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Predictors of Contralateral Breast Cancer in BRCA Negative Women

Ann E. Simmons

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PREDICTORS OF CONTRALATERAL BREAST CANCER IN *BRCA* NEGATIVE
WOMEN

by

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WOMEN

A

THESIS

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In Partial Fulfillment

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for the Degree of

MASTER OF SCIENCE

by

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Houston, TX

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PREDICTORS OF CONTRALATERAL BREAST CANCER IN *BRCA* NEGATIVE
WOMEN

Publication No. _____

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Breast cancer is the most common cancer diagnosis and second leading cause of death in women. Risk factors associated with breast cancer include: increased age, alcohol consumption, cigarette smoking, white race, physical inactivity, benign breast conditions, reproductive and hormonal factors, dietary factors, and family history. Hereditary breast and ovarian cancer syndrome (HBOC) is caused by mutations in the *BRCA1* and *BRCA2* genes. Women carrying a mutation in these genes are at an increased risk to develop a second breast cancer. Contralateral breast cancer is the most common second primary cancer in patients treated for a first breast cancer. Other risk factors for developing contralateral breast cancer include a strong family history of breast cancer, age of onset of first primary breast cancer, and if the first primary was a lobular carcinoma, which has an increased risk of being bilateral.

A retrospective chart review was performed on a select cohort of women in an IRB approved database at MD Anderson Cancer Center. The final cohort contained 572 women who tested negative for a *BRCA1* or *BRCA2* mutation, had their primary invasive breast cancer diagnosed under the age of 50, and had a BRCAPro risk assessment number over 10%. Of the 572 women, 97 women developed contralateral breast cancer. A number of predictors of contralateral breast cancer were looked at between the two groups. Using

univariable Cox Proportional Hazard model, thirteen statistically interesting risk factors were found, defined as having a p-value under 0.2. Multivariable stepwise Cox Proportional Hazard model found four statistically significant variables out of the thirteen found in the univariable analysis. In our study population, the incidence of contralateral breast cancer was 17%. Four statistically significant variables were identified. Undergoing a prophylactic mastectomy was found to reduce the risk of developing contralateral breast cancer, while not having a prophylactic mastectomy, a young age at primary diagnosis, having a positive estrogen receptor status of the primary tumor, and having a family history of breast cancer increased a woman's risk to develop contralateral breast cancer.

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BACKGROUND

BREAST CANCER FACTS

Breast cancer is the most common cancer diagnosis and second leading cause of death in women. It represents 32% of all newly diagnosed cancers and 15% of all deaths from cancer in women [1]. An average of 180,000 women per year in the United States will be diagnosed with breast cancer [2]. There are currently more than 2.4 million women in the United States who have a history of breast cancer [3]. Breast cancer can occur in three familial clusterings: sporadic, familial, and hereditary. Approximately 75% of breast cancer is considered sporadic, while 20% is considered familial and 5% is considered hereditary. Lifestyle, demographic, and personal medical history risk factors have been identified to help portray a women's risk to develop breast cancer.

BREAST CANCER RISK FACTORS

The high prevalence of breast cancer in the general population has led to numerous studies that have tried to identify factors that predispose a woman to developing breast cancer. Many of these predictors that are thought to increase an individuals risk of breast cancer have been extensively studied. Those risk factors associated with breast cancer include, but are not limited to: increased age, alcohol consumption, being Caucasian, physical inactivity, benign breast conditions, dietary factors, and family history [1]. Li et al (2011) found that diabetic women have a 15-20% increased risk of developing breast cancer over non-diabetic women. Another study found that having a healthy diet can actually lower a woman's risk to develop breast cancer [4]. Some reproductive factors found to be risk

factors for breast cancer include early age at menarche, late age at menopause, and nulliparity [5].

Environmental exposures to radiation, have also been associated with a higher risk for developing breast cancer [1]. Gao et al (2003) suggests that all women diagnosed with early-stage breast cancer should avoid unnecessary radiation exposure so as to lower their risk of developing contralateral breast cancer.

Of the 5% of breast cancer considered hereditary, the majority of increased risk is associated with mutations in the *BRCA1* or *BRCA2* genes. However, there are other syndromes that can cause an increased risk of breast cancer including Li Fraumeni syndrome, PTEN, and heterozygous Ataxia Telangiectasia [6]. Since these syndromes are rarer, Hereditary Breast and Ovarian Cancer Syndrome caused by mutations in *BRCA1* and *BRCA2* is looked at more closely and is more commonly tested for in the breast cancer population.

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

Hereditary breast and ovarian cancer (HBOC) is caused by mutations in the *BRCA1* and *BRCA2* genes. Approximately 0.1% of the population carries a mutation in either *BRCA1* or *BRCA2* [7]. Almost 10% of women diagnosed with breast cancer in Poland carry a genetic mutation that causes them to develop their cancer [8] and there are other genetic isolates such as Ashkenazi Jewish women or women from Iceland. Women with mutations in either *BRCA1* or *BRCA2* are at a higher risk to develop breast cancer, especially at a younger age [8]. There is a 47-66% lifetime risk of breast cancer in *BRCA1* mutation carriers and a 40-57% lifetime risk of breast cancer in *BRCA2* mutation carriers [7]. There

have been numerous studies that have found that the breast cancer found in *BRCA1* mutation carriers has a different pathology than breast cancer found in *BRCA2* mutation carriers. *BRCA1* mutation-caused breast cancer has a higher frequency of being a basal epithelial phenotype and is usually associated with estrogen receptor (ER) negative, progesterone receptor (PR) negative and HER2/neu negative breast cancer. In contrast, *BRCA2* mutation-caused breast cancer has a higher frequency of being estrogen receptor (ER) positive and progesterone receptor (PR) positive [5].

HBOC GENETIC TESTING AND SCREENING RECOMMENDATIONS

There are certain criteria set forth to determine which women should be offered *BRCA* mutation testing. The US Preventative Services Task Force has a strict set of guidelines aimed at determining which women should receive genetic testing. These guidelines are:

"two first-degree relatives with breast cancer, with one diagnosed at or before age 50 years; three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis; a combination of both breast and ovarian cancers among first- and second-degree relatives; a first-degree relative with bilateral breast cancer; two or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis; a first- or second-degree relative with both breast and ovarian cancers at any age; a history of breast cancer in a male relative; or a woman of Ashkenazi Jewish heritage with any first-degree relative (or any two second-degree relatives) with breast or ovarian cancer" [9].

These guidelines help the clinician determine who should be tested for a *BRCA* mutation.

Individuals who test positive have specific screening and management guidelines. Increased screening guidelines put out by the National Comprehensive Cancer Network are recommended for women who carry a mutation in *BRCA1* or *BRCA2*. These guidelines include breast self exam beginning at the age of 18 and a clinical breast exam every year beginning at the age of 25. It is also recommended that these women receive mammograms and MRIs starting at the age of 25. Women who test positive can be offered prophylactic mastectomies to reduce their risk of breast cancer up to 97% [7]. They can also undergo a prophylactic bilateral salpingo-oophorectomy, at 35 to 40 years of age or after childbearing is completed, to reduce their risk of ovarian cancer by up to 96% [10]. If women choose not to have a bilateral salpingo-oophorectomy, they can undergo transvaginal ultrasounds and a CA-125 blood draws every six months beginning at the age of 35 or 5-10 years before the earliest age of ovarian cancer diagnosis in the family, but this screening has not been proven very effective at catching ovarian cancer early [11]. Tamoxifen can also be recommended for breast cancer prevention for women with estrogen receptor positive tumors [7]. Tamoxifen is a selective estrogen receptor modulator that is used to lower a woman's risk to develop invasive and non-invasive breast cancer. It has also been shown to decrease the risk of contralateral breast cancer by about 50% [12].

A negative *BRCA1* or *BRCA2* test result does not rule out an underlying genetic cause of breast cancer in a family [13]. Women with a strong family history of breast and/or ovarian cancer who test negative are considered to have an 'uninformative' test result. This means that there could be other genes involved in their family's risk that have not been identified [13]. Women who test negative for a known familial mutation are considered true negatives for a *BRCA1* or *BRCA2* mutation. Women with a previous unilateral breast cancer,

and a strong family history who are *BRCA* 1/2 negative, have screening guidelines on how to screen or prevent a contralateral breast cancer from developing. It is unknown if certain *BRCA* negative women should undergo more screening than others. This unknown can cause anxiety among this cohort of women. Women with uninformative results have also been found to show more worry after finding out their results [14].

CONTRALATERAL BREAST CANCER

Contralateral breast cancer is the most common second primary cancer in patients treated for a first breast cancer, and is thought to account for about 50% of all second cancers in women [1]. When defining contralateral breast cancer, it is important to categorize according to timing of presentation of the second cancer. Synchronous contralateral breast cancer occurs when the second breast tumor develops at the same time or close to the same time as the first primary cancer. Metachronous contralateral breast cancer occurs when a time period of more than 3 months has elapsed since the first primary breast cancer [15]. Kollias et al (1999) defined metachronous breast cancer as not being found and treated at the time of the first primary breast cancer. Most of the literature about contralateral breast cancer focuses on metachronous contralateral breast cancer, since it can be hard to distinguish a synchronous breast cancer from a metastases of the first primary. This is also the case because the incidence of primary bilateral breast cancer is low, occurring between 1-14% in women diagnosed with a primary invasive breast cancer [8].

It is known that women who have been previously diagnosed with breast cancer have an estimated two- to six-fold higher risk of developing contralateral breast cancer at some point in their life over the general population's risk to develop a primary breast cancer

[2,16,17,18]. This amounts to approximately 5-10% of women who have been treated for breast cancer getting a second primary in the opposite breast [19]. Gao et al (2003) found that the risk of developing contralateral breast cancer at 10-, 15-, and 20-years after the first primary was 6.1%, 9.1%, and 12%, respectively. Once a woman has developed contralateral breast cancer her 1-, 5-, 10-, and 15-year survival rate was found to be 94%, 70%, 55%, and 49%, respectively [20]. This same study found that survival after a contralateral breast cancer diagnosis was worse among the youngest women, those patients who were diagnosed within 5 years of their first diagnosis, poor African American women, women with either of their primary's diagnosed at a later stage, those with less than 12 years of school, single women, and those with major weight gain between age 18 and adulthood [20]. A different study looked at the survival rates of those diagnosed with contralateral breast cancer versus those with unilateral breast cancer. They found that if the contralateral breast cancer was diagnosed within 5 years of the initial primary breast cancer that the prognosis was worse than for those whom the contralateral breast cancer was diagnosed after five years and for those diagnosed with unilateral breast cancer [21]. This same study found that patients that had positive lymph nodes with their contralateral breast cancer had double the risk of dying from their breast cancer as opposed to patients who's lymph nodes were negative and also that a higher stage of the contralateral breast cancer lead to a poorer prognosis [21].

