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Factors Associated with Early Versus Late Development of Breast and Ovarian Cancer in BRCA1 and BRCA2 Positive Women

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FACTORS ASSOCIATED WITH EARLY VERSUS LATE DEVELOPMENT OF BREAST AND OVARIAN CANCER IN *BRCA1* AND *BRCA2* POSITIVE WOMEN

A

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Hereditary breast and ovarian cancer (HBOC) is caused by a mutation in the *BRCA1* or *BRCA2* genes. Women with a *BRCA1*/2 mutation are at increased risks for breast and ovarian cancer and often develop cancer at an earlier age than the general population. However, some women with a *BRCA1*/2 mutation do not develop breast or ovarian cancer under the age of 50 years. There have been no specific studies on *BRCA* positive women with no cancer prior to age 50, therefore this study sought to investigate factors within these women with no cancer under age 50 with respect to reproductive risk factors, BMI, tumor pathology, screening history, risk-reducing surgeries, and family history. 241 women were diagnosed with cancer prior to age 50, 92 with cancer at age 50 or older, and 20 women were over age 50 with no cancer. Data were stratified based on *BRCA1* and *BRCA2* mutation status. Within the cohorts we investigated differences between women who developed cancer prior to age 50 and those who developed cancer at age 50 or older. We also investigated the differences between women who developed cancer at age 50 or older and those who were age 50 or older with no cancer. Of the 92 women with a *BRCA1*/2 mutation who developed cancer at age 50 or older, 46 developed ovarian cancer first, 45 developed breast cancer, and one had breast

and ovarian cancer diagnosed synchronously. *BRCA2* carriers diagnosed age 50 or older were more likely to have ER/PR negative breast tumors when compared to *BRCA2* carriers who were diagnosed before age 50. This is consistent with one other study that has been performed. Ashkenazi Jewish women with a *BRCA1* mutation were more likely to be diagnosed age 50 or older than other ethnicities. Hispanic women with a *BRCA2* mutation were more likely to be diagnosed prior to age 50 when compared to other ethnicities. No differences in reproductive factors or BMI were observed. Further characterization of *BRCA* positive women with no cancer prior to age 50 may aid in finding factors important in the development of breast or ovarian cancer.

TABLE OF CONTENTS

Page Number

LIST OF FIGURES

Page Number

LIST OF TABLES

Page Number

BACKGROUND

INTRODUCTION

Hereditary breast and ovarian cancer (HBOC) is a hereditary cancer syndrome caused by mutations in the *BRCA1* and *BRCA2* genes. HBOC has an autosomal dominant mode of inheritance and a high penetrance in mutation carriers. Women with a *BRCA1* or *BRCA2* mutation are more likely to have an HBOC-related cancer, such as breast or ovarian, and may be diagnosed at a younger age than the general population. Although individuals with this syndrome are at the greatest risk of developing breast or ovarian cancer, other cancers, such as prostate and pancreatic, are also associated with HBOC.

BRCA1 was first cloned in 1994, followed by *BRCA2* in 1995 (1). *BRCA2* consists of 3,418 amino acids and, while little is known about its function, it is known to be involved in homologous recombination (1). *BRCA1* is 1,863 amino acids and plays a role in DNA repair, protein ubiquitinylation, chromatin remodeling, and cell-cycle-checkpoint control (1). Both of these genes play a role in preventing cancer from developing, specifically in the breasts and ovaries. A mutation in one of these two genes leads to an increased risk of breast and ovarian cancer.

The median age of ovarian cancer diagnosis in the general population is 63 years of age (2). Women with a *BRCA1* or *BRCA2* mutation often have a younger age at diagnosis than the general population. The average age of ovarian cancer diagnosis in women with a *BRCA1* mutation is 52.6 years and is 58.8 years in those with a *BRCA2* mutation (3). The lifetime chance for a woman in the general

population to develop ovarian cancer is 1.4% (2). Individuals with a *BRCA1* or *BRCA2* mutation have a significantly increased chance to develop ovarian cancer with *BRCA2* mutation carriers having a 27% risk for ovarian cancer by age 70 (4). *BRCA1* carriers have an estimated ovarian cancer risk of 11-42% by age 60 (5).

According to Surveillance, Epidemiology, and End Results (SEER) data, women in the general population have a 12.08% chance to develop breast cancer during their lifetime and the average age at diagnosis is 61 years of age (2). Estimates for female breast cancer in *BRCA* carriers are that 90% of *BRCA1* carrier women will develop breast cancer and 41% of *BRCA2* carrier women will develop breast cancer (3). In addition to having higher lifetime risks of breast cancer, women with a *BRCA1* or *BRCA2* mutation are often diagnosed at significantly younger ages than the general population.

A meta-analysis of 22 studies unselected for family history showed that by age 50, it was estimated that approximately 40% of *BRCA1* carriers would develop breast cancer and that approximately 12% would develop ovarian cancer (6). In *BRCA2* carriers it was estimated that approximately 15% would develop breast cancer by age 50 and approximately 3% would develop ovarian cancer by age 50. A study of 676 Ashkenazi Jewish families and 1,272 families of other ethnicities in the US showed that the cumulative risk to age 50 for *BRCA1* carriers was 28% (CI 24-34) for breast cancer and 13% (CI 9.7-17) for ovarian cancer (6). The cumulative risks for *BRCA2* carriers were 23% (CI 19-29) for breast cancer and 4% (CI 2.2-6.2) for ovarian cancer by age 50 (6). These two studies differ in their breast cancer risk estimates among *BRCA1* and *BRCA2* carriers (40% vs. 28% for

BRCA1 and 15% vs. 23% for *BRCA2*), however the ovarian cancer risk estimates are quite similar (12% vs. 13% for *BRCA1* and 3% vs. 4% for *BRCA2*).

There have been many studies investigating breast and ovarian cancer risk factors in women with a *BRCA1* or *BRCA2* mutation, however many of these studies have focused on women with early-onset breast or ovarian cancer. There is very limited information about these factors in women with a later-onset of breast or ovarian cancer or in older women who have not developed breast or ovarian cancer. There may be factors that influence the chance that a woman with a *BRCA1* or *BRCA2* mutation does not develop breast cancer at a younger age. To our knowledge, there have been no studies performed to identify factors in *BRCA* positive women with later-onset (≥50 years old) breast or ovarian cancer and compare the factors to women who developed breast or ovarian cancer at an earlier age (<50 years old).

REPRODUCTIVE RISK FACTORS

In addition to *BRCA* mutation status, there are other risk factors known to influence whether or not a woman will develop breast or ovarian cancer. Certain reproductive factors can increase risk or play a protective role in whether or not a woman develops breast or ovarian cancer. These factors include parity, age at first full-term pregnancy, age of menarche, age at menopause, breastfeeding, oral contraceptive use, and hormone replacement therapy use.

Later age of menarche has been associated with a decreased risk of breast cancer in the general population. Early menarche may induce an early proliferation

of mammary gland cells through early exposure to high hormonal levels causing an increased risk of breast cancer (7), therefore early menarche (prior to age 12) is associated with a higher lifetime risk of breast cancer in the general population (8). One study found a later age of menarche in *BRCA1* mutation carriers was associated with a decreased breast cancer risk, however no protective effect was observed in *BRCA2* mutation carriers (9). Another study showed no association with age at menarche and breast cancer risk in *BRCA1* or *BRCA2* mutation carriers(10).

Ovarian cancer risk is decreased among women with a later age of menarche. Among *BRCA1* and *BRCA2* carriers, there has not been any significant evidence that age at menarche is positively or negatively associated with ovarian cancer risk (11).

Women in the general population have an increased risk of breast cancer if they undergo menopause at a later age. This is likely due to the increased duration and amount of estrogen and progesterone (7). A study of *BRCA1* and *BRCA2* mutation carriers found no overall association with menopause and breast cancer risk (10). Early menopause has also been found to be protective against ovarian cancer. One particular study found early menopause to confer an odds ratio of 0.6 when women who underwent menopause prior to age 45 were compared to those who underwent menopause after age 45 (12). There have been no studies that explore the relationship between age at menopause and ovarian cancer in women with a *BRCA1* or *BRCA2* mutation.

Early age at first full-term pregnancy is associated with a decreased risk for breast cancer in the general population. Women under age 18 at their first full-term pregnancy have only 40% of the breast cancer rates of women with no pregnancies (13). In addition, late pregnancies may increase breast cancer risk for women in the general population. Women with their first full-term pregnancy occurring after age 35 showed a 20% higher risk of developing breast cancer than those who were nulliparous (13). The role of pregnancy in the etiology of *BRCA*-breast cancer is not clear. In women with a *BRCA1* or *BRCA2* mutation, early full-term birth was not found to be protective against breast cancer (14), suggesting that the factors playing a role in the general population may not be applicable to women who are genetically predisposed to developing breast cancer. In *BRCA2* carriers, first childbirth at later ages has been associated with an increased risk for breast cancer when compared to those with their first childbirth prior to age 20 (11). In *BRCA1* mutation carriers, first full-term pregnancy after age 30 has been associated with a reduction of breast cancer risk compared to those whose first full-term pregnancy occurred before age 20 (15). As this is in contradiction to findings in the general population, this further suggests that factors playing a role in the general population may not be applicable to *BRCA* carriers. In the general population, later age at first birth is associated with a reduced risk of ovarian cancer. This same association has been seen in both *BRCA1* and *BRCA2* carriers (16).

An increasing number of full-term pregnancies has been associated with a decreased risk for breast cancer in the general population. Some studies suggest that this may be due to decreased levels of estrogen and progesterone, increased

levels of sex hormone-binding globulin, and pregnancy-induced differentiation of breast tissue (12). A study performed in a population of *BRCA1* and *BRCA2* mutation carriers found a decreased risk of breast cancer as the number of full-term pregnancies increased (9), however the results were not statistically significant. Another study found no statistically significant difference in the risk of breast cancer between parous and nulliparous women (15). For carriers and noncarriers of a *BRCA1* or *BRCA2* mutation, women who have had four or more full-term pregnancies had a near fifty percent reduction of breast cancer risk when compared to nulliparous women (9). This protective effect was mainly limited to women who had their first full-term pregnancy prior to age 25. Among women over age 40 with a *BRCA* mutation who have had a full-term pregnancy, an increasing number of full-term pregnancies was associated with a 14% decrease in the breast cancer risk for each pregnancy (15).

Women in the general population have a decreased ovarian cancer risk as parity increases. One study found that parity was associated with a decreased risk of ovarian cancer in *BRCA1* carriers and an increased risk of ovarian cancer in *BRCA2* carriers (17). Another study identified the same protective effects of parity in *BRCA1* carriers but did not identify any significant association between parity and ovarian cancer risks in *BRCA2* carriers (16).

A longer duration of breastfeeding has been found to decrease the breast cancer risk in the general population. Several theories have been proposed to explain this observation, including postponed resumption of ovulatory menstrual cycles, breast tissue differentiation, decreased estrogen levels, and excretion of

carcinogens from the breast ductal tissue (9)**.** A longer duration of breast-feeding has not been found to have a decreased risk of breast cancer in *BRCA2* mutation carriers (9, 15, 18). While some studies have shown breast-feeding to have no effect in *BRCA1* mutation carriers (9, 15), one study found that women with a *BRCA1* mutation who breast-fed for more than one year were 45% less likely to have breast cancer than those who had never breast fed (13).

Breastfeeding among the general population confers a decreased risk of developing ovarian cancer. In one study of women with a *BRCA1* mutation, breast-feeding was shown to be protective against ovarian cancer (17), however other studies have found no association among *BRCA1* or *BRCA2* carriers' ovarian cancer risk and breastfeeding (11).

Studies on the use of oral contraceptives and its influence on breast cancer have not been conclusive. Some studies show that oral contraceptive use is not associated with breast cancer risk in the general population or in *BRCA1* or *BRCA2* mutation carriers (9). In a meta-analysis, women currently using combined oral contraceptives or women who had used them in the past 10 years were found to have a slightly increased risk of breast cancer (19). They found no evidence of an increased risk of breast cancer diagnosed 10 or more years after discontinuing use. Women who had ever used oral contraceptives had a relative risk of 1.07 of developing breast cancer when compared to women who had never used oral contraceptives (19). One study showed a decreased risk of breast cancer among *BRCA1* mutation carriers, although the results were not statistically significant (9). Another study found that *BRCA1* mutation carriers who used oral contraceptives for

5 years or longer had an increased risk for breast cancer when compared to *BRCA1* carriers who did not use oral contraceptives (odds ratio 1.33) (20). However, oral contraceptive use after age 30 was not likely to increase the risk of breast cancer among *BRCA1* mutation carriers (20). This study did not find an association among *BRCA2* carriers and oral contraceptive use, although the sample size for this group was small (20). Given that numerous studies have been done on this topic and there are contradictions between them, there is currently no real consensus on the effect of oral contraceptives on breast cancer risk. However, oral contraceptive use has consistently been found to reduce the risk of ovarian cancer in the general population as well as in women with a *BRCA1* or *BRCA2* mutation (17).

Hormone replacement therapy (HRT) has been found to increase the risk of breast cancer in the general population and the risk of breast cancer increases with increasing duration of HRT (21). A study of *BRCA1* mutation carriers did not find that HRT was associated with an increased risk of breast cancer (22). This study also did not find an association between the duration of HRT use and the risk of breast cancer among women with a *BRCA1* mutation. An increased risk of ovarian cancer has been associated with HRT use in the general population, however there have been some conflicting studies and the ovarian cancer and HRT relationship is not quite clear in the literature (23-25). There was no association between HRT and ovarian cancer risk seen in a study looking at *BRCA* positive women (26).

BODY MASS INDEX (BMI)

Body mass index (BMI) is calculated from a person's height and weight. A higher BMI has been associated with a decreased risk of breast cancer prior to menopause and is minimally associated with an increased risk for breast cancer after menopause (27). The increased risk for breast cancer in heavier postmenopausal women may be attributed to higher levels of estrogen in the woman since the primary source of estrogen after menopause is the conversion of androstenedione to estrone in adipose tissue (28). When comparing postmenopausal women who have the highest BMI to postmenopausal women who have the lowest BMI, studies report a relative risk of breast cancer of 1.5-2.0 (28). In women with a *BRCA* mutation, increases or decreases in body weight during early adult life may be more important in determining the risk for breast cancer than current weight or BMI (29).

