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Jacob Comeaux

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Risk Reducing Mastectomies among Women with Mutations in Moderate Penetrance Breast  
Cancer Susceptibility Genes

By

Jacob Comeaux

Submitted in Partial Fulfillment of the Requirements  
For the Degree of Master of Science in Human Genetics and Genetic Counseling  
School of Pharmacy and Health Sciences  
Keck Graduate Institute

2020

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## **DEDICATION**

I would like to dedicate this manuscript to my parents, Gregory and Nicole Comeaux. Their endless and unconditional support enabled me to focus on advancing my education in a field that I'm passionate about. My aspirations are to make the most of the opportunities they have given me by making a positive impact on patients' lives and the field of cancer genetics.

## ACKNOWLEDGMENTS

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were on trajectories to make contributions to the field of genetic counseling. She has remained unwavering in her commitment to all her students, and she provided reliable feedback to me and my class over the entire two year process of this project. Her tireless dedication and encouragement as a member of the thesis committee inspired me to undertake a study of this magnitude. In the same vein, I want to thank Ashley Mills, MS, LCGC Program Director, for founding the KGI genetic counseling program. Her vision for enlarging the Southern California community of genetic counselors and admitting me into the inaugural class allowed this study to take form. Both Ashley and Emily provided me with the tools to successfully complete this study, including a key partnership with statistician and professor Nicholas Gorman, PhD, who went above and beyond to help guide study design, data collection, and ultimately data analysis. Thank you, Dr. Gorman, for offering your time and providing comprehensive analyses.

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**ABSTRACT**

Women who harbor mutations in breast cancer susceptibility genes are at an increased lifetime risk of developing breast cancer and are faced with decisions about managing their risks, including the decision of whether to undergo a risk reducing mastectomy (RRM). While decision making for risk management has been studied extensively for *BRCA1* and *BRCA2* carriers, there is much less information surrounding risk management for women with mutations in moderate penetrance genes. This is a retrospective study of 280 women undergoing genetic counseling at a Los Angeles-based academic hospital between 2009 and 2019. The study used medical records to examine rates of RRM in both affected and unaffected women with 1) no known mutation (N=92), 2) a mutation in a moderate penetrance gene *CHEK2*, *ATM*, *NBN*, or *PALB2* (N=90), or 3) a *BRCA* mutation (N=98). Participants had a mean age of 45.7 years and were 78% Caucasian, 34% affected with breast cancer, and 31% never married. Results showed that mutation status was associated with RRM decision ( $p<.001$ ), with 8.6% (8/92) of women with no known risk mutations, 30% (27/90) of moderate penetrance gene carriers, and 39.8% (39/98) of *BRCA* mutation carriers undergoing RRM. Women were more likely to undergo RRM if they were affected with breast cancer ( $p<.001$ ), had a younger age at diagnosis ( $p<.001$ ), were presented with a higher lifetime risk ( $p=.006$ ), and were married or partnered ( $p=0.02$ ). Participants with a moderate risk mutation without breast cancer were more likely to have RRM if they had a first degree relative with breast cancer ( $p=.03$ ). The NCCN Guidelines® does not typically recommend consideration of RRM for moderate penetrance carriers, but their rates of RRM approach those of *BRCA* carriers. Genetics providers must better equip surgeons and patients with knowledge of risks associated with moderate penetrance mutations, and healthcare providers must strive to understand why surgical decisions are made.

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## INTRODUCTION

Breast cancer is the most common female cancer worldwide and the second most common cancer overall (Rojas, 2016; Ullah, 2019). While most breast cancers are sporadic, hereditary cancers comprise approximately 5-10% of all breast cancer cases (*Genetics of Breast and Gynecologic Cancers*, 2020). These hereditary cancers are largely caused by inherited single-gene mutations in tumor suppressor genes. The most common genes involved in hereditary breast (and ovarian) cancer syndromes are *BRCA1* and *BRCA2*, which were discovered in the mid-1990s and remained synonymous with hereditary breast cancer until recently (Familial Breast Cancer, 2001). Mutations in *BRCA1* and *BRCA2* are considered “high penetrance” because they confer, by some estimates, over an 80% lifetime risk for female breast cancer. Mutations in these two genes account for just half of all hereditary breast cancers (Easton, 1999; Easton, 2015; Kapoor, 2015; Kuchenbaecker 2017; Tedaldi, 2017). Other gene contributors to hereditary breast cancer remained largely unidentified until the past decade, as the advent and implementation of next-generation DNA sequencing brought the possibility of simultaneous analysis of multiple newly-discovered genes implicated in hereditary cancers (Powers, 2018). These genes include “moderate penetrance” breast cancer susceptibility genes such as *ATM*, *CHEK2*, *NBN*, and *PALB2*, which are generally estimated to have a 23-43%, or 2-4 fold increased lifetime risk of female breast cancer (Antoniou, 2014, Easton, 2015; LaDuca, 2020; Leedom, 2016; Marabelli, 2016).

For women who are considered at higher risk for breast cancer, such as gene mutation carriers, current risk management options include screening, chemoprevention, risk reducing mastectomy (RRM), and controversially, prophylactic oophorectomy (Domchek 2006; Jatoi, 2016; Jernstrom, 2004; Kotsopoulos 2018). Unaffected women are therefore left with few non-

invasive options to consider when presented with a significant lifetime risk. Women who have been diagnosed with breast cancer also decide whether their surgical approach entails removing 1) solely the affected area of the breast or 2) the entire breast with the cancer or 3) additionally removing the contralateral breast to reduce the risk of a new primary breast cancer. The most risk-conservative, efficacious, and invasive procedure indicated for women at a high risk of breast cancer is the RRM, which reduces breast cancer risk for *BRCA1/2* carriers by 90-95% (Domchek, 2010; Singh, 2013).

Decision making for RRM requires comprehension of both the efficacy of the procedure and the adverse events and risks involved (Scott, 2013). While decision making for risk management has been studied for *BRCA1* and *BRCA2* carriers, there is a paucity of information surrounding risk management for women with moderate penetrance genes such as *ATM*, *CHEK2*, *NBN*, and *PALB2*. There are many factors at play during the RRM decision making process. In this manuscript, we assess whether the number of first, second, and third degree relatives with a history of breast cancer influences the likelihood of undergoing a RRM among a) women with mutations in the moderate penetrance genes (*ATM*, *CHEK2*, *NBN*, and *PALB2*), b) women with *BRCA1* and *BRCA2* mutations, and c) women with no known mutations. We also explore whether the decision regarding RRM in these three genetic-risk-stratified groups depends on patient age and marital status. Our study population of 280 women includes both women who have and who have not been diagnosed with breast cancer. For women who have not been diagnosed, we investigate whether the estimated remaining lifetime risk presented to them at the time of genetic testing influences their decision-making for RRM.

**BACKGROUND:****A. Breast Cancer Screening and Risk Reduction Options**

While breast cancer is one of the most common cancers, it ranks fifth in cancer mortality due to its relatively favorable prognosis compared to other cancer types (Ullah, 2019). Population screening for unaffected women and the tailoring of these screening methods to women based on their lifetime risks contributes to breast cancer's relatively favorable prognosis. Women without signs or symptoms undergo breast screening so that if a cancer does develop, it can be detected and treated at an early stage. The etiology of breast cancer is multifactorial and can be caused by genetic as well as environmental factors. Some lifestyle factors that may also contribute to a women's lifetime risk for developing breast cancer include combined estrogen/progesterone therapy for more than three to five years, alcohol consumption, lack of exercise, excess weight, and not breastfeeding (NCCN v.1.2020). A number of these lifestyle factors are used in conjunction with age and family history to generate an estimated lifetime risk for women who have no known gene mutation using empirical risk models, such as the Tyrer-Cuzick model (Stevanato, 2019).

Women who are identified as having a higher risk secondary to her family history, gene mutation, lifestyle, or very early age of onset of breast or ovarian cancer, may be offered additional screening options. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are the gold standard for the treatment and management of an array of cancers, including recommendations for detection, prevention, and risk reduction. The NCCN Guidelines® for Breast Cancer Screening and Diagnosis state that screening modalities depend on age, medical history, and family history. Screening may include "breast awareness, regular clinical encounters, clinical breast exam, breast imaging with screening mammography, and in selected cases, breast MRI" (NCCN, v1.2020).

The NCCN Guidelines® offer information on risk reduction for breast cancer and recommend that women at an increased risk for developing breast cancer receive genetic counseling. Risk reducing chemoprevention such as aromatase inhibitors or tamoxifen may be considered and discussed based on the woman's age, potential contraindications, and associated adverse effects. Finally, the NCCN supports consideration of RRM for women not only with gene mutations conferring a high risk for breast cancer such as *BRCA1* or *BRCA2*, but also for women with a compelling family history or possibly for women with prior thoracic radiation therapy at or before age 30. The NCCN also offers gene-specific management guidelines which are delineated in subsequent sections of this background.

## **B. Surgical Approaches and Management for Breast Cancer Patients**

Surgical treatment for breast cancer has been studied extensively. The radical mastectomy, or the removal of the breast containing the cancer and the underlying pectoral muscle, was considered the standard of care from the 1950s to the 1970s, until it was challenged by emerging breast conservation strategies in combination with other approaches including radiation, chemotherapy, and endocrine therapy (Lerner, 2001). In 1990, the National Institute of Health (NIH) Consensus conference established that “breast conservation treatment...is preferable because it provides survival equivalent to total mastectomy...while preserving the breast” (NIH, 1990). Since then multiple randomized controlled trials have shown that breast conservation strategies such as lumpectomy with radiation result in similar local recurrence and survival outcomes to invasive techniques such as the radical mastectomy (Beaulieu, 1998; Fisher, 2002).

Today, women with unilateral breast cancer have options regarding surgical treatment, both for the affected breast and for the contralateral, unaffected breast. Contralateral prophylactic



mastectomy (CPM) is the removal of the unaffected breast in breast cancer patients and remains a choice for women who wish to decrease the risk of developing contralateral breast cancer (CBC) (Herrington, 2005). There are two groups that are at a substantially increased risk for contralateral breast cancer development: women with *BRCA1/2* mutations and women with a history of mantle radiation during childhood and adolescence (Metcalf, 2004). The role of CPM is generally accepted for *BRCA1/2* carriers, but the benefit is not evident in women who are diagnosed with breast cancer at early ages but do not carry a mutation or those who have a strong family history but no known mutation (Teoh, 2020). For women with *BRCA1/2* mutations, CPM reduces the risk of CBC by over 90% (Li, 2016; van Sprundel, 2005). Studies also show that CBC rates are higher for women who have a positive family history of breast cancer and are stratified by degree of relation (Bernstein, 1992; Boughey, 2010; Ji, 2007; Kuchenbaecker, 2017; Narod, 2016; Reiner, 2018; Teoh, 2020; Vaittinen, 2000). Decision-making for surgical approach for breast conservation surgery (BCS), i.e. unilateral mastectomy or lumpectomy, versus CPM is discussed in a subsequent section of this background.

