Metcalfe, Quan, Eisen, Cil, Sun, & Narod, 2013). Studies have demonstrated a correlation between stress and breast cancer in family members (Metcalfe et al., 2013). Likewise, since the inception of genetic testing for breast cancer susceptibility, studies have examined how the results of BRCA1 or BRCA2 mutations influence stress levels and preventative measures to reduce breast cancer in patients (Hamann et al., 2005; Patenaude, Tung, Ryan, Ellisen, Hewitt, Schneider, & Garber, 2013).

When it comes to stress in breast cancer research, studies have largely focused on stress experienced by the daughters of breast cancer patients, and the fears faced by the daughters that are associated with inheritance of BRCA1 or BRCA2 mutations (Patenaude et al., 2013). However, daughters of patients are not the only individuals largely affected by a breast cancer diagnosis (Metcalfe et al., 2013). In 2013 results of a study examining cancer-related distress and risk perception among biological sisters of newly diagnosed breast cancer patients was published (Metcalfe et al., 2013). This investigation was unique from others of its kind in that the 205 sisters studied were from families with no history of the disease (Metcalfe et al., 2013). The sisters responded to questionnaires that were scored and analyzed (Metcalfe et al., 2013). This research found that approximately half of the 205 sisters studied were placed in the moderate or severe distress range regarding their perception and risk of developing breast cancer following their biological sister's diagnosis (Metcalfe et al., 2013).

Genetic testing for cancer susceptibility has shown many benefits. However, results from genetic testing that reveal a BRCA1 or BRCA2 mutation can have a profound impact on an individual's emotional stability and stress levels (Hamann, Somers, Smith, Inslicht, & Baum, 2005). A study examining 84 women was conducted to determine if the women had experienced threshold or subthreshold Post Traumatic Stress Disorder (PTSD) related to the results from genetic testing for BRCA1 and BRCA2 mutations (Hamann et al., 2005). A total of 65 women completed both the genetic testing and the PTSD module interview (Hamann et al., 2005). In this study the PTSD module interview consisted of an interview by a clinical psychologist that followed the clinical interview criteria for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (Hamann et al., 2005). In order to receive a diagnosis of PTSD patients needed to meet the minimum threshold levels in intrusion, avoidance and hyperarousal for one month following testing (Hamann et al., 2005). Of the 65 total women that underwent the testing for BRCA1 or BRCA2 mutations and PTSD interview module, 12 were found to be mutation carriers (Hamann et al., 2005). The results found that five women presented with threshold PTSD at 3-6 months that was related to the genetic testing process (Hamann et al., 2005). Despite the lack of significance due to small sample sizes in this study, some evidence exists that genetic testing and the results of the tests can serve as significant stressors for patients (Hamann et al., 2005).

Given the rise in individuals undergoing genetic testing for BRCA1 or BRCA2 gene mutations, research has aimed to reveal the efficacy and stress related to the information obtained from the genetic testing. One of these investigations examined three components in analyzing the efficacy and stress related to genetic testing, and how

the results of the testing impacted future generations (Patenaude et al., 2013). The first component of the investigation was to determine what daughters of mutation carriers of BRCA1 or BRCA2 understood about their risk of carrying the mutation (Patenaude et al., 2013). Additionally, the research aimed to measure the daughter's cancer-related distress and the effect the mother's mutation had on the daughter's plans for breast cancer prevention (Patenaude et al., 2013). In this study 40 daughters between the ages of 18-24 with mothers whom were positive for the BRCA1 or BRCA2 mutations were contacted to participate in a telephone interview (Patenaude et al., 2013). Following the interview, the subjects completed demographic and family history questionnaires, the Brief Symptom Inventory-18, Impact of Event Scale, and the Breast Cancer Genetic Counseling Knowledge Questionnaire (Patenaude et al., 2013). The subjects were scored on their knowledge of screening strategies, current health status, future plans regarding prevention of breast cancer, and their knowledge of risk reducing surgeries that could be performed. Following analysis of the interviews and questionnaires, the results revealed that the test subjects' knowledge in all areas was suboptimal (Patenaude et al., 2013). The subjects exhibited many gaps in knowledge and had numerous misconceptions regarding their risks (Patenaude et al., 2013). The study also found that more than 1/3 of the subjects exhibited high cancer-related stress regarding knowledge of their mother's status as a BRCA1 or BRCA2 mutation carrier (Patenaude et al., 2013). Ultimately, this investigation revealed that daughters of BRCA1 or BRCA2 mutation carriers lack much of the information needed to make adequate decisions regarding their health and the preventative measures that should be taken (Patenaude et al., 2013). The study suggested that improved patient education regarding risks and recommendations for screenings by

age 25 could improve long term patient survival as well as breast cancer prevention (Patenaude et al., 2013).

The above studies document the stress that exists among patients and family members after evidence of carrying a BRCA1 or BRCA2 gene mutation. Not only is consideration of this stress important in creating an ideal treatment plan for patients with BRCA1 or BRCA2 mutations, but also it is important to understand the enormous implications and impacts that stress can have on an individual. With this in mind, working to alleviate stress and anxiety experienced by patients should be a goal undertaken by health care providers. Much of the stress experienced by a patient comes from uncertainty. Fortunately, patients may experience a reduction in stress with increased knowledge of what is to come. In other words, patients' anxieties may be partially alleviated with increased knowledge. The research conducted in our investigation sought to eliminate some of the stress accompanying the BRCA1 or BRCA2 mutation carrier state by providing patients with guidelines of what they can expect in terms of preventative practices and measures.