The association of ovarian cancer and BMI has not been consistent. Some studies show that ovarian cancer risk increases in the general population as BMI increases (30, 31). In a meta-analysis of 28 studies, the risk of epithelial ovarian cancer among obese women was estimated to be 30% higher than women with a normal BMI and women considered overweight had a 16% increased risk of ovarian cancer when compared to women with a normal BMI (30). The association between ovarian cancer and BMI may depend on a woman's menopausal status. BMI has been associated with an approximately 2-fold increased ovarian cancer risk among premenopausal women (age <50 years), however among postmenopausal women there was no significant association between BMI and

ovarian cancer (32). There have been no studies, to our knowledge, looking at the association between BMI and ovarian cancer in women with a *BRCA1*/2 mutation. However, some studies have shown that in women who have a family history of ovarian cancer, there is no association between BMI and ovarian cancer (31).

SCREENING MODALITIES AND FREQUENCIES

There have been specific recommendations made for women who have a *BRCA1* or *BRCA2* mutation in order to screen for breast and ovarian cancer. These recommendations are in place to help detect these types of cancer at a stage that is, ideally, earlier and more treatable. The National Comprehensive Cancer Network (NCCN) has developed a set of practice guidelines for cancer screening in women with a *BRCA1* or *BRCA2* mutation. The 2009 guidelines include breast self-examination monthly beginning at age 18 as well as clinical breast exams semiannually beginning at age 25. Annual mammograms and breast MRI should begin at age 25. To screen for ovarian cancer, the NCCN guidelines recommend concurrent transvaginal ultrasound and CA-125 blood test every 6 months beginning at age 35 or 5-10 years prior to the earliest age of ovarian cancer onset in the family. Ovarian cancer screening has not been shown to be effective, therefore it is recommended that women with an increased risk to develop ovarian cancer undergo risk-reducing bilateral salpingo-oophorectomy (33).

CHEMOPREVENTION

Chemopreventive agents, such as tamoxifen, may be offered to women at an increased risk of breast cancer based on personal history, family history, or *BRCA* mutation status. Tamoxifen targets the estrogen receptor (ER) in breast cells, therefore tamoxifen may not have as great an effect on ER negative breast cancers. Given that many *BRCA1*-related breast cancers tend to be ER negative, tamoxifen may not significantly reduce breast cancer risk among *BRCA1* mutation carriers. Tamoxifen use does not have an effect on ovarian cancer risk (34).

Women in the general population receive protection against breast cancer when taking tamoxifen. Women who took tamoxifen for seven years had a rate of breast cancer of 24.8 per 1000 as compared to 42.5 per 1000 women in the placebo group (35).

While no large studies to date have assessed the effect of tamoxifen on *BRCA1* and *BRCA2* carriers that do not have a history of breast cancer, studies have shown a decreased risk of contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers (36). The risk of contralateral breast cancer was decreased by greater than 50% in *BRCA1*/2 mutation carriers when tamoxifen was used as treatment for their initial breast cancer diagnosis (36). Given this data, it is reasonable to assume that tamoxifen use in women with a *BRCA1* or *BRCA2* mutation who have never had a breast cancer diagnosis would experience a decreased risk of developing breast cancer, however no large studies have been reported. One study observed women with no previous breast cancer diagnosis and found that of the 8 women with a *BRCA1* mutation who developed breast

cancer, 5 were taking Tamoxifen and 3 were in the placebo group (risk ratio 1.67) (34). In this same study, of 11 women with *BRCA2* mutations who developed breast cancer, 3 were taking tamoxifen and 8 were in the placebo group (risk ratio 0.38) (34). Given the small sample size, general inferences cannot be made, however it appears that tamoxifen use may be effective in *BRCA2* mutation carriers, but not in those with a *BRCA1* mutation.

RISK-REDUCING SURGERIES

Bilateral mastectomy and bilateral salpingo-oophorectomy (BSO) are often recommended to women with a *BRCA1* or *BRCA2* mutation to decrease the chance of developing breast and/or ovarian cancer. Mastectomy reduces the risk of breast cancer while BSO reduces the risk of both breast and ovarian cancer (37-42). The hypothesis for why BSO affects breast cancer risk is that estrogen deprivation reduces the risk of breast cancer (37).

Prophylactic BSO decreases the chance for ovarian cancer to develop in women with a *BRCA1* or *BRCA2* mutation. Prospective studies identified a reduced risk of ovarian cancer in *BRCA1* carriers (39). While protection was suggested for *BRCA2*-associated ovarian cancer in this study, it did not reach statistical significance, likely due to the small number of *BRCA2* carrier (39). A meta-analysis of 10 studies found an 80% reduction of ovarian cancer after BSO (42). Another study that was performed showed a 96% reduction of ovarian cancer risk after BSO (43).

BSO has been associated with a 57% reduction in breast cancer risk in *BRCA1* carriers and a 46% risk reduction in *BRCA2* carriers (37). Another study showed a hazard ratio of 0.53 for breast cancer risk in *BRCA1* mutation carriers who had undergone prophylactic BSO when compared to *BRCA1* carriers who had not undergone the surgery (38). While oophorectomy at a premenopausal age decreases the risk for breast cancer throughout a woman's lifetime, the effect appears greater for breast cancers diagnosed before age 50 (37-39). A prospective study found that prophylactic BSO was associated with a significant decreased risk of breast cancer in *BRCA2* mutation carriers (39). Other studies have shown an approximately 50% risk reduction of developing breast cancer following a premenopausal BSO (42, 43).

Bilateral mastectomy reduces a woman's risk of breast cancer by approximately 90% if she carries a *BRCA1* or *BRCA2* mutation (41). In a group of 76 women with a *BRCA1* or *BRCA2* mutation who chose to undergo prophylactic mastectomy, none of them developed breast cancer whereas in a group of 63 women with a *BRCA1* or *BRCA2* mutation who did not undergo the surgery, 8 women developed breast cancer (40). Another study showed that 1.9% of *BRCA1*/2 carriers were diagnosed with breast cancer after prophylactic mastectomy whereas 48.7% of controls were diagnosed with breast cancer (41).

Women may choose to undergo prophylactic mastectomy and/or BSO in order to greatly reduce their chances of developing breast and/or ovarian cancer, however there are many psychosocial concerns that may also affect whether or not a woman chooses to have the surgery done. In addition, even if a woman chooses

to undergo these procedures, there is still a risk for her to develop breast and/or ovarian cancer (primary peritoneal cancer) as the procedures do not confer a 100% reduction of cancer risk.

HORMONE RECEPTOR STATUS

Hormone receptor status has been found to vary among breast cancers and can also have prognostic factors for the cancer. Estrogen and progesterone are important in the development and progression of breast cancer. Estrogen receptor (ER) and progesterone receptor (PR) status have been found to be the most important predictors of endocrine therapy response (44). Approximately 65% of female breast cancers are ER positive and 50% are PR positive (45). ER and PR status tend to be positive more often in patients whose tumor developed at an older age (45). Tumors that are ER and PR positive tend to have a better response to endocrine therapies and have a better prognosis when compared to women with ER and PR negative tumors (46).

Studies have found that women with a *BRCA1* mutation are more likely to have ER/PR negative breast cancers than women with a *BRCA2* mutation or women with no *BRCA* mutation (47-49). A study by Atchley et al (47) found that women with triple-negative breast cancer who were *BRCA2* mutation carriers were diagnosed at a later age than *BRCA1* mutation carriers and noncarriers.

Her-2/*neu* status is another pathological characteristic found in breast cancer. Her-2/*neu* is a proto-oncogene that has been identified in up to 34% of breast cancers (50). The amplification and protein overexpression of Her-2/*neu* is

associated with an adverse outcome in breast cancer (50). There have been inconsistent findings when identifying the relationship between Her-2/*neu* status and *BRCA1* and *BRCA2* mutations. Some studies have found that Her-2/*neu* status among *BRCA1* mutation carriers does not differ when compared to noncarriers (47), however other studies have reported that *BRCA1* status is associated with Her-2/*neu*-negative breast cancers (51).

Many studies have looked at early-onset breast cancer and the association with ER, PR, and Her-2/*neu* status. We could not find any studies that look at this association between women with a *BRCA1* or *BRCA2* mutation who were diagnosed with breast cancer at a later age. It is largely unknown whether or not there is a difference in ER, PR, and Her-2/*neu* status when comparing women with early- vs. late-onset breast cancer.

ETHNICITY

The incidence of breast cancer in the general population varies by race/ethnicity. White women have the highest breast cancer incidence (141.1 in 100,000 females) followed by African Americans (119.4), Asian Americans/Pacific Islanders (96.6) and Hispanics/Latinas (89.9) (52). American Indians/Alaska Natives have the lowest incidence of breast cancer (54.8) (52). White women in the United States are at a higher risk for developing ovarian cancer (13.1 in 100,000) than American Indians (10.2), Hispanics (9.4), African Americans (9.0) and Asian/Pacific Islanders (8.0) (53).

Given that white women are at the highest risk to develop breast and ovarian cancer, it is reasonable to presume that a white woman with a *BRCA1* or *BRCA2* mutation may be at higher risk to develop breast and/or ovarian cancer than a Hispanic/Latina with a *BRCA1*/2 mutation. In individuals with a breast cancer diagnosis, *BRCA1* and *BRCA2* mutation rates across ethnic groups are fairly similar with a rate of 1-4% for each gene (54). Therefore, the differences in prevalence of breast and ovarian cancer among different ethnic/racial populations cannot be explained exclusively by the rate of mutations in the *BRCA1* and *BRCA2* genes in those populations. There are likely other genetic factors within racial groups that influence a woman's risk of developing breast or ovarian cancer.

FAMILY HISTORY

A family history of breast or ovarian cancer increases the risk for a woman to develop these types of cancers. One study showed that having two or more first-degree female relatives with breast cancer is associated with an increased risk to develop ovarian cancer (OR 9.5; CI 1.0-87.0), however there were very few cases and this may be due to chance (55). In a meta-analysis of women with a family history of ovarian cancer, the relative risk to first-degree relatives was 3.1 (56). Sisters of a woman with ovarian cancer had a higher relative risk (3.8) of ovarian cancers than mothers of cases (1.1) (56). Daughters of cases had the highest relative risk of ovarian cancer (6.0) (56).

A family history of breast cancer confers a greater risk of breast cancer in an individual. In a meta-analysis of 74 studies of breast cancer risk and family history,

it was found that a woman with any first-degree relative affected with breast cancer has a relative risk of 2.1 when compared to women with no family history of breast cancer (57). A woman with a mother diagnosed with breast cancer has a 2.0 relative risk to develop breast cancer and a woman with a sister diagnosed with breast cancer has a 2.3 relative risk (57). Women with a second-degree relative diagnosed with breast cancer have a relative risk of 1.5 to develop the same type of cancer (57). All of these risks were increased if the relative was diagnosed at a younger age (57).

One study found that the age of breast cancer onset in a woman with a *BRCA* mutation and a family history of breast cancer can be predicted to a small extent by the youngest age of diagnosis within the family and the mean age of diagnosis in the family (58). This effect was slightly significant in *BRCA2* carriers but not in *BRCA1* carriers. Based on this study, they concluded that it appears that an unaffected carrier may have an earlier age at diagnosis if the youngest diagnosis in the family is less than 35 years when compared to families were all cases were over age 35 (58). In a study of Polish women with a *BRCA1* mutation, they found that relatives of women diagnosed with breast cancer had a higher risk of breast cancer than relatives of women diagnosed with ovarian cancer (OR=1.7; p=0.03) (59). Some researchers theorize that there may be other modifier genes contributing to a greater cancer risk within certain families with a *BRCA* mutation (60). While the effect of family history on *BRCA* mutation carriers' cancer risk does not seem to be entirely clear, it does seem to play a role.

In conclusion, there are many factors that play a role in the development of breast and/or ovarian cancer in the general population. These factors have not been investigated in the development of later-onset breast or ovarian cancer among women with a *BRCA1* or *BRCA2* mutation. In addition, these factors have not been explored among women with a *BRCA1* or *BRCA2* mutation living at older ages with no history of breast or ovarian cancer. In this study, we attempt to investigate reproductive risk factors, hormone receptor status, screening frequencies and modalities, risk-reducing surgeries, as well as family history among women with a *BRCA* mutation who did not develop cancer before the age of 50 years and are followed at MD Anderson Cancer Center.

MATERIALS AND METHODS

Study Design

This study was a retrospective chart review of a select population of women with a *BRCA1* or *BRCA2* mutation. The specific aims of this study were to 1) determine if any factors influence whether a woman with a *BRCA1* or *BRCA2* mutation develops breast or ovarian cancer at an early age (<50 years of age) or a later age (≥50 years) and to identify which factors are important and 2) determine if any factors influence whether or not a woman with a *BRCA1* or *BRCA2* mutation develops cancer and determine which factors are important. The factors observed in this study include reproductive factors, BMI, risk-reducing surgeries, and family history.

Differences in these factors between women with a *BRCA* mutation who developed breast or ovarian cancer under age 50 and women with a *BRCA* mutation who developed breast or ovarian cancer at age 50 or older were investigated. In addition, differences in these factors between women with a *BRCA* mutation over age 50 with no cancer diagnosis and women with a *BRCA* mutation who developed cancer at age 50 or older were investigated. The MD Anderson Cancer Center electronic medical records (EMR) of this population were reviewed and relevant information was extracted and analyzed to identify trends and differences in the data. We hypothesized that there would be differences among women who developed breast or ovarian cancer at age 50 or older, women who developed breast or ovarian cancer prior to age 50, and women over age 50 who had never developed breast or ovarian cancer.

Study Approval

Approval for this study was granted by the University of Texas-Houston Health Science Center and the Committee for the Protection of Human Subjects of MD Anderson and the on September 1, 2009 and November 5, 2009, respectively.

Study Population

The study population consisted of 353 MD Anderson Cancer Center patients with a *BRCA1* or *BRCA2* mutation. Of these women, 20 women are ≥50 years of age and have never had a breast or ovarian cancer diagnosis. Ninety-two women were diagnosed with breast or ovarian cancer ≥50 years of age. There were 241 MD Anderson Cancer Center patients with a *BRCA1* or *BRCA2* mutation who had a breast or ovarian cancer develop prior to age 50. Myriad Genetics Laboratory in Salt Lake City, Utah performed the genetic testing.