Despite the poorer prognosis after a diagnosis of contralateral breast cancer, the incidence of contralateral breast cancer has been declining in the United States since 1985 by about 3% per year [3]. The study contributes this decline to the increased use of Tamoxifen adjuvant therapy in patients with ER-positive breast cancer. There was no decrease in contralateral breast cancer in patients with ER-negative breast cancer, due to the fact that these patients

do not take Tamoxifen. A different study reported an increase of 150% from 1998 to 2003 in contralateral prophylactic mastectomy [22]. This could also contribute to the decrease of contralateral breast cancer by removing the unaffected breast at the same time as the affected breast.

HBOC AND CONTRALATERAL BREAST CANCER

Women carrying a mutation in *BRCA1* or *BRCA2* are also at an increased risk to develop a second breast cancer [16]. The risk to develop breast cancer in the opposite breast is up to 53%, vs 2% for the general population [8,23]. In general, *BRCA1* and *BRCA2* mutation carriers have a 4-fold increase of developing contralateral breast cancer after a first primary breast cancer, which computes to a 4.5-fold increase in *BRCA1* mutation carriers and a 3.4-fold increase in *BRCA2* mutation carriers [2]. *BRCA1* mutation carriers have a 36.1% to 43.4% 10-15 year risk of developing contralateral breast cancer and *BRCA2* mutation carriers have a 28.5% to 34.6% 10-15 year risk [7,24]. This risk of developing contralateral breast cancer in *BRCA1/2* mutation carriers depends mostly on age at first breast cancer and whether the mutation is in *BRCA1* or *BRCA2* [23] .

The risk can also be changed based on whether the patient had radiation as part of her treatment for the first breast cancer. Paradiso et al. (2011) found that a mutation in *BRCA1* or *BRCA2* can be found to impair DNA repair and in vitro hypersensitivity to radiation of *BRCA*-null cells. This raises a woman's risk to develop radiation complications, including second cancers [7].

Metcalf et al (2011) found that the risk to develop contralateral breast cancer in *BRCA 1/2* mutation carriers decreases with older age of diagnosis and increases with the

number of first degree relatives affected with breast cancer, in a cohort of 810 women where a *BRCA1* or *BRCA2* mutation had been found in the family. In women who carry a mutation in *BRCA1*, the risk to develop contralateral breast cancer increases by 1.2 fold for each first degree relative diagnosed with breast cancer under the age of 50 and for women who carry a mutation in *BRCA2* the risk increases by 1.7 fold [24]. They also found that a bilateral salpingo oophorectomy will reduce the risk of contralateral breast cancer in young women who carry a *BRCA 1/2* mutation.

It is thought that known *BRCA 1/2* mutation carriers have a higher incidence of contralateral breast cancer because their first breast cancer is picked up at younger ages and therefore they have more time to develop a second breast cancer than someone diagnosed at an older age [16]. *BRCA1* carriers are usually diagnosed with their first primary breast cancer at younger ages as well as being diagnosed with contralateral breast cancer at younger ages [23]. Malone et al. (2010) looked at *BRCA1* mutation carriers relative risk of developing contralateral breast cancer by age of first diagnosis. They found that women diagnosed with a first primary breast cancer under the age of 35 had an 11-fold increase in developing contralateral breast cancer, women between the ages of 35-44 at the time of their first diagnosis had a 4-fold increase, and women between the ages of 45-54 at the first diagnosis had a 2.6-fold increase in contralateral breast cancer risk. Since contralateral breast cancer is the most common second primary cancer in patients previously diagnosed with breast cancer, knowing the risk factors associated with contralateral breast cancer is important to treating these women.

CONTRALATERAL BREAST CANCER RISK FACTORS: AGE AND ETHNICITY

Certain risk factors for developing contralateral breast cancer have been studied. Some factors include a strong family history of breast cancer, age of onset of first primary breast cancer, and if the first primary was a lobular carcinoma, which has about a 20% risk of being bilateral [1,8,16,17,19,23,25]. Gao et al (2003) found that being over the age of 55 was a risk factor for developing contralateral breast cancer compared to being between the ages of 45 and 55 years old. They also found that being younger than 45 years of age was a risk factor for developing contralateral breast cancer as opposed to being between 45 and 55 years old. It was also found that African-American women had a 20% higher risk to develop contralateral breast cancer over non-hispanic Caucasian women [1]. Having a significant family history of breast cancer and a previous unilateral breast cancer diagnosis under the age of 50 also increased a patient's risk to develop contralateral breast cancer [19].

PREVIOUS PRIMARY CANCER CHARACTERISTICS

Gao et al (2003) was the first study to find that radiation therapy used as treatment of the first primary breast cancer would increase the patients risk to develop contralateral breast cancer in a cohort of patients treated for early-stage primary breast cancer. They found that contralateral breast cancer risk doubled in the population that was less than 45 years old at primary tumor diagnosis and received radiation therapy during a 15-20 year follow up period [1]. One study found that the estrogen receptor status of the first primary breast cancer was very highly associated with estrogen receptor status of the second primary breast cancer [26]. Alkner et al (2011) found that receiving chemotherapy as a treatment for primary breast cancer was associated with a more aggressive form of contralateral breast

cancer. However, receiving chemotherapy does not increase the risk to get contralateral breast cancer [24]. Imyanitov et al. (2003) showed that premenopausal women had a higher level of similarity in their primary and contralateral tumor characteristics than those women who underwent menopause between their two diagnoses. They used this finding to suggest that hormonal factors influence tumor characteristics [16].

LIFESTYLE

One study found that regular alcohol intake increased the risk of metachronous contralateral breast cancer and this increased with longer duration of use [27]. This is consistent with the finding that alcohol is also a risk factor for primary breast cancer. Knight et al. (2009) found that smoking was not related to metachronous contralateral breast cancer. Li et al (2011) looked at the relationship between diabetes and the risk of developing contralateral breast cancer. They found that diabetic women had a 2.2 fold increase in developing contralateral breast cancer over women who were not diabetic and this risk was increased when women were diagnosed with their primary breast cancer before the age of 60 [28]. The link between diabetes and obesity has been looked at in these studies. Li et al (2011) recognized that obesity is a risk factor for diabetes and breast cancer as well. A different study looked specifically at the risk of contralateral breast cancer in obese women. They found that obese postmenopausal patients that had a first primary breast cancer that was ER negative had an increased risk of developing contralateral breast cancer compared to non-obese women with ER-negative primary breast cancer [29]. They did not find an increased risk in pre- or postmenopausal women with an primary breast cancer that was ER

positive. This study also found that weight change between the primary and secondary tumors was not associated with increased risk of contralateral breast cancer [29].

REPRODUCTIVE RISK FACTORS

Reproductive factors and their associated risk to develop contralateral breast cancer have been studied. It was found that having menarche before the age of 13 can be associated with a slight increase in contralateral breast cancer risk [5,30]. It has been found that having a full-term pregnancy can reduce a postmenopausal woman's risk to develop contralateral breast cancer, although having the first pregnancy in their 30's or 40's actually increases a woman's risk for breast cancer over a nulliparous woman [30]. Going through menopause has not been found to be associated with an increase in contralateral breast cancer risk [30]. Metcalfe et al. (2011) found that women who were diagnosed with a primary breast cancer under the age of 50 and who had a bilateral salpingo-oophorectomy had a decreased risk of contralateral breast cancer [24].

Figueiredo et al. (2010) looked at the association between oral contraceptive use and post-menopausal hormone use and the risk to develop contralateral breast cancer in carriers of *BRCA 1/2* mutations and non-carriers. They found that the association between oral contraceptive use and post-menopausal hormone use and the risk of contralateral breast cancer did not differ between carriers and non-carriers. They also speculate that since carriers have a higher risk of developing contralateral breast cancer, that even a small increase risk from oral contraceptive use might be pertinent in the assessment of contralateral breast cancer risk [31]. In the study by Poynter et al. (2010), it was noted that there was no difference in contralateral breast cancer risk between *BRCA 1/2* mutation

carriers and non-carriers when comparing reproductive risk factors. Imkampe et al (2011) found that the use of oral contraceptive pills was one of the strongest predictors of developing breast cancer at a young age. This study states that the use of oral contraceptive pills will increase a woman's breast cancer risk by inducing high breast proliferation rates, especially in nulliparous women. They also found that the duration of use had no effect on the development of breast cancer [32].

DECREASE IN RISK

The risk of developing contralateral breast cancer is significantly decreased if the woman undergoes a bilateral mastectomy at the time of the first primary and if they use Tamoxifen [17,18,23]. One study found that a prophylactic bilateral mastectomy can lower the risk of contralateral breast cancer up to 97% [7]. Poynter et al. (2010) found a lower risk of developing contralateral breast cancer in women who were older when they entered menopause, in women who had more full term births, and women who were younger at the time of parity.

BREAST CANCER RISK ASSESSMENT MODELS

There are several risk assessment models that assess a woman's risk of developing breast cancer as well as their risk to carry a *BRCA* mutation. One of these risk assessment models is the BRCAPro model found in CancerGene 5.1 software. The BRCAPro risk assessment model is used to calculate the likelihood of identifying a mutation in *BRCA1* or *BRCA2* in an individual. The model is based on a Bayesian probability that uses a patient's personal and family history of breast and ovarian cancer to determine their personal risk to

carry a mutation. The model includes information about the patient's first and second degree relatives history of unilateral or contralateral breast cancer and ovarian cancer and their ages of diagnosis. This model also takes into account a patients unaffected relatives and their ages [9]. BRCAPro was developed by Parmigiani et al and has been validated in numerous studies [33]. The BRCAPro model is run on all of the genetic counseling patients seen at MD Anderson Cancer Center's Breast Center.