Current Prophylactic Actions

Providers use a variety of preventative services when caring for carriers of BRCA1 or BRCA2 mutation. However, no set systematic protocols exist for providers to follow (Grann, Jacobson, Thomason, Hershman, Heitjan, Neugut, 2002). Currently, four prevention or detection options are utilized. Providers can continue to follow surveillance guidelines, perform prophylactic surgery, utilize chemopreventive drug approach, or carry out a combination of these strategies (Grann et al., 2002). Prophylactic surgeries such as oophorectomy and mastectomy have been shown to reduce

the risk of breast cancer by nearly 90% (Grann et al., 2002). It has also been shown that women between the ages of 20 and 40 have the most benefit in reducing cancer risk when prophylactic surgery is performed (Grann et al., 2002).

Chemopreventative drugs have also been shown to increase the survival rate (Grann et al., 2002). Tamoxifen is the drug of choice and was approved by the United States Food and Drug Administration to reduce the risk of breast cancer (Grann et al., 2002). Tamoxifen has been shown to reduce the risk of invasive breast cancer by 49% (Grann et al., 2002). In many cases, both chemopreventative drugs and prophylactic surgery have been used in high-risk patients to further reduce the risk of breast cancer development (Grann et al., 2002).

Routine surveillance has been another option for healthcare providers (Grann et al., 2002; Warner, Plewes, Hill, Causer, Zubovits, Jong, Cutrara, DeBoer, Yaffe, Messner, Meschino, Piron, Narod, 2004). A common surveillance protocol includes monthly self-breast examinations starting at age 18, semiannual clinical breast examinations beginning at age 20, and annual mammography beginning at age 25 (Warner et al., 2004). However, no solid evidence of mortality benefit in these patients exist (Warner et al., 2004). This echoes what was noted previously when discussing USPSTF guidelines for women who are not at risk for having familial breast cancer. They described self-breast examination as unreliable and found insufficient evidence for starting mammograms earlier than age 50 (US Preventative Task Force, 2005). Even though women carrying the BRCA1 or BRCA2 mutation are at an increased risk, the notion that increased surveillance for early detection to prevent mortality may not be enough.

Conclusion

The current lack of guidelines for preventative measures for women possessing the BRCA 1 or BRCA 2 deleterious mutations drove our investigation to ascertain what guidelines were being used at various oncology clinics. We had hoped that our work would highlight the need for other investigations to examine current recommendations for BRCA carriers at oncology clinics nationwide. The perceived lack of guidelines and standardized preventative recommendations for women who possess these mutations may then begin to be made apparent. That in turn may ultimately lead to a nationwide effort to study effective preventative measures to reduce breast cancer in BRCA1 or BRCA2 carriers and establish United States Preventative Task Force Recommendations for these individuals.

Chapter 3: Methods

Introduction

The purpose of this investigation was to determine if preventative service recommendations made by oncology clinicians for patients possessing the BRCA1 or BRCA 2 mutation are age independent. Furthermore, this study analyzed exactly what recommendations clinicians would make for three hypothetical patients possessing BRCA 1 or BRCA 2 mutations at varying ages of 25, 45, and 55. The three patients have the same medical, family, and social histories (Appendix A). The participants of the study, materials used, study design, procedures, and statistical methods of the study are included in this chapter.

Participants

The research utilized the opinions of oncology physicians, physician assistants and nurse practitioners employed by Minnesota Oncology and Allegheny Health Network. It was thought that the use of providers from different health systems would aid in reducing any bias that may exist toward preventative measure practices within health systems. Likewise, it was thought that the use of physicians, physician assistants and nurse practitioners were used to help reduce any biases that may exist within a profession. The age, gender, ethnicity, economic and health status of the participants were not expected to influence results.

Materials Used

The researchers created the three hypothetical case studies (Patients A, B and C) in order to ensure validity of the investigation. The case studies were reviewed and validated by other healthcare providers to ensure that the cases were realistic. The three

case studies included a review of systems as well as a brief medical, family, and social history for a patient with a positive BRCA 1 or BRCA 2 mutation. All three of the cases possessed the exact same review of systems, medical, family, and social histories. The only variation among the three cases was the patient's age; age 25, age 45 and age 55 respectively. For each of the three cases the provider was asked to complete a short questionnaire selecting the options of preventative services they deemed most appropriate for each patient.

Study Design

The research was a descriptive, qualitative survey study targeting oncology physicians, physician assistants and nurse practitioners employed by Minnesota Oncology and Allegheny Health Network. The study was a comparison between study participants to determine overall preventative screening recommendations. The preventative service recommendations for three patients possessing BRCA 1 or BRCA 2 mutations were based on web-accessed case studies. The case studies were accessed via a hyperlink received through the work e-mail of oncology physicians, physician assistants and nurse practitioners at the designated sites. The use of a web-based program to access the case studies ensured confidentiality in provider response. It was also thought that it would result in an increased participant response rate. The research utilized three case studies for patients possessing BRCA 1 or BRCA 2 mutations.

The dependent variable was:

1. Physician, physician assistant and nurse practitioner responses

The independent variable was:

1. The three case studies

Procedures

In the fall of 2014 an email was sent to the work email addresses of oncology physicians, physician assistants and nurse practitioners employed by Minnesota Oncology and Allegheny Health Network. The email consisted of a cover letter describing the purpose of the research and a hyperlink to access the web-based case studies and subsequent questionnaires. The email indicated that by accessing the hyperlink to complete the case studies the provider was giving informed consent to participate. A reminder email was sent 14 days following the initial email. This reminder was intended to increase response rates. After 30 days the researchers no longer accepted responses.

Statistical Methods

An initial sample size of 50 participants was anticipated. Data received from the online case study and subsequent questionnaire underwent analysis. Each preventative service provided on the web-based case study was scored in order to analyze the response numerically. Microsoft's SPSS tool was utilized to create an ANOVA comparison of providers' recommendations for preventative services for each of the three patients. The responses of the survey were scored to determine the statistical analysis. The primary aim of the study was to determine whether the age of the patient had an effect on the number of recommended preventative screenings. The secondary aim was to determine what treatment option was preferred for each patient case.

Conclusion

Chapter 4 analyzes the results of the questionnaires utilizing statistical analyses. Detailed descriptions of the preventative recommendations are found in chapter 5.