Ascertainment

Study subjects were ascertained through an IRB approved research database at MD Anderson Cancer Center. The study population included patients at MD Anderson between 2/1/1997 and 11/16/2009. A total of 434 patients were identified as potential study participants and their fulfillment of the inclusion criteria was confirmed during review of their medical records. Of the 434 patients, 81 participants were excluded because they did not meet the inclusion criteria for the study. The following individuals were excluded from our data: men, individuals with a variant of uncertain significance and no deleterious mutation, and individuals with

no *BRCA1* or *BRCA2* mutation found. Women who had a variant of uncertain significance identified along with a known deleterious *BRCA1* or *BRCA2* mutation were included in our population. Women with ductal carcinoma in situ (DCIS) were not included in our study unless they also had an invasive cancer and we recorded their age at diagnosis at the time that they developed the invasive cancer.

Data Collection

The study population's medical records at MD Anderson Cancer Center were reviewed December 2009 through February 2010. The information extracted from the medical records is presented in table 1.

Table 1. Information Obtained through Medical Record Review

General Information
Date of birth Ethnicity Age of last contact with MD Anderson Cancer Center *BRCA* mutation status Age at breast or ovarian cancer diagnosis
Reproductive Risk Factor Information and BMI
Age at menarche Age at menopause (if applicable) Age at first full term pregnancy Parity (prior to diagnosis) Breastfeeding history Hormone replacement therapy use Oral contraceptive use Chemopreventive use (Tamoxifen) BMI (Based on height and weight at time of testing)
Screening History
Type of screening received (Mammography, Breast MRI, Clinical breast exam, Transvaginal ultrasound, or CA-125 blood test) Frequency of screening
Risk-Reducing Surgery
Type of surgery (Bilateral mastectomy or bilateral salpingo-oophorectomy) Age at surgery
Tumor Pathology Information
ER and PR Status Her2/neu status Type of cancer
Family History Information
Number of first and second degree relatives with a breast or ovarian cancer diagnosis Age of cancer diagnosis in first and second degree relatives Number of unaffected first and second degree relatives

Statistical Analysis

STATA 10.0, Microsoft Office Excel 2007, and Microsoft Office Access 2007 were used to analyze the data that was obtained from the MD Anderson electronic medical records. Descriptive statistics were performed to summarize the content of each variable for *BRCA1* carriers with cancer under age 50, *BRCA1* carriers with

cancer over age 50, *BRCA1* carriers with no cancer diagnosis, *BRCA2* carriers with cancer under age 50, *BRCA2* carriers with cancer over age 50, and *BRCA2* carriers with no cancer diagnosis. All of these variables were analyzed to identify differences based on mutations status and we compared women who developed cancer at age 50 or older to women who developed cancer before age 50 and those who had no cancer diagnosis. P-values less than 0.05 were considered to be statistically significant.

We used contingency tests (eg. Pearson's chi square) to compare frequencies among our groups. T-tests were used to analyze normally distributed continuous variables between the two groups and Mann-Whitney tests were used to compare non-normally distributed continuous variables among the groups. We performed four analyses on most variables and compared the differences between the following cohorts as shown in figure 2 and 3. Women diagnosed with cancer at or after age 50 were our referent group for all analyses. As shown in figure 2, we analyzed the differences in *BRCA1* or *BRCA2* mutation carriers who developed cancer before age 50 and those who developed cancer at age 50 or older. These data were stratified by *BRCA* mutation status. As shown in figure 3, we analyzed differences in women who developed cancer at age 50 or older and women who had never developed cancer stratified on their *BRCA* mutation status.

Figure 1. Analysis between women with cancer <50 and women with cancer ≥50 years of age

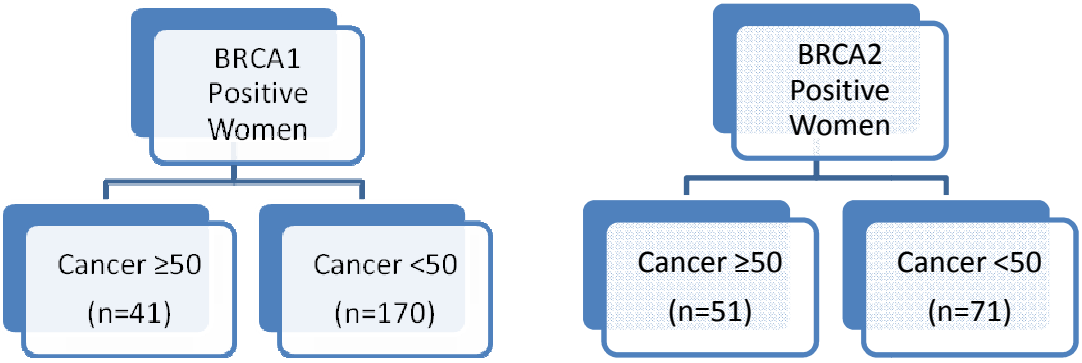
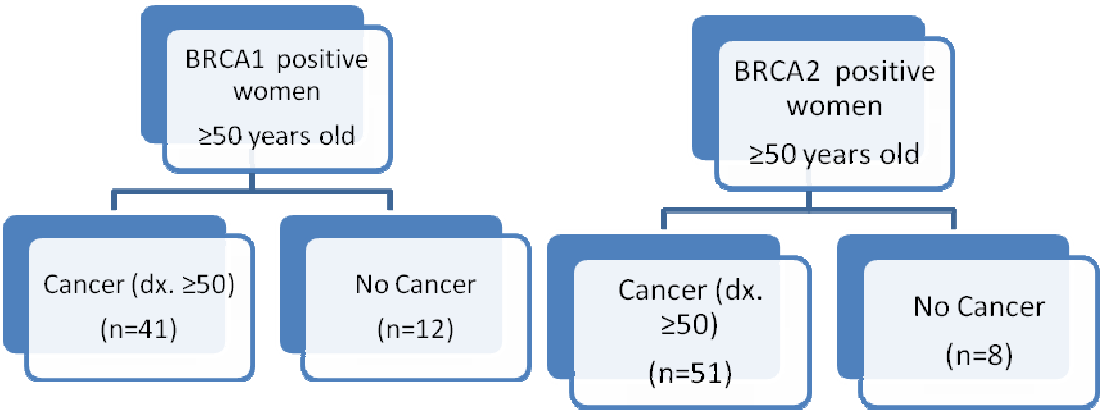


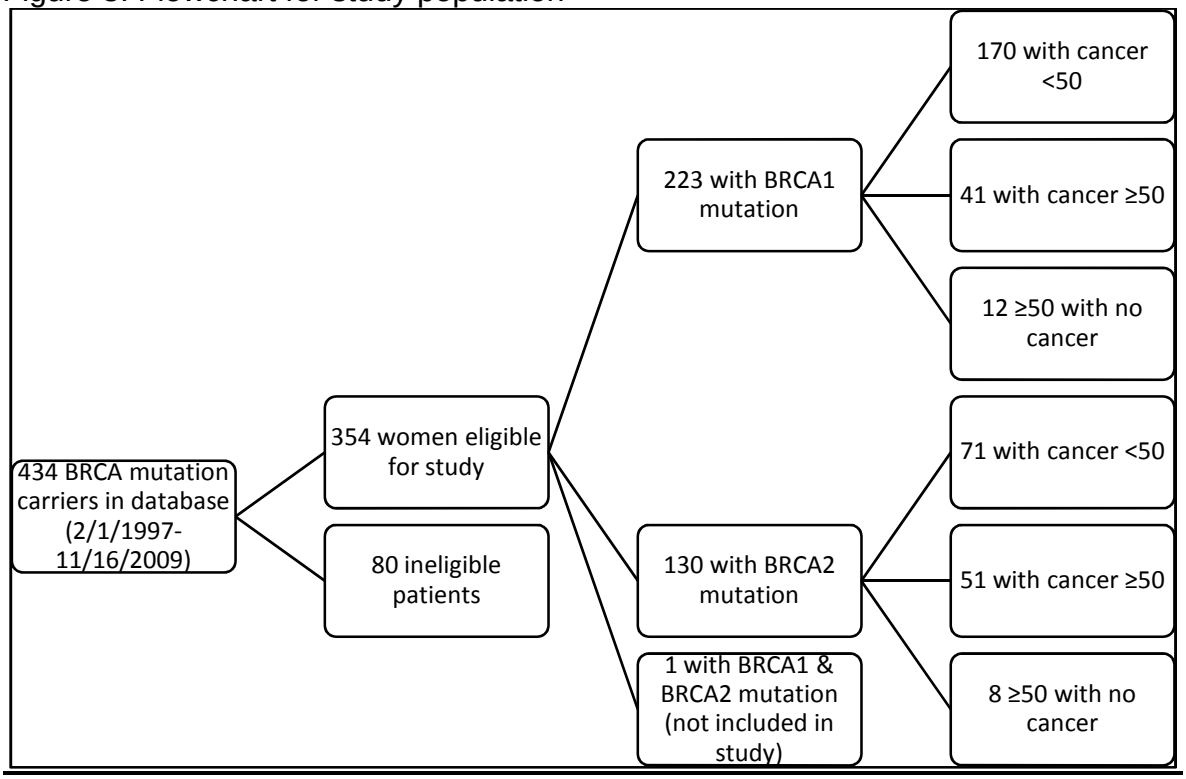
Figure 2. Analysis between women with cancer ≥50 years of age and those with no cancer



RESULTS

The population for our study is shown in figure 2. *BRCA1* and *BRCA2* mutation carriers were analyzed separately for reproductive risk factors, tumor characteristics, ethnicity, risk-reducing surgeries, and family history. There was one woman with a *BRCA1* and *BRCA2* mutation. She was not included in the analysis because the effect of having a mutation in both *BRCA* genes may impact the risk of developing breast or ovarian cancer when compared to women who have a mutation in only one of the genes.

Figure 3. Flowchart for study population



Average Age of Population

The average age at diagnosis was not statistically significant between *BRCA1* and *BRCA2* women diagnosed prior to age 50. There was also no

statistically significant difference in age at diagnosis between *BRCA1* and *BRCA2* women diagnosed at age 50 or older. No statistically significant difference was found between the current average age of women with a *BRCA1* or *BRCA2* mutation who are over age 50 with no cancer diagnosis. The mean ages for these groups, as well as p values for this analysis, are presented in tables 2-4.

Table 2. Age at Diagnosis (<50) based on *BRCA* mutation status

Cancer dx. <50	Mean Age (SD)	P-Value
BRCA1	38.87 (6.69)	0.3166
BRCA2	39.79 (5.92)	

Table 3. Age at Diagnosis (≥50) based on *BRCA* mutation status

Cancer dx. ≥50	Mean Age (SD)	P-Value
BRCA1	57.68 (5.46)	0.2742
BRCA2	56.41 (5.55)	

Table 4. Average Current Age based on *BRCA* mutation status

≥50 with no cancer dx.	Mean Age (SD)	P-Value
BRCA1	59.5 (9.56)	0.5046
BRCA2	56.88 (6.31)	

Type of Cancer First Diagnosed

There was a statistically significant difference ($p<0.0001$) between the type of cancer diagnosed in women before age 50 and at age 50 or older in women with a *BRCA1* mutation. Results were similar in women with a *BRCA2* mutation ($p<0.0001$). Women who developed cancer prior to age 50 were more likely to have breast cancer whereas those who developed cancer at age 50 or older were more likely to have ovarian cancer as their first cancer diagnosis.

The numbers and percentages of women with each type of cancer diagnosis are shown in figures 4-5.

Figure 4: Type of cancer first diagnosed in *BRCA1* mutation carriers, by age at diagnosis

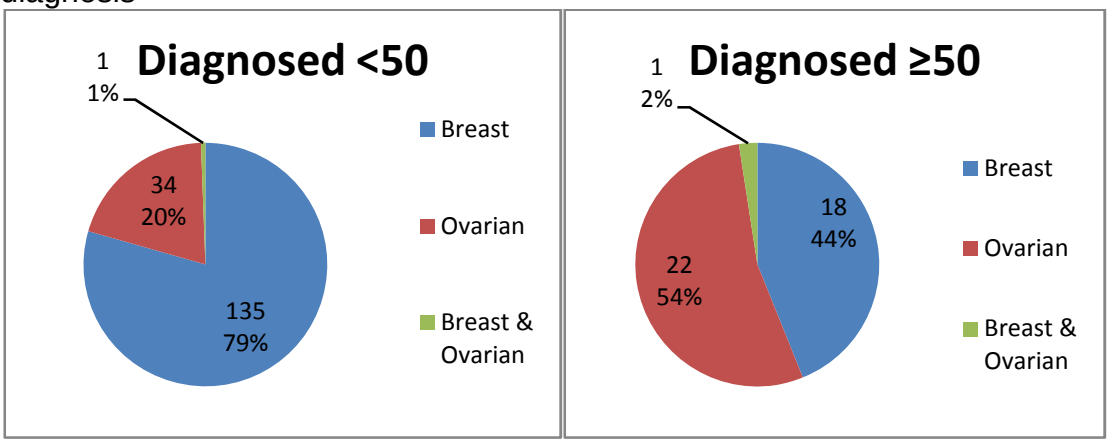
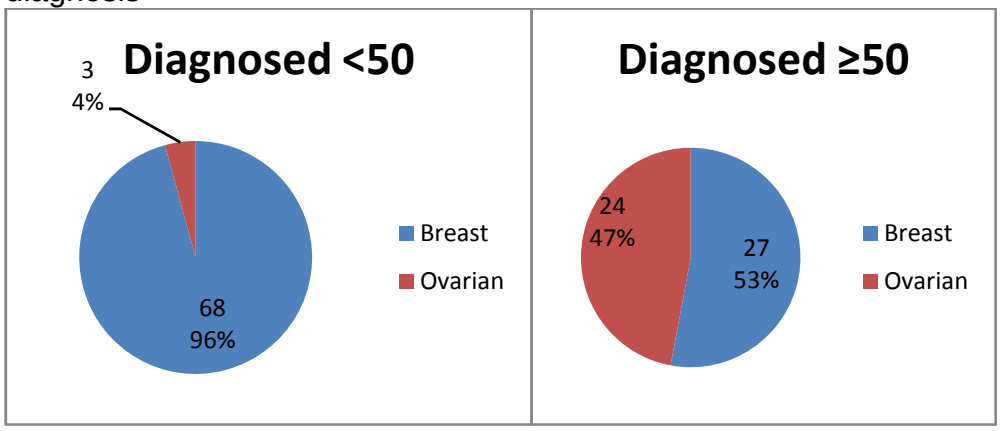


Figure 5: Type of cancer first diagnosed in *BRCA2* mutation carriers, by age at diagnosis



REPRODUCTIVE FACTORS

Mean age Menarche

There was no difference in the mean age at menarche between women with a *BRCA1* or *BRCA2* mutation who developed cancer prior to age 50 or those who had never developed cancer when compared to women who developed cancer at age 50 or older. The mean age at menarche as well as p-values are shown in tables 5-6.