PREVIOUS STUDIES

There have been previous studies evaluating women with sporadic breast cancer and women with *BRCA1* and *BRCA2* mutations with breast cancer and their risks for developing a contralateral breast cancer. Kollias et al (1999) studied the risk of contralateral breast cancer in women previously treated for a breast cancer. Gao et al (2003) studied women treated for early-stage breast cancer and their risk to develop contralateral breast cancer. Kirova et al (2005) studied whether a woman's mutation carrier status would influence her risk to develop contralateral breast cancer after having breast-conserving surgery and treatment. Yi et al (2009) studied the clinical features that predict contralateral breast cancer that may help a patient with unilateral breast cancer and her decision to undergo a contralateral prophylactic mastectomy. Graeser et al (2009) studied the risk for contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers. To our knowledge, there have been no studies specifically on uninformative *BRCA* negative women who have familial breast cancer and their risk to develop contralateral breast cancer.

OBJECTIVE

The objective of this study is to evaluate and determine risk factors for the development of contralateral breast cancer among women who test negative for *BRCA1* or *BRCA2* and who have high BRCAPro (>10%) scores. Our cohort is comprised of women who have been previously diagnosed with invasive breast cancer and who tested negative for a mutation in the *BRCA1* and *BRCA2* genes. We then study the time to contralateral breast cancer development and evaluate which predictors associate with increased breast cancer risk. We studied women with a BRCAPro score of greater than 10% because this has been proven previously to be associated with higher *BRCA1/BRCA2* mutation rates [34], and so this groups of women are at a higher probability of having inherited susceptibility to breast cancer and of developing another cancer. This study can help clinician's assess a *BRCA* negative woman's risks to develop a contralateral breast cancer and to determine the correct screening protocol for these patients. Some patients with high BRCAPro scores may be sufficiently anxious about their risks for developing a contralateral breast cancer that they consider prophylactic mastectomy even in the absence of a known mutation. Therefore, it is of interested to evaluate specific risk factors for contralateral breast cancers.

MATERIALS AND METHODS

STUDY DESIGN

A retrospective chart review was performed on a select cohort of women in an MD Anderson database. These women had a previous diagnosis of invasive breast cancer and had tested negative for a mutation in the *BRCA1* or *BRCA2* genes. Women included in the study were under the age of 50 at their first diagnosis and had a BRCAPro score of greater than 10%. The specific aim of this study was to determine predictors of contralateral breast cancer and the incidence of contralateral breast cancer in *BRCA* negative women with a BRCAPro >10% who had an invasive breast cancer diagnosed under the age of 50. The electronic medical records of the women at MD Anderson were reviewed and data was entered into a database. Some of the factors studied included: family history of breast and/or ovarian cancer, primary tumor characteristics, and reproductive factors. The factors were then analyzed to determine what predictors, if any, predicted an increased risk for developing a contralateral breast cancer. The study also looked at the incidence of contralateral breast cancer in this population. The hypothesis of the study was that there are many predictors associated with contralateral breast cancer and an associated incidence for women with a previous unilateral breast cancer who have tested negative for a *BRCA* mutation and have a BRCAPro greater than 10%.

STUDY APPROVAL

The study received approval from the University of Texas Health Science Center of Houston- Graduate School of Biomedical Sciences on July 25, 2011. It also received approval from MD Anderson on October 6, 2011.

STUDY POPULATION

The study population contained 572 women who had an invasive breast cancer diagnosed under the age of 50, had tested negative for a *BRCA* mutation, and had a BRCAPro score of greater than 10%. The women were tested between 1997 and August, 31, 2011. A total of 97 women in the population developed contralateral breast cancer.

ASCERTAINMENT

The study population was obtained from a MD Anderson database. The original cohort consisted of 1,641 patients who met the criteria of having an invasive breast cancer diagnosed under the age of 50 and had tested negative for a *BRCA* mutation. Of the 1,641 patients, 1,069 were excluded because they did not meet the study criteria. The exclusion criteria included women diagnosed with DCIS, women diagnosed over the age of 50 with their first primary tumor, women with a BRCAPro score of less than 10%, men, women with a true negative result, and women with a different hereditary condition.

DATA COLLECTION

Data was reviewed and collected from November 2011 through February 2012. The data was then entered into a database and the information obtained is displayed in Table 1.

Table 1: Variables Obtained from Electronic Medical Record

General Information
<p>Ethnicity</p> <p>Age at Diagnosis of first invasive breast cancer</p> <p>BRCAPro number</p> <p>Smoker/Smoking Length</p> <p>Alcohol Use</p> <p>Ashkenazi Jewish ancestry</p> <p>BMI</p>
Reproductive Risk Factors
<p>Age at menarche</p> <p>Ever Parous/Age at first full term pregnancy</p> <p>Menopause/Age at Menopause</p> <p>Hormone replacement use/Length</p> <p>Oral Contraceptive Use/Length</p>
Risk Reducing Surgery
<p>Prophylactic mastectomy</p> <p>Bilateral Salpingo-oophorectomy</p> <p>Total Abdominal Hysterectomy</p> <p>Age at BSO/TAH</p>
Genetic Testing Type
<p>Sequencing</p> <p>BART</p>

Ashkenazi Jewish panel
Family History Information
Number of First Degree Relatives with Breast Cancer Number of Second Degree Relatives with Breast Cancer Number of First Degree Relatives with Ovarian Cancer Number of Second Degree Relatives with Ovarian Cancer
First Primary Tumor Pathology Information
Tumor receptor status Her2/neu Status Grade Lymphovascular Invasion Pathology of Tumor Previous Biopsy/Previous Biopsy Number Tumor Size
Treatment
Radiation Exposure Chemotherapy Tamoxifen Use/Length
Contralateral Tumor Pathology Information
Pathology of Tumor Tumor Receptor Status Grade Lymphovascular Invasion

Synchronous/Metachronous diagnosis

Tumor Size

STATISTICAL ANALYSIS

Statistical analysis was performed on the data to determine if any trends were present that would help identify predictors of contralateral breast cancer in this population.

Microsoft Office Excel 2010, Microsoft Office Access 2010, and STATA 12.0 were all used to study this population's data. Descriptive analysis of the data was used to describe the cohort. The frequencies of each variable as well as the mean and range of the variables was determined to help summarize the cohort.

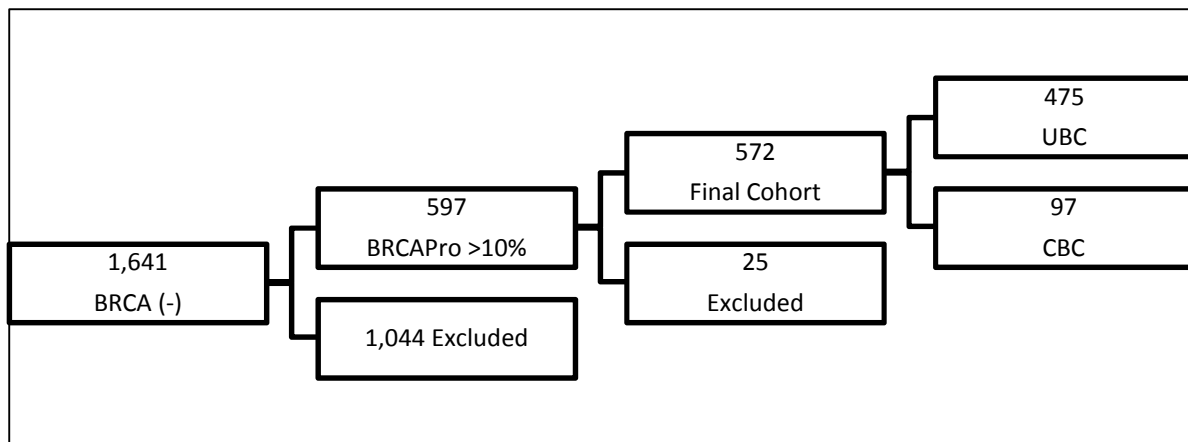
Cox Proportional Hazard Model was used to assess the relationship between the time to develop contralateral breast cancer to the covariables used in the study. The Cox model analyzes time to recurrence of breast cancer allowing for incomplete information about the time to breast cancer development caused by censoring. Censoring is when the patient either did not develop contralateral breast cancer, they were lost to follow-up or they passed away before they developed contralateral breast cancer, so it is unknown when they would have developed contralateral breast cancer. In our Cox Proportional Hazard Model, we set the time variable as follow-up time after primary, time to death after primary or time to develop contralateral breast cancer after primary. Our failure event was whether the patient developed contralateral breast cancer or not. Univariable Cox Proportional Hazard Model was performed on each variable to determine which covariables could be of statistical interest. We used a p-value of 0.2 to screen for potentially interesting covariates to include in the multivariable analysis. Kaplan-Meier curves represent graphical presentation for each

covariate identified in the univariable Cox model as potentially interesting. Stepwise multivariable Cox Proportional Hazard Model was then performed on the selected covariates to arrive at a final parsimonious multivariable model consisting of only significant covariates, defining statistically significant variables with different thresholds, i.e. as having a p-value of less than 0.05 or less than 0.1. We then performed recursive partitioning using a decision tree that represents an optimal way of combining the significant covariates to classify the women into risk groups represented by the different times they develop contralateral breast cancer. A Kaplan-Meier curve was plotted for each of the five terminal nodes. These five nodes were then grouped into three different risk groups and a new Kaplan-Meier curve was made on these final three groups. The three groups were defined as being low-risk, medium-risk or high-risk.

RESULTS

The cohort for our study is described in the flow chart in Figure 1. We began with 1,641 women who had a previous unilateral invasive breast cancer, had tested negative for a mutation in the *BRCA1* or *BRCA2* genes, and were diagnosed with a primary invasive breast cancer under the age of 50 years. We then evaluated the BRCAPro risk assessment probability for each woman in the cohort. This excluded 1,044 woman from the cohort based on the exclusion criteria of: a BRCAPro probability of less than 10%, women who had DCIS as their first primary diagnosis, women with a true negative result, women with a different hereditary condition, and men. After reviewing the 597 woman left in the cohort, 25 more women were excluded because they were true negatives or they had a different hereditary condition, i.e. Li Fraumeni syndrome or Cowden syndrome, leaving a final cohort of 572. This included 475 women with unilateral breast cancer and 97 women who developed contralateral breast cancer (CBC).