Chapter 5 also contains research limitations and a discussion of conclusions that can be made from the statistical analysis. Finally, possibilities for future research are discussed.

Chapter 4: Result

Primary Analysis: ANOVA Test

Microsoft's SPSS statistical package was utilized to carry out a one-way ANOVA test. The mean number of preventative services recommended for each of the three patients was found. The null hypothesis was that no difference exists in regards to the number of preventative services recommended for each of the three patients; H_o: Patient A = Patient B = Patient C. The alternative hypothesis is H_1: Patient A≠ Patient B≠ Patient C (one or more of the group means is different). A total of 25 individuals responded to each of the three patient cases. The summary of data is presented in Table 1 for each patient. Table 2 displays an abbreviated summary of the data utilized to carry out the one-way ANOVA Test.

Table 1

Data Summary

	Patient A	Patient B	Patient C	Total
N	25	25	25	75
Summation X	75	112	125	312
Mean	3	4.48	5	4.16
Summation X^2	225	534	651	1410
Variance	0	1.3433	1.0833	1.5146
St. Deviation	0	1.159	1.0408	1.2307
Standard Error	0	0.2318	0.2082	0.1421

Table 2

Factor Means

Patient	N	Mean	Standard Error
A	25	3	0
B	25	4.48	0.2318
C	25	5	0.2082

The one-way ANOVA Test resulted in a F ratio of 48.17, and a p-value <0.0001 (Table 3). The F ratio is the ratio of two mean squares. An F ratio with a value close to 1.0 suggests that the null hypothesis is true. A large F ratio suggests that the variation among group means is more than one would expect to see by chance alone. The P-value is calculated from the F ratio and the degrees of freedom (df) indicated in Table 3. The P-value of p <0.0001 indicates statistical significance, indicating that the null hypothesis is rejected, and that the alternative hypothesis, stating that mean values differ among patients, is accepted. The results of the graph correspond to the results of the ANOVA Test in that there appears to be an effect of patient age on number of preventative services recommended (Figure 1).

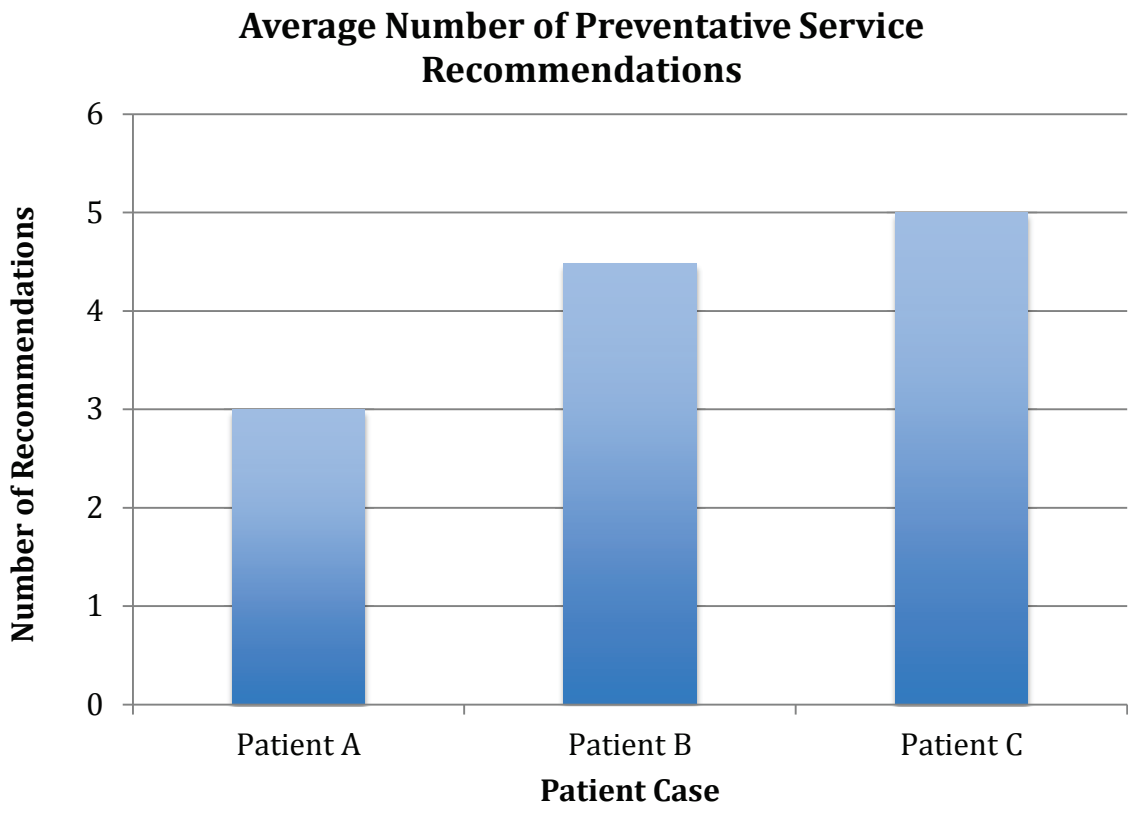
Table 3

ANOVA Table

Source	df	SS	MS	F ratio	P-value
Treatments	2	53.84	26.92	48.17	<0.0001*
Error	48	26.8267	0.5589		
Total	74	112.08			

**Note*. A P-value of p<0.05 shows statistical significance.

Figure 1.



Secondary Analysis: Preferred Service Recommendations

The secondary analysis examined which preventative service was recommended most often for each particular case, and examined the frequency in which services were recommended for each patient. In examining the survey results for Patient A, 100% of respondents recommended a clinical breast exam annually, and 96% of respondents recommended a monthly self-breast exam (Table 4). Annual mammogram screening beginning "this year" was recommended by 60% of respondents, while 20% of respondents recommended that annual mammogram screening begin in 5 years (Table 4).

Table 4.