### **C. Breast Cancer Risks for Women with *BRCA1/2* Mutations**

As mentioned, breast cancer screening, risk reduction, and surgical decision making are often considered in the context of a woman's lifetime risk for breast cancer. A woman's lifetime risk for breast cancer may be most drastically affected by germline mutations in genes that function to prevent the development of cancer. i.e. tumor suppressor genes. Cancer genetics is a relatively new field within genetic counseling, but if there is any gene that spearheaded its push into its current paradigm, it's *BRCA1*. Mary-Claire King et al began to link early-onset familial breast cancer to chromosome 17q21 in 1990. They localized the *BRCA1* gene in 1991, then mapped *BRCA1* in 1993, and isolated and sequenced *BRCA1* in 1994, thus making it the first cloned

hereditary cancer susceptibility gene known to mankind (Anderson, 1993; Friedman, 1994; Hall, 1990; King, 1991, 1993; Miki, 1994). In 1995, scientists at the National Institutes of Health (NIH) discovered the prevalence of this gene in the general Ashkenazi Jewish population at a frequency of 1% (FitzGerald, 1996). Subsequent studies implicated *BRCA1* in coding for tumor suppressors, though its molecular mechanism remained unknown (Jensen, 1996). By 1998, researchers had shown that *BRCA1* and *BRCA2* coexist in a protein complex, leading them to believe that they work in concert in the DNA repair pathway and that perturbations or mutations in either gene could be a cause for both breast and ovarian cancers, among other cancers (Chen, 1998).

Since their implication in breast cancer and other diseases, *BRCA1* and *BRCA2* have been the focus of dozens of studies that have aimed to classify the risk they each confer to an individual for breast cancer. In 1994, the same year that *BRCA1* was discovered, researchers homed in on 33 families with known *BRCA1* linkage and found that female carriers faced an 87% percent chance of developing breast cancer by age 70 (Ford, 1994). Luckily, this proved to be the apex for breast cancer risk estimates for *BRCA1* to date. Larger studies including more than 20 times the number of families and taking into account ethnic origin, including Ashkenazi Jewish ancestries, estimated the risk conferred by the *BRCA1* gene to be 46%, which was ultimately accepted as the lowest risk estimate to date. *GeneReviews* takes into account the many studies conducted to calculate the breast cancer risks for women with *BRCA1* and *BRCA2* mutations and compiles those into a table for referencing: the risk of breast cancer in a woman with a germline *BRCA1* pathogenic variant is 46-87%; the risk of breast cancer in a woman with a germline *BRCA2* pathogenic variant is 38-84%; and the general population risk of breast cancer is 12%

(Breast Cancer Linkage Consortium 1999; Easton, 1995; Lee, 2011; Mavaddat, 2013; Rakha, 2008; Satagopan 2001).

One study that stands apart from the others in scope and thoroughness is *Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers*. In 2017, Kuchenbaecker et al published prospective results estimating age-specific risks of breast and contralateral breast cancer for *BRCA1/2* carriers and modifications of risks due to family history and mutation location. Out of 6036 *BRCA1* female carriers and 3820 *BRCA2* female carriers, 49% were affected with either breast or ovarian cancer while 51% were unaffected during the duration of the study from 1997-2011. *BRCA1* carriers were estimated to have a 72% chance of developing breast cancer by 80 while *BRCA2* carriers were estimated to have a risk of 69% based on the data collected. This percentage risk approaches the higher end of the range previously defined, but researchers took their analysis a step further by analyzing risks per decade. For *BRCA1*, women's risk increased rapidly through ages 30-40, while for *BRCA2*, the risk increased quickly through ages 40 to 50. Both genes' conferred risks leveled off until 80 years of age. Not surprisingly, more affected first and second degree relatives translated into higher hazard ratios for women with both *BRCA1* and *BRCA2* mutations. Interestingly, but not ostensibly germane to *BRCA1/2* perceived risk and management, the location of the mutation in both *BRCA1* and *BRCA2* were positively correlated with breast cancer risk (Kuchenbaecker, 2017). Finally, a recently published study indicates that the absolute risk by age 80 for *BRCA1* and *BRCA2* carriers is 75% and 76%, respectively (LaDuca, 2020).

In the aforementioned paper, Kuchenbaecker et al also demonstrated that the cumulative risk for contralateral breast cancer (CBC) 20 years after the original diagnosis was 40% for *BRCA1* and 26% for *BRCA2* (Kuchenbaecker, 2017). This estimate is taken in the context of previously

conducted studies including published data by Metcalfe et al wherein the risk of developing contralateral breast cancer in *BRCA1/2* carriers was estimated to be approximately 40% at 10 years (Metcalfe, 2004). A more recent study by Metcalfe et al provided *BRCA1/2* gene-specific estimates: the 15 year risk of CBC for *BRCA1* was estimated to be 36.1% and 28.5% for women with a *BRCA2* mutation. Another retrospective study estimated the risk of CBC in *BRCA1/2* patients to be 47.4% over the course of 25 years from a woman's first breast cancer (Graeser, 2009). Kuchenbaecker's study also demonstrated, in alignment with these previously conducted retrospective studies, that women were at a higher risk for contralateral breast cancer (CBC) when diagnosed before age 40 versus after age 50 (Graeser, 2009; Kuchenbaecker, 2017; Metcalfe, 2011).

#### **D. *BRCA1/2*-Specific Management Options**

Mary-Claire King, the discoverer of *BRCA1*, discussed a “scientific purgatory” surrounding the utility of genetic testing when *BRCA* testing was first entering the clinical realm: even if we could identify a woman at high risk, it was futile to intervene reliably (Bouchard, 2004; Holtzman, 1998; Koenig, 1998). Since then, our knowledge for reliably intervening for *BRCA* management has developed considerably. Domchek states, “there should no longer be a sense of nihilism about genetic testing for *BRCA1/2*. If we can identify the women who have these genetic mutations, we can improve their overall mortality with [proper] interventions” (Domchek, 2010; Printz, 2011).

The diagnosis of Hereditary Breast and Ovarian Cancer Syndrome (HBOC) begins with offering molecular genetic testing to identify a germline pathogenic/likely pathogenic variant in *BRCA1* or *BRCA2*. Following a molecular diagnosis, women should be offered follow up options

in accordance with current guidelines. Regarding breast cancer risk, the NCCN Guidelines® (v.1.2020) recommend that women who have tested positive for mutations in *BRCA1/2* begin breast awareness at age 18, initiate clinical breast examination (CBE) every six to twelve months at age 25, and increase radiological screening beginning at age 25 to at least age 75 with age-dependent frequency and age-dependent modalities including annual breast MRIs and mammograms. Similar to NCCN Guidelines®, *GeneReviews* guidelines for surveillance of breast cancer for women with HBOC include monthly breast self-exams, initiate CBEs every 6 months to 1 year at age 25, yearly breast MRI beginning at age 25, and annual mammograms starting at age 30 (Petrucelli, 1993; *updated 2016*). A Dutch study set out to validate this model of screening based on risk group, found that screening for *BRCA1* should begin at 25 years, screening for *BRCA2* should begin at 30 years, and screening for familial risk should begin at 35 years (Tilanus-Linthorst, 2013). Some studies suggest that more than 80% of *BRCA* carriers adhere to the commonly adopted screening methods of MRI and mammogram (Gilbert, 2017; Schwartz, 2012).

Data in support of chemoprevention and prophylactic oophorectomies to reduce breast cancer risks for *BRCA1/2* carriers is somewhat limited. In a retrospective study, King et al showed that tamoxifen, a selective estrogen receptive modulator (SERM), reduced breast cancer risk for healthy women with a hereditary *BRCA1/2* mutation by 62% (King, 2001). However, there have been no prospective trials to test if SERMs are as effective as chemoprevention. There are other breast cancer risk-reducing agents including raloxifene and aromatase inhibitors. The NCCN offers guidelines regarding use of tamoxifen, raloxifene, and aromatase inhibitors, though they are not tailored specifically to *BRCA1/2* mutation carriers. Only 15% of *BRCA1/2* carriers are

offered a chemoprevention trial and just 8.5% *BRCA1/2* carriers begin chemoprevention within the first 4 years of genetic testing results (Padamsee, 2017; Pujol, 2012).

There are mixed reviews on whether prophylactic oophorectomies as a primary means of decreasing risk for ovarian cancer also decrease the risk for breast cancer (Metcalf, 2005). Metcalfe et al also demonstrated that women with *BRCA1/2* mutations taking tamoxifen or who have undergone an oophorectomy diminish their risk of developing CBC (Metcalf, 2004).

RRMs are a common consideration among *BRCA1/2* carriers. Recent data shows that RRM in unaffected *BRCA1* carriers is associated with lower mortality but that for unaffected *BRCA2* carriers, surveillance versus RRM led to similar survival rates (Heemskerk-Gerritsen, 2019). The NCCN Guidelines® state to, “discuss the option of risk-reducing mastectomy [in regard to] degree of protection, reconstruction options, and risks for *BRCA1* and *BRCA2*.” Life expectancy and residual breast cancer risk should be considered when counseling these patients as well. Importantly, the NCCN Guidelines® recommend addressing psychosocial and quality-of-life aspects of undergoing RRM.

## **E. Breast Cancer Risks for Families and Populations with *ATM*, *CHEK2*, *NBN*, and *PALB2* Mutations**

### **a. Overview**

The distinction between moderate and high penetrance genetic risk stratification is defined arbitrarily, but researchers have previously defined moderate penetrance in terms of gene carrier cancer incidence that is two to four fold higher than in the general population (Easton, 2015; Tung, 2016). 2-5% of those who are referred for cancer genetic testing are identified as carriers of moderate penetrance gene mutations (Tung, 2016). Per the National Cancer Institute, these moderate penetrant mutations are thought to be more frequent in the general population

than those conferring higher risks and are the cause for a small fraction of cancers, but a significant percentage of familial breast cancers (Smith, 2015). Therefore, it is paramount for clinicians to understand the risks conferred by moderate penetrance mutations and appropriately counsel patients based on those risks to ensure that women are making the most informed and rational decisions that best suit their circumstances. Each of the moderate penetrance genes discussed below—*ATM*, *CHEK2*, *NBN*, and *PALB2*—have estimates that fall within the two to four-fold increased lifetime risk windows, but vary in degree of breast cancer risk.

#### **b. ATM and breast cancer risks**

*ATM* is a protein kinase that functions to monitor and repair double-stranded DNA breaks and maintain genomic stability (Shiloh, 2003). The ATM protein was discovered as part of the gene that is responsible for the autosomal recessive human genetic disorder ataxia telangiectasia (AT), a disease characterized by cerebellar degeneration leading to progressive neuromotor dysfunction, immunodeficiency, genomic instability and sensitivity to ionizing radiation (Savitsky, 1995). Studies then began to compare the incidence of breast cancer and mortality in relatives of AT patients to the general population. A review of four of these studies estimated that the relative risk of breast cancer to be 3.9 (CI=95%, 2.1 to 7.2) (Easton, 1994; Inskip, 1999; Janin, 1999; Olsen, 2001; Swift, 1987; Swift, 1991; Su, 2000). Studies estimating relative risks for heterozygous mutations in *ATM* following that analysis reported a range of 2.4 to 3.4, with younger women experiencing a higher degree of relative risk (Easton, 1994; Geoffroy-Perez, 2001; Olsen, 2005; Swift, 1987). Thompson et al then conducted a study congruent with these findings, stating that the relative risk of breast cancer for *ATM* carriers was 2.23 (CI=95%, 1.16 to 4.28) but as high as 4.94 (CI=95%, 0.76 to 2.00) in women younger than 50. These findings confirmed a moderate penetrance risk status for *ATM*, but ultimately failed to support a

genotype-phenotype risk relationship (Thompson, 2005). The following year, Renwick et al published a study combining *ATM* truncating, splicing, and missense mutations which are strongly implicated in AT and found that the relative risk of breast cancer to be 2.37 (CI=95%, 1.51 to 3.78) using a segregation analysis (Renwick, 2006).