Table 5. Age at menarche based on cohort (*BRCA1*)

BRCA1	**Mean (SD)**	**P-value**
<50 w/ cancer	12.81 (1.59)	0.4522
≥ 50 w/ cancer *	13.03 (1.78)	
≥50 w/o cancer	12.18 (0.98)	0.1406
* Referent Group		

Table 6. Age at menarche based on cohort (*BRCA2*)

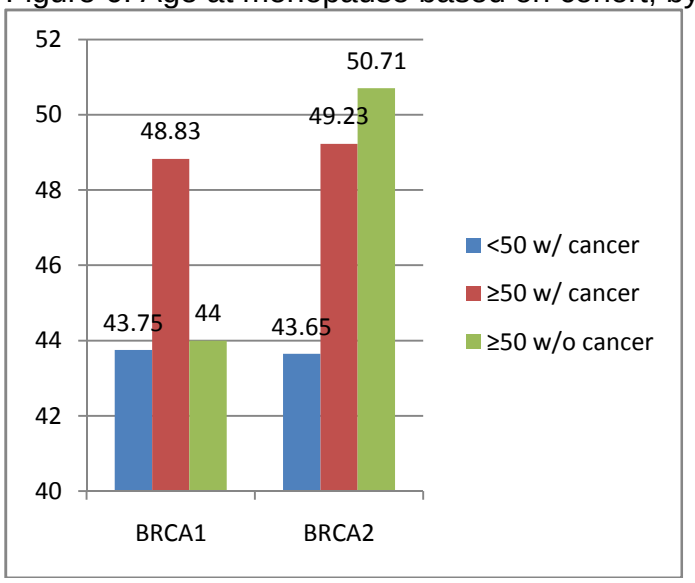
BRCA2	**Mean (SD)**	**P-value**
<50 w/ cancer	12.83 (1.31)	0.5455
≥ 50 w/ cancer *	12.68 (1.27)	
≥50 w/o cancer	13.13 (1.73)	0.3899
* Referent Group		

Mean age Menopause

Women with a *BRCA1* or *BRCA2* mutation diagnosed with cancer under age 50 underwent menopause at a statistically significant younger age than those diagnosed with cancer at age 50 or older ($p<0.0001$ for *BRCA1*; $p=0.0007$ for *BRCA2*). In addition, women with a *BRCA1* mutation diagnosed with cancer at age 50 or older underwent menopause at a statistically significant older age than women

with a *BRCA1* mutation who had never had a cancer diagnosis (p=0.0312). Women with a *BRCA2* mutation diagnosed with cancer at age 50 or older had no statistically significant difference from those never diagnosed with cancer (p=0.5204). Figure 6 shows the average age of menopause among the different cohorts.

Figure 6. Age at menopause based on cohort, by age at diagnosis



Mean Age at First Full Term Pregnancy

There was no difference in the age at first full-term pregnancy between women with a *BRCA1* or *BRCA2* mutation who developed cancer before age 50 when compared to those who developed cancer at age 50 or older. In addition, there was no difference between *BRCA1* or *BRCA2* positive women who developed cancer at age 50 or older when compared to women who had not developed cancer. Mean age at first full term pregnancy and p-values are shown in tables 7-8.

Table 7. Mean age at first full term pregnancy based on cohort (*BRCA1*)

BRCA1	**Mean (SD)**	**P-value**
<50 w/ cancer	24.82 (5.75)	0.1081
≥ 50 w/ cancer *	23.06 (3.93)	
≥50 w/o cancer	24.89 (4.31)	0.2376
* Referent Group		

Table 8. Mean age at first full term pregnancy based on cohort (*BRCA2*)

BRCA2	**Mean (SD)**	**P-value**
<50 w/ cancer	25.64 (5.66)	0.8075
≥ 50 w/ cancer *	25.35 (5.58)	
≥50 w/o cancer	26.67 (6.66)	0.6999
* Referent Group		

Parity

There was no difference in parity between women with a *BRCA1* or *BRCA2* mutation diagnosed with cancer over age 50 and those never diagnosed with cancer. In addition, there was no statistically significant difference between women with a *BRCA1* or *BRCA2* mutation who developed cancer prior to age 50 and those who developed cancer at age 50 or older. The median parity and p-values for each cohort are shown in tables 9-10.

Table 9. Median parity based on cohort (*BRCA1*)

***BRCA1* Group**	**Median (Range)**	**P-value**
<50 w/ cancer	2 (0-8)	0.0710
≥50 w/ cancer *	2 (0-10)	
≥50 w/o cancer	2 (0-4)	0.5962
* Referent Group		

Table 10. Median parity based on cohort (*BRCA2*)

***BRCA2* Group**	**Median (Range)**	**P-value**
<50 w/ cancer	2 (0-6)	0.0595
≥50 w/ cancer *	2 (0-7)	
≥50 w/o cancer	2.5 (0-4)	0.8546
* Referent Group		

When parity was broken into groups of 0, 1, 2, 3, or ≥4 children, there was no statistically significant difference between any of the groups. The p-value for *BRCA1* positive women with cancer development prior to age 50 vs. those who developed cancer at age 50 or older was 0.6839. When *BRCA1* positive women who developed cancer at age 50 or older were compared to those who had never developed cancer, the p-value was 0.8508. When *BRCA2* positive women who developed cancer prior to age 50 were compared to those who did not develop cancer until at age 50 or older, the p-value was 0.5886. *BRCA2* positive women who developed cancer at age 50 or older and those who had not developed cancer did not differ significantly in respect to their parity group (p=0.8281).

There was no statistically significant difference between parous women and non-parous women with a *BRCA1* mutation who developed cancer at age 50 or older when compared to those who developed cancer prior to age 50 (p=0.166) or those who had not developed cancer (p=0.924). There was no difference between parous and non-parous women with a *BRCA2* mutation who developed cancer at age 50 or older when compared to those who developed cancer prior to age 50 (p=0.664) and those who had not yet developed cancer (p=0.309).

Mean time breastfeeding (if parity >0)

There was no statistically significant difference between women with a *BRCA1* mutation who developed breast cancer prior to age 50 (p=0.3700) or had never developed cancer (p=0.9218) when compared to those who had developed cancer at age 50 or older. Women with a *BRCA2* mutation who developed cancer

prior to age 50 did not differ significantly from women who developed cancer at age 50 or older (p=0.0805). There was also no statistical difference in the median breastfeeding time period when comparing *BRCA2* mutation carriers who developed cancer at age 50 or older to those who had never developed cancer (0.6371). The median number of months of breastfeeding and p-values for each cohort are presented in tables 11-12.

Table 11. Median months of breastfeeding based on cohort (*BRCA1*)

***BRCA1* Group**	**Median (Range)**	**P-value**
<50 w/ cancer	3 (0-44)	0.3700
≥50 w/ cancer *	1.5 (0-9)	
≥50 w/o cancer	4 (0-10)	0.9218
* Referent Group		

Table 12. Median months of breastfeeding based on cohort (*BRCA2*)

***BRCA2* Group**	**Median (Range)**	**P-value**
<50 w/ cancer	4 (0-24)	0.0805
≥50 w/ cancer *	3 (0-18)	
≥50 w/o cancer	0 (0)	0.6371
* Referent Group		

There was no difference between the cohorts when comparing whether or not they had ever breastfed their children. The number of women who breastfed their children and the p-values associated are shown in tables 13-14.

Table 13. Breastfeeding status based on cohort (*BRCA1*)

Breastfeeding *BRCA1*	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=10	**n, (%) Total n=48**	**P-value**	**n, (%) Total n=3**	**P-value**
Yes	6 (60)	34 (71)	0.501	2 (67)	0.835
No	4 (40)	14 (29)		1 (33)	
* Referent Group					

Table 14. Breastfeeding status based on cohort (*BRCA2*)

Breastfeeding ***BRCA2***	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=11	**n, (%) Total n=23**	**P-value**	**n, (%) Total n=0**	**P-value**
Yes	7 (64)	15 (65)	0.928	0 (0)	0.217
No	4 (36)	8 (35)		1 (100)	
* Referent Group					

HRT and OCP Use

Oral contraceptive use did not affect the development of cancer among *BRCA1* or *BRCA2* women who developed cancer at age 50 or older when compared to those who developed cancer prior to age 50 or had never developed cancer. The numbers and percentages of women who used oral contraceptives are shown in tables 15-16.

Table 15. Oral Contraceptive use based on cohort (*BRCA1*)

OCP Use ***BRCA1***	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=33	**n, (%) Total n=151**	**P-value**	**n, (%) Total n=10**	**P-value**
Yes	25 (76)	120 (79)	0.636	6 (60)	0.186
No	8 (24)	31 (21)		4 (40)	
* Referent Group					

Table 16. Oral contraceptive use based on cohort (*BRCA2*)

OCP Use ***BRCA2***	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=46	**n, (%) Total n=60**	**P-value**	**n, (%) Total n=8**	**P-value**
Yes	34 (74)	49 (82)	0.337	7 (88)	0.407
No	12 (26)	11 (18)		1 (12)	
* Referent Group					

Women with a *BRCA1* or *BRCA2* mutation who developed cancer at age 50 or older were more likely to have taken a hormone replacement therapy than women who developed cancer prior to age 50. There was no difference in women with a *BRCA1* or *BRCA2* mutation diagnosed at age 50 or older when compared to those who had never developed cancer. The numbers and percentages of women who used HRT are shown in tables 17-18.

Table 17. HRT use based on cohort (*BRCA1*)

HRT Use ***BRCA1***	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=36	**n, (%) Total n=118**	**P-value**	**n, (%) Total n=10**	**P-value**
Yes	20 (56)	20 (17)	**<0.001**	7 (70)	0.412
No	16 (44)	98 (83)		3 (30)	
* Referent Group					

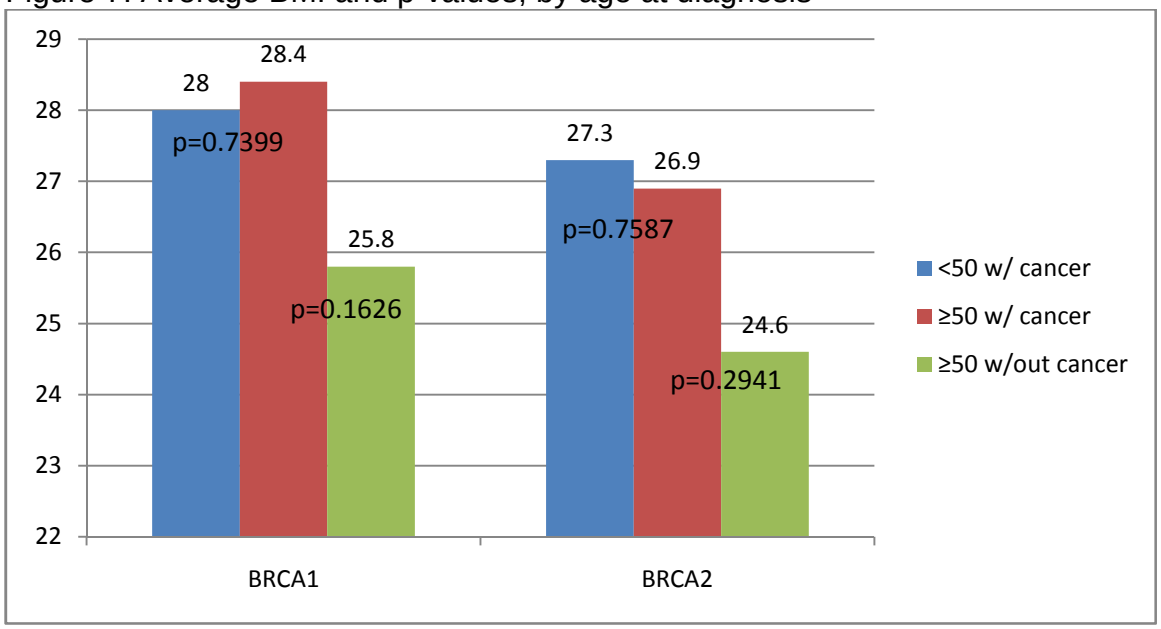
Table 18. HRT use based on cohort (*BRCA2*)

HRT Use *BRCA2*	≥50 w/ cancer *	<50 w/ cancer		≥50 w/out cancer	
	n, (%) Total n=46	n, (%) Total n=51	P-value	n, (%) Total n=7	P-value
Yes	27 (59)	8 (16)	**<0.001**	5 (71)	0.521
No	19 (41)	43 (84)		2 (29)	
* Referent Group					

BMI

No statistically significant differences in mean BMI were found between women diagnosed before age 50 and those diagnosed at age 50 or older with a *BRCA1* or *BRCA2* mutation. There were also no statistically significant differences between women diagnosed with cancer at age 50 or older and those with no cancer diagnosis. The average BMI for each group, as well as p values, are shown in Figure 7.

Figure 7. Average BMI and p-values, by age at diagnosis



SCREENING FREQUENCY AND MODALITY

There was a statistically significant difference between the number of women with a *BRCA1* mutation who received mammograms when comparing those diagnosed with cancer prior to age 50 and those who developed cancer at age 50 or older (p=0.009). Women who developed their cancer at a later age were more likely to have undergone mammography than those who developed cancer at an earlier age. There was no difference between women with a *BRCA1* or *BRCA2* mutation who developed cancer at age 50 or older and those who had never developed cancer (p=0.448, 0.896). In women with a *BRCA2* mutation, there was no significant difference in whether or not the woman had received a mammogram when comparing women who developed cancer prior to age 50 to those who developed cancer at age 50 or older (p=0.535).