Figure 1: Flowchart of Study Cohort



DEMOGRAPHIC AND LIFESTYLE

Follow-Up Time

The average follow-up time was 7.11 years. Follow-up time included time to develop contralateral breast cancer, time to death, and time at last follow-up; all calculated from the time of the primary diagnosis in years. The range of follow-up time was 0.1 years to 46 years. The standard deviation was 7.36. The final cohort had 51 women who were deceased at the closing of the data collection. 521 women were still living at the end of data collection.

Ethnicity

There were 413 Non-Hispanic White women in the population, which is approximately 72% of the cohort. There were 84 Hispanic women (15%), 51 African-American women (9%), 13 Asian women (2%), and 11 (2%) women of 'Other' ethnicity.

Age at Primary Diagnosis

The average age at the first primary diagnosis was 41.05 years with the minimum age being 22 years and the maximum age being 50 years old. The standard deviation was 6.22.

BRCAPro Risk Assessment Number

The average BRCAPro risk assessment probability of the cohort was 23.23%. This ranged from 10%-100% over the entire cohort. The standard deviation was 18.58.

Ashkenazi Jewish

There were 502 women who were not of Ashkenazi Jewish ancestry (87.76%) and 70 (12.24%) women who were Ashkenazi Jewish.

Smoker/Smoking Length

There were 347 (60.66%) women who reported no history of smoking and 206 (36.01%) women who had a history of smoking. There were 19 women who did not have information regarding their smoking habits. The average number of years women in the cohort smoked was 15.70 years with a range of 1 year to 50 years. There were 164 women who had information regarding how long they smoked cigarettes. The standard deviation of smoking length was 10.95.

Alcohol Use

There were 203 (35.49%) women who had no history of ever drinking alcohol and 350 (61.19%) women who drank alcohol in some amount. There were 19 women who did not have information regarding ever drinking alcohol.

Body Mass Index (BMI)

The average body mass index (BMI) for the cohort at the initial diagnosis was 27.21 with a range of 17 to 61. The standard deviation was 6.41. There was information regarding BMI for 521 women in the cohort.

Ovarian Cancer

There were 9 (1.57%) women in the cohort who developed ovarian cancer and 563 (98.43%) women who did not get ovarian cancer.

The demographic and lifestyle covariables' categorical data are summarized in Table 2 and the discrete data are summarized in Table 3. The ethnicity of the population is summarized in Figure 2.

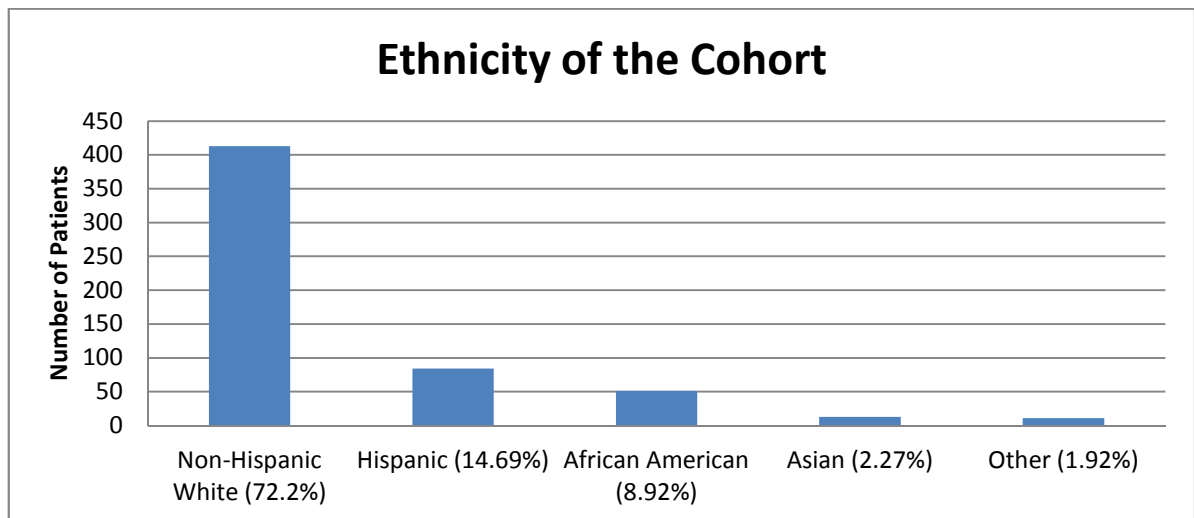
Table 2: Categorical Data of Demographic and Lifestyle Covariables

Variable	Observations	Mean	Std. Dev.	Min	Max
Follow-Up Time	572	7.11	7.36	0	46
Diagnosis Age	572	41.05	6.22	22	50
BRCAPro	572	23.23	18.58	10	100
Smoking Length	164	15.70	10.95	1	50
BMI	521	27.21	6.41	17	61

Table 3: Discrete Data of Demographic and Lifestyle Covariables

Variable	No	Yes	Unknown
Ashkenazi Jewish	502 (87.76%)	70 (12.24%)	0
Smoker	347 (60.66%)	206 (36.01%)	19 (3.32%)
Alcohol Use	203 (35.49%)	350 (61.19%)	19 (3.32%)
Ovarian Cancer	563 (98.43%)	9 (1.57%)	0

Figure 2: Ethnicity of the Cohort



REPRODUCTIVE RISK FACTORS

Age at Menarche

The average age of menarche for the cohort was 12.45 years old with a range of 8 years old to 18 years old. Of note, there are 40 women who did not have information about the age of menarche. The standard deviation was 1.49.

Parity/Age at First Full Term Birth

There were 103 (18.01%) nulliparous women and 469 (81.99%) parous women. The average age at parity was 25.82 years old with a range of 14 years old to 43 years old. There were 2 women who did not have information regarding the age at parity. The standard deviation for age at the first birth was 5.51.

Experienced Menopause/Age at Menopause

There were 250 (43.71%) women who had not gone through menopause and 283 (49.48%) who had experienced menopause. There were 39 women who did not have information in their medical record regarding menopausal status. The average age at menopause was 43.25 years with a range from 27 to 58 years of age. There was information regarding the average age of menopause for 263 women in the cohort. The standard deviation for the age at menopause was 5.65.

Hormone Replacement Use/Length of Use of Hormone Replacement

There were 425 (74.30%) women who had never used hormonal replacement and 85 (14.86%) women who had used hormones. There were 62 (10.84%) women who did not have information regarding hormonal use in their medical records. The average length of use of hormone replacement was 3.30 years with a range from 0.08 years to 18 years. There were 74 women who had information regarding how many years they were on hormone

replacement therapy. The standard deviation of the length of hormone replacement use was 4.21 years.

Oral Contraceptive Pills Use/Length of Use of Oral Contraceptive Pills

There were 416 women who had information regarding how long they used oral contraceptive pills. There were 93 (16.26%) women who never used oral contraceptive pills and 431 (75.35%) women who had used oral contraceptive pills for some length of time. The average length of use of oral contraceptive pills was 8.62 years with a range from 0.02 years to 35 years. The standard deviation of the length of oral contraceptive pill use was 6.87.

The reproductive risk factors’ quantitative data is summarized in Table 4 and the discrete data is summarized in Table 5.

Table 4: Reproductive Risk Factors’ Quantitative Data

Variable	Observations	Mean	Std. Dev.	Min	Max
Age at Menarche	532	12.45	1.49	8	18
Age at First Birth	467	25.82	5.51	14	43
Age at Menopause	263	43.25	5.65	27	58
Hormone Use Length	74	3.30	4.21	0.08	18
OCP Use Length	416	8.62	6.87	0.02	35

Table 5: Reproductive Risk Factors' Discrete Data

Variable	No	Yes	Unknown
Ever Parous	103 (18.01%)	469 (81.99%)	0
Menopause	250 (43.71%)	283 (49.48%)	39 (6.82%)
Hormone Use	425 (74.30%)	85 (14.86%)	62 (10.84%)
OCP Use	93 (16.26%)	431 (75.35%)	48 (8.39%)

RISK REDUCING SURGERY RISK FACTORS

Prophylactic Mastectomy

There were 445 (79.79%) women who did not undergo a prophylactic mastectomy and 124 (20.21%) women who did undergo a prophylactic mastectomy. One woman developed contralateral breast cancer after having a prophylactic mastectomy.

Bilateral Salpingo-Oophorectomy/Age at Bilateral Salpingo-Oophorectomy

In this cohort, there were 380 (66.43%) women did not have a bilateral salpingo-oophorectomy (BSO) and 113 (19.76%) who had a bilateral salpingo-oophorectomy. There were 79 (13.81%) women who did not have this information in their medical records. The average age of bilateral salpingo-oophorectomy in this cohort was 43.21 years old with a range of 27 years old to 70 years old. The standard deviation of the age at the time of a bilateral salpingo-oophorectomy was 7.46.

Total Abdominal Hysterectomy/Age at Total Abdominal Hysterectomy

There were 351 (61.36%) women who have not had a total abdominal hysterectomy (TAH) and 143 (25%) women who have. There were 78 (13.64%) women who did not have this information in their medical records. The average age of undergoing a total abdominal

hysterectomy was 41.78 years old with a range of 23 years old to 70 years old. There were 138 women in our cohort who underwent a TAH and had information regarding the age at the time of the procedure. The standard deviation of the age at the time of the total abdominal hysterectomy was 8.03.

The risk reducing surgery covariables' quantitative data are summarized in Table 6 and the discrete data are summarized in Table 7.