A meta-analysis of the three large cohort studies of family members with AT revealed that truncating variants are “likely moderate penetrance”, conferring a relative risk of 2.8 (CI=90%, 2.2 to 3.7; p-value=4E-11) and a 27% absolute risk by 80 years of age (Easton, 2015). Approximately 70% of *ATM* mutations are truncating variants (Shiloh, 2003). Easton et al also predict that missense variants are likely to confer increased breast cancer risks (Easton, 2015). In fact, Goldgar et al previously demonstrated that *ATM* p.Val2424Gly confers higher risks than truncating variants (8.0; 90% CI, 2.8 to 22.5; p-value=0.0005) (Goldgar, 2011). The most recent study cited here estimates an odds ratio of 2.91 (N=79912, p-value=9.53E-44) for female *ATM* carriers (LaDuca, 2020). *ATM* mutation carrier frequency in Western populations has been estimated to be as high as 1% (Fitzgerald, 1997; Swift, 1986).

In general, the relationship between *ATM* variants and risk for CBC remains contentious. Four common variants of *ATM* have been demonstrated to be associated with lower CBC risk (RR=0.8) compared to rare, missense *ATM* mutations (Concannon, 2008; Teoh, 2020). Bernstein postulates that this can be explained by deleterious rare *ATM* variants acting in tandem with radiation exposure to increase the risk of a tumor developing (Bernstein, 2017). While overall breast cancer risk is unknown, radiation at least appears to contribute to contralateral breast cancer risk (Broeks, 2008).



### c. **CHEK2 and breast cancer risks**

*CHEK2* is activated as an effector kinase when DNA damage occurs and is integral in signaling downstream repair proteins (Stracker, 2009). One of the most well-known mutations in *CHEK2* is a founder mutation denoted as c.1100delC which was first described in 1999 in an individual who was suspected to have Li-Fraumeni syndrome (Bell, 1999). Founder mutations are ancient mutations found in individuals who share a common ancestor, and are therefore primarily unique to certain populations, in this case Western European populations. The 1100delC variant was subsequently shown to be present in 5.1% of women with breast cancer who were confirmed to not harbor *BRCA1/2* mutations (Meijers-Heijboer, 2002). In 2002, researchers published additional studies identifying *CHEK2*\*1100delC as a “cancer susceptibility allele” (Consortium, 2002; Vahteristo, 2002). Following that discovery, the *CHEK2* Breast Cancer Case-Control Consortium evaluated 10,860 cases and 9,065 controls from a number of studies, finding that the 1100delC allele conferred a two-fold increase in breast cancer risk (*CHEK2* Consortium, 2004). Since then, multiple studies have characterized risks for both founder mutation carriers and non-founder mutation carriers. A study conducted in 2013 indicated that women with *CHEK2* mutations are at a 25-37% lifetime risk for developing breast cancer (Apostolou, 2013). A meta-analysis conducted by Easton et al in 2015, indicated that truncating variants in *CHEK2* are “likely moderate penetrance,” conferring a three-fold relative risk and a 29% absolute risk by age 80 (p-value 8E-37) (*CHEK2* breast cancer Case Control Consortium, 2004; Easton, 2015; Kilpivaara, 2004; Meijers-Heijboer, 2002; Weischer, 2012). The most recently published study providing a risk estimate for *CHEK2* mutations predicted an odds ratio of 2.38 (p-value 3.66E-52) (LaDuca, 2020).

Data shows that breast cancer risks are similar between founder mutation carriers, such as c.1100delC, p.S428F, c.444+1G>A etc., and non-founder mutation carriers (Leedom, 2016). One should note, however, that location and type of variant may affect the lifetime risk provided to a patient. For instance, a *CHEK2* missense variant, p.Ile157Thr, is associated with a lower breast cancer risk than the well-characterized c.1100delC variant, which is a truncating variant (Kilpivaara, 2004). This generalization is confounded by the fact that missense variants in highly conserved functional domains are likely to be associated with disease risk versus missense variants occurring in different, less evolutionarily conserved regions of the genes (Calvez-Kem, 2011). The NCCN Guidelines® for *CHEK2* are “based only on frameshift pathogenic/likely pathogenic variants”; therefore, the risks for most missense variants remain uncertain at this time with the exception of variants such as Ile157Thr, which appears to have a lower breast cancer risk (NCCN, v1.2020).

Data from multiple studies also demonstrate an increased risk for CBC among *CHEK2* 1100delC carriers, with a range of associated risks spanning from a relative risk of 2.75 to 5.74 and 10-year risks of CBC as high as 28.9% (Akdeniz, 2019; Broeks, 2004; De Bock, 2004; Kriege, 2014; Schmidt, 2007; Teoh, 2020). Another study shows no significant association between the 1100delC variant and rates of CBC (Mellemkjaer, 2008).

#### **d. NBN and breast cancer risks**

Akin to *ATM*, *NBN* was discovered to be a breast cancer susceptibility gene only after exploring its relation to an autosomal recessive genetic disease, Nijmegen Breakage Syndrome 1 (NBS1) (Huang, 2008; Seemanova, 2007; Tauchi, 2002). NBS1 is associated with short stature, progressive microcephaly, a weakened immune system, increased risks of cancer, and intellectual disabilities, among other health problems (Varon, 1993). Among the moderate

penetrance breast cancer genes, perhaps the least is known about *NBN*. Much of what is known regarding *NBN* surrounds risks associated with the c.657\_661del5 mutation, which has been observed in breast cancer, prostate cancer, medulloblastoma, and melanoma (Steffen, 2004; Ciara, 2010; Cybulski, 2004;). This specific deletion occurs in populations of Slavic descent and confers approximately a three-fold increase in breast cancer within these populations (Buslov, 2005; Gorski, 2003, 2005; Steffen, 2004, 2006).

In 2014, Damiola et al established that *NBN* is indeed an “intermediate-risk breast cancer susceptibility gene,” justifying its inclusion on cancer gene panels. Specifically, they showed that truncating variants and rare missense mutations in conserved areas of the gene confer a two to three fold increase in breast cancer risk (Damiola, 2014). Easton et al found that the protein-truncating variant of *NBN* mentioned above, c.657del5, was found frequently enough in Eastern European populations to conduct a meta-analysis of 10 case control studies. They found that truncating variants likely confer a moderate penetrance relative risk of 2.7 (p-value 5E-7) and an absolute risk of 23% by age 80 (Easton 2015; Zhang, 2013). Bogdanova et al published data on the missense variant I171V, indicating that it is likely a “low-penetrance susceptibility allele for breast cancer,” but that a specific lifetime risk could not be predicted (Bogdanova, 2008). In this vein, the NCCN acknowledges that “current data suggest that breast cancer risks are not increased for pathogenic/likely pathogenic variants other than 657del5” (NCCN, v1.2020). For variants deemed pathogenic, LaDuca et al estimate the odds ratio for breast cancer to be 1.37 (N=75818, p-value 0.0491) (LaDuca, 2020).

There are no studies providing overall risk assessments for contralateral breast cancer in women with *NBN* mutations.

### **e. PALB2 and breast cancer risks**

*PALB2*, the “partner and localizer of *BRCA2*,” was originally discovered in 2006 while looking for *BRCA2* associating complexes. It was implicated as a breast cancer susceptibility gene in 2007 when monoallelic truncation of *PALB2* was shown to increase breast cancer risks by 2.3-fold (Rahman 2007; Xia 2006). A subsequent study conducted in 2011 showed between a two and four-fold increase in breast cancer risk, moving the needle up on risk estimates but ultimately calling for further research (Casadei, 2011). Two years later, Teo et al published their findings after analyzing Australasian families fraught with breast cancer. They concluded that about 1.5% families with multiple cases were attributable to protein truncations in *PALB2*, and supported clinical testing of *PALB2* (Teo, 2013). In the wake of the Teo et al study, Catucci et al screened 575 Italian women from families with histories of breast cancer, finding that 2.1% had *PALB2* mutations (Catucci, 2014). At that time, *PALB2* was listed as a moderate-risk gene in breast cancer (Tischkowitz, 2010; Evans, 2014).

However, given the shortage of large-scale *PALB2* mutation data generated in the aforementioned studies, Antoniou et al embarked on a prospective international study to more accurately characterize *PALB2* cancer risks. In a landmark study aiming to identify breast cancer risks based on monoallelic loss of function mutations in *PALB2*, Antoniou et al tracked 363 women with *PALB2* loss-of-function mutations from 154 families from age 20 until they were diagnosed with any cancer (primarily focusing on breast cancer), passed away, or turned 80 years old. Since this was a longitudinal study with a large, international study population, researchers were able to confirm or clarify previous estimations of cancer risk for mutation carriers. They found that breast cancer risks for *PALB2* were up to nine times higher for *PALB2* carriers younger than 40 years old, eight times as high for those between 40 and 60, and five times as

high for those over 60. Another important finding was that by age 70, female *PALB2* carriers had a 35% chance of developing breast cancer (Antoniou, 2014).

Antoniou's study is extremely valuable to consider with regards to familial risk because the best fitting model it uses to categorize risks for *PALB2* takes into consideration family history and affected first degree relatives. For instance, if a woman who tests positive for the *PALB2* mutation has no affected family members, her risk for breast cancer by age 70 is 33%; however, a woman who tests positive for *PALB2* and has two first-degree relatives with breast cancer diagnosed by age 50 is at a 58% risk for developing breast cancer. These family factors should be considered with respect to medical decision making for women who have either affected family members, known *PALB2* mutations, or both.

Antoniou's study is the gold standard for understanding risks for this population, but it was based on a specific group of those receiving diagnoses between 1930 and 2014, and the disparities of risk ratios based on which decade a woman was born are cause for skepticism—if their findings are correct, a woman's risk factor if she was born in 1960 is 6.3 times as high than if she was born in 1940. After this critique, Antoniou et al acknowledged that their risk estimations could not be directly applied to patients (2014) seen in the clinic, pointing to the wide confidence intervals. The data collected for certain populations during Antoniou's landmark study is also scant. Antoniou et al agreed that more research was needed for underrepresented populations, including those of Asian ancestry (*Editorial*, Antiniou, 2014). In a subsequent study of 100 Asian women seen in a high risk breast clinic, 4% presented with *PALB2* mutations, warranting a closer look at this high frequency mutation in this population (Sopik, 2014). Contrary to Narod et al, Phuah et al had previously demonstrated that *PALB2* mutations are rare in multi-ethnic Asian populations and are not always associated with a family

history of breast cancer (Phuah, 2013). Most recently, a study of 7051 Japanese women with breast cancer and 11,241 controls identified a significant contribution to breast cancer risk from *PALB2* in agreement with previously reported risks. In consideration of Phuah et al, Momozawa et al confirm *PALB2*'s role as a major hereditary breast cancer gene in Japanese women (Momozawa, 2018). Lower risks for a Finnish founder variant, c.1592delT have been demonstrated with case-control studies (Errko, 2007; Heikkinen, 2009). Yang et al also take into consideration 524 families with *PALB2* mutations from 21 countries, providing country specific relative risks which are explained below (Yang, 2019).

Both reviews and subsequent studies since Antoniou's pivotal publication support the fact that Antoniou's study is successful in determining breast cancer risks for women who have mutations in *PALB2*, though newer studies report slightly different risks (Wesola, 2017; Easton, 2015; Yang, 2019). Easton et al conducted a meta-analysis to estimate the combined relative risk which was found to be 5.3 (CI=90%, 3.0 to 9.4) and a 45% absolute risk by age 80; therefore, "*PALB2* mutations may fall into the high-risk category" which is defined as greater than or equal to four times the general population risk (Easton, 2015). There have been two studies published in 2020 that estimate the breast cancer risk for women with *PALB2* mutations. LaDuca et al determined the odds ratio for *PALB2* carriers as 5.1 (N=83862, p-value 1.89E-57). Yang et al report the relative risk for breast cancer to be 7.18 (95% CI, 5.82 to 8.85; p-value=6.5E-76), and to be declining with age with an estimated risk of 53% at age 80 for *PALB2* carriers (Yang, 2019).