There was a statistically significant difference in women with a *BRCA1* or *BRCA2* mutation who had received a breast MRI when comparing women who developed cancer prior to age 50 to those who developed cancer at age 50 or older (p=0.017, <0.001). Women diagnosed at age 50 or older were more likely to have had a breast MRI than those who developed cancer before age 50. There was no statistically significant difference in *BRCA1* or *BRCA2* positive women who developed cancer at age 50 or older when compared to those with no cancer diagnosis (p=0.095, 0.788).

Women with a *BRCA1* mutation with no cancer development were less likely to have had a clinical breast exam than those who had developed cancer at age 50 or older (p=0.003). There was no statistically significant difference between *BRCA1*

and *BRCA2* women diagnosed with cancer at an earlier age when compared to those diagnosed at a younger age when observing whether or not they had a clinical breast exam performed (p=0.585, 0.532). In addition, there was no difference between *BRCA2* women who developed cancer at age 50 or older when compared to those who had no cancer (p=0.939).

There was no difference in the number of *BRCA1* or *BRCA2* positive women who had had a CA-125 blood test when comparing those who developed cancer prior to age 50 or those who had never developed cancer to women who developed cancer at age 50 or older. P-value for *BRCA1* positive women who developed cancer prior to age 50 when compared to those who developed cancer at age 50 or older was 0.378. When comparing those with a *BRCA1* mutation who developed cancer at age 50 or older to those who had never developed cancer, the p-value was 0.252. In women with a *BRCA2* mutation who developed cancer at a later age, the p-value was 0.131 when compared to those who developed cancer at an earlier age. The p-value when comparing women with a *BRCA2* mutation who had never developed cancer to those who had developed cancer at age 50 or older was 0.397.

There was no difference in the number of women with a *BRCA1* or *BRCA2* mutation who had had a transvaginal ultrasound when comparing women who developed cancer at a later age to women who developed cancer at a younger age or who had never had a cancer diagnosis (p=0.872, 0.103, 0.842, 0.726).

The percentage of women who underwent the different screening procedures are shown in figures 8-9.

Figure 8. Percentage of women undergoing screening procedures based on cohort (*BRCA1*), by age at diagnosis

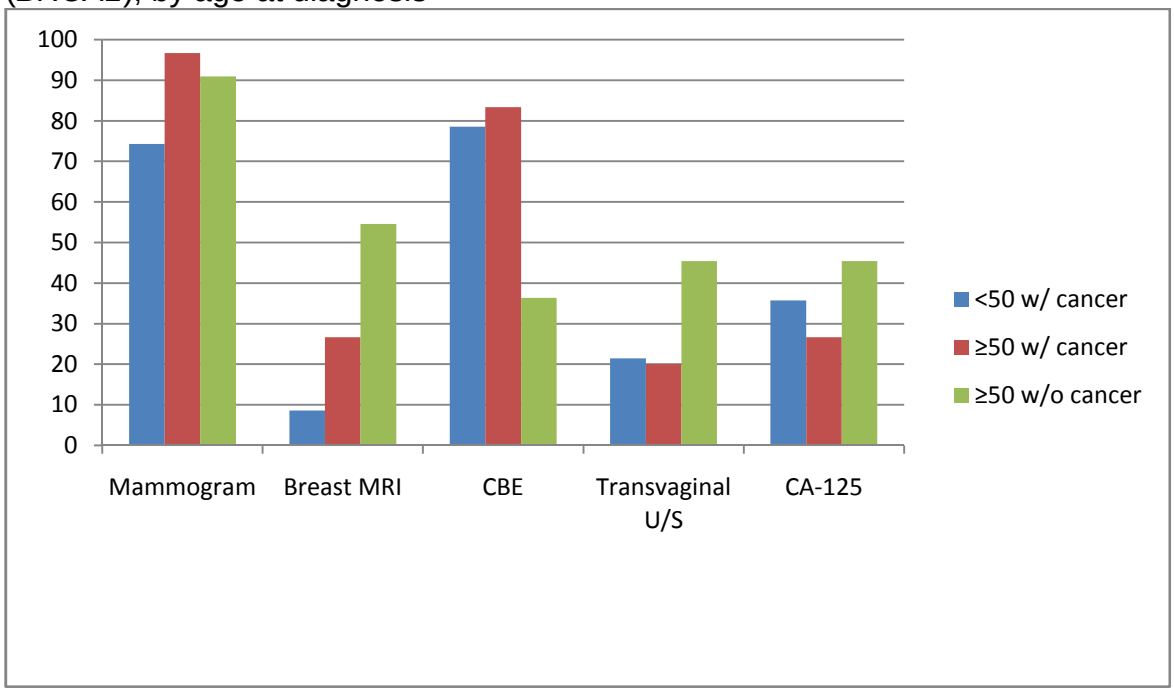
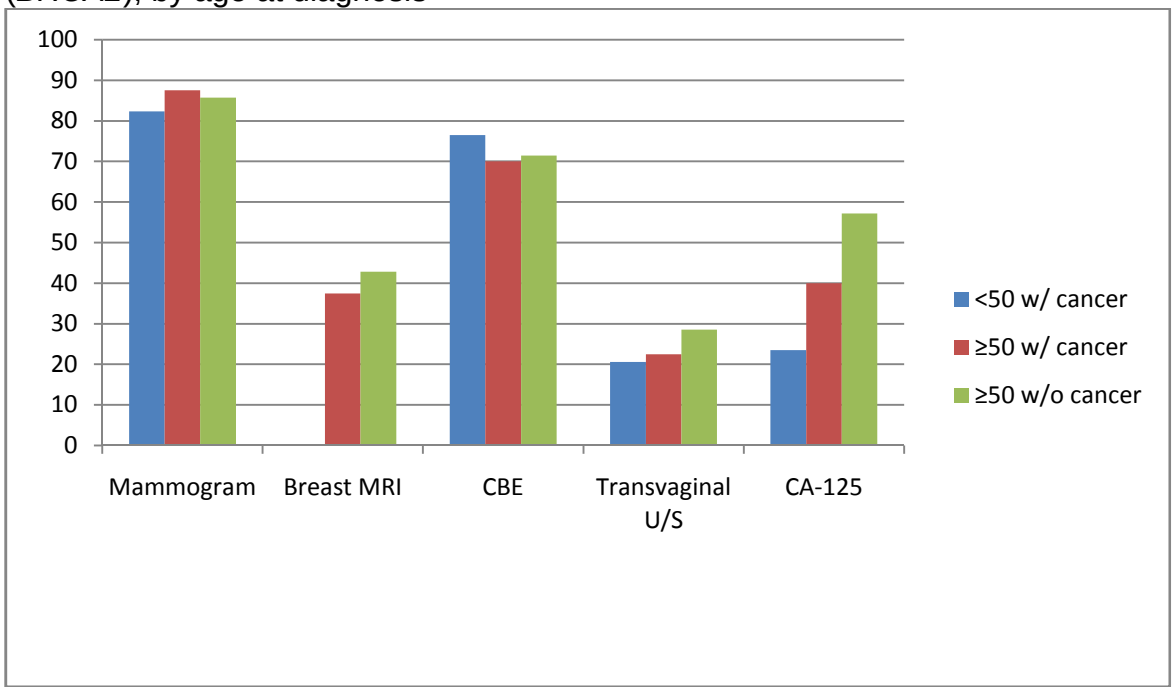


Figure 9. Percentage of women undergoing screening procedures based on cohort (*BRCA2*), by age at diagnosis



There was no difference in the screening frequency when comparing women with a *BRCA1* or *BRCA2* mutation diagnosed with cancer at age 50 or older to those who had never developed cancer (p=0.738, 0.825). Women with a *BRCA1* or *BRCA2* mutation who developed cancer at age 50 or older had a different distribution of screening frequency when compared to women who developed cancer prior to age 50 (p= 0.006, 0.009). The number of women who performed screening at certain time intervals are shown in tables 19-20.

Table 19. Screening frequency based on cohort (*BRCA1*)

Screening Frequency (*BRCA1*)	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=29	**n, (%) Total n=67**	**P-value**	**n, (%) Total n=11**	**P-value**
>Once per year	15 (52)	12 (18)	**0.006**	6 (55)	0.738
Annually	11 (38)	47 (70)		5 (45)	
<Once per year	2 (7)	7 (10)		0 (0)	
Never	1 (3)	1 (2)		0 (0)	
* Referent Group					

Table 20. Screening frequency based on cohort (*BRCA2*)

Screening Frequency (*BRCA2*)	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=39	**n, (%) Total n=34**	**P-value**	**n, (%) Total n=7**	**P-value**
>Once per year	16 (41)	3 (9)	**0.009**	3 (43)	0.825
Annually	20 (51)	24 (70)		3 (43)	
<Once per year	3 (8)	5 (15)		1 (14)	
Never	0 (0)	2 (6)		0	
* Referent Group					

CHEMOPREVENTION USE

There was not enough data to determine the differences in tamoxifen use between women with a *BRCA1* or *BRCA2* mutation who had developed cancer before or at age 50 or older. This information was not available in the medical records for the majority of these women. We did find that of the women who had not developed cancer, 56% of *BRCA1* positive women and 88% of *BRCA2* positive women had used tamoxifen.

RISK-REDUCING PROCEDURES

There was no difference in whether or not women with a *BRCA1* mutation underwent risk-reducing surgery when comparing women diagnosed at age 50 or older to those diagnosed prior to age 50. Women with a *BRCA2* mutation who developed cancer under age 50 were more likely to undergo risk-reducing surgery than those who developed cancer at age 50 or older. Women with a *BRCA1* or *BRCA2* mutation who had no cancer history were more likely to have undergone risk-reducing surgery than those who had developed cancer at age 50 or older. The numbers and percentages of women who underwent risk-reducing mastectomy or BSO are shown in tables 21-22.

The vast majority of women underwent risk-reducing BSO. Four women with a *BRCA1* mutation underwent a prophylactic mastectomy; three diagnosed prior to age 50 and one diagnosed at age 50 or older. There were only two women who underwent both a prophylactic bilateral mastectomy and BSO; both were over age

50 with no cancer diagnosis, one of whom had a *BRCA1* mutation and one who had a *BRCA2* mutation.

Table 21. Number of women who underwent risk-reducing mastectomy or BSO based on cohort (*BRCA1*)

Underwent Surgery (*BRCA1*)	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=40	**n, (%) Total n=169**	**P-value**	**n, (%) Total n=11**	**P-value**
Yes	13 (32.5)	86 (51)	0.092	9 (82)	**0.009**
No	27 (67.5)	83 (49)		2 (18)	
* Referent Group					

Table 22. Number of women who underwent risk-reducing mastectomy or BSO based on cohort (*BRCA2*)

Underwent Surgery (*BRCA2*)	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=51	**n, (%) Total n=67**	**P-value**	**n, (%) Total n=8**	**P-value**
Yes	13 (25)	35 (52)	**0.003**	7 (87.5)	**<0.001**
No	38 (75)	32 (48)		1 (12.5)	
* Referent Group					

Women with a *BRCA1* or *BRCA2* mutation diagnosed with cancer under age 50 underwent risk-reducing surgeries at a statistically significant younger age than those diagnosed at age 50 or older ($p<0.0001$ and 0.0149, respectively). There was no difference between the age of risk-reducing surgery for women over 50 with no cancer and those diagnosed at age 50 or older. The mean ages at risk-reducing surgery and p-values are shown in tables 23-24.

Table 23. Mean age at risk-reducing mastectomy or BSO based on cohort (*BRCA1*)

BRCA1	**Mean (SD)**	**P-value**
<50 w/ cancer	43.77 (7.01)	**<0.0001**
≥ 50 w/ cancer *	54.86 (12.03)	
≥50 w/o cancer	51.78 (11.20)	0.5452
* Referent Group		

Table 24. Mean age at risk-reducing mastectomy or BSO based on cohort (*BRCA2*)

BRCA2	**Mean (SD)**	**P-value**
<50 w/ cancer	45.32 (9.15)	**0.0149**
≥ 50 w/ cancer *	52.23 (6.06)	
≥50 w/o cancer	53.57 (6.63)	0.6530
* Referent Group		

TUMOR CHARACTERISTICS

There was no statistically significant difference in ER status among women with a *BRCA1* mutation who were diagnosed with breast cancer prior to age 50 when compared to those who developed breast cancer at age 50 or older. Women with a *BRCA2* mutation who developed cancer prior to age 50 were more likely to have an ER positive breast cancer than those who developed cancer at age 50 or older. The numbers of women with ER positive and ER negative breast tumors are shown in tables 25-26.

Table 25. ER status based on cohort (*BRCA1*)

***BRCA1* Group**	**<50 w/ cancer n, (%) Total n=96**	**≥50 w/ cancer n, (%) Total n=18**	**P-value**
ER positive	24 (25)	8 (44)	0.092
ER negative	72 (75)	10 (56)	

Table 26. ER status based on cohort (*BRCA2*)

***BRCA2* Group**	**<50 w/ cancer n, (%) Total n=43**	**≥50 w/ cancer n, (%) Total n=24**	**P-value**
ER positive	33 (77)	9 (37)	**0.001**
ER negative	10 (23)	15 (63)	

The PR status of breast tumors in women with a *BRCA1* mutation who developed breast cancer prior to age 50 was not statistically significant when compared to women who developed breast cancer at age 50 or older. Women with a *BRCA2* mutation who developed cancer prior to age 50 were more likely to have a PR positive breast cancer when compared to those with cancer at age 50 or older. The numbers of women with PR positive and PR negative breast tumors are shown in tables 27-29.

Table 27. PR status based on cohort (*BRCA1*)

***BRCA1* Group**	**<50 w/ cancer n, (%) Total n=92**	**≥50 w/ cancer n, (%) Total n=17**	**P-value**
PR positive	21 (23)	5 (29)	0.558
PR negative	71 (77)	12 (71)	

Table 28. PR status based on cohort (*BRCA2*)

***BRCA2* Group**	**<50 w/ cancer n, (%) Total n=41**	**≥50 w/ cancer n, (%) Total n=24**	**P-value**
PR positive	31 (76)	7 (29)	**<0.001**
PR negative	10 (24)	17 (71)	

There was no difference in the Her2/neu status when comparing women with a *BRCA1* or *BRCA2* mutation diagnosed with cancer under age 50 to those

diagnosed at age 50 or older. The numbers of women with Her2/neu positive and Her2/neu negative breast tumors are presented in tables 29-30.