Preventative Services Recommended for Patient A (age 25)

Preventative Service	**# of respondents**	**% of respondents**
Clinical breast exam annually	25	100%
Self breast exam monthly	24	96%
Mammograms annually starting this year	15	60%
Mammograms annually starting within 5 years	5	20%
No mammogram recommendation at this time	5	20%
Self breast exam annually	1	4%

In Patient B, the most frequently recommended preventative services were clinical breast exams annually and a monthly self breast exam, with 84% of respondents selecting these services (Table 5). For this patient, 80% of providers recommended a

double mastectomy and salpingo-oophrectomy within five years (Table 5). Other recommendations made for this patient included annual mammograms beginning this year (60%), mammograms biennially starting this year (40%), and hysterectomy within five years (20%) (Table 5).

Table 5.

Preventative Services Recommended for Patient B (age 45)

Preventative Service	**# of respondents**	**% of respondents**
Clinical breast exam annually	21	84%
Self breast exam monthly	21	84%
Double mastectomy within 5 years	20	80%
Salpingo-oophrectomy within 5 years	20	80%
Mammograms annually starting this year	15	60%
Mammograms biennial starting this year	10	40%
Hysterectomy within 5 years	5	20%

When the providers analyzed Patient C, the most frequently recommended preventative service was a double mastectomy within 5 years (Table 6). Every single provider that completed this case recommended that Patient C receive a double mastectomy within 5 years, and 96% of providers recommended a monthly self-breast exam (Table 6). Other services frequently recommended for Patient C included a salpingo-oophrectomy within 5 years and clinical breast exams annually, receiving an 80% response rate (Table 6).

Table 6.

Preventative Services recommended for Patient C (age 55)

Preventative Service	**# of respondents**	**% of respondents**
Double mastectomy within 5 years	25	100%
Self breast exam monthly	24	96%
Salpingo-oophrectomy within 5 years	20	80%
Clinical breast exam annually	20	80%
Mammograms annually starting this year	15	60%
Mammograms biennially starting this year	10	40%
Hysterectomy within 5 years	5	20%
Tamoxifen	5	20%
Self breast exam annually	1	4%

Chapter 5: Discussion

Summary of Primary Analysis

The primary analysis data revealed that the null hypothesis was rejected and the alternative hypothesis was accepted. The null hypothesis stated that no difference exists in regards to the number of preventative services recommended for each of the three patients; Ho: Patient A = Patient B = Patient C. The alternative hypothesis was H1: one or more of the group means is different. These results demonstrated that each patient in the case study was assigned a different number of average recommendations, and that these recommendation averages were different enough to indicate statistical significance.

From these results the reader can infer that the number of preventative service recommendations made for a BRCA1 or BRCA2 mutation carriers is dependent on patient age. The data shows that for Patient A, a 25 year old female, the average number of services recommended by oncology providers was 3 services. When the patient's age was 45, providers recommended an average of 4.48 preventative services. Finally, a patient age 55, or Patient C, had an average of 5 preventative services recommendations. While these averages indicated that patient age has a direct correlation with the number of services recommended in the hypothetical patient cases, it is important to acknowledge that each patient in the clinical setting has a very unique medical history and a very different genetic basis.

Summary of Secondary Analysis

The secondary analysis examined the preferred preventative services recommended for each patient ,as well as the frequency in which those recommendations were made. In Patient A, 100% of providers recommended to have a clinical breast exam annually.

From this data, a 25-year-old female with a BRCA1 or BRCA2 mutation can expect a clinical breast exam performed by an advanced practice provider or physician annually. Likewise, in the same patient, 96% of providers recommended that the patient perform monthly self-breast, and over half of the providers (60%) recommended that mammograms be performed annually at this. While a few providers made additional screening recommendations for Patient A (age 25), a 25 year old BRCA1 or BRCA2 mutation carrier can infer that at minimum an annual clinical breast exam and a monthly self-breast exam will be recommended services.

These secondary analysis recommendations closely correlate with those set forth by the National Comprehensive Cancer Network (NCCN) for women with hereditary breast and/or ovarian cancer syndrome (HBOCS) (women with a strong family history of breast cancer and found to have a BRCA1 or BRCA2 deleterious mutation) (National Comprehensive Cancer Network, 2014). The NCCN recommends that breast awareness begin at age 18 and clinical breast exams be carried out yearly starting at age 25 (National Comprehensive Cancer Network, 2014). Additionally, the NCCN recommends screening mammograms or MRIs for individuals age 25-29 based on the age of family member presenting with breast cancer (National Comprehensive Cancer Network, 2014). While only 60% of providers recommended mammograms be performed annually starting at age 25 in our research, an additional 20% of respondents (n=5) recommended mammograms annually starting within 5 years. In contrast, a total of 20% of respondents (n=5) stated that no mammogram recommendation would be made at this time. Due to the nature of the questionnaire, it is not completely clear if some survey respondents may have selected the option, “no mammogram recommendation at this time” in addition to

the option "mammograms annually starting within 5 years." However, based on a respondent number of 25 responses regarding a mammogram recommendation and a total of 25 individuals completing the survey, it is unlikely that a survey respondent would have selected both options. The NCCN recommendations are solely guidelines that numerous clinicians and oncologists utilize to help direct patient care. This research reveals that these recommendations closely align with the recommendations made by survey respondents to the 25 year-old patient in Case A.

In Patient B, where the patient was 45 years of age, 84% of providers recommended an annual clinical breast exam and a monthly self-breast exam and 80% of providers recommended a double mastectomy and a salpingo-oophrectomy within 5 years. An additional 60% of providers recommended annual mammograms. While these recommendations for Patient B are significantly more invasive than those for Patient A, the majority of providers apparently deemed these services to be appropriate considering the patient's age.