Antoniou's study in 2014 became the impetus for researchers to investigate the frequency of *PALB2* mutations across geographical locations and within subpopulations. In the Czech Republic, the frequency of *PALB2* is high, up to 5.5% in a subgroup of hereditary breast cancer

patients (Janatova, 2016). Recurrent germline *PALB2* mutations were found also in 7/460 (1.5%) of Polish women studied with breast cancer (Kluska, 2017). Notably, and as expanded upon below, these were recurrent mutations in the population which have the potential to be linked by origin. Finally, in Jamaica, which has the highest breast cancer rates in the Caribbean, 8 of 179 (4.5%) breast cancer patients had a mutation in *BRCA1* (1), *BRCA2* (2) or *PALB2* (5) (Lerner-Ellis, 2017).

*PALB2* founder mutations have been identified in Finnish and French-Canadian populations. In Finland, the mutation discovered in approximately 1% of women with breast cancer irrespective of family history conferred a six times higher risk of breast cancer, approaching that of *BRCA2* for the same population (Errko, 2007). Additionally, researchers discovered a founder mutation in about 0.5% of French-Canadian women with frequencies of up to 2.7% in women with early onset breast cancer who are also irrespective of family history. Breast cancer risk for this mutation was approximately 40% by age 70, and the researchers leading this study suggested that the highly penetrant *PALB2* be added to breast cancer genetic testing panels (Foulkes 2007). Identical mutations found in certain populations and traced back also allow researchers to identify the origin on mutations. Such is the case for a common *PALB2* mutation found in Polish families, suggesting that this particular mutation has origins in central Europe (Dansonka-Mieszkowska, 2010).

The *PALB2* carrier frequency is estimated to be 0.08%, resulting in the estimation that 2.4% of all familial aggregation is due to these loss-of-function mutations (Antoniou, 2014). Accounting for all studies published until 2017, the occurrence rate of *PALB2* mutation ranges in the population from 0.1% to 1.5% (Wesola, 2017). Clearly, both the frequency of *PALB2*

mutations and its penetrance for cancer vary widely between populations and researchers present consistently similar, but not always congruent, frequency and risk data for *PALB2* mutations.

There is currently no published literature on CBC risks in *PALB2* carriers who have been diagnosed with breast cancer (Teoh, 2020; Song, 2018).

#### **F. Management of Moderate Penetrance Gene Carriers**

Similar to the management of *BRCA1/2*, management of moderate penetrance genes begins once a germline mutation has been identified in one of the moderate penetrance genes. The NCCN Guidelines® recommend that female carriers of *ATM*, *CHEK2*, and *NBN* undergo annual mammogram and consider breast MRI starting at age 40. Evidence for recommendations regarding RRM is insufficient, so the guidelines recommend to manage “based on family history.” In other words, there currently exists insufficient evidence to provide guidance for risk reducing mastectomies for these moderate penetrance genes. Interestingly, at the outset of this study in 2019, the NCCN management recommendations (v.3.2019) for *PALB2* were the same as *ATM*, *CHEK2*, and *NBN*, but recent publications offering a substantially higher lifetime risk for breast cancer in *PALB2* carriers has shifted the suggested management. Specifically, guidance shifted from “RRM: Evidence insufficient, manage based on family history” in 2019 to “RRM: discuss option of risk-reducing mastectomy” in 2020 (v.1.2020). Based on large epidemiologic studies, the NCCN Guidelines® acknowledge that in general the value of RRM in women with mutations in genes associated with a greater than two-fold risk without a significant family history of breast cancer is unknown.

Management surrounding the treatment of women who have been diagnosed with cancer and harbor a moderate penetrance mutation is evolving and can be gene specific. For example, there was prior controversy as to whether women who have *ATM* mutations should receive



radiation therapy given associated ionizing radiation sensitivity, but recent studies indicate that decisions about radiation or systemic therapy should not be influenced by *ATM* carrier status (Jerzak, 2018). Another example is the use of PARP inhibitors as systemic therapy for certain gene mutation carriers. PARP inhibition has proven effective for eligible *BRCA1/2* mutation carriers, but remains experimental for women harboring *PALB2* mutations, which are involved in the same double strand break pathway as *BRCA1/2*, as well as both *ATM* and *NBN* mutation carriers (Macedo, 2019; Nielsen, 2016). Treatment considerations outside the scope of surgical approach are not fully considered in the current study. Gene-dependent management is further complicated by genotype-phenotype correlations of risk. For example, *CHEK2* missense variants are not well-characterized so the NCCN Guidelines® suggest to manage patients “based on best estimates of cancer risk for the specific pathogenic/likely pathogenic variant” (NCCN, 2020).

### **G. Decision Making Overview**

For the purposes of this manuscript, we make the distinction between two groups in decision-making: those who have been diagnosed with breast cancer and those who have not. Those who have not been diagnosed with breast cancer must make a decision about RRM given what they know about their own risks. Similarly, women diagnosed with breast cancer are faced with a decision to undergo CPM in addition to surgical management for the affected breast bearing in mind their risks. For both groups, a high-quality decision is one that is fully informed and aligned with one’s principles (Sepucha, 2004). Women who have higher perceived risks are more likely to undergo RRM, though all determinants of perceived risks are not well known (Haroun, 2011; Hartmann, 2016; Meiser, 2003). The nexus of decision making is largely shaped by personal experiences which dominate analytic decision making. Diverse psychological,

social, and emotional factors complicate comprehension of genetic information (Heiniger, 2015; Hesse-Biber, 2016). Our study highlights what is known primarily about four surgical decision-making elements: lifetime risk, family history, age, and marital status.

## **H. Decision Making for Women Without Breast Cancer**

### **a. Overview**

Most of the literature regarding surgical decision making for gene mutation carriers is based on women who have been diagnosed with breast cancer. This imbalance in knowledge regarding surgical decision-making for unaffected women is more pronounced for moderate penetrance genes since there is currently much less published literature on these carriers as compared to *BRCA1/2* carriers. A study published in February of 2020 by Napoli et al explores surgical decisions among women with mutations in moderate penetrance breast cancer genes, but of the 16 women included, just four were unaffected with breast cancer (Napoli, 2020). Nonetheless, the study is unprecedented and sheds an important light upon themes of robust decision making that vary between women with moderate penetrance mutations who are both unaffected and affected with breast cancer. This study by Napoli et al included semi-structured, qualitative interviews to determine decisional influences and themes among women with *ATM*, *CHEK2*, and *PALB2* mutations, and offers unique patient perspectives. Two out of the four women without breast cancer chose to have RRM. For all four unaffected patients, decision-making themes emerging from the semi-structured interviews included family history, physician opinions, risk perception, sibling influence, and health insurance. The authors of this study explain that presence of children or grandchildren was also a distinctive factor for how women decided to manage their risks, which conforms with other published literature (Stuckey, 2010;

Friebel, 2007; Skytte, 2010; Litton, 2009; Julian-Reynier, 2000; Napoli, 2020). RRM for unaffected *BRCA1/2* carriers is dependent on an array of factors including country of origin and when a woman received genetic testing, among the many other factors mentioned above, which do not amount to an exhaustive list, nor provide evidence that the factors mentioned above are unequivocal in their influence (Henry, 2019; Metcalfe, 2008, 2009, 2019; Evans, 2019).

### **b. Family History as an Influence for Unaffected Women**

Processing of the cancer experiences of relatives may influence surgical decision-making for an unaffected woman. The degree to which a woman “personally lived” the cancer experience of a relative is based on the amount of sharing of the cancer experience (e.g. closeness of woman and relative, developmental stage of women, and number/type of competing pressures), phase and variability of illness trajectory (emotional and social adjustments), and extent to which suffering was witnessed (Thomson, 1996).

A family history of breast cancer is one of the strongest predictors breast cancer risk; however, women with *BRCA1/2* mutations and a negative family history are still at a considerable lifetime risk for breast cancer: 60% by age 80, versus 63% for those with a family history of breast cancer (Pharoah, 1997; Metcalf, 2017). A study conducted by Singh et al on unaffected women at the same teaching hospital as this study population assessed rates of RRM among 136 women with *BRCA1/2* mutations. There was a significant uptake of RRM for women with more total first and second-degree relatives who have been affected and who have died from breast cancer (Singh, 2013). If, for instance, a woman has a mother who passed away from breast cancer at a young age, she may request RRM at a younger age than is medically recommended. A family history significant for a first degree relative with breast cancer as well as higher total number of relatives with breast cancer have been associated with a higher

likelihood of choosing RRM versus surveillance (Henry, 2019). It's worth noting that there's the potential for these family factors to work in the opposite way as well—women who carry a deleterious mutation with little to no family history of breast cancer may perceive their risk as being lower than it actually is.

### **c. Age as an Influence for Unaffected Women**

In general, unaffected younger women are more likely to undergo RRM than unaffected older women, which seems logical given that they have more of a risk to live through (Evans, 2009, 2019; Hoskins, 2012; Metcalfe, 2008, 2019). One of the largest studies of *BRCA1/2* carriers found that 950 out of 3413 (27.8%) women without breast cancer had a RRM: the mean age was 41.8 and just 3.4% of mastectomies among this population were performed at age 60 and above (Metcalfe, 2019). Perhaps a more relevant finding to this current study would be that 3515 women including both those who were at a greater than 25% lifetime risk without known mutations and *BRCA1/2* mutation carriers were assessed for RRM, and uptake was significantly related to younger age regardless of which group they were a part of (Evans, 2009).

### **d. Marital Status as an Influence for Unaffected Women**

Although studies have assessed whether marital status influences surgical decision-making for RRM, there has been no evidence to support that marital status significantly influences these decisions for unaffected women (Henry, 2019).

### **e. Lifetime Risk as an Influence for Unaffected Women**

There is also limited information surrounding whether lifetime risk alone influences surgical decision-making for unaffected women. The best comparisons can only be made between rates of two major groups of unaffected women that have been studied: *BRCA1/2* mutation carriers and those with no known mutations. In the United States, approximately 20% of *BRCA1/2* carriers without breast cancer opt for RRM (Domchek, 2010; Printz, 2011). In women who harbored no known mutation, 6.4% of women estimated at a 40-45% lifetime risk, 2.5% of women estimated at 33-39% lifetime risk, and 1.8% of women at 25-32% lifetime risk elected for RRM ( $p\text{-value}=\leq 0.005$ ). Lifetime risks for this study were estimated similarly to our study, with the vast majority of unaffected women receiving lifetime risk estimates based on the Tyrer-Cuzick empiric risk model (Evans, 2009). The degree to which RRM reduces the risk of breast cancer differs between women with solely a positive family history of breast cancer and *BRCA1/2* carriers. RRM decreases a *BRCA1/2* carrier's lifetime risk by 90-95%, and RRM decreases the risk of breast cancer in women with solely a family history by around 80%; therefore, women with *BRCA1/2* mutations stand to benefit from a larger net risk reduction with a RRM (Metcalf, 2008; Hartmann, 1999, 2001).