Table 6: Risk Reducing Surgery Quantitative Data

Variable	Observations	Mean	Std. Dev.	Min	Max
Age at BSO	108	43.21	7.46	27	70
Age at TAH	138	41.78	8.03	23	70

Table 7: Risk Reducing Surgery Discrete Data

Variable	No	Yes	Unknown
Prophylactic Mastectomy	445 (79.79%)	124 (20.21%)	0
BSO	380 (66.43%)	113 (19.76%)	79 (13.81%)
TAH	431 (75.35%)	141 (24.65%)	78 (13.64%)

FAMILY HISTORY

Number of First Degree Relatives with Breast Cancer

There were 362 (63.29%) women who did not have a first degree relative with breast cancer and 210 (36.71%) women who had at least one first degree relative with breast

cancer. Of the 210 women, 178 (31.12%) women had one first degree relative affected with breast cancer. 29 (5.07%) women had two first degree relatives affected with breast cancer. Two women (0.35%) had three first degree relatives affected with breast cancer and one woman (0.17%) had five first degree relatives affected with breast cancer.

Number of Second Degree Relatives with Breast Cancer

There were 223 (38.99%) women who did not have a second degree relative with breast cancer and 349 (61.01%) women who had a second degree relative with breast cancer. Of the 349 women, 199 (34.79%) had one second degree relative with breast cancer. 91 (15.91%) women had two second degree relatives affected with breast cancer. 41 (7.17%) women had three second degree relatives affected. 10 (1.75%) had four second degree relatives affected. Five (0.87%) had five second degree relatives affected. Two (0.35%) had six second degree relatives affected and one (0.17%) woman had eleven second degree relatives affected with breast cancer.

Number of First Degree Relatives with Ovarian Cancer

There were 547 (95.63%) women who did not have a first degree relative with ovarian cancer and 25 (4.37%) women who had one first degree relative with ovarian cancer.

Number of Second Degree Relatives with Ovarian Cancer

There were 467 (81.64%) women who did not have a second degree relative with ovarian cancer and 105 (18.36%) women who had at least one second degree relative with ovarian cancer. In the 105 women, 97 (16.96%) women had one second degree relative with ovarian cancer, six (1.05%) had two relatives affected, one (0.17%) had three affected relatives, and one (0.17%) had five affected relatives with ovarian cancer.

The family history data is summarized in Table 8. The number of first degree relatives affected with breast cancer is summarized in Table 9. The number of second degree relatives affected with breast cancer is summarized in Table 10. The number of first degree relatives affected with ovarian cancer is summarized in Table 11. The number of second degree relatives affected with ovarian cancer is summarized in Table 12.

Table 8: Family History of Having or Not Having Affected Relatives

Variable	No	Yes
FDR with Breast Cancer	362 (63.29%)	210 (36.71%)
SDR with Breast Cancer	223 (38.99%)	349 (61.01%)
FDR with Ovarian Cancer	547 (95.63%)	25 (4.37%)
SDR with Ovarian Cancer	467 (81.64%)	105 (18.36%)

Table 9: Number of First Degree Relatives Affected with Breast Cancer

Number of Relatives Affected	Number of Patients in Cohort
0	362 (63.29%)
1	178 (31.12%)
2	29 (5.07%)
3	2 (0.35%)
5	1 (0.17%)

Table 10: Number of Second Degree Relatives Affected with Breast Cancer

Number of Relatives Affected	Number of Patients in Cohort
0	223 (38.99%)
1	199 (34.79%)
2	91 (15.91%)
3	41 (7.17%)
4	10 (1.75%)
5	5 (0.87%)
6	2 (0.35%)
11	1 (0.17%)

Table 11: Number of First Degree Relatives Affected with Ovarian Cancer

Number of Relatives Affected	Number of Patients in Cohort
0	547 (95.63%)
1	25 (4.37%)

Table 12: Number of Second Degree Relatives Affected with Ovarian Cancer

Number of Relatives Affected	Number of Patients in Cohort
0	467 (81.64%)
1	97 (16.96%)
2	6 (1.05%)
3	1 (0.17%)
5	1 (0.17%)

PRIMARY TUMOR CHARACTERISTICS

Estrogen Receptor Status

There were 183 (32%) women who had a negative ER status. There were 386 women who had a positive ER status. There were 3 (0.52%) women who did not have information about ER status of their primary tumor.

Progesterone Receptor Status

There were 251 (43.88%) women who had a negative PR status and 318 (55.60%) women who had a positive PR status. There were 3 (0.52%) women who did not have information about PR status in their medical records.

Her2/neu Status

There were 477 (83.40%) women who had a negative Her2/neu status. There were 92 (16.08%) women who had positive Her2/neu status. There were 3 (0.52%) women who did not have Her2/neu status of the primary tumor in their medical records.

Pathology of Tumor

There were 34 (5.94%) women who had invasive lobular carcinoma. There were 445 (77.80%) women who had invasive ductal carcinoma. There were 8 (1.40%) women who had invasive tubular carcinoma. There were 9 (1.57%) women who had inflammatory breast cancer and 32 (5.59%) women who had mixed ductal carcinoma. There were 11 (1.92%) women who had an 'other' pathology subtype of their tumor. There were 33 (5.78%) women who did not have any information regarding the pathology of their primary tumor.

Previous Biopsy/Previous Biopsy Number

There were 485 (84.79%) women who had never had a previous biopsy and 84 (14.69%) women who had previous biopsies. There were 3 (0.52%) women who did not

have information regarding previous biopsies. The average previous biopsy number was 0.63 with a range of 0 to 10. The standard deviation of the previous biopsy number was 1.32.

Tumor Size

The average tumor size for the primary tumor was 2.56cm and the range was 0.07cm to 12cm. There was information regarding tumor size of the primary tumor for 504 patients. The standard deviation of the size of the primary tumor was 1.92.

Grade of Tumor

There were 61 women who had a grade 1 primary tumor, which is 12.35% of the patient population. There were 209 women who had a grade 2 primary breast cancer tumor, which was 42.31% of the study population. There were 224 women who had a grade 3 primary cancer tumor, which was 45.34% of the patient population. The majority of our study cohort had a high grade primary breast cancer tumor.

Lymphovascular Invasion

There were 339 (59.58%) women who did not have lymphovascular invasion during their first primary and 230 (40.42%) women who had positive lymphovascular invasion during their first primary diagnosis treatment.

The primary tumor characteristics' quantitative data is summarized in Table 13. The primary tumor characteristics' discrete data is summarized in Table 14. The grade of the primary tumor is summarized in Figure 3. The pathology subtype of the primary tumor is summarized in Table 15.

Table 13: Primary Tumor Characteristics' Quantitative Data

Variable	Observations	Mean	Std. Dev.	Min	Max
Prev. Biopsy Number	263	0.63	1.32	0	10
Tumor Size	504	2.56	1.92	0.07	12

Table 14: Primary Tumor Characteristics' Discrete Data

Variable	Negative	Positive	Missing
ER Status	183 (32%)	386 (67.48%)	3 (0.52%)
PR Status	251 (43.88%)	318 (55.60%)	3 (0.52%)
Her2/neu Status	477 (83.40%)	92 (16.08%)	3 (0.52%)
Previous Biopsy	485 (84.79%)	84 (14.69%)	3 (0.52%)
Lymphovascular Invasion	339	230	0

Figure 3: Grade of Primary Tumor

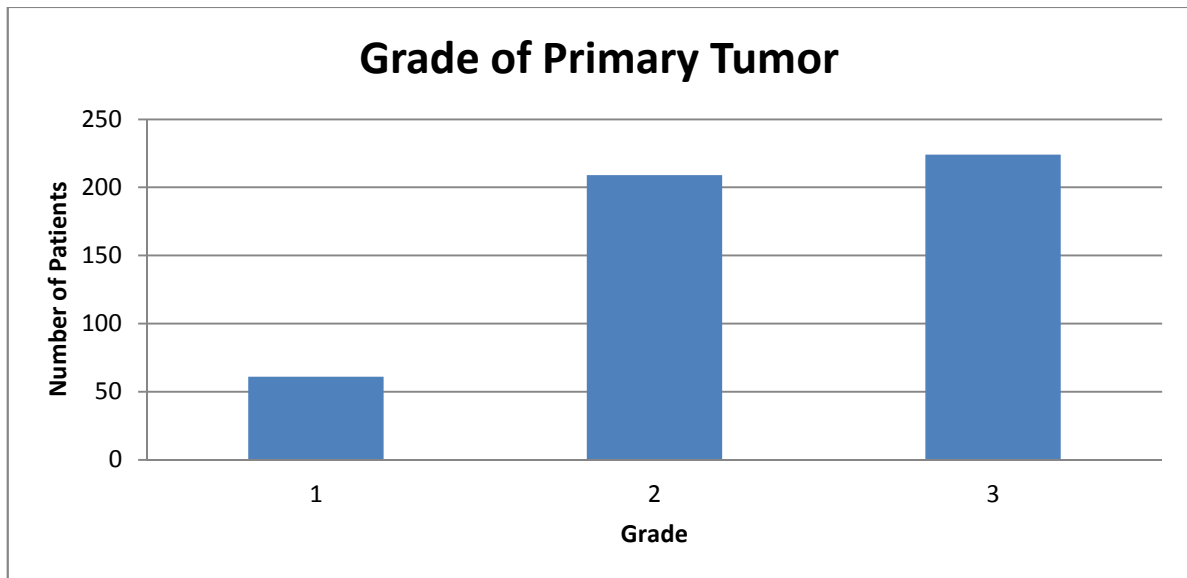


Table 15: Pathology Subtype of Primary Tumor

Pathology Subtype	Number of Patients with Subtype
Invasive Lobular Carcinoma	34 (5.94%)
Invasive Ductal Carcinoma	445 (77.80%)
Invasive Tubular Carcinoma	8 (1.40%)
Inflammatory	9 (1.57%)
Mixed Ductal Carcinoma	32 (5.59%)
Other Subtype	11 (1.92%)
Missing	33 (5.78%)

TREATMENT

Radiation Therapy

There were 215 (37.59%) women who were not treated with radiation during their first primary diagnosis treatment and 354 (61.89%) women who received radiation treatment. There were 3 (0.52%) women who did not have this information.

Chemotherapy

There were 105 (18.36%) women who did not receive chemotherapy as part of their treatment and 464 (81.12%) women who had chemotherapy. There were 3 (0.52%) women missing this information.

Tamoxifen Use/Tamoxifen Length of Use

There were 268 (46.85%) women who did not use Tamoxifen and 304 (53.15%) women who did use Tamoxifen. The average length of use of Tamoxifen was 3.24 years

with a range of 0.04 years to 10 years. There was information regarding length of Tamoxifen use for 194 patients. The standard deviation of the length of use of Tamoxifen was 2.03.