The NCCN recommendations for a 45 year-old female with hereditary breast and ovarian cancer syndrome include breast awareness at age 18 and a clinical breast exam yearly (National Comprehensive Cancer Network, 2014). Additionally, recommendations include annual mammograms beginning at age 25 or 30 and a salpingo-oophrectomy ideally carried out between the ages of 35 and 40 (National Comprehensive Cancer Network, 2014). These recommendations also note that those individuals who have not elected a salpingo-oophrectomy should then receive transvaginal ultrasounds and a CA-125 every 6 months starting at age 30 (National Comprehensive Cancer Network, 2014). While the recommendation of the clinical breast exam and the salpingo-oophrectomy

found in the research study aligns closely with the NCCN recommendations, a discrepancy exists in the double mastectomy recommendation. The research investigation shows that 80% of providers recommended a double mastectomy within 5 years while the NCCN guidelines make no recommendation for when a double mastectomy should be discussed or carried out (National Comprehensive Cancer Network, 2014). These guidelines simply state, "discuss risk-reducing mastectomy" without an age group attached (National Comprehensive Cancer Network, 2014).

In Patient C (age 55), 100% of providers recommended a double mastectomy within 5 years, and 96% of providers recommended a monthly self-breast exam. In this patient population, the research reveals that providers thought it was more important to carry out a monthly self-breast exam (96% of providers) than to receive an annual clinical breast exam by a provider (80% of providers) or to have a salpingo-oophrectomy within 5 years (80% of providers). This indication revealing the need for self-breast exams being seen as a more appropriate service recommendation than having clinical breast exams (96% compared to 80% of providers) may be linked to the idea that 100% of providers in this case had recommended a double mastectomy for the patient. Over half of providers (60%) indicated that an annual mammogram should be carried out. Carrying out a hysterectomy within 5 years was recommended as a service for both Patients B and C, but was only recommended by 20% of providers in each case. It is likely that no recommendation for a hysterectomy in Patient A was due to the patient being in the childbearing years.

In Patient C, the use of Tamoxifen was recommended by 20% of providers. Tamoxifen was found as a unique recommendation to Patient C, as it was not indicated as

a relevant preventative service in either Patient A or Patient B. Tamoxifen was initially included in the list of preventative service recommendations because it is the only option available for breast cancer prevention in women that can be utilized in both premenopausal women and postmenopausal women (Chen & Colditz, 2015). Raloxifene, which is a similar drug to tamoxifen that works to prevent breast cancer in postmenopausal women, is not yet utilized in premenopausal women due to the lack of safety data in this population, and therefore was not included as a choice of recommendations for providers to select (Chen & Colditz, 2015). Other drugs used for breast cancer prevention like aromatase inhibitors have been shown to increase estrogen production in premenopausal women, which can ultimately increase the rate of cancer growth, and thus were excluded from the recommendation list (Chen & Colditz, 2015). Published guidelines that indicate appropriate use for Tamoxifen as a breast cancer prevention drug recommend the drug for those over age 60, or those individuals ages 35 to 59 years who have a calculated five-year risk of developing breast cancer of 1.66 percent or higher according to a system called the Gail model (Chen & Colditz, 2015). While the Gail model accounts for women's age, age at first live birth, number of first-degree relatives with breast cancer, age at first menstrual period and the number of breast biopsies with pathological findings to calculate the five-year risk of developing breast cancer, it doesn't take into consideration inherited BRCA1 or BRCA2 mutations (Chen & Colditz, 2015). Information needed to calculate the Gail score was purposely excluded from the patient cases in the research to deter use of this score for provider recommendations during the survey. Due to the relatively small population of women that Tamoxifen is recommended for among those ages 35-59 years of age, it is not

surprising that this was a rarer preventative service recommendation by providers, and a recommendation seen only in Patient C (age 55).

The NCCN guidelines for a 55 year old women with HBOCS includes yearly clinical breast exams, annual mammograms, a risk reducing salpingo-oophrectomy carried out ideally between the ages of 35 and 40 and discussion of a risk reducing mastectomy (National Comprehensive Cancer Network, 2014). Although the NCCN doesn't tag the discussion of a risk-reducing mastectomy to a specific age group, the research investigation demonstrates that 100% of providers recommend a double mastectomy within 5 years. While the NCCN recommendations are useful guidelines for providers to follow, it is evident that gaps in these guidelines ultimately places the provider responsible for recommendations made and the age at which such recommendations are carried out for patients. Additionally, the research we conducted demonstrates that despite the existence of these guidelines, large variation still exists in recommendations.

Limitations

Limited health clinics and systems were targeted in this investigation to ensure the results could be generalized to individuals in a particular area. As a consequence of targeting specific clinics and health systems, our investigative results cannot be utilized to describe the attitudes of providers outside of the two health systems studied, Minnesota Oncology and Allegheny Health Network. Due to a lack of personal contact with the sites we utilized to participate in the case study and questionnaire, the response rate of 25 was lower than anticipated. Fortunately, there was an adequate sample size and enough variation to receive statistically significant results, however, a larger sample size would

provide stronger results regarding the opinions of providers. Utilizing in person contact with the sites and health systems in the future may influence more providers to participate, and thus lead to a higher response rate. In sending out case studies via email a possible bias to providers who do not utilize email as often or as comfortably as other providers was created. In choosing the method of email delivery, those providers who do not have a work computer or work email that they check regularly or at all were excluded. In an attempt to limit the data that would undergo analysis, a brief list of common screenings and treatment options that the providers could select from was created. The use of this close-ended questionnaire method was not all inclusive of every possible recommendation the provider may have for a patient with a positive BRCA1 or BRCA 2 mutation. Finally, collaboration among providers participating in the case study questionnaire may have affected the research. Despite strict instructions in the email that the cases should be completed individually, it is possible that providers could discuss the cases and the options that they would subsequently recommend for each patient, ultimately impacting research results.