## **I. Decision Making: CPMs for Breast Cancer Patients**

### **a. Overview**

Decision-making for patients became a focus in the 1980s, and subsequent legislation required "full disclosure of surgical options" for breast cancer patients. Since the 1980s, rates of mastectomy have sharply dropped from nearly 100 percent to about one-third for breast cancer patients today (Lerner, 2001; Lantz, 2002). The mortality for those choosing unilateral mastectomy versus breast conserving lumpectomy is equivalent (Habermann, 2010). Tumor

staging and location may hinder the use of breast conservation approaches, but most women remain candidates for Breast Conserving Surgery (BCS) (Morrow, 1998). Moreover, results from multiple studies suggest that there may be better quality-of-life outcomes, including positive body image, for women who choose lumpectomy versus unilateral mastectomy (de Haes, 2003).

Patients overestimate their risks of CBC and the degree of risk reduction attained by CPM (Ager, 2016). With a substantial amount (43.9%) of women diagnosed with breast cancer considering CPM, it's alarming that just 38.1% were aware that CPM does not improve overall survival (Jagsi, 2017). One study demonstrated that just 16% of breast cancer patients know that recurrence rates were not equivalent between mastectomy and lumpectomy and only 48% understood that the survival rates were equivalent between mastectomy and breast conservation surgery (BCS) with radiation (Fagerlin, 2006). Women with stage I and stage II breast cancer were studied, and overall women preferred a collaborative and active role over a passive role in decision-making for their treatment (Katz, 2007). Most women (88.1%) were pleased with their cancer treatment choice (Sabo, 2006). Nonetheless, the majority of patients frequently make decisions regarding surgery without accurate knowledge of the risks and benefits involved, which suggests that often times high-quality decisions are not being made with regards to surgery (Fagerlin, 2006). Luckily, most women are pleased with their selection of CPM; however, dissatisfaction with body appearance, femininity, and sexual relationships may be observed in some patients (Frost, 2005).

Women opt for bilateral mastectomy based on a desire to avoid radiation, on how aggressive their disease is, on decreased need for surveillance, and on the fear of contralateral breast cancer or disease recurrence (Haberman, 2010; Rodby, 2016). Rates of unilateral mastectomies and CPMs have changed through time and have been shown to differ between regions and between

patients of different races, socioeconomic classes, smoking history, marital status, residence type, cancer stage and grade, and with different insurance coverage (Dores, 2010; Yakoub, 2014; Bhat, 2017; Metcalfe, 2019). Published data are not congruent on associations between these factors and decision-making, and there remains some uncertainty as to the factors that most influence decision making for breast cancer patients with regards to surgery. For example, Bhat et al analyzed bilateral mastectomy decisions for patients with unilateral breast cancer based on an array of factors including patient's age, insurance status, urban versus rural residence, subsequent reconstruction, marital status, smoking history, family history of cancer, and cancer stage and grade. Patients who were less than 50, who had private insurance, who had residence in urban settings, and who planned for subsequent reconstruction were all more likely to undergo bilateral mastectomy versus unilateral mastectomy (Bhat, 2017). Another study observing rates of mastectomies from 1998 to 2013 found a six-fold increase in that time period. It was also found that rates of CPM positively correlated with younger, white, married, metropolitan, college educated and wealthier patients, while also finding, on the contrary, no correlation of CPMs with pathological characteristics including tumor stage and grade (You, 2018). A comprehensive literature review performed by Teoh et al indicates that CPM decision is based largely on a age, stage of disease, whether she has a genetic predisposition, whether family members have been diagnosed with breast cancer, fear of disease recurrence, desire for breast symmetry, and physician recommendations (Teoh, 2020; Bhat, 2017; Arrington, 2009; Buchanan, 2016; Brewster, 2011; Chung, 2012). Patients' propensity to pursue mastectomies probably reflects uncertainty about the cancer they face and the treatment's influence on their survival and well-being (Katz, 2007). Those who are offered radiation or who are concerned about recurrence, for example, elect to undergo mastectomy more often (Sepucha, 2007).

In the aforementioned study conducted by Napoli et al exploring decision making among women with moderate penetrance gene mutations, four of twelve women with a personal history of breast cancer chose to have a RRM. Robust themes surrounding decision making for all breast cancer patients in this study included physician options, autonomy, sibling influence, family history, whether the woman had a breast cancer diagnosis, and perceived risk. Once again, our study highlights what is known primarily about four surgical decision-making elements: lifetime risk, family history, age, and marital status.

**b. Lifetime Risk as an Influence for Breast Cancer Patients**

As with unaffected women, presented lifetime risk for breast cancer patients has not been shown to play a significant role in a patient's likelihood of pursuing RRM and reconstruction.

**c. Family History as an Influence for Breast Cancer Patients**

Family history can influence surgical choice for breast cancer patients. *BRCA1/2* mutation carriers with a first-degree relative diagnosed with breast or ovarian cancer are more likely to undergo RRM (Singh, 2013; Mæland, 2014). Furthermore, breast cancer patients who have had relatives with breast cancer are more likely to undergo CPM rather than BCS (Metcalf, 2008; Haroun, 2011; Metcalfe, 2009). Other published research, on the contrary, did not find that family cancer history influenced decision making for unilateral versus bilateral mastectomy for breast cancer patients (Bhat, 2017).

**d. Age as an Influence for Breast Cancer Patients**

Patient age has been implicated as an independent predictor of surgical approach for breast cancer patients, though there exists discordance between studies. Some suggest that older patients trend towards undergoing RRM versus BCS (Chagpar, 2006; Lazovich, 1999; Nold, 2000; Newcomb, 1993; Ward, 1989). In contrast, other studies show high rates of BCS in



patients in their 80s, an uptake of RRM in women younger than 50, and still others found no statistically meaningful difference in age influencing BCS versus RRM (Rodby, 2016; Ballard-Barbash, 1996; Bhat, 2017; Chapgar, 2006; Hussien, 2003; Hoskins, 2012).

Age-specific breast cancer risk varies by gene, and thus the timing of preventative surgery should be discussed among women contemplating a RRM. For example, a RRM at age 25 increased the probability of being alive at age 80 by 8.7% (from 42.7 to 51.3%) versus 2.8% at age 50 (from 42.7 to 45.5%) for *BRCA1/2* mutation carriers. The consideration of RRM may therefore look much different for a *BRCA1/2* carrier younger than 50, who stands to maximize risk-reduction benefits, versus a woman over age 50 (Giannakeas, 2018).

Studies also suggest that age-related factors influence treatment plans for breast cancer patients, which influences the likelihood of pursuing RRM (Rodby, 2016). For example, age at diagnosis is an important consideration in disease feature and treatment—younger women typically present with more aggressive breast cancers which require chemotherapy and radiation—as well as surgical approach. Advances in radiation techniques may also factor into whether elderly patients are able to receive adjuvant radiation therapy, and therefore may impact decision making for BCS (Chapgar, 2006).

Furthermore, age-dependent body habitus and breast shape factor into a woman's decision to pursue RRM and reconstruction. Studies have suggested that older patients are less worried about cosmetic outcome and choose mastectomy versus BCS more often than younger patients who may have anatomical concerns such as desired breast shape, availability of tissue, and potential need for additional surgeries to achieve breast symmetry (Nold, 2000; Degner, 1997).

### **e. Marital Status as an Influence for Breast Cancer Patients**

There are conflicting data on whether marital status of a woman influences her likelihood of undergoing a RRM, and Bhat et al did not find that marital status had a statistically significant impact on decision-making for unilateral versus bilateral mastectomies for breast cancers; however, other studies have shown increasing trends of CPM associated with married women (Bhat, 2017; You, 2018; Howard-McNatt, 2011). Napoli et al also describe that partners may have a greater influence for women affected with breast cancer due to the support they provide during the diagnosis process (Napoli, 2020). Marital status has been associated with decision-making regarding breast reconstruction, with more women with relationship support of a marriage or partner undergoing reconstruction after mastectomy than women who were separated, single, or widowed. This study indicates only that relationship factors may influence decision making regarding post-surgery decisions, but does not verify anything about pre-surgery decision making. However, it is important to consider support networks of patients with and without breast cancer in tailoring preoperative counseling (Sergesketter, 2019).

### **J. Objectives and Hypotheses**

The primary research objective of this study is to determine whether women with moderate penetrance gene mutations are influenced by their family history of breast cancer in their decision-making to undergo RRM. Our hypothesis is that women who have more first, second, and third degree relatives with breast cancer are more likely to undergo RRM across all risk stratified groups. Secondary research objectives include assessing whether presented lifetime risk of breast cancer, age, and marital status predict the likelihood of undergoing RRM across all three groups. We hypothesize that women presented with higher lifetime risks, younger women, and women in relationships are more likely to undergo RRMs.

## MATERIALS AND METHODS

### A. Study Population

See Table 1: *Summary of Patient Demography by RRM Status*

After receiving approval from the CS-Investigational Review Board, we performed retrospective chart review of electronic medical records on a master list of patients seen through cancer genetics at an academic teaching hospital with genetic test results reported 6/1/2009 through 6/1/2019. Data on each subject was collected at the time of her genetic test result.

Eligible subjects include females at least 18 years of age with an available pedigree or family history on file, a documented management plan or surgical decision, and a known mutation status before any surgical decisions were made. Both breast cancer patients and women unaffected with breast cancer were included in this study population.

Subjects with prior breast surgery before receiving genetic testing results, an unknown family history, stage 4 breast cancer, being actively treated for other cancers, or with breast cancer gene mutations other than those defining their study arm were excluded from eligibility.

There are three arms of this study, each defined by cancer gene mutation status: moderate penetrance, high penetrance, and no known mutation. Those in moderate penetrance and high penetrance arms must have pathogenic variants or likely pathogenic variants, referred to as mutations in this paper, in the genes that define each arm as listed below. Only reports from Clinical Laboratory Improvement Amendments (CLIA) certified laboratories were included for entry into this study.

The moderate penetrance arm contains 90 women with *ATM*, *CHEK2*, *NBN*, and *PALB2* mutations. 35 women from this arm were diagnosed with breast cancer. The high penetrance arm contains 98 women with *BRCA1* and *BRCA2* mutations. 30 women from this arm were

diagnosed with breast cancer. The no mutation arm contains 92 women with no known mutation. 30 women in this arm were diagnosed with breast cancer.

## **B. Study Instruments**

The master list of patients seen through cancer genetics at Cedars-Sinai Medical Center with variants in a number of genes and was created and populated by the team of genetic counselors at that institution and contains medical record number, first name, last name, date of birth, date of test result, laboratory at which testing was performed, name of test/panel, test results, gene, site of mutation, whether the subject was diagnosed with cancer, and ancestry for each subject.

A Cedars-Sinai Utilization Report issued by Invitae was used to generate the no mutation status arm of this study and includes subjects who did not have a positive result on their testing panel. This report includes report release date, date of birth, requisition number, name of test/panel, ICD-10 Codes, and Cedars-Sinai genetic counselor contact for each subject at Cedars-Sinai who underwent genetic testing through Invitae. The following testing panels were included: Invitae Breast and Gyn Cancers Guidelines-Based Panel, Invitae Breast and Gyn Cancers Panel, Invitae Breast Cancer Panel, Invitae Breast Cancer STAT Panel, Invitae Common Hereditary Cancers Panel, Invitae Common Hereditary Cancers Panel (Breast, Gyn, GI), Invitae Multi-Cancer Panel.

A random integer generator through [www.random.org](http://www.random.org) allowed for collection of a systematic random selection of the positive and negative control groups.

The EPIC electronic medical record and Progeny pedigree tool were both used to locate subject data, which was abstracted and stored directly into a HIPAA-compliant REDCap electronic data portal.