The treatment covariables' quantitative variables are summarized in Table 16 and the discrete data is summarized in Table 17.

Table 16: Treatment Quantitative Data

Variable	Observations	Mean	Std. Dev.	Min	Max	P-Value
Tamoxifen Use Length	194	3.24	2.03	0.04	10	0.99

Table 17: Treatment Discrete Data

Variable	No	Yes	Missing
Radiation Therapy	215 (37.59%)	354 (61.89%)	3 (0.52%)
Chemotherapy	105 (18.36%)	464 (81.12%)	3 (0.52%)
Tamoxifen Use	268 (46.85%)	304 (53.15%)	0

CONTRALATERAL BREAST CANCER COVARIABLES

Synchronous vs. Metachronous Contralateral Breast Cancer

There were 27 (27.84%) women who had their contralateral breast cancer diagnosed at the same time or within 3 months of their primary breast cancer diagnosis. There were 64 (65.98%) women who had their contralateral breast cancer diagnosed at least 3 months after their primary breast cancer diagnosis. There were 6 (6.19%) women missing this

information. The average time to develop contralateral breast cancer in our cohort was 9.40 years and the median time to develop contralateral breast cancer was 24.5 years.

Age at Contralateral Breast Cancer

The average age of the women at the diagnosis of contralateral breast cancer was 50.57 years with a range of 33 years to 78 years. The standard deviation was 9.27.

Body Mass Index at Time of Contralateral Breast Cancer

The average BMI at the time of contralateral breast cancer diagnosis was 29.05 with a range of 19 to 44. There was only information on BMI at contralateral breast cancer for 61 women. The standard deviation was 6.05.

Pathology of Contralateral Tumor

There were 7 (7.22%) women who had invasive lobular carcinoma and 58 (59.79%) women who had invasive ductal carcinoma. There were 11 (11.34%) women who had DCIS as their contralateral breast cancer diagnosis. There were 7 (7.22%) women who had mixed ductal carcinoma and 8 (8.79%) women who had an 'other' subtype. There were 6 (6.19%) women who did not have this information.

Estrogen Receptor Status of Contralateral Tumor

There were 31 (31.96%) women who had a negative ER tumor status or who had missing ER status data. There were 60 (61.86%) women who had a positive ER status in their contralateral breast cancer tumor. There were 6 (6.19%) women who did not have this information.

Progesterone Receptor Status of Contralateral Tumor

There were 40 (41.24%) women who had a negative PR status of their contralateral breast cancer tumor or who had missing PR tumor status information. There were 51

(52.58%) women who had a positive progesterone receptor status of their contralateral breast cancer tumor. There were 6 (6.19%) women missing this information.

Her2/neu Status of Contralateral Tumor

There were 83 (85.87%) women who had a negative Her2/neu tumor status or were missing this information. There were 8 (8.25%) women who had a positive Her2/neu contralateral breast cancer tumor. There were 6 (6.19%) women who did not have this information.

Size of Contralateral Tumor

The average size of the contralateral tumor was 1.94cm with the range being 0.1cm to 15cm. There was information regarding the size of the contralateral tumor for 82 tumors. The standard deviation was 1.93.

Grade of Contralateral Breast Cancer Tumor

There were 12 women who had a grade 1 contralateral breast cancer tumor, which was 12.37% of the contralateral tumors. There were 40 women who had a grade 2 contralateral breast cancer tumor, which was 41.24% of the contralateral tumors. There were 28 women who had a grade 3 contralateral breast cancer tumor, which was 28.87% of the contralateral tumors. There were 17 contralateral breast cancer tumors that did not have information regarding the grade of the tumor, which was about 17.53% of the contralateral tumors.

Lymphovascular Invasion

There were 70 (72.16%) women who did not have lymphovascular invasion and 21 (21.65%) women who had lymphovascular invasion. There were 6 (6.19%) women who did not have this information.

The contralateral breast cancer characteristics quantitative data is summarized in Table 18 and the discrete data is summarized in Table 19. The grade of the contralateral tumor is summarized in Figure 4. The pathology of the contralateral breast cancer tumor is summarized in Table 20. Whether the contralateral breast cancer was synchronous or metachronous with the primary breast cancer is summarized in Figure 5.

Table 18: Contralateral Breast Cancer Quantitative Data

Variable	Observations	Mean	Std. Dev.	Min	Max
Age at CBC	97	50.57	9.24	33	78
BMI at CBC	61	29.05	6.05	19	44
Tumor Size of CBC	82	1.94	1.93	0.1	15

Table 19: Contralateral Breast Cancer Discrete Data

Variable	No/Negative	Yes/Positive	Missing
Lymphovascular Invasion of CBC	70 (72.16%)	21 (21.65%)	6 (6.19%)
ER Status	31 (31.96%)	60 (61.85%)	6 (6.19%)
PR Status	40 (41.24%)	51 (52.58%)	6 (6.19%)
Her2/neu Status	83 (85.57%)	8 (8.24%)	6 (6.19%)

Figure 4: Grade of Contralateral Breast Cancer Tumor

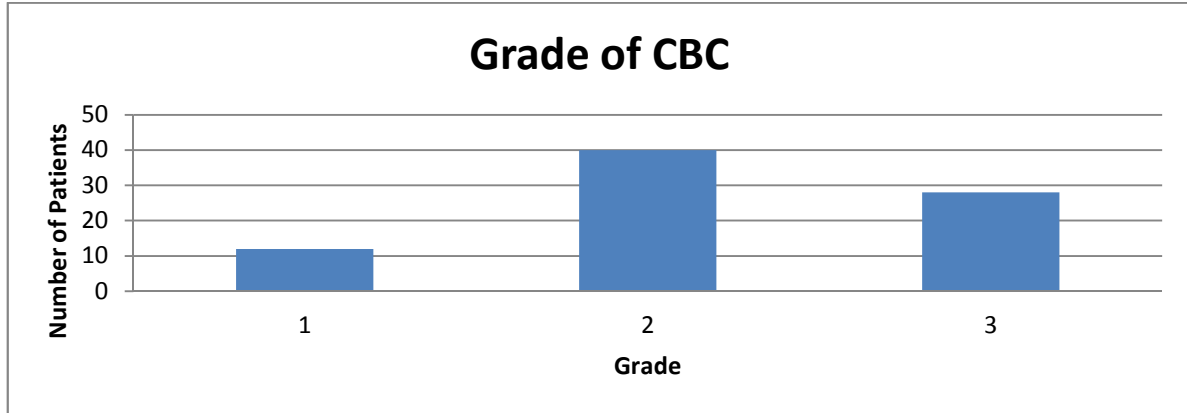
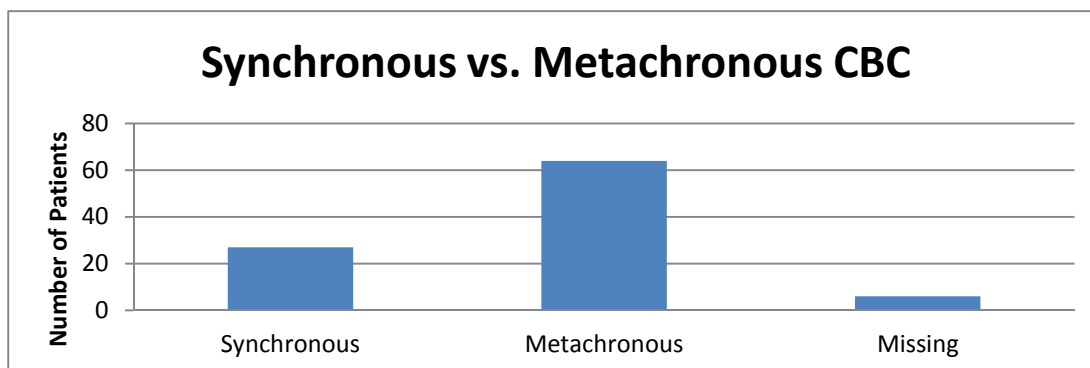


Table 20: Contralateral Breast Cancer Tumor Pathology Subtype

Pathology Subtype of CBC	Frequency	Percentage
Lobular	7	7.22%
Ductal	58	59.79%
DCIS	11	11.34%
Mixed Ductal	7	7.22%
Other	8	8.24%
Missing	6	6.19%

Figure 5: Synchronous vs. Metachronous Contralateral Breast Cancer



MOLECULAR GENETIC TESTING SUBTYPE

565 of the women received full sequencing of both the *BRCA1* and *BRCA2* genes. 35 women received the Ashkenazi Jewish panel test. In some cases but not all, the women who tested negative on the Ashkenazi Jewish panel were then retested to full sequencing. 205 women received BART testing after being negative by full sequencing. BART testing looks for large rearrangements and large duplications/deletions that sequencing is unable to detect. This is summarized in Table 21.

Table 21: Molecular Genetic Testing Subtype

Test Type	Count
Sequencing	565 (70.19%)
Ashkenazi Jewish Panel	35 (4.35%)
BART	205 (25.47%)
Total	805

UNIVARIABLE ANALYSIS

Univariable Cox Proportional Hazard Model was performed on each covariate with time to contralateral breast cancer as the response variable. We used a p-value of <0.2 to determine whether the covariate was of potential interest. The p-values that are in bold in the following tables were considered potentially interesting with a p-value less than 0.2.

DEMOGRAPHIC AND LIFESTYLE COVARIABLES

Ethnicity

The ethnicity of the cohort had a hazard ratio of 1.05 with a p-value of 0.72 (95% CI: 0.82-1.34) which was not statistically significant.

Age at Primary Diagnosis

The age at primary breast cancer diagnosis had a hazard ratio of 1.04 with a statistically significant p-value of 0.019 (95% CI: 1.01-1.08).

BRCAPro Risk Assessment Number

The BRCAPro risk assessment number of the patient cohort had a hazard ratio of 1.00 and was not statistically significant with a p-value of 0.46.

Ashkenazi Jewish

If the woman was of Ashkenazi Jewish ancestry, the hazard ratio was 0.99 with a p-value of 0.98, which was not statistically significant (95% CI: 0.58-1.71).