Research Opportunities and Conclusion

The overall data trends suggest that both the number of services as well as the invasiveness of the service recommendation increases as patient age increases. This trend is also often seen in other preventative service guidelines established by the United States Preventative Task Force. The information revealed in this study showing that preventative service recommendations change with age is by no means an astounding revelation. However, the data shown in the secondary analysis revealing the wide variation of recommendations made by providers further affirms the need for additional

research to be carried out regarding the use of BRCA mutation testing results, and the adequate use of these results in implanting preventative services. While recent advances in science have allowed us to identify those women possessing a BRCA 1 or BRCA 2 mutation, this research exposes an obvious shortcoming regarding the utilization of these BRCA testing results.

Aside from the need for further investigations exposing the usefulness of BRCA testing results, this research can be used to assist patients of Minnesota Oncology or Allegheny Health Network possessing a BRCA mutation on what to expect for preventative service recommendations. This research was initially conducted to serve as a tool for BRCA mutation carriers and to reduce stress alleviated with BRCA mutation carrier status. Obviously, in medicine every patient is very unique, but the information revealed in this study may indeed alleviate stress or tension surrounding the unknown, in patients with a positive BRCA mutation. However, it is also a likely possibility that the information in the study may elicit further anxiety in individuals with a positive BRCA mutation; especially if they may be facing an invasive procedure such as a double mastectomy that was recommended by 100% of providers in Patient Case C. Overall, this research exposes the obvious need for further investigations regarding preventative services in BRCA mutation carriers and questions the use of BRCA mutation testing until those preventative services for BRCA mutation carriers are adequately implemented.

References:

American Cancer Society guidelines for early protection of cancer. (2013). Retrieved from American Cancer Society website: http://www.cancer.org/healthy/findcancerearly/cancerscreeningguidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer

Billings, P. (2005). Genetic nondiscrimination. *Nature Genetics, 37,* 559-560.

Bray, F., McCarron, P., Parkin, D.M. (2004). The changing global patterns of female breast cancer incidence and mortality. *Breast Cancer Research,* 6, 229-239.

Breast Cancer Prevention. (2013). Retrieved from National Cancer Institute website: http://www.cancer.gov/cancertopics/pdq/prevention/breast/Patient/page3#Keypoint11

Brose, M.S., Rebbeck, T., Calzone, K., et al. (2002). Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. *Journal of the National Cancer Institute,* 94(18), 1365-1372

CDC - Breast Cancer Home Page. (2013). Retrieved from Center for disease control and prevention website: http://www.cdc.gov/cancer/breast/

Chen S. & Parmigiani G. (2007) Meta-analysis of BRCA1 and BRCA2 entrance. *Journal of Clinical Oncology*. 25(11):1329–1333. Retrieved from http://jco.ascopubs.org/content/25/11/1329.full.pdf+html

Chen, W. & Colditz, G. (2015) Patient information: medications for the prevention of breast cancer. Retrieved from http://www.uptodate.com/contents/medications-for-the-prevention-of-breast-cancer-beyond-the-basics

Cook-Deegan, R., DeRienxo, C., Carbone, J., Chandrasekharan, S., Heaney, C., & Conover, C. (2010). Impact of gene patents and licensing practices on access to genetic testing for inherited susceptibility to cancer: comparing breast and ovarian cancers with colon cancers. *Genetics in Medicine, 12,* S15-S38.

Deborah Schrag, MD, MPH; Karen M. Kuntz, ScD; Judy E. Garber, MD, MPH; Jane C. Weeks, MD, MSC. (2000). Life expectancy gains from cancer prevention strategies for women with breast cancer and BRCA1 or BRCA2 mutations. *The Journal of the American Medical Association.* 283(5); 617-624.

Deng C. & Scott F. (2000). Role of the tumor suppressor gene BRCA1 in genetic stability and mammary gland tumor formation. *Oncogene*. 19, 8;1059-1064.

Feero, G., Guttmacher, A., & Collins, F. (2008). The genome gets personal- almost. *Journal of the American Medical Association, 300,* 1351-1352.

Foulkes, W., and Shuen, A. (2013). In brief: BRCA1 and BRCA2. *The Journal of Pathology,* 230, 347-349.

Grann, R.V., Jacobson, S.J., Thomason, D., Hershman, D., Heitjan, F.D., Neugut, I.A. (2002). Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA1/2 mutations: an updated decision anlysis. *Journal of Clinical Oncology*, *20(*10), 2520-2529.

Hamann, H., Somers, T., Smith, A., Inslicht, S., & Baum, A. (2005). Posttraumatic stress associated with cancer history and BRCA1/2 genetic testing. *Psychosomatic Medicine, 67,* 766-772.

Kobayashi, H. Ohno, S. Sasaki, Y. Matsuura, M. (2013). Hereditary breast and ovarian cancer susceptibility genes (review). *Oncology Reports*. 30;1019-1029.

Korf BR. Principles of Genetics. In: Goldman L, Ausiello D, eds. Cecil Medicine. 24th ed. Philadelphia, Pa: Saunders Elsevier; 2011:chap 39.

Kumar, V., Abbas, A.K., Fausto, N., & Aster, J.C. (2010). *Pathologic basis of disease* (8th ed.). Philadelphia, PA: Saunders Elsevier.

Lucassen, A., & Parker, M. (2010) Confidentiality and sharing genetic information with relatives. *The Lancet, 375,* 1508-1509.

Matloff, E., Shappell, H., Brierley, K., Bernhardt, B., McKinnon, W., & Peshkin, B. (2000). What would you do? Specialists' perspectives on cancer genetic testing, prophylactic surgery, and insurance discrimination. *Journal of Clincal Oncology 18,* 2484-2492.

Matloff, E., Shappell, H., Brierley, K., Bernhardt, B., McKinnon, W., & Peshkin, B. (2000). What would you do? Specialists' perspectives on cancer genetic testing, prophylactic surgery, and insurance discrimination. *Journal of Clincal Oncology 18,* 2484-2492.