### **C. Data Collection**

The moderate penetrance was principal arm of interest and guided data collection for this study. The master list of genetic test results was filtered to include pathogenic and likely pathogenic variants in the genes of interest: *ATM*, *CHEK2*, *NBN*, and *PALB2*. This yielded a list of 203 potentially eligible subjects. Each was reviewed and 90 met eligibility criteria for this study after medical chart review.

The high penetrance *BRCA1* and *BRCA2* arm was also populated using the same master list. Filtering the master list by *BRCA1* and *BRCA2* yielded a list of 300 potentially eligible subjects. A random integer generator was used to select a comparator group in a systematic random selection until 30 eligible subjects diagnosed with breast cancer and harboring *BRCA1* and *BRCA2* mutations were gathered. 68 eligible women with *BRCA1* and *BRCA2* mutations who were not diagnosed with breast cancer were accrued in the process.

The no mutation status arm was populated using the Invitae Cedars-Sinai Utilization Report. This report includes 813 potentially eligible subjects. A random integer generator was used to select a comparator group in a systematic random selection until 30 eligible subjects diagnosed with breast cancer were gathered. 62 eligible women with no mutation who were not diagnosed with breast cancer were accrued in the process.

Common reasons for ineligibility across all three arms include male sex, previous surgery, active treatment for another cancer, stage 4 breast cancer, multiple mutations, and insufficient records.

The following data was collected for each subject:

1. Demographics: age, ethnicity, race, sex, marital status
2. Mutation status: CLIA lab certified result, gene, variant information date of report
3. Breast Cancer Risk: breast cancer lifetime risk for unaffected women, age at which lifetime risk provided, method by which lifetime risk calculated.
4. Personal History: breast cancer diagnosis, age of diagnosis if diagnosed, type of breast cancer if diagnosed, stage of breast cancer if diagnosed, whether subject was diagnosed with any other type of cancer, type of other cancers if diagnosed and age at which diagnosed.
5. Family History: whether first, second, and third degree relatives were diagnosed with breast cancer, how many of each were diagnosed, relation to the subject (i.e. mother, aunt etc.), ages of diagnoses, age passed away, if applicable.
6. Surgical Decision: recommendation for surgery, reason for surgical recommendation, surgical decision, age surgical decision made, motivation for surgery
7. Previous Genetic Testing: whether subject previously underwent genetic testing, years since testing, whether subject previously underwent genetic counseling, years since genetic counseling
8. Children Status: whether the subject has children, how many children the patient has, ages of children

#### **D. Data Analysis**

Demographic categories were separated by “No RRM” and “RRM” among the study population and were compared using independent samples t-tests or chi square tests of independence, where appropriate. See Table 1.

Logistic Regression Models were run on each research question, producing odds ratios based on exposure versus outcome. The exposures retrospectively analyzed were number of 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> degree relatives with a history of breast cancer, presented lifetime risk, age, and marital status. Outcome in our model was whether the patient received a RRM or did not receive a RRM. For this study, “bilateral mastectomy” for unaffected and affected subjects was considered RRM. For affected patients, a unilateral mastectomy was not considered a RRM.

Family history was separated into 6 models, which were created based on mutation status and whether the patient had breast cancer at the time of surgical decision. Within each model odds ratios were assessed independently by degree of relative. See Table 2.

Remaining lifetime risk of breast cancer was collected solely for those women who did not have a diagnosis of breast cancer. Chart abstraction yielded percentage values for remaining lifetime risk that each patient was presented during their decision making period. When ranges were provided, the mean value of the two numbers was used. See Table 3 and 4.

The age at time of surgical decision was analyzed as an exposure. See Table 5.

Logistic regression models for marital status were conducted with “Married/Unmarried” couple as the reference group, and “Never married” and “Divorced/Separated/Widowed” as groups illustrating the effects of marital status on decision making. The rationale for combining “widowed” with the divorced/separated stems from the fact that each subject in this group once had a partner’s support and no longer have that partner’s support. See Table 6.

## RESULTS

### A. Patient Demographics

Patient demographics are listed in Table 1. The groups comprising the risk stratified groups were fairly balanced: 32.9% had no known risk mutations, 32.1% had moderate penetrance gene mutations, and 35% had *BRCA* mutations. Most of the subjects included in this study were non-Hispanic, white (78.1%). The average age at which surgical decision was made was 45.7 years. For patients who were diagnosed with breast cancer, most were diagnosed with IDC (70.5%) and most were either stage 1 or 2 breast cancer (77.9%). Most patients in this study did not have previous genetic counseling (97.4%) or genetic testing (93.5%). Documented surgical decisions vary between women with and without breast cancer and are shown in Figure 1 and Figure 2.

The average number of first, second, and third degree relatives with breast cancer was not shown to independently influence surgical decision making for this study population.

There were statistically significant differences between RRM and no RRM for the following categories: age of diagnosis, marital status, mutation status, and whether a patient was diagnosed with breast cancer.

For breast cancer patients, women who underwent RRM were on average 13.2 years younger at age of diagnosis than those who didn't undergo RRM (45.7 vs 58.9).

Women who have never been married underwent RRM less often than the other two marital status groups. 15.9% (14/88) of women who were never married underwent RRM, while 31.1% (53/170) of women who were either married or in a relationship underwent RRM. 31.8% (7/22) who were either divorced, separated, or widowed underwent RRM, but the sample size for this group was relatively small compared to the other two groups.



For both women with and without breast cancer, rates of RRM increased with mutation status stratification. 8.6% (8/92) of women with no known risk mutations, 30% (27/90) of moderate penetrance gene carriers, and 39.8% (39/98) of *BRCA* mutation carriers underwent RRM.

Finally, rates of RRM were higher among women who were diagnosed with breast cancer. 56.8% (54/95) of women with breast cancer underwent RRM while 10.8% (20/185) of women who were unaffected underwent RRM. The breakdown of mutation status stratification among these women with breast cancer is demonstrated in Figure 2.

Table 1

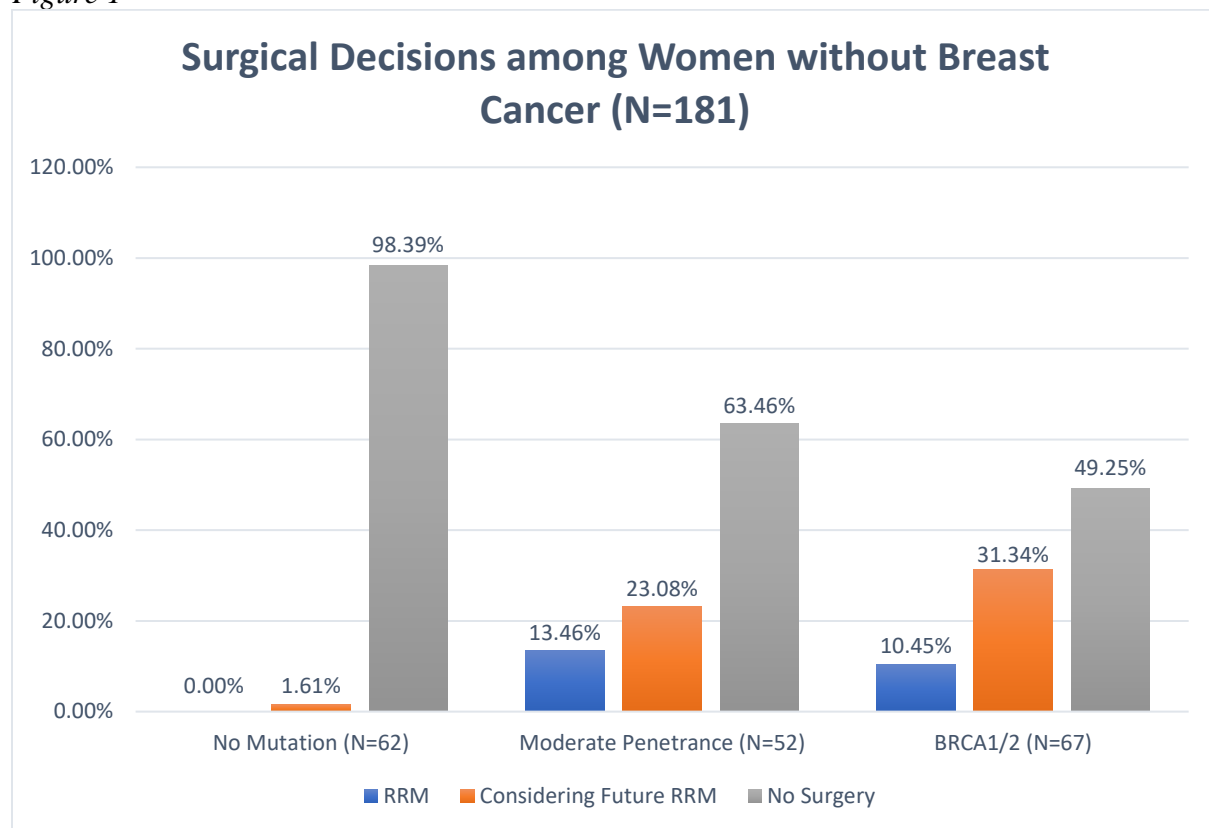
Summary of Patient Demography by RRM Status (n = 7 - 279)

Demographics	Overall		No RRM		RRM		p*
	M (SD)	Freq (%)	M (SD)	Freq (%)	M (SD)	Freq (%)	
Age Surgical Decision Made	45.7 (14.6)		45.8 (16.0)		45.2 (10.0)		.71
Age Dx (if applicable)	51.4 (12.8)		58.9 (12.9)		45.7 (9.3)		< .001
Race/Ethnicity							.87
Asian/API		21 (7.5)		13 (61.9)		7 (33.3)	
Black/African American		12 (4.3)		9 (75)		3 (25)	
White, Hispanic		9 (3.2)		6 (66.7)		3 (33.3)	
White, Non-Hispanic Latino		218 (78.1)		57 (26.1)		161 (73.9)	
Other		19 (6.8)		15 (78.9)		4 (21.1)	
Marital Status							.02
Never Married		88 (31.4)		74 (84.1)		14 (15.9)	
Married/Unmarried Couple		170 (60.7)		117 (68.8)		53 (31.2)	
Divorced/Separated/Widowed		22 (7.9)		14 (63.6)		7 (31.8)	
Mutation Status							< .001
No known risk mutations		92 (32.9)		84 (91.3)		8 (8.7)	
Moderate penetrance (ATM, CHEK2, NBN, PALB2)		90 (32.1)		63 (70)		27 (30)	
BRCA1/2		98 (35.0)		58 (59.2)		39 (39.8)	
Diagnosed with breast cancer							< .001
Yes		95 (33.9)		41 (43.2)		54 (56.8)	
No		185 (66.1)		164 (88.6)		20 (10.8)	
Breast Cancer Type							.24
Mixed DCIS and IDC		5 (5.3)		1 (20)		4 (80)	
DCIS		15 (15.8)		8 (53.3)		7 (46.7)	
IDC		67 (70.5)		26 (38.8)		41 (61.2)	
ILC		4 (4.2)		3 (75)		1 (25)	
Other		4 (4.2)		3 (75)		1 (25)	
Stage of Breast Cancer							.38
0		15 (15.8)		8 (53.3)		7 (46.7)	
1		39 (41.1)		17 (43.6)		22 (56.4)	
2		35 (36.8)		12 (34.3)		23 (65.7)	
3		6 (6.3)		4 (66.7)		2 (33.3)	
Number of Relatives with Breast Cancer							
1 <sup>st</sup> Degree	1.2 (0.5)		1.2 (0.5)		1.3 (0.6)		.43
2 <sup>nd</sup> Degree	2.2 (5.6)		2.0 (4.6)		2.9 (7.7)		.39
3 <sup>rd</sup> Degree	1.4 (0.8)		1.4 (0.7)		1.5 (0.9)		.45
Previously Received Genetic Counseling							.30
Yes		7 (2.6)		4 (57.1)		3 (42.9)	
No		263 (97.4)		195 (74.1)		67 (25.5)	
If yes, years since	0.03 (0.2)		5.8 (2.2)		4.3 (5.8)		.67
Previously Received Genetic Testing							.22
Yes		18 (6.5)		11 (61.1)		7 (38.9)	
No		261 (93.5)		193 (73.9)		67 (25.7)	
If yes, years since	7.7 (4.7)		8.8 (5.0)		6.0 (4.1)		.33

\* Comparisons between “No RRM” and “RRM” using independent samples t-tests or chi square tests of independence, where appropriate.