Table 29. Her2/neu status based on cohort (*BRCA1*)

***BRCA1* Group**	**<50 w/ cancer n, (%) Total n=72**	**≥50 w/ cancer n, (%) Total n=14**	**P-value**
Her2/neu positive	6 (8)	2 (14)	0.483
Her2/neu negative	66 (92)	12 (86)	

Table 30. Her2/neu status based on cohort (*BRCA2*)

***BRCA2* Group**	**<50 w/ cancer n, (%) Total n=34**	**≥50 w/ cancer n, (%) Total n=20**	**P-value**
Her2/neu positive	6 (18)	1 (5)	0.182
Her2/neu negative	28 (82)	19 (95)	

ETHNICITY

There was no difference in the ethnicity distribution when women with a *BRCA1* or *BRCA2* mutation who developed cancer at age 50 or older were compared to those who had never developed cancer. There was a statistically significant difference in the distribution of ethnicity between women with a *BRCA1* or *BRCA2* mutation who developed cancer prior to age 50 when compared to women who developed cancer at age 50 or older (p=0.006 for *BRCA1* and p=0.019 for *BRCA2*). Ashkenazi Jewish women with a *BRCA1* mutation are more likely to have their cancer diagnosed at age 50 or older when compared to Caucasian women with a *BRCA1* mutation (p=0.002). In addition, women with a *BRCA1* mutations whose race was listed as “other” were found to be more likely to have their cancer diagnosed at age 50 or older when compared with Caucasian women

(p=0.026). Hispanic women with a *BRCA2* mutation were more likely to be diagnosed with cancer prior to age 50 when compared to Caucasian women (p=0.008).

The number and percentage of women from each ethnicity category are shown based on their cohort in figures 10-11.

Figure 10. Ethnicity based on cohort (*BRCA1*), by age at diagnosis

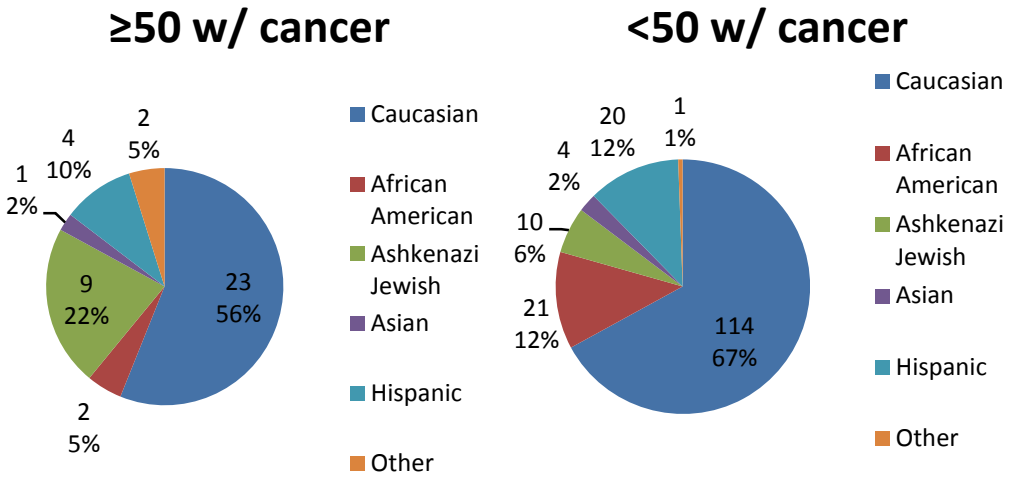
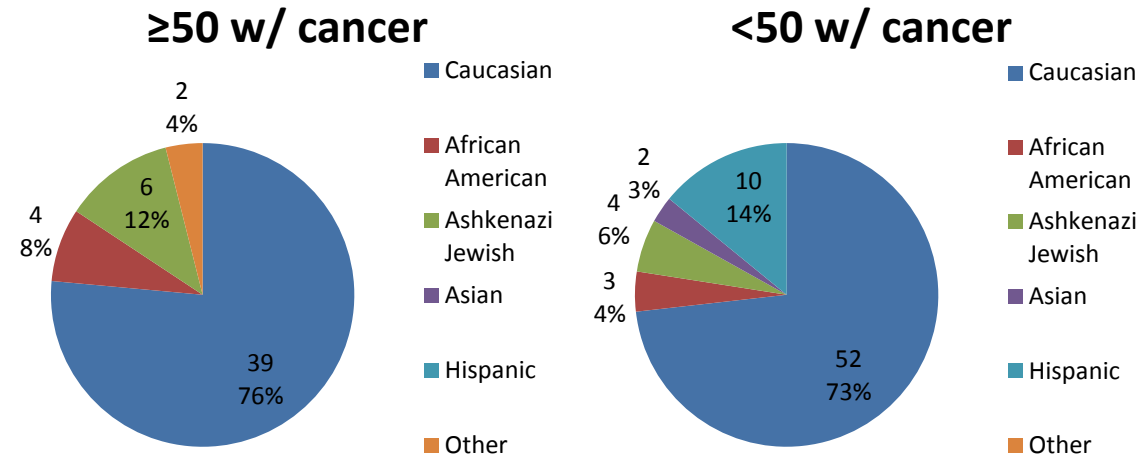


Figure 11. Ethnicity based on cohort (*BRCA2*), by age at diagnosis



FAMILY HISTORY

For family history information, we collected data about first and second degree relatives (FDR and SDR).

First Degree Relatives in BRCA1 Carriers

Women with a *BRCA1* mutation diagnosed at age 50 or older were more likely to have 0 or 1 affected first degree relative whereas those who had not developed cancer were more likely to have 2 or 3 first degree relatives. We did not find any statistically significant results when comparing the percentage of family members diagnosed with a breast or ovarian cancer among the *BRCA1* mutation carriers.

The number of families and number and percentage of first degree relatives with a breast or ovarian cancer diagnosis are shown in tables 31-32.

Table 31. First degree relatives with breast or ovarian cancer based on cohort (*BRCA1*)

Number of Families with N cases of Breast or Ovarian Cancer in FDR	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=41	**n, (%) Total n=153**	**P-value**	**n, (%) Total n=11**	**P-value**
n=0	10 (24)	49 (32)		0 (0)	
n=1	18 (44)	73 (48)		1 (9)	
n=2	13 (32)	21 (14)	0.053	8 (73)	**0.001**
n=3	0 (0)	8 (5)		2 (18)	
n≥4	0 (0)	2 (1)		0 (0)	
* Referent Group					

Table 32. Percentage of first degree relatives with breast or ovarian cancer based on cohort (*BRCA1*)

Percentage of FDRs with Breast or Ovarian Cancers	≥50 w/ cancer *	<50 w/ cancer		≥50 w/out cancer	
	n, (%) Total n=41	n, (%) Total n=153	P-value	n, (%) Total n=11	P-value
0%	10 (24)	49 (32)	0.094	0 (0)	0.054
1-24%	17 (42)	48 (31)		4 (36)	
25-49%	11 (27)	24 (16)		6 (55)	
50-74%	0 (0)	12 (8)		1 (9)	
100%	3 (7)	20 (13)		0 (0)	
* Referent Group					

There was a statistically significant difference in whether or not a woman with a *BRCA1* mutation had first degree relatives diagnosed with breast or ovarian cancer prior to age 50 when comparing women who developed cancer at age 50 or older to those who had never had cancer (p=0.030). This data is shown in table 33. We did not find any statistical significance when comparing whether or not each of the groups had a first degree relative diagnosed with breast or ovarian cancer after the age of 50. The number of women with first degree relatives diagnosed with breast or ovarian cancer under age 50 and p-values are presented in table 33. The number of women with first degree relatives diagnosed with breast or ovarian cancer over the age of 50 and p-values are presented in table 34.

Table 33. Cancer diagnoses <50 years of age in first degree relatives based on cohort (*BRCA1*)

First Degree Relatives Diagnosed Under Age 50	≥50 w/ cancer *	<50 w/ cancer		≥50 w/out cancer	
	n, (%) Total n=38	n, (%) Total n=137	P-value	n, (%) Total n=10	P-value
Yes	25 (66)	79 (58)	0.367	10 (100)	**0.030**
No	13 (34)	58 (42)		0 (0)	
* Referent Group					

Table 34. Cancer diagnoses ≥50 years of age in first degree relatives based on cohort (*BRCA1*)

First Degree Relatives Diagnosed ≥50	≥50 w/ cancer *	<50 w/ cancer		≥50 w/out cancer	
	n, (%) Total n=38	n, (%) Total n=121	P-value	n, (%) Total n=11	P-value
Yes	14 (37)	37 (31)	0.471	3 (27)	0.557
No	24 (63)	84 (69)		8 (73)	
* Referent Group					

First Degree Relatives in BRCA2 Carriers

When comparing *BRCA2* mutation carriers who developed cancer at age 50 or older to those who developed cancer prior to age 50, we found a statistically significant difference between the number of first-degree relatives diagnosed with breast or ovarian cancer. When we compared these data and looked at the percentage of family members diagnosed with a breast or ovarian cancer, we still found statistical significance between women with a *BRCA2* mutation who developed cancer prior to age 50 and those who developed cancer at age 50 or older. The number of families and number and percentage of first degree relatives with a breast or ovarian cancer diagnosis are shown in tables 35-36.

Table 35. Number of first-degree relatives with breast or ovarian cancer based on cohort (*BRCA2*)

Number of Families with N cases of Breast or Ovarian Cancer in FDR	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=49	**n, (%) Total n=66**	**P-value**	**n, (%) Total n=8**	**P-value**
n=0	10 (20)	35 (53)	**0.005**	1 (12.5)	0.319
n=1	29 (59)	21 (32)		3 (37.5)	
n=2	8 (17)	7 (11)		3 (37.5)	
n=3	1 (2)	3 (4)		1 (12.5)	
n≥4	1 (2)	0 (0)		0 (0)	
* Referent Group					

Table 36. Percentage of first degree relatives with breast or ovarian cancer diagnosis based on cohort (*BRCA2*)

Percentage of Families with N cases of Breast or Ovarian Cancer in FDR	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=49	**n, (%) Total n=66**	**P-value**	**n, (%) Total n=8**	**P-value**
0%	10 (20)	35 (53)	**0.001**	1 (12.5)	0.527
1-24%	24 (49)	12 (18)		3 (37.5)	
25-49%	9 (19)	7 (11)		3 (37.5)	
50-74%	2 (4)	4 (6)		1 (12.5)	
100%	4 (8)	8 (12)		0 (0)	
* Referent Group					

There was no difference between women with a *BRCA2* mutation who developed cancer at age 50 or older and those who developed cancer prior to age 50 when investigating whether they had any first degree relatives with a breast or ovarian cancer diagnosis under age 50. We found statistical significance when comparing *BRCA2* mutation carriers who developed cancer prior to age 50 to those who developed cancer at age 50 or older when comparing whether or not they had

a first degree relative diagnosed with breast or ovarian cancer at age 50 or older. The number of women with first degree relatives diagnosed with breast or ovarian cancer under age 50 and p-values are presented in table 37. The number of women with first degree relatives diagnosed with breast or ovarian cancer over the age of 50 and p-values are presented in table 38.

Table 37. Cancer diagnoses <50 based on cohort (*BRCA2*)

First Degree Relatives Diagnosed Under Age 50	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=43	**n, (%) Total n=58**	**P-value**	**n, (%) Total n=5**	**P-value**
Yes	17 (40)	26 (45)	0.595	3 (60)	0.380
No	26 (60)	32 (55)		2 (40)	
* Referent Group					

Table 38. Cancer diagnoses ≥50 based on cohort (*BRCA2*)

First Degree Relatives Diagnosed ≥50	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=44	**n, (%) Total n=54**	**P-value**	**n, (%) Total n=7**	**P-value**
Yes	26 (59)	7 (13)	**<0.001**	4 (57)	0.923
No	18 (41)	47 (87)		3 (43)	
* Referent Group					

Second Degree Relatives

When looking at second degree relatives who developed breast or ovarian cancer, there was no difference between *BRCA1* or *BRCA2* positive women who developed cancer prior to age 50 or had never developed cancer when compared to those who developed cancer after the age of 50. The number of first-degree

relatives with a breast or ovarian cancer and p-values are presented in tables 39-40.

Table 39. Number of first degree and second degree relatives with breast or ovarian cancer based on cohort (*BRCA1*)

Number of Families with N cases of Breast or Ovarian Cancer in FDR & SDR	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=41	**n, (%) Total n=163**	**P-value**	**n, (%) Total n=12**	**P-value**
n=0	2 (5)	19 (12)	0.507	0 (0)	0.312
n=1	13 (32)	51 (31)		1 (8)	
n=2	15 (37)	47 (29)		6 (50)	
n=3	6 (15)	33 (20)		4 (34)	
n≥4	5 (12)	13 (8)		1 (8)	
* Referent Group					

Table 40. Number of first degree and second degree relatives with breast or ovarian cancer based on cohort (*BRCA2*)

Number of Families with N cases of Breast or Ovarian Cancer in FDR & SDR	**≥50 w/ cancer ***	**<50 w/ cancer**		**≥50 w/out cancer**	
	n, (%) Total n=49	**n, (%) Total n=70**	**P-value**	**n, (%) Total n=8**	**P-value**
n=0	3 (6)	15 (21)	0.246	0 (0)	0.366
n=1	15 (31)	20 (29)		1 (12.5)	
n=2	17 (35)	19 (27)		4 (50)	
n=3	6 (12)	7 (10)		0 (0)	
n≥4	8 (16)	9 (13)		3 (37.5)	
* Referent Group					

DISCUSSION

To our knowledge, there has been no previous research specifically evaluating the older population of women with a *BRCA1* or *BRCA2* mutation who do not have cancer or who developed cancer at a later age (age 50 or older). The aim of this study was to evaluate reproductive risk factors, family history, BMI, and tumor pathology among women with a *BRCA1* or *BRCA2* mutation who developed breast or ovarian cancer age 50 or older and determine if there were statistically significant differences between any of these factors when compared to women with a *BRCA1* or *BRCA2* mutation who developed cancer prior to age 50. An additional aim of this study was to evaluate reproductive risk factors, family history, BMI, and tumor pathology among women with a *BRCA1* or *BRCA2* mutation who are over the age of 50 and have not developed cancer and determine if there were any significant differences in these factors when compared to women with a *BRCA1* or *BRCA2* mutation who developed cancer at age 50 or older. The goal of the analyses was to determine whether or not there are factors in *BRCA1* or *BRCA2* positive women that determine whether a woman develops early or late onset breast cancer as well as to determine whether there are factors that determine whether or not a woman with a *BRCA1* or *BRCA2* mutation ever develops breast or ovarian cancer.