National Cancer Institute. (2012) FY 2012 research funding by cancer type. Retrieved from http://fundedresearch.cancer.gov/nciportfolio/search/funded?fy=PUB2012&type=site

National Comprehensive Cancer Network. (2014). NCCN clinical practice guidelines in oncology genetic/familial high-risk assessment breast and ovarian. Retrieved from http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf

Natowicz, M., Alper, J., & Aper, I. (1992). Genetic discrimination and the law. *American Journal of Human Genetics 50,* 465-475.

Neslson, H. D., Tyne, K., Naik, A., Boughatsos, C., Chan, B. K., & Humphery, L. (2009). Screening for Breast Cancer: Systematic Evidence Review Update for the U. S. Preventive Services Task Force. *Annals of Internal Medicine*, *151*(10), 727-742.

O'Neill, S., Luta, G., Walker, L., Peshkin, B., Abraham, A., & Tercyak, K. (2010) Primary care providers' willingness to recommend BRCA1/2 testing to adolescents. *Familial Cancer 9,* 43-50.

Patenaude, A. F., Tung, N., Ryan, P. D., Ellisen, L. W., Hewitt, L., Schneider, K. A., & Garber, J. E. (2013). Young adult daughters of BRCA1/2 positive mothers: What do they know about hereditary cancer and how much do they worry? *Psycho-Oncology, 22*(9), 2024-2031.

Samani, N., Tomaszewski, M., & Schunkert, H. (2010). The personal genome- the future of personalized medicine? *The Lancet, 375,* 1497-1498.

Saslow D, Boetes C, Burke W, Harms, S., Leach, O.M., Lehman, D.C., Morris, E. Pisano, E., Schnall, M., Sener, S., Smith, A.R., Warner, E., Yaffe, M., Andrews, S., Russell A.C. (2007). American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer Journla Clinicians*. 2007;57:75-89.

Surbone, A. (2001). Ethical implications of genetic screening for breast cancer predisposition. *Critical Review in Oncology Hematology Journal 40,* 149-157.

Surbone, A. (2011). Social and ethical implications of BRCA testing. *Annals of Oncology, 22,* i60-i66.

United States National Library of Medicine. (2013, November). *What is direct-to-consumer genetic testing?* Retrieved from http://ghr.nlm.nih.gov/handbook/testing/directtoconsumer

U.S. Preventive Services Task Force. (2005). Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. *Annals of Internal Medicine, 143,* 355-61. Retrieved from http://www.uspreventiveservicestaskforce.org/uspstf05/brcagen/brcagenrs.htm

U.S. Preventive Services Task Force. (2009). Screening for breast cancer: U.S. Preventive Service Task Force recommendation statement. *Annals of Internal Medicine, 151,* 716-726.

Van Hoyweghen, I., & Horstman, K. (2008). European practices of genetic information and insurance. Lessons from the Genetic Information Nondiscrimination Act. *Journal of the American Medical Association 300,* 326-327.

Wagner, J. (2005). Practical and ethical issues with genetic screening. *American Society of Hematology, 1,* 498-502.

Warner, E., Plewes, D.B., Hill K.A., Causer, A.P., Zubovits, T.J., Jong, A.R., Cutrara, R.C., DeBoer G., Yaffe, J.M., Messner, J.S., Meschino, S.W., Piron, A.C., Narod, A.S., (2004). Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *Journal of American Medical Association.* 292(11):1317-1325.

Wolf, S. (1995). Beyond genetic discrimination: toward the broader harm of geneticism. *Journal of Law Medicine and Ethics 23,* 345-353.

Yabroff, K.R., Lund, J., Kepka, D., Mariotto, A. (2011) Economic burden of cancer in the United States: estimates, projections, and future research. *Cancer Epidemiology, Biomarkers & Prevention*, 20(10), 2006–2014.

APPENDIX A:

Case Studies

Patient: A: 25 year old female

Due to a strong family history of breast cancer patient A was genetically tested and found positive for a BRCA1/BRCA2 mutation. Her ROS on physical exam today was unremarkable and medical history is as follows:

PMH:
Meds:
Allergies: penicillin
Surgeries/ Hospitalizations: denies
Immunizations: current
Standing Medical Problems: unremarkable

Family History:
Father – alive and well
Mother- alive, Hx of breast cancer age of onset 40
Maternal Grandmother- deceased at age (65), hx of breast cancer age of onset 55
Maternal aunt- alive, Hx of breast cancer age of onset 45
Brother- alive with hyperlipidemia
Denies any other cancer, HTN, hyperlipidemia, diabetes, heart, lung and thyroid disease, bleeding and clotting disorders, or psychiatric history

Social History:
Tobacco- denies
Alcohol- denies
Caffeine- denies
Exercise- frequently cardio and weight bearing
Sleep- 8 hours nightly
Diet: balanced diet
Occupation: teacher
Marital status: single
Sexual history: denies

OBJECTIVE:
Vitals:

T- 37.2 C (ear)	Wt- 145lbs
HR- 70	BMI: 24.1
R- 16	
BP-126/83	
O2 sat- 99%	
Ht- 65”	

Patient A presents to your clinic what recommendations would you advise for prevention of breast cancer?