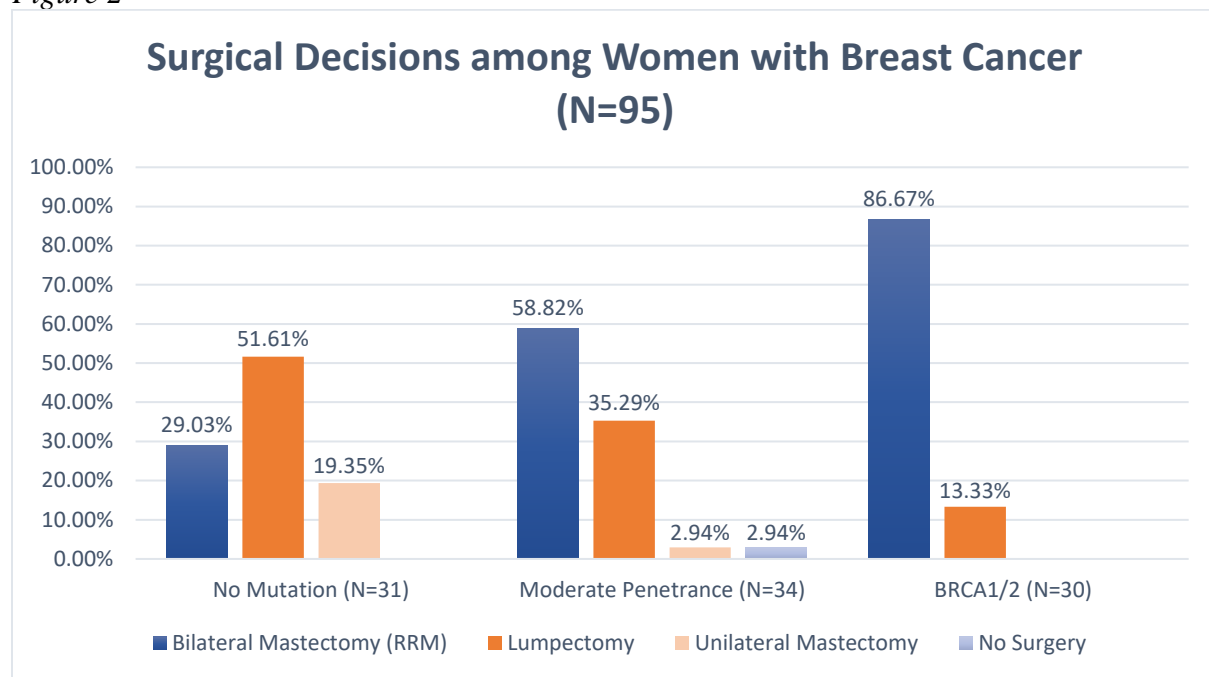
One participant’s RRM status was listed as “unknown” and was excluded from the “No RRM” and “RRM” columns

Figure 1



*Surgical Decisions among Women without Breast Cancer:* For the no mutation group, one subject (1/62; 1.61% stated that she was considering a future RRM and 98.39% (61/62) decided against RRM. For the moderate penetrance arm, 13.46% (7/52) received a RRM, 23.08% (12/52) were considering a future RRM, and 63.46% (33/52) elected to not undergo RRM. Finally, for the *BRCA1/2* group 10.45% (7/67) underwent RRM, 31.34% (21/67) indicated that they were considering a RRM in the future, and 49.25% (33/67) decided against RRM. Subjects whose surgical decision was listed as “other” (N=3) and whose surgical decision was unknown (N=1) are excluded from this figure.

Figure 2



*Surgical Decisions among Women with Breast Cancer:* For the no mutation group, 29.03% (9/31) elected for bilateral mastectomy, 51.61% (16/31) elected for lumpectomy, and 19.35% (6/31) elected for a unilateral mastectomy. For the moderate penetrance group, 58.82% (20/34) underwent bilateral mastectomy, 35.29% (12/34) received a lumpectomy, one (2.94%) received a unilateral mastectomy, and of note, there was one breast cancer patient who declined surgical treatment. For the *BRCA1/2* group, 86.67% (26/30) elected to undergo bilateral mastectomy and 13.33% (4/30) received a lumpectomy. One patient whose surgical decision was listed as “Considering future mastectomy” was excluded from this figure.

## B. Family History and RRM Odds Ratios

A series of multiple logistic regression models were conducted in order to determine whether the number of first, second, and third degree relatives with a history of breast cancer influences the odds of undergoing a RRM 1) among patients with mutations in *BRCA1/2*, 2) among patients with the moderate penetrance genes (*ATM*, *CHEK2*, *NBN*, and *PALB2*), and 3) among patients

with no known mutation. Whether or not the patient had breast cancer was also taken into account. As shown in Table 2, the number of relatives with a history of breast cancer served as a statistically significant predictor of undergoing RRM in just a single model (see Model 3;  $\chi^2_{(3)} = 25.30, p < .001$ , Nagelkerke's  $R^2 = .69$ , Cox & Snell  $R^2 = .37$ ). Specifically, among patients without breast cancer who tested positive for a mutation in moderately penetrant genes (*ATM*, *CHEK2*, *NBN*, or *PALB2*), the odds of undergoing RRM increased over a hundredfold per first degree relative with a history of breast cancer.

Table 2

Summary of Logistic Regression Models of Number of 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> Degree Relatives with History of Breast Cancer on Odds of Undergoing RRM ( $n = 30, 55, 35, 67, 30$ )

Variable	<i>B</i>	<i>SE B</i>	Exp ( <i>B</i> )	<i>p</i>
<b>Model 1: No breast cancer; no known mutations</b>				
Model could not be run; RRM is a constant (i.e. no subjects underwent RRM)				
<b>Model 2: Breast cancer; no known mutations</b>				
Constant	-1.30	0.67	0.27	
1 <sup>st</sup> Degree Relatives with History of BC	-0.001	0.68	1.00	.99
2 <sup>nd</sup> Degree Relatives with History of BC	-0.06	0.54	0.94	.91
3 <sup>rd</sup> Degree Relatives with History of BC	1.33	0.99	3.79	.18
<b>Model 3: No breast cancer; moderate penetrance genes (ATM, CHEK2, NBN, and PALB2)</b>				
Constant	-9.37	3.52	0.00	
1 <sup>st</sup> Degree Relatives with History of BC	4.65	2.10	104.82	.03
2 <sup>nd</sup> Degree Relatives with History of BC	2.00	1.20	7.37	.10
3 <sup>rd</sup> Degree Relatives with History of BC	0.91	0.72	2.47	.21
<b>Model 4: Breast cancer; moderate penetrance genes (ATM, CHEK2, NBN, and PALB2)</b>				
Constant	0.003	0.50	1.00	
1 <sup>st</sup> Degree Relatives with History of BC	-0.46	0.93	0.63	.62
2 <sup>nd</sup> Degree Relatives with History of BC	1.02	0.56	2.77	.07
3 <sup>rd</sup> Degree Relatives with History of BC	-0.68	0.56	0.51	.22
<b>Model 5: No breast cancer; BRCA 1/2</b>				
Constant	-1.82	0.59	0.16	
1 <sup>st</sup> Degree Relatives with History of BC	0.67	0.39	1.95	.09
2 <sup>nd</sup> Degree Relatives with History of BC	-0.31	0.39	0.74	.43
3 <sup>rd</sup> Degree Relatives with History of BC	0.37	0.49	1.44	.35
<b>Model 6: Breast cancer; BRCA 1/2<sup>a</sup></b>				
Constant	1.74	0.68	5.68	
1 <sup>st</sup> Degree Relatives with History of BC	-0.19	1.29	0.83	.88
2 <sup>nd</sup> Degree Relatives with History of BC	0.25	0.66	1.28	.71

Overall model statistics, Model 2:  $C^2_{(3)} = 1.93$ ,  $p = .59$ , Nagelkerke's  $R^2 = .09$ , Cox & Snell  $R^2 = .06$

Overall model statistics, Model 3:  $C^2_{(3)} = 25.30$ ,  $p < .001$ , Nagelkerke's  $R^2 = .69$ , Cox & Snell  $R^2 = .37$

Overall model statistics, Model 4:  $C^2_{(3)} = 5.28$ ,  $p = .15$ , Nagelkerke's  $R^2 = .18$ , Cox & Snell  $R^2 = .14$

Overall model statistics, Model 5:  $C^2_{(3)} = 5.05$ ,  $p = .17$ , Nagelkerke's  $R^2 = .12$ , Cox & Snell  $R^2 = .07$

Overall model statistics, Model 6:  $C^2_{(2)} = 0.44$ ,  $p = .80$ , Nagelkerke's  $R^2 = .03$ , Cox & Snell  $R^2 = .02$

<sup>a</sup> Note: Due to a radically inflated SE and Exp (*B*) attributable to limited sample size, 3<sup>rd</sup> degree relatives were omitted from Model 6

### C. Lifetime Risks and RRM Odds Ratio

In order to determine whether lifetime risk of breast cancer estimates influence the odds of undergoing a RRM among patients without breast cancer, a simple logistic regression model was run. As shown in Table 3, lifetime risk of breast cancer estimates did serve as a statistically significant predictor of the odds of undergoing RRM ( $\chi^2_{(1)} = 7.94, p = .005$ ), with the odds of undergoing a RRM increasing 1.03 times per percentage point of lifetime risk. While the results were statistically significant, lifetime risk of breast cancer estimates were modest predictors of patients' actual behaviors, explaining only approximately 5-10% of the observed variability in RRM (Nagelkerke's  $R^2 = .10$ , Cox & Snell  $R^2 = .05$ ). Average lifetime breast cancer risks and average ages at time of results disclosure are demonstrated in Table 4.

Table 3

*Summary of Logistic Regression Model of Lifetime Risk Estimate on Odds of Undergoing RRM (n = 185)*

Variable	B	SE B	Exp (B)	p
Constant	-3.57	0.67	0.03	
Lifetime Risk	0.03	0.01	1.03	.006

Overall model statistics:  $\chi^2_{(1)} = 7.94, p = .005$ , Nagelkerke's  $R^2 = .10$ , Cox & Snell  $R^2 = .05$

Table 4

*Average Presented Lifetime Breast Cancer Risks for Unaffected Women at Results Disclosure*

	No Mutation (N=39)	Moderate Penetrance (N=53)	BRCA1/2 (N=62)
Average Lifetime Risk (SD)	20.25 (7.34)	32.27 (11.70)	63.69 (17.30)
Average Age at Results Disclosure (SD)	44.21 (13.44)	44.02 (12.14)	34.66 (11.74)

#### D. Patient Age and RRM Odds Ratio

In order to determine whether age at time of surgical decision influences the odds of undergoing a RRM, a simple logistic regression model was run. As shown in Table 5, age at time of surgical decision failed to statistically significantly predict the odds of undergoing RRM ( $\chi^2_{(1)} = 0.09, p = .76$ ).