Women with a *BRCA1* or *BRCA2* mutation who developed cancer prior to age 50 were more likely to develop breast cancer as their first cancer diagnosis than those who developed cancer at age 50 or older. The vast majority of women diagnosed under age 50 (79% of *BRCA1* and 96% of *BRCA2* mutation carriers)

were diagnosed with breast cancer whereas only 42% of *BRCA1* and 53% of *BRCA2* mutation carriers diagnosed at age 50 or older were diagnosed with breast cancer. Ovarian cancer was more likely to be diagnosed in the women who developed cancer at age 50 or older than those who developed cancer prior to age 50. The fact that women are more likely to be diagnosed with ovarian cancer at age 50 or older is consistent with the literature, as ovarian cancer often develops at an older age (6, 61), however it is interesting to note that women who developed cancer at age 50 or older were had an approximately equal likelihood to develop ovarian cancer as they did to develop breast cancer. In women with a *BRCA1* or *BRCA2* mutation, the lifetime risk of breast cancer is greater than that of ovarian cancer (3-6, 61), however from this study, it appears as though at age 50 or older, the chance for a woman with a *BRCA1* or *BRCA2* mutation to develop breast cancer is approximately the same as that to develop ovarian cancer.

REPRODUCTIVE RISK FACTORS

Age at Menarche

Age at menarche did not show statistical significance between any of the groups in our study. This is consistent with one previous study that did not find an association between age at menarche and breast cancer risk in *BRCA1* or *BRCA2* carriers (10). Other studies have found that a later age of menarche is associated with a decreased breast cancer risk in *BRCA1* mutation carriers (9, 15), however this was not observed in our population. Our study suggests that the age at menarche does not affect whether or not a woman with a *BRCA1* or *BRCA2*

mutation will develop breast or ovarian cancer before age or after age 50. It also suggests that age at menarche does not determine whether a woman will develop cancer at age 50 or older or not develop cancer at all.

Age at Menopause

Women with a *BRCA1* or *BRCA2* mutation who developed cancer prior to age 50 underwent menopause at a statistically significant younger age than women who developed cancer at age 50 or older. Those with a *BRCA1* mutation who developed cancer at age 50 or older underwent menopause at an average age of 44 years and those who developed cancer after 50 underwent menopause at an average age of 49. This is not consistent with current literature. Early age at menopause is associated with a decreased risk of breast and ovarian cancer (7, 10, 12). We would expect that women diagnosed with cancer at age 50 or older would have an earlier age of menopause. The reason for the difference in our study is likely that women diagnosed under age 50 underwent menopause earlier due to chemotherapy or surgery. When observing age at prophylactic surgery, women diagnosed with cancer at a younger age were more likely to undergo prophylactic BSO at a younger age when compared to those who developed cancer at a later age. When ascertaining the age at menopause, we did not distinguish between women who had naturally undergone menopause from women whose menopause was surgically or chemotherapy induced. This likely accounts for the difference seen in ages at menopause between women diagnosed with cancer at a younger age. Because these women were more likely to have undergone chemotherapy or

surgery that induced menopause, these women went through menopause at a statistically significant younger age. Future studies should investigate whether the natural age at menopause differs between women who developed cancer at a late vs. early age or those who have not developed cancer.

Women with a *BRCA1* mutation who developed cancer at age 50 or older went through menopause at an average age of 49 while those who had never developed cancer underwent menopause at an average age of 44. Women who developed cancer at a later age underwent menopause at a statistically significant older age than those with no cancer diagnosis. This is not consistent with the current literature. It is not known why this difference was seen in *BRCA1* mutation carriers, but not in *BRCA2* mutation carriers. In *BRCA2* carriers, the average age at menopause in women who developed cancer at age 50 or older was 49 and those who had never developed cancer underwent menopause at an average age of 50. This is more consistent with the current literature. We are unable to explain the difference in age at menopause between *BRCA1* mutation carriers whose cancer developed at age 50 or older and those who had never developed cancer. This is a factor that needs further investigation.

Age at First Full-Term Pregnancy

Age at first full-term pregnancy did not appear to have an effect on whether a woman with a *BRCA1* or *BRCA2* mutation had early or late onset cancer. It also did not appear to have an effect on whether or not a woman with a *BRCA1* or *BRCA2* mutation developed cancer at age 50 or older or had never developed cancer. The

literature about age at first full-term pregnancy in women with a *BRCA1* or *BRCA2* mutation is not consistent. Some studies have found that early age at full-term birth was not protective against breast cancer in women with a *BRCA1* or *BRCA2* mutation (14). Other studies have shown that later ages of first childbirth was associated with an increased risk of breast cancer in *BRCA2* mutation carriers (15). Our study did not find any statistically significant differences between the groups, suggesting that age at first full-term pregnancy does not significantly affect whether or not a woman will develop cancer at an early or later age or whether she will develop cancer during her lifetime.

Parity

Women with a *BRCA1* mutation who developed cancer at age 50 or older had more children (2.73) than those who developed cancer prior to age 50 (1.96) and Women with a *BRCA2* mutation who developed cancer at age 50 or older had more children (2.33) than those who developed cancer prior to age 50 (1.86). While these results were not statistically significant, they did approach significance for individuals with a *BRCA1* mutation (p=0.0710 for *BRCA1* and p=0.595 for *BRCA2*). Previous studies have found that the risk for breast and ovarian cancer in women with a *BRCA1*/2 mutation decreases as parity increases (9, 15-17), however we did not find any statistical significance in our data. We did not find any differences in parous and non-parous women with a *BRCA1* or *BRCA2* mutation who developed cancer at age 50 or older when compared to those who developed cancer prior to

age 50 or who had never developed cancer. This has been seen in previous studies (15).

There was a woman with a *BRCA1* mutation diagnosed at age 50 or older who had 10 children. Because of the possibility of skewed data, we analyzed parity in such a way that those with four or more children were put into one group. When we attempted to correct for this possibility of skewed data, there was no statistical significance between any of the groups and the p-values did not approach significance. Parity does not appear to have an effect on whether or not a woman with a *BRCA1* or *BRCA2* mutation will develop cancer at an earlier or later age. It also does not seem to have an effect on whether a woman develops cancer at age 50 or older or does not develop cancer. Because we saw statistically significant values or values approaching significance when looking at total parity for the groups, it may be that having many children (more than 4) has an effect on breast or ovarian cancer risk, however the data may be skewed in our analysis.

Breastfeeding

There was no statistical difference in the mean time of breastfeeding among *BRCA1* or *BRCA2* mutation carriers who developed cancer prior to age 50 when compared to those who developed cancer at age 50 or older. There was also no difference in women who had never developed cancer when compared to those who developed cancer at age 50 or older. We also investigated whether there was a difference in any of the groups when comparing whether or not they had ever breastfed at all and found no significance between any of the groups. From our

study, it does not appear that breastfeeding has an impact on the breast or ovarian cancer risk in women with a *BRCA1* or *BRCA2* mutation. This is consistent with previous studies (9, 11, 15, 18).

Overall Reproductive Factors

Many of the reproductive factors that are known to have an effect on a woman's breast or ovarian cancer risk do not seem to have an effect on this risk in *BRCA1* or *BRCA2* mutation carriers. Parity may have some effect, however it seems as though this effect may only be evident if a woman has more than 4 children. The fact that reproductive factors do not appear to have an effect on whether a woman is diagnosed with cancer at an early or later age likely means that the woman's risk from her *BRCA1* or *BRCA2* mutation overrides any protective effect that reproductive factors may have.

OCP AND HRT USE

We did not find any difference in whether or not a woman had used oral contraceptives when comparing women who developed cancer at age 50 or older to those who developed cancer before age 50 or had never developed cancer. It does not appear, from our study, that oral contraceptive use affects breast or ovarian cancer development in *BRCA1* or *BRCA2* mutation carriers.

We found that women who developed cancer at age 50 or older were more likely to have used hormone replacement therapy than women who developed cancer prior to age 50. This is likely due to the ascertainment of the two groups.

Most of the women who developed cancer under age 50 had not yet gone through menopause, therefore they were less likely to have needed hormone replacement therapy. No conclusions can be drawn about hormone replacement therapy use and breast and ovarian cancer development from this data.

BMI

While there were no statistically significant differences in women with a *BRCA1* or *BRCA2* mutation who developed cancer at age 50 or older when compared to those who developed cancer prior to age 50 or had never developed cancer, we did note that women who were over age 50 with no cancer diagnosis had a lower average BMI than the other groups. While this difference was not statistically significant, it was consistent among the *BRCA1* and *BRCA2* groups. Previous literature has shown that women in the general population with a lower BMI after menopause have a decreased risk of breast cancer (27, 28). For this study, BMI was ascertained at the time the individual presented to MD Anderson for their genetic testing. Women diagnosed at a younger age may have had their genetic testing performed at a younger age compared to women who were diagnosed at an older age, therefore the data may be somewhat biased. A woman's body weight fluctuation throughout life may have more impact on her breast cancer diagnosis than BMI at a specific time in her life (29, 62), therefore a more accurate way to assess whether BMI impacts breast or ovarian cancer may be to record a woman's BMI at different time points in her life.

SCREENING

We observed screening frequency and screening modalities of women with a *BRCA1* or *BRCA2* mutation prior to their cancer diagnosis. In looking at screening frequency, we found a difference in frequency of screening when comparing women with a *BRCA1* or *BRCA2* mutation who developed cancer at age 50 or older to those who developed cancer prior to age 50. Women who developed cancer at age 50 or older underwent more frequent screening than those who developed cancer prior to age 50. This is likely because many of the women who were diagnosed under age 50 were diagnosed prior to 40 years of age and the breast cancer screening recommendations for women in the general population is to begin mammography at age 40. Because many of these women were not yet 40 years of age, it is likely that their first mammogram was for diagnostic purposes, not for screening purposes. In addition, some of the women who developed cancer under age 50 may not have had knowledge of their *BRCA* mutation prior to their cancer diagnosis, so they were likely not undergoing the increased surveillance recommendations that have been developed for women with a *BRCA1* or *BRCA2* mutation. Women who developed cancer at age 50 or older were likely already getting their annual breast cancer screening, even without knowledge of their *BRCA* mutation, due to the screening recommendations that are in place for the general population.

There was no difference in screening frequency between women who developed breast cancer at age 50 or older and those who had never developed

cancer. This is likely because these women are following current medical recommendations to undergo screening annually since they are over the age of 40.

When looking specifically at mammography screening, we found that women with a *BRCA1* mutation who developed cancer at age 50 or older were more likely to have had a mammogram when compared to those who developed cancer prior to age 50. Again, this is quite likely due to current breast cancer screening for the general population and younger women most likely received their first mammogram for diagnostic purposes. We did not see this difference in *BRCA2* mutation carriers. We cannot explain the difference between these two groups.

In women with a *BRCA1* or *BRCA2* mutation who developed cancer at age 50 or older, we found that they were more likely to have had a breast MRI than women who developed cancer prior to age 50. This was an interesting result given that breast MRI is recommended to all women with a *BRCA* mutation. It is possible that women who developed cancer at age 50 or older may have known about their *BRCA* mutation prior to developing cancer and began screening recommendations for that population whereas those who developed cancer prior to age 50 may have not had knowledge of their *BRCA* mutation prior to developing their own cancer and had not received screening recommendations for *BRCA* carriers. Women who developed their cancer later in life are more likely to have had other family members diagnosed with cancer, given the older ages of their relatives, and therefore may have had knowledge of their *BRCA* mutation, or may have been receiving breast MRIs due to their family history, prior to their own cancer diagnosis.

We found that *BRCA1* carriers with no cancer were less likely to have had a clinical breast exam when compared to those who developed cancer at age 50 or older. Women undergoing more screening are more likely to have a breast cancer diagnosis because the cancer may be detected by screening. This same difference, however, was not seen in *BRCA2* mutation carriers; there was no difference when comparing those who developed cancer at age 50 or older to those with no cancer diagnosis. We found no difference in the proportion of women who had received a clinical breast exam when comparing those diagnosed at age 50 or older to those who were diagnosed before age 50.

We found no difference in the proportion of women undergoing ovarian cancer screening (CA-125 blood test or transvaginal ultrasound) when comparing those who developed cancer prior to age 50 and those who developed cancer at age 50 or older. In addition, there was no difference in the proportion of women undergoing ovarian cancer screening when comparing those who developed cancer at age 50 or older and those who had never developed cancer.

CHEMOPREVENTION USE

We were unable to analyze data comparing the use of chemopreventive agents among the groups. Chemoprevention use was not mentioned in the majority of the medical records for women who had a cancer diagnosis. In women who had not had a cancer diagnosis we found that 56% of *BRCA1* carriers and 88% of *BRCA2* carriers had used tamoxifen. The use of tamoxifen in *BRCA1* mutation carriers may be less than *BRCA2* carriers because it is known that *BRCA1* positive

women are more likely to have a triple-negative (ER/PR/Her2/neu status) breast cancer and tamoxifen is not protective against triple-negative breast cancers. Women with a *BRCA1* mutation may feel as though tamoxifen is not as effective against breast cancer as it is in the general population, so fewer women may choose to use it. In addition, it has been previously reported that women are concerned about the side effects of tamoxifen, leading some women to decline its use as a chemopreventive agent (63).