Smoker/Smoking Length

If a woman ever smoked, the hazard ratio was 0.95 with a non-statistically significant p-value of 0.83 (95% CI: 0.62-1.46). The length of time a woman smoked had a hazard ratio of 1.00 and a p-value of 0.97, which was not statistically significant (95% CI: 0.96-1.04).

Alcohol Use

If the woman ever drank alcohol, the hazard ratio was 0.94 with a non-statistically significant p-value of 0.78 (95% CI: 0.62-1.43).

Body Mass Index (BMI)

The body mass index at the primary breast cancer had a hazard ratio 1.02 with a non-statistically significant p-value of 0.24 (95% CI: 0.98-1.06).

Ovarian Cancer

If the woman had been diagnosed with ovarian cancer, the hazard ratio was 0.32 with a non-statistically significant p-value of 0.25 (95% CI: 0.04-2.28).

Table 22: Demographic and Lifestyle Risk Factors Univariable Cox Proportional Hazard Model

Variable	Hazard Ratio	P-Value	Confidence Interval (95%)
Ethnicity	1.05	0.72	0.82-1.34
Diagnosis Age	1.04	<0.02	1.01-1.08
BRCAPro	1.00	0.46	0.99-1.01
Ashkenazi Jewish	0.99	0.98	0.58-1.71
Smoker	0.95	0.83	0.62-1.46
Smoking Length	1.00	0.97	0.96-1.04
Alcohol Use	0.94	0.78	0.62-1.43
BMI	1.02	0.24	0.98-1.06
Ovarian Cancer	0.32	0.25	0.04-2.28

REPRODUCTIVE RISK FACTORS

Age at Menarche

The age of menarche had a hazard ratio of 1.04 and a p-value of 0.61, which was not statistically significant (95% CI: 0.89-1.21).

Parity/Age at First Full Term Birth

If the women had ever had a live birth, the hazard ratio was 0.79 and was not statistically significant with a p-value of 0.39 (95% CI: 0.47-1.34). The age of the woman at their first live birth had a hazard ratio of 1.03 and a statistically interesting p-value of 0.17 (95% CI: 0.99-1.08).

Experienced Menopause/Age at Menopause

If the woman had gone through menopause, the hazard ratio was 0.76 with a non-statistically significant p-value of 0.30 (95% CI: 0.46-1.27). The age the woman was at the time of menopause had a hazard ratio of 1.03 and a p-value of 0.073, which was statistically interesting (95% CI: 1.00-1.08).

Hormone Replacement Use/Length of Use of Hormone Replacement

If the woman ever used hormone replacement therapy, the hazard ratio was 1.05 with a non-statistically significant p-value of 0.87 (95% CI: 0.62-1.78). The length of use of hormone replacement therapy had a hazard ratio of 0.96 and a p-value of 0.64, which was not statistically significant (95% CI: 0.83-1.12).

Oral Contraceptive Pills Use/Length of Use of Oral Contraceptive Pills

If the woman ever used oral contraceptive pills, the hazard ratio was 0.65 with a statistically significant p-value of 0.078 (95% CI: 0.40-1.05). The length of use of oral

contraceptive pills had a hazard ratio of 1.01 with a p-value of 0.46, which was not statistically significant (95% CI: 0.98-1.05).

Table 23: Reproductive Risk Factors Univariable Cox Proportional Hazard Model

Variable	Hazard Ratio	P-Value	Confidence Interval (95%)
Age at Menarche	1.04	0.61	0.89-1.22
Ever Parous	0.79	0.39	0.47-1.34
Age at First Birth	1.03	0.17	0.99-1.08
Menopause	0.76	0.30	0.46-1.27
Age at Menopause	1.04	0.07	1.00-1.08
Hormone Use	1.05	0.87	0.62-1.78
Hormone Use Length	0.96	0.64	0.83-1.12
OCP Use	0.65	0.08	0.40-1.05
OCP Use Length	1.01	0.46	0.98-1.05

RISK REDUCING SURGERY RISK FACTORS

Prophylactic Mastectomy

If the woman had a prophylactic mastectomy, the hazard ratio was 0.05 with a p-value of 0.004 (95% CI: 0.01-0.38), which was statistically significant.

Bilateral Salpingo-Oophorectomy/Age at Bilateral Salpingo-Oophorectomy

If the woman had a bilateral salpingo-oophorectomy, the hazard ratio was 0.79 and the p-value was 0.36, which was not statistically significant (95% CI: 0.47-1.32). The age at

which the woman had her bilateral salpingo-oophorectomy had a hazard ratio of 0.99 and a non-statistically significant p-value of 0.82 (95% CI: 0.95-1.04).

Total Abdominal Hysterectomy/Age at Total Abdominal Hysterectomy

If the woman had a total abdominal hysterectomy, the hazard ratio was 0.65 with a statistically interesting p-value of 0.084 (95% CI: 0.40-1.06). The age at which a woman received her total abdominal hysterectomy had a hazard ratio of 0.98 and a non-statistically significant p-value 0.35 (95% CI: 0.94-1.02).

Table 24: Risk Reducing Surgery Univariable Cox Proportional Hazard Model

Variable	Hazard Ratio	P-Value	Confidence Interval (95%)
Prophylactic Mastectomy	0.05	<0.01	0.01-0.38
BSO	0.79	0.36	0.47-1.32
BSO Age	0.99	0.82	0.95-1.04
TAH	0.65	0.08	0.40-1.05
TAH Age	0.98	0.35	0.94-1.02

FAMILY HISTORY

Number of First Degree Relatives with Breast Cancer

If the woman did not have any first degree relatives with breast cancer, the hazard ratio was 0.65 with a p-value of 0.015 (95% CI: 0.46-0.92), which was statistically significant.

Number of Second Degree Relatives with Breast Cancer

If the woman did not have a second degree relative with breast cancer, the hazard ratio was 0.79 with a statistically significant p-value of 0.025 (95% CI: 0.65-0.97).

Number of First Degree Relatives with Ovarian Cancer

If the woman did not have a first degree relative with ovarian cancer, the hazard ratio was 0.83 with a p-value of 0.69 (95% CI: 0.33-2.06), which was not statistically significant.

Number of Second Degree Relatives with Ovarian Cancer

If the woman did not have a second degree relative with ovarian cancer, the hazard ratio was 0.91 with a non-statistically significant p-value of 0.71 (95% CI: 0.55-1.51).

Table 25: Family History Univariable Cox Proportional Hazard Model

Variable	Hazard Ratio	P-Value	Confidence Interval (95%)
FDR Breast Cancer	0.65	<0.02	0.46-0.92
SDR Breast Cancer	0.79	<0.03	0.65-0.97
FDR Ovarian Cancer	0.83	0.69	0.33-2.06
SDR Ovarian Cancer	0.91	0.71	0.55-1.51

PRIMARY TUMOR CHARACTERISTICS

Estrogen Receptor Status

If the ER tumor status was positive, the hazard ratio was 1.45 with a statistically interesting p-value 0.096 (95% CI: 0.94-2.20).

Progesterone Receptor Status

If the PR tumor status was positive, the hazard ratio was 1.46 with a p-value of 0.070 (95% CI: 0.97-2.21), which was statistically interesting.

Her2/neu Status

If the Her2/neu status was positive, the hazard ratio was 0.63 and had a p-value of 0.25 (95% CI: 0.29-1.38), which was not statistically significant.

Pathology of Tumor

The pathology of the primary tumor had a hazard ratio of 0.93 and a p-value of 0.58 (95% CI: 0.73-1.19), which was not statistically significant.

Previous Biopsy/Previous Biopsy Number

If the woman ever had a previous biopsy, the hazard ratio was 1.41 with a p-value of 0.193 (95% CI: 0.84-2.36), which was statistically interesting. The number of previous biopsies had a hazard ratio of 1.07 and a non-statistically significant p-value of 0.45 (95% CI: 0.90-1.27).

Tumor Size

The size of the primary tumor had a hazard ratio of 1.04 and a p-value of 0.60 (95% CI: 0.91-1.18), which was not statistically significant.

Grade of Tumor

The grade of the primary tumor had a hazard ratio of 0.85 with a p-value of 0.38 (95% CI: 0.60-1.21), which was not statistically significant.

Lymphovascular Invasion

If the woman had lymphovascular invasion at the time of the primary breast cancer diagnosis, the hazard ratio was 1.48 with a statistically interesting p-value of 0.064 (95% CI: 0.98-2.25).

Table 26: Primary Tumor Characteristics Cox Proportional Hazard Model

Variable	Hazard Ratio	P-Value	Confidence Interval (95%)
ER Status	1.44	<0.10	0.94-2.20
PR Status	1.46	<0.10	0.97-2.21
Her2/neu Status	0.63	0.25	0.29-1.38
Pathology	0.93	0.58	0.73-1.19
Previous Biopsy	1.41	0.19	0.84-2.36
Previous Biopsy Number	1.07	0.45	0.90-1.27
Tumor Size	1.04	0.60	0.91-1.18
Grade	0.85	0.38	0.60-1.21
Lymphovascular Invasion	1.48	0.06	0.98-2.25

TREATMENT

Radiation Therapy

If the woman was treated with radiation at the primary breast cancer diagnosis, the hazard ratio was 1.54 with a statistically interesting p-value of 0.054 (95% CI: 0.99-2.39).

Chemotherapy

If the woman was treated with chemotherapy at the time of the primary breast cancer diagnosis, the hazard ratio was 1.32 with a non-statistically significant p-value of 0.29 (95% CI: 0.79-2.23).

Tamoxifen Use/Tamoxifen Length of Use

If the woman used Tamoxifen, the hazard ratio was 1.07 and the p-value was 0.76, which was not statistically significant (95% CI: 0.71-1.60). The length of time the woman took Tamoxifen had a hazard ratio of 1.04 and a non-statistically significant p-value of 0.62 (95% CI: 0.90-1.20).