- ☐ Mammograms biennially starting this year
- ☐ Mammograms biennially starting within 5 years
- ☐ Mammograms every 5 years starting this year
- ☐ Mammograms annually starting this year
- ☐ No mammogram recommendation at this time
- ☐ Clinical breast exams annually
- ☐ No clinical breast exam recommendation at this time
- ☐ Self breast exams annually
- ☐ Self breast exams monthly
- ☐ No self breast exam recommendation at this time
- ☐ Hysterectomy within 5 years
- ☐ Salpingo-oophrectomy within 5 years
- ☐ Double mastectomy within 5 years
- ☐ Tamoxifen therapy
- ☐ No preventative recommendations at this time

Patient: B: 45 year old female

Due to a strong family history of breast cancer patient B was genetically tested and found positive for a BRCA1/BRCA2 mutation. Her ROS on physical exam today was unremarkable and medical history is as follows:

PMH:
Meds:
Allergies: penicillin
Surgeries/ Hospitalizations: denies
Immunizations: current
Standing Medical Problems: unremarkable

Family History:
Father – alive and well
Mother- alive, Hx of breast cancer age of onset 40
Maternal Grandmother- deceased at age (65), hx of breast cancer age of onset 55
Maternal aunt- alive, Hx of breast cancer age of onset 45
Brother- alive with hyperlipidemia
Denies any other cancer, HTN, hyperlipidemia, diabetes, heart, lung and thyroid disease, bleeding and clotting disorders, or psychiatric history

Social History:
Tobacco- denies
Alcohol- denies
Caffeine- denies
Exercise- frequently cardio and weight bearing
Sleep- 8 hours nightly
Diet: balanced diet
Occupation: teacher
Marital status: single
Sexual history: denies

OBJECTIVE:
Vitals:
T- 37.2 C (ear)
HR- 70
R- 16
BP-126/83
O2 sat- 99%
Ht- 65”
Wt- 145 lbs
BMI: 24.1

Patient B presents to your clinic what recommendations would you advise for prevention of breast cancer?

- ☐ Mammograms biennially starting this year
- ☐ Mammograms biennially starting within 5 years
- ☐ Mammograms every 5 years starting this year
- ☐ Mammograms annually starting this year
- ☐ No mammogram recommendation at this time
- ☐ Clinical breast exams annually
- ☐ No clinical breast exam recommendation at this time
- ☐ Self breast exams annually
- ☐ Self breast exams monthly
- ☐ No self breast exam recommendation at this time
- ☐ Hysterectomy within 5 years
- ☐ Salpingo-oophrectomy within 5 years
- ☐ Double mastectomy within 5 years
- ☐ Tamoxifen therapy
- ☐ No preventative recommendations at this time

Patient: C: 55 year old female

Due to a strong family history of breast cancer patient C was genetically tested and found positive for a BRCA1/BRCA2 mutation. Her ROS on physical exam today was unremarkable and medical history is as follows:

PMH:
Meds:
Allergies: penicillin
Surgeries/ Hospitalizations: denies
Immunizations: current
Standing Medical Problems: unremarkable

Family History:
Father – alive and well
Mother- alive, Hx of breast cancer age of onset 40
Maternal Grandmother- deceased at age (65), hx of breast cancer age of onset 55
Maternal aunt- alive, Hx of breast cancer age of onset 45
Brother- alive with hyperlipidemia
Denies any other cancer, HTN, hyperlipidemia, diabetes, heart, lung and thyroid disease, bleeding and clotting disorders, or psychiatric history

Social History:
Tobacco- denies
Alcohol- denies
Caffeine- denies
Exercise- frequently cardio and weight bearing
Sleep- 8 hours nightly
Diet: balanced diet
Occupation: teacher
Marital status: single
Sexual history: denies

OBJECTIVE:
Vitals:
T- 37.2 C (ear)
HR- 70
R- 16
BP-126/83
O2 sat- 99%
Ht- 65”
Wt- 145 lbs
BMI: 24.1

Patient C presents to your clinic what recommendations would you advise for prevention of breast cancer?

- ☐ Mammograms biennially starting this year
- ☐ Mammograms biennially starting within 5 years
- ☐ Mammograms every 5 years starting this year
- ☐ Mammograms annually starting this year
- ☐ No mammogram recommendation at this time
- ☐ Clinical breast exams annually
- ☐ No clinical breast exam recommendation at this time
- ☐ Self breast exams annually
- ☐ Self breast exams monthly
- ☐ No self breast exam recommendation at this time
- ☐ Hysterectomy within 5 years
- ☐ Salpingo-oophrectomy within 5 years
- ☐ Double mastectomy within 5 years
- ☐ Tamoxifen therapy
- ☐ No preventative recommendations at this time

BETHEL UNIVERSITY

September 10, 2014

Rebecca Crissman

Bethel University St. Paul, MN 55112

Re: Project FA-01-14 Oncology Provider Opinions on Preventative Recommendations for Patients with BRCA1 and/or BRCA2 Breast Cancer Mutation(s)

Dear Rebecca,

On September 10, 2014, the Bethel University Institutional Review Board completed the review of your proposed study and approved the above referenced study with the following qualification:

(1) As per the Bethel IRB guidelines, please provide written documentation of permission from an appropriate institutional authority from the Allegheny Health Network to conduct your proposed study at their site and/or with their constituents (see http://www.bethel.edu/academics/irb/guidelines/instructions).

Please note that this approval is limited to the project as described on the most recent Human Subjects Review Form. Also, please be reminded that it is the responsibility of the investigator(s) to bring to the attention of the IRB any proposed changes in the project or activity plans, and to report to the IRB any unanticipated problems that may affect the welfare of human subjects. Last, the approval is valid until September 9, 2015.

Sincerely,

Peter Jankowski, Ph.D. Chairperson Bethel University IRB

Cc: Dr. Gregory Ekbom, Research Advisor

Kathleen Dunsmore

Institutional Review Board 3900 Bethel Drive PO2322 St. Paul, MN 55112

To Whom It May Concern:

I am writing to grant permission as the Director of Clinical Services for West Penn Allegheny Oncology Network for Rebecca Crissman and Kathleen Dunsmore of Bethel University to complete their research using surveys administered to physicians, nurse practitioners and physician assistants employed by West Penn Allegheny Oncology Network a part of Allegheny Health Network.

Sincerely,

Marjorie Leslie
(412) 770- 3579

To Whom It May Concern:

I am writing to grant permission as the Director of Managed Care and Quality for Minnesota Oncology for Rebecca Crissman and Kathleen Dunsmore to complete their research using surveys administered to Minnesota Oncology employed providers.

Sincerely,

Rhonda Henschel

Rhonda Henschel
(651)-602-5347