RISK-REDUCING SURGERIES

Women with a *BRCA1* or *BRCA2* mutation who developed cancer prior to age 50 underwent prophylactic surgeries at a statistically significant younger age than those who developed cancer at age 50 or older. Studies have found that the median time to risk-reducing surgery is approximately four months after learning about a positive *BRCA* result (64). Women who developed cancer under age 50 likely found out about their *BRCA* status earlier than those who developed cancer at age 50 or older and, therefore, underwent their risk-reducing surgery at an earlier age.

We found that women over age 50 with no cancer diagnosis were more likely to have undergone a risk-reducing surgery than those who had developed cancer at age 50 or older. This is expected because these women have not developed cancer and it is likely that this is due to their risk-reducing surgery. Risk-reducing BSO reduces breast cancer risk by approximately 50% and ovarian cancer by up to 96% (37, 38, 41-43). However, the average age that women over age 50 with no

cancer diagnosis underwent their risk-reducing surgery was 51.78 in *BRCA1* mutation carriers and 53.78 in *BRCA2* mutation carriers. They did not undergo surgery at a younger age than women who developed cancer at age 50 or older.

When comparing average age at diagnosis and average age of surgery, it is interesting to note that women who developed cancer prior to age 50 appear to have undergone risk-reducing surgery after their cancer diagnosis and women who developed cancer at age 50 or older seem to have undergone risk-reducing surgery prior to developing their first cancer. This may be due to the risk-reducing surgery delaying the development of cancer in these individuals. From this observation, it seems as though women diagnosed with cancer will undergo a risk-reducing surgery sooner than those with no cancer diagnosis, however this may also be due to these women finding out about their *BRCA* status at a younger age as well. In our study, in each of the groups of women over the age of 50, they underwent their surgeries at a similar age. It appears as though with no cancer diagnosis, women will wait until a later age to pursue risk-reducing surgery, however it does not seem as though a cancer diagnosis impacts their decision. It is likely that the woman's family history of cancer, knowledge of cancer risks, knowledge of *BRCA* status, and recommendations from physicians impact her decision to undergo risk-reducing procedures.

There was no difference in the age at risk-reducing surgery among *BRCA1* or *BRCA2* women who developed cancer at age 50 or older when compared to those who had never had a cancer diagnosis. Again, it appears as though the

cancer diagnosis in the women diagnosed at a younger age probably impacts their decision to undergo risk-reducing surgery at a younger age.

There were only three women over the age of 50 who had not developed cancer that had never undergone any risk-reducing surgeries. These women were last seen at MD Anderson at ages 51, 53, and 82. Because of the small number of women who have not undergone risk-reducing surgeries, it is difficult to draw conclusions about some of the findings when comparing women who developed cancer at age 50 or older to those who have never developed cancer. The other women in this category may have developed cancer if it were not for their risk-reducing surgeries. While risk-reducing surgeries are not 100% preventive, it is known that bilateral mastectomy reduces the breast cancer risk by 90% (41) and BSO reduces breast cancer risk by 50% and ovarian cancer risk by up to 96% (37, 38, 42, 43). The majority of women who underwent risk-reducing surgery did not undergo bilateral mastectomy, so they do still have a risk to develop breast cancer.

TUMOR CHARACTERISTICS

We found that women with a *BRCA2* mutation who developed cancer at age 50 or older were more likely to have an ER/PR negative breast cancer than those who developed breast cancer prior to age 50. While women with early-onset breast cancer are more likely to have ER/PR negative tumors than women with later-onset breast cancer, one study did find that *BRCA2* mutation carriers whose cancer was diagnosed at a later age were more likely to have ER/PR negative tumors (47). The reason for this finding is unknown at this time and more research about women with

BRCA2 mutations and ER/PR negative tumors is warranted as this may lead to clinical implications when discussing endocrine therapies for breast cancer.

There was no difference in ER or PR status in women with a *BRCA1* mutation when comparing those who developed cancer prior to age 50 to those who developed cancer at age 50 or older. This is likely because women with a *BRCA1* mutation are more likely to have a triple-negative breast cancer, therefore women with early or late onset breast cancer do not differ significantly in their ER/PR status.

We did not find a difference in Her2/neu status when comparing women with a *BRCA1* or *BRCA2* diagnosed prior to age 50 to those diagnosed at age 50 or older. In the study by Atchley et al, (47) they found that women with a *BRCA2* mutation with later-onset breast cancer were more likely to have Her-2/*neu* negative breast cancers. In our study, there was no statistically significant difference in Her-2/*neu* status in women diagnosed before age 50 and those diagnosed at age 50 or older.

ETHNICITY

We identified a difference in the ethnicity distribution in both *BRCA1* and *BRCA2* mutation carriers when comparing women who developed cancer prior to age 50 to those who developed cancer at age 50 or older. From our data, it appears as though Ashkenazi Jewish women and women of “other” race develop cancer at an older age when compared to other ethnicities. It also appears as though Hispanic women with a *BRCA2* mutation develop cancer at a younger age when compared to other ethnicities. The majority of the women included in our

study were Caucasian, therefore it would be beneficial to look at these populations in greater numbers to determine whether there is a significant difference in their cancer risks based on ethnicity. To our knowledge, there have been no published reports about early vs. late cancer diagnosis in *BRCA1* or *BRCA2* mutation carriers among different ethnicities.

FAMILY HISTORY

We found that women over the age of 50 with no cancer diagnosis were more likely to have 2 or 3 first-degree relatives diagnosed with a breast or ovarian cancer while those diagnosed with cancer at age 50 or older were more likely to have 0 or 1 relative with a breast or ovarian cancer diagnosis. Women with no breast cancer were more likely to have undergone a risk-reducing surgery than those who had developed breast cancer at age 50 or older and this may be due to having seen more relatives affected with a breast or ovarian cancer or having prior knowledge of a *BRCA* mutation in the family. While the p-value approached significance ($p=0.054$), we did not identify any statistical significance between these groups when looking at the percentage of first-degree relatives diagnosed with a breast or ovarian cancer.

All of the women with a *BRCA1* mutation in our study who had not developed cancer had at least one first-degree relative who developed breast or ovarian cancer prior to age 50. This was statistically different than the group of women who developed cancer at age 50 or older. We found that 66% of women diagnosed with cancer at age 50 or older had a first-degree relative who was diagnosed with breast

or ovarian cancer before 50 years of age and 34% of them did not have a first-degree relative diagnosed under age 50. From this data, it appears as though women with no cancer have more early-onset breast and/or ovarian cancer in their first-degree relatives, however the majority of the women with no cancer had a risk-reducing surgery. It is likely that these women underwent their surgery due to many family members having a breast or ovarian cancer diagnosis or may be due to prior knowledge of a *BRCA* mutation in the family.

Women who developed cancer prior to age 50 were not more likely to have a first-degree relative diagnosed under age 50 when compared to the group of women who developed cancer at age 50 or older. From this information, it does not appear that early-onset breast cancer in a first-degree relative predicts early-onset breast cancer in another first-degree relative. Likewise, it does not appear that having a first-degree relative with cancer diagnosed at age 50 or older predicts later-age of cancer onset in women with a *BRCA1* mutation. When comparing women with cancer at age 50 or older to those diagnosed before 50 or those who had not had a cancer diagnosis, there was no difference in whether or not they had a first-degree relative diagnosed with breast or ovarian cancer at age 50 or older.

Women with a *BRCA2* mutation who developed cancer before age 50 were more likely to have no breast or ovarian cancer diagnoses in their first-degree relatives when compared to women who developed cancer at age 50 or older. When we looked at the percentage of first-degree relatives with a cancer diagnosis, we found that women who developed cancer before age 50 were more likely to have 0% of their relatives affected with breast cancer while those who developed

cancer at age 50 or older were more likely to have 1-25% of their first-degree relatives affected. These results may likely be due to the ages of first-degree relatives in the family because women under age 50 may have younger relatives than those who developed cancer at age 50 or later. Women over age 50 are more likely to have more relatives that are of older ages when compared to the women who developed cancer under age 50. Because age is a risk factor for breast and ovarian cancer, it may be that the first-degree relatives of women who had cancer under age 50 have not yet developed cancer but may have a cancer diagnosis in the future. This result is likely due to ascertainment bias.

Women with a *BRCA2* mutation who developed cancer at age 50 or older did not differ in the number or percentage of family members with breast or ovarian cancer when compared to women who had not developed cancer. From this data, it does not appear that the number of family members with a cancer diagnosis affects the chance that a woman will develop cancer.

There was no difference between women with a *BRCA2* mutation who developed cancer at age 50 or older and those who developed cancer prior to age 50 when investigating whether they had any first degree relatives with a breast or ovarian cancer diagnosis under age 50. Similarly, we did not find any difference in whether or not a woman had a first-degree relative with breast or ovarian cancer under 50 when comparing women who developed cancer at age 50 or older to those who had never developed cancer. It does not appear that having a first-degree relative with a cancer diagnosis under age 50 increases the risk for early-onset breast or ovarian cancer in women with a *BRCA2* mutation.

We found that women with a *BRCA2* mutation who developed cancer at age 50 or older were more likely to have a first-degree relative diagnosed with cancer at age 50 or older when compared to women who developed cancer prior to age 50. This trend may be present for two different reasons. Women with a history of later-onset breast cancer may develop later-onset breast cancer themselves or it may be that women who developed cancer before age 50 have fewer first-degree relatives over the age of 50 and, therefore, are less likely to have cancer diagnosed at age 50 or older. This finding may be due to ascertainment bias, therefore more studies on age at diagnosis in family members may be warranted.

When combining first- and second-degree family members' cancer histories, it does not appear that there is any significant difference between any of the groups. It does not appear that the number of first- and second-degree relatives with a cancer diagnosis has an impact on early vs. late cancer diagnosis in women with a *BRCA1* or *BRCA2* mutation. From our study, it is not evident that the age of onset within a family with a *BRCA1* or *BRCA2* mutation can predict the age of onset for other individuals within the family.

SUMMARY OF ASSOCIATIONS

Among our population of women with a *BRCA1* or *BRCA2* mutation we identified several significant and interesting observations. We found that women who developed their first cancer at or after age 50 appear to have an approximately equal chance to develop ovarian cancer as they do to develop breast cancer. We also found that reproductive risk factors and BMI do not appear to play a significant

role in the development of breast or ovarian cancer among these women, however further studies on the effect of age at menopause should be performed. Women with a *BRCA2* mutation who developed breast cancer at or after age 50 were more likely to have an ER/PR negative tumors than those who developed their breast cancer prior to age 50. Ethnicity may play a role in the development of early vs. late onset of breast or ovarian cancer. Women of Ashkenazi Jewish descent with a *BRCA1* mutation appear to be more likely to develop late-onset breast or ovarian cancer, whereas Hispanic women with a *BRCA2* mutation seem to be more likely to have an early-onset of breast or ovarian cancer. Family history of breast and ovarian cancer may have an impact on the development of these cancers in an individual, however this is not clear in our study and additional investigation on this topic is warranted.

STUDY LIMITATIONS

There have been several limitations of the current study noted. The main limitation to our study is ascertainment bias. All of the women included in this study were patients at MD Anderson and, therefore, they likely either had a diagnosis of breast or ovarian cancer or had a relative with breast or ovarian cancer. Therefore, our population is highly skewed toward women who have a family history of cancer or have had a breast or ovarian cancer diagnosis. In addition, our study only included women who have knowledge of their *BRCA* mutation, so we were unable to evaluate factors among women who have a *BRCA* mutation but do not have knowledge of their *BRCA* status. This information would have likely been very

helpful when studying reproductive risk factors, however would likely not play a significant role when exploring screening frequencies/modalities and risk-reduction surgeries.

Because this was a retrospective study, we were unable to obtain all relevant information on every patient. In identifying some factors, there was information missing on certain individuals. It is possible that this information would lead us to find some significance in our analyses, however it is unlikely that this missing information would alter the analyses a significant amount.

Another limitation to our study is that the family history information obtained was via patient report and was not validated using medical records. It is possible that some cancer diagnoses were misreported or under-reported due to patients not recalling certain cancer diagnoses or recalling cancer diagnoses that did not truly exist.

An additional limitation to this study is that we are unable to predict whether the women who have not yet developed cancer will develop cancer in the future. The average age of women with no cancer diagnosis in this study was 59.5 and 56.88 in *BRCA1* and *BRCA2* mutation carriers, respectively. These women may still develop cancer in their lifetime, however we cannot predict whether or not they will develop cancer, so this is a limitation in that we do not know which women will go on to develop cancer or when they will develop it. Some women in this group may be more similar to women diagnosed with cancer at age 50 or older, however we are not able to ascertain which individuals may develop cancer.

Only those women who underwent risk-reducing bilateral mastectomy were recorded. Women who underwent a unilateral prophylactic mastectomy following a breast cancer diagnosis in the contralateral breast were not recorded as having a prophylactic mastectomy. Because we were interested in the age at the first breast or ovarian cancer diagnosis, we did not feel it was necessary as the prophylactic mastectomy was part of the treatment for the cancer in the contralateral breast. There were no cases where a unilateral mastectomy was performed without a breast cancer diagnosis.

We did not analyze the date at which a woman underwent *BRCA* mutation analysis and at what age she learned of her *BRCA1*/2 mutation status. This information would be beneficial in order to determine whether women underwent risk-reducing surgeries prior learning of their *BRCA* status or if they were more likely to undergo risk-reducing surgeries after a cancer diagnosis.

IMPLICATIONS AND FUTURE RESEARCH

The further characterization of women with a *BRCA1* or *BRCA2* mutation who do not develop early-onset breast or ovarian cancer may aid in determining what factors are important in early vs. late-onset breast or ovarian cancer development. A larger cohort of *BRCA1* and *BRCA2* mutation carriers with no cancer diagnosis prior to age 50 would be beneficial to determine whether or not the results are consistent with those in this study. Additional research may also include investigating when a woman received knowledge of her *BRCA1* or *BRCA2* mutation and investigating whether this knowledge delays or prevents a cancer diagnosis,

perhaps through a prospective study. Because there have not been any reports on *BRCA1* or *BRCA2* carriers with later-onset breast or ovarian cancer, confirmation of the results from this study as well as additional analyses in another population would be valuable. In addition to further exploring the factors included in this study, research on the effect of possible modifier genes and their role in early or late development of breast and ovarian cancer may also be advantageous.

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VITA

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