Table 27: Treatment Univariable Cox Proportional Hazard Model

Variable	Hazard Ratio	P-Value	Confidence Interval (95%)
Radiation Exposure	1.54	0.05	0.99-2.39
Chemotherapy	1.32	0.29	0.79-2.23
Tamoxifen Use	1.07	0.76	0.71-1.60
Tamoxifen Use Length	1.04	0.62	0.90-1.20

MULTIVARIABLE ANALYSIS

After selecting the potentially interesting covariates by using univariable analyses, a stepwise multivariable Cox Proportional Hazard model was performed to build a final parsimonious multivariable model with only significant covariates (with adjustments for other covariates). The first multivariable analysis included all the potentially interesting

variables with a point of entry of 0.1. There were 37 failures with this model and not the 97 failures expected. The failures indicate how many women developed contralateral breast cancer. The results are summarized in Table 28.

Table 28: Multivariable Cox Proportional Hazard Model: All Interesting Covariables with Point of Entry = 0.1

Variable	Hazard Ratio	P-Value	Confidence Interval (95%)
Radiation Exposure	2.02	0.09	0.90-4.53
NumFDRBreast	0.50	0.03	0.27-0.95
DiagAge	1.07	0.03	1.01-1.13
ProphylacticMastectomy	0.11	0.03	0.01-0.79

It was determined that the covariable ‘Age at Menopause’ had 60 failures and the covariable ‘Age at First Birth’ had 80 failures due to missing data. Multivariable Cox Proportional Hazard model was repeated without including age at menopause so as to retain a reasonable sample size. In this model, there were 59 failures. We ran this model with a point of entry at 0.1. The results of running this model are summarized in Table 29.

Table 29: Multivariable Cox Proportional Hazard Model, Excluding Age of Menopause

Point of Entry =0.1

Variable	Hazard Ratio	P-Value	Confidence Interval (95%)
Prophylactic Mastectomy	0.06	0.005	0.00-0.42
NumFDRBreast	0.44	0.002	0.26-0.75
DiagAge	1.06	0.011	1.01-1.11
AgeFirstBirth	1.04	0.080	1.00-1.09

We then reran the stepwise multivariable Cox Proportional Hazard model excluding both age at menopause and age at first birth. In this model, there were 73 failures. This model was also run with a point of entry at 0.1. The results are summarized in Table 30.

Table 30: Multivariable Cox Proportional Hazard Model, Excluding Age of Menopause and Age at First Birth, Point of Entry =0.1

Variable	Hazard Ratio	P-Value	Confidence Interval (95%)
Prophylactic Mastectomy	0.06	0.004	0.01-0.41
NumFDRBreast	0.53	0.007	0.34-0.84
DiagAge	1.05	0.030	1.00-1.09
NumSDRBreast	0.74	0.017	0.57-0.95
ER	1.65	0.060	0.98-2.78
OCPUse	0.62	0.073	0.36-1.05

We then reran the stepwise multivariable Cox Proportional Hazard Model excluding age at menopause, age at first birth, and total abdominal hysterectomy due to a low number of failures in these covariables. In this new model there were 85 failures. We used a point of entry at 0.1 and 0.05, which gave the same results. The results are summarized in Table 31.

Table 31: Multivariable Cox Proportional Hazard Model, Excluding Age at Menopause, Age at First Birth, and Total Abdominal Hysterectomy, Point of Entry =0.1 and 0.05

Variable	Hazard Ratio	P-Value	Confidence Interval (95%)
Prophylactic Mastectomy	0.05	0.003	0.01-0.37
NumFDRBreast	0.50	0.002	0.32-0.77
DiagAge	1.06	0.004	1.01-1.10
NumSDRBreast	0.71	0.005	0.56-0.90
ER	1.65	0.038	1.03-2.64

KAPLAN-MEIER CURVES

After univariable Cox Proportional Hazard Model was performed, Kaplan-Meier curves and log-rank tests were calculated on the statistically interesting or statistically significant predictors, classified as having a p-value <0.2. Figure 6 shows the Kaplan-Meier curve for the time to develop contralateral breast cancer, with a median time at 24.5 years after the first primary diagnosis.

Figure 6: Kaplan-Meier Curve for Time to Contralateral Breast Cancer Development

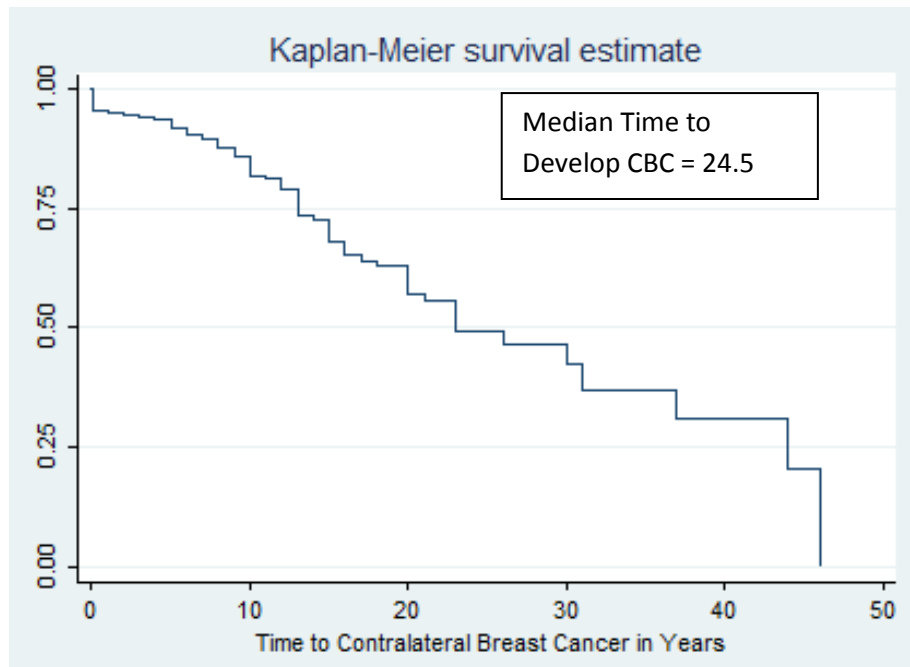


Figure 7A shows the Kaplan-Meier curve for age at the first primary diagnosis when divided into three groups. Group one is women who were diagnosed with their primary breast cancer under the age of 30. Group two is women who were diagnosed with their primary breast cancer between the ages of 30 and 40. Group three is women who were diagnosed with their primary breast cancer between the ages of 40 and 50. The p-value for this curve was 0.14. Figure 7B shows the Kaplan-Meier curve for age at the first primary diagnosis when divided into two groups. Group one is women who were diagnosed under the age of 40 and group two is women who were diagnosed between the ages of 40 and 50. The p-value for this curve was 0.01.

Figure 7: Kaplan-Meier Curves for Age at Primary Diagnosis in Different Subgroups

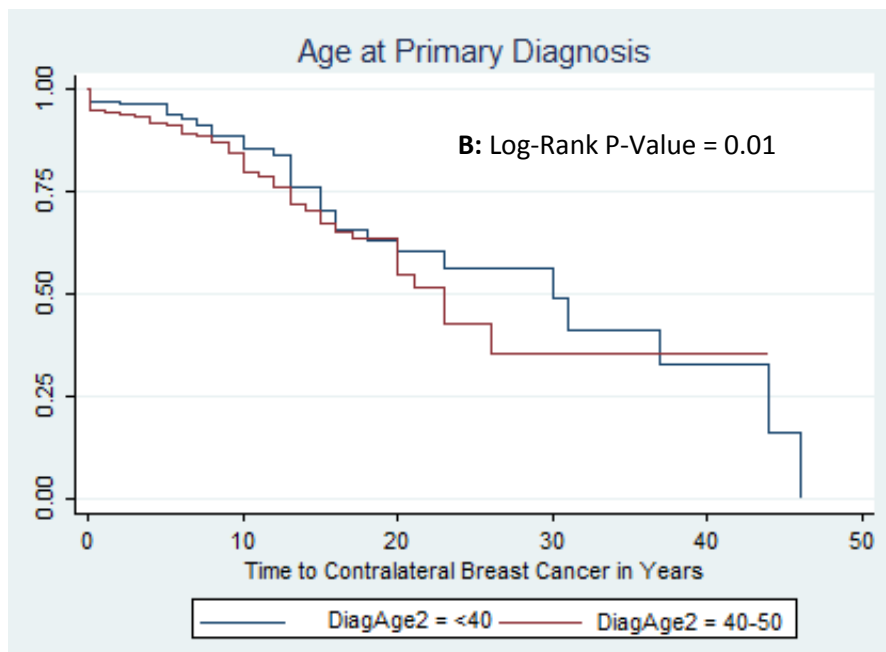
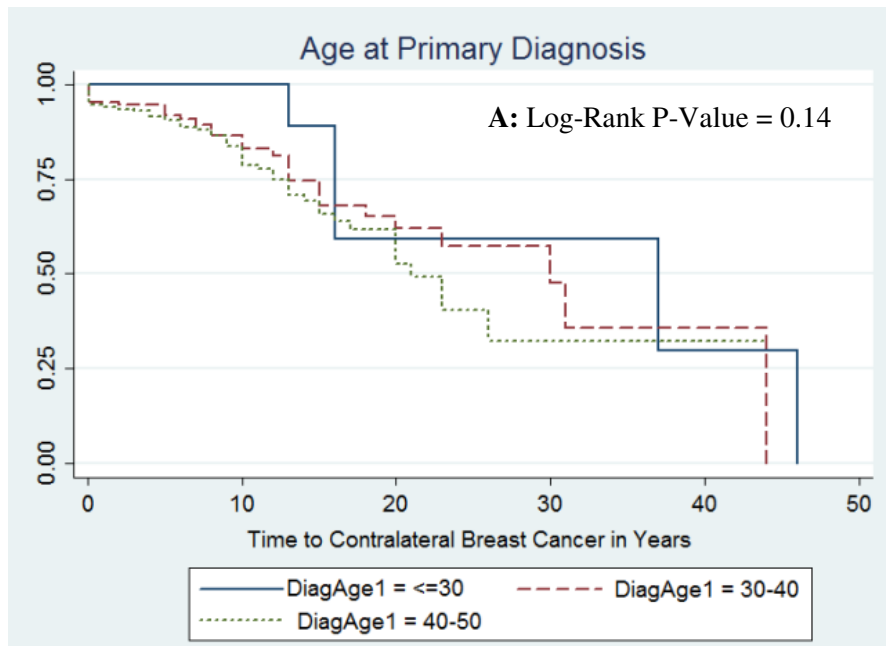