Table 5

*Summary of Logistic Regression Model of Age at Time of Surgical Decision on Odds of Undergoing RRM (n = 280)*

Variable	B	SE B	Exp (B)	p
Constant	-0.88	0.45	0.41	
Age at Time of Surgical Decision	-0.003	0.01	1.00	.76

Overall model statistics:  $C^2_{(1)} = 0.09, p = .76$ , Nagelkerke's  $R^2 < .001$ , Cox & Snell  $R^2 < .001$



### E. Marital Status and RRM Odds Ratios

In order to determine whether marital status influences the odds of undergoing a RRM, a simple logistic regression model was run. As shown in Table 6, marital status did serve as a statistically significant predictor of the odds of undergoing RRM ( $\chi^2_{(2)} = 7.96, p = .02$ ), with the odds of undergoing a RRM being 0.42 times as likely for never married patients compared to married/unmarried couples. While the results were statistically significant, marital status was a modest predictor of patients' actual behaviors, explaining only approximately 3-4% of the observed variability in RRM (Nagelkerke's  $R^2 = .04$ , Cox & Snell  $R^2 = .03$ ).

Table 6

*Summary of Logistic Regression Model Marital Status on Odds of Undergoing RRM (n = 279)*

Variable	B	SE B	Exp (B)	p
Constant	-0.79	0.17	0.45	
Never Married <sup>a</sup>	-0.87	0.34	0.42	.01
Divorced/Separated/Widowed <sup>a</sup>	0.10	0.49	1.10	.84

Overall model statistics:  $\chi^2_{(2)} = 7.96, p = .02$ , Nagelkerke's  $R^2 = .04$ , Cox & Snell  $R^2 = .03$

<sup>a</sup> Reference Category: Married/Unmarried Couple

## **DISCUSSION**

### **A. Overview**

Women who have access to genetic counselors are provided more thorough information about risk and prevention and are more supported to process information and make decisions (Padamsee, 2017; Connors, 2014). All of the women in this study had access to genetic counseling, yet women's risk perceptions differ greatly than those of healthcare providers (Salant, 2006; Hesse-Biber, 2014). Clarity on decisional facets explored in this study may assist providers in better understanding the perceived risks of their patients and ultimately facilitate informed decision making.

### **B. Family History**

Assessing RRM rates in regard to family history and in the context of gene mutation status proved valuable to draw comparison between what was observed on a study population level versus within subgroups, especially moderate penetrance gene carriers. Although potentially attributable to modest sample size in each model, the only statistically significant predictor of undergoing a RRM was the presence of affected first degree relatives, and only for unaffected moderate penetrance gene carriers. Perhaps these women, in the absence of pressure from a breast cancer diagnosis or high penetrance mutation, turn to shared experiences of their sisters or mothers in their decision-making. In other studies, presence of first degree relatives, especially sisters, as well as a higher number of total relatives with breast cancer has been shown to increase the rates of RRM among both *BRCA1/2* carriers and in a cohort combining high and moderate penetrance gene carriers (Henry, 2019; Metcalfe, 2008). This current study did not assess decision making in the context of the total number of affected relatives; however, number of first, second, and third degree relatives separately did not increase the odds of RRM for the entire study population. This study is novel in illuminating the effect of family history

independently within genetic risk stratified groups and has shown that family history influences surgical decision making for moderate penetrance gene carriers.

### C. Lifetime Risk

As predicted, lifetime risk presented to unaffected patients at time of results disclosure was a statistically significant predictor of decision to undergo RRM. Surprisingly, however, higher lifetime risks only modestly increased the odds of undergoing RRM, increasing 1.03 times per percentage point and thus explaining only 5-10% of variability in RRM. This may explain why there were similar rates in RRM between unaffected moderate penetrance carriers and unaffected *BRCA1/2* carriers in this cohort. It may also explain the similar rates of women considering future RRM between the same two groups. For unaffected women in this study, the average presented lifetime risk was 20.25% for no mutation carriers, 32.27% for moderate penetrance carriers, and 63.69% for *BRCA1/2* carriers. The American Cancer Society recommends that all women with a greater than 20% lifetime risk of breast cancer undergo a breast mammogram and a breast MRI every year. Average lifetime risks for each of these groups cross this “high-risk” threshold, yet evidently mutation status itself may be a stronger predictor than actual presented lifetime risk given the rates of RRM in this unaffected group of women. Intriguingly, the average ages of presentation of this lifetime risk were the same for the no mutation group and moderate penetrance group, and average lifetime risk differed only by 12%; however, not a single unaffected no mutation carrier underwent RRM. Surprisingly, the rates of RRM between moderate penetrance and BRCA groups were similar despite the fact that lifetime risk of breast cancer is 30% higher in the BRCA group than in the moderate penetrance group. It should be noted, however, that the average age of women in the *BRCA1/2* group when presented with their lifetime risk was 10 years younger than the moderate penetrance group (Table 4). It

might be that younger women in this group are less inclined to undergo an RRM even though the literature suggests that younger women who are unaffected with breast cancer are more likely to undergo RRM than unaffected older women since they stand to gain a higher net risk reduction with a RRM (Evans, 2009, 2019; Hoskins, 2012; Metcalfe, 2008, 2019).

#### **D. Age**

Age has been contended as a decisional influencer for RRM for women with breast cancer (Ballard-Barbash, 1996; Bhat, 2017; Chagpar, 2006; Hoskins, 2012; Hussien, 2003; Lazovich, 1999; Nold, 2000; Newcomb, 1993; Rodby, 2016; Ward, 1989). However, literature suggests that younger women who are unaffected with breast cancer are more likely to undergo RRM than unaffected older women (Evans, 2009, 2019; Hoskins, 2012; Metcalfe, 2008, 2019). This current study found no relationship between surgical decision and age, but included a combined cohort of unaffected (N=185) and affected (N=95) women. Our hypothesis that younger women across both groups would elect to undergo RRM more than older women was founded upon the principle that a greater net reduction in risk of a future diagnosis of breast cancer was attainable at a younger age. This consideration is seemingly eclipsed by other decision making factors such as marital status for women in this study.

#### **E. Marital Status**

Having a partner purportedly has a greater influence on RRM decision making for women affected with breast cancer than those not facing a diagnosis due to the support partner provides during the diagnosis process (Napoli, 2020). It is, however, crucial to consider support networks of patients both with and without cancer in the preoperative counseling period since no studies to date have indicated that marital status either increases or decreases the rates of RRMs among unaffected high risk women. The findings of this study in regard to marital status did not

draw a comparison between affected and unaffected women, but suggest that women who have never been married are 0.42 as likely to undergo RRM than women who are either married or in a relationship. Once again, marital status was only a modest predictor of RRM rates. This could be a matter of support network, as previously implied, but one cannot rule out other competing factors such as age-dependent body habitus and desired cosmetic outcome which have been shown to influence surgical decision making (Nold, 2000; Degner, 1997). For this study population, women in relationships were older by 11 years on average than single women ( $M(SD)= 48 (13.24)$  vs.  $37 (13.02)$ ) and while age at time of surgical decision-making did not influence the odds of undergoing a RRM for the entire study population, the difference in ages between these two marital status groups cannot be ruled out as a potential confounding variable. Women may also think that RRM may adversely impact their likelihood of finding a future partner or prevent them from breastfeeding, though these factors are at this point conjectures in light of the scope of this study and currently published research.

#### **F. Limitations:**

Many of the limitations of this study stem from it being a retrospective study looking solely at patients at one academic hospital in an urban setting. The patient population, like so many others, constituted majority Non-Hispanic white women and underrepresents the general population demographics. It's reported that women located in urban residence are more likely to undergo RRM with an odds ratio of 2.22, so total RRM rates may be higher compared with other settings (Bhat, 2017). This study population comes from one center in the US, and researchers have shown that rate of RRM differs by country (Metcalf, 2019).

Additionally, chart abstraction by nature is imperfect. For example, it may be impossible to know whether a woman was truly considering a RRM if she did not tell the genetic counselor or

if it was not documented in the clinic note within the EMR. Comprehensive searches of EMRs may yield no results as to whether a surgery occurred, and assumptions are made that if a subject's intentions towards surgery were not explicitly noted and she had no follow up with surgeons within the medical network or EMR-collaborators, that she ultimately decided to not undergo surgery at that time. Exhaustive risk factors were not collected for gene mutation carriers, though some were integrated with empiric risk models for non-mutation carriers using Tyrer-Cuzick. For example, it was not captured whether a woman received a risk reducing salpingo-oophorectomy, whether she breast fed, age of menarche, etc., which have been shown to impact *BRCA1* carriers (Kotsopoulos 2018). In the same vein, presented remaining lifetime risks may be inaccurate based on insufficient data, especially for moderate penetrance gene carriers. For example, Tyrer-Cuzick produces a remaining lifetime risk based on the current age of a woman, and currently age-related risks are more unclear for mutation carriers such as those with *NBN* mutations. Discussions in clinic may take a woman's age into consideration, but may not be reflected in clinician notes. For example, a woman identified to have a *NBN* mutation may be told in clinic, "women with a *NBN* mutation are at a two to four fold increase risk for breast cancer over their lifetimes, but since you're 65, you've outlived a substantial portion of this risk," but the note may include solely the first portion of this compound sentence.

There are analytical limitations given how subjects were grouped in this study. For example, many decision-making variables were assessed in a combined cohort of affected and unaffected women. As stated previously, decision-making factors such as age and possibly marital status have been shown to be dependent on whether a woman has a breast cancer diagnosis. In addition, models of family history and breast cancer subdivide influences of first, second, and third degree relative on odds of undergoing RRM, but total number of relatives affected with breast cancer is

not assessed in these models nor across the entire study population. Data also shows that whether a woman has children may influence her odds of undergoing RRM. While collected, this study did not analyze whether a woman with children was more likely to undergo a RRM.

### **G. Future Research**

The completion of this study leaves more questions unanswered than answered. The limitations of analyzing research questions regarding age and marital status with combined cohorts of unaffected and affected women is that we still don't know whether marital status is dependent upon whether a woman is affected or not. The findings that marital status is a modest predictor of patient behavior warrants further investigation into whether this is primarily in the context of a new diagnosis. Additionally, women may also think that RRM may adversely impact their likelihood of finding a future partner or prevent them from breastfeeding. This is something that should be explored further qualitatively. A prospective study designed to assess decision-making factors of women found to harbor breast cancer susceptibility gene mutations would illuminate reasons for the observed rates of RRM among women considered at high risk. Eventually, understanding these factors may open the door for interventions and educational tools to better inform patients in their decision making process.

## CONCLUSION

Women identified to have a higher risk for developing breast cancer choose whether to have a RRM, and make this decision based on a number of factors. This retrospective study of 280 women demonstrates that mutation status, breast cancer diagnosis, and age of diagnosis influence decision making for RRM for women with no mutations, moderate penetrance mutations, and *BRCA1/2* mutations. Unaffected moderate penetrance carriers who had first degree relatives with breast cancer were significantly more likely to undergo RRM, but family history otherwise didn't influence decision making for the entire study population. Lifetime risks presented to unaffected women and marital status for all patients were both modest predictors of subjects' propensity to undergo RRM, and age did not influence the odds of undergoing RRM. As healthcare providers, we should continue to strive to understand decisional influences so that we can support patients in informed decision making.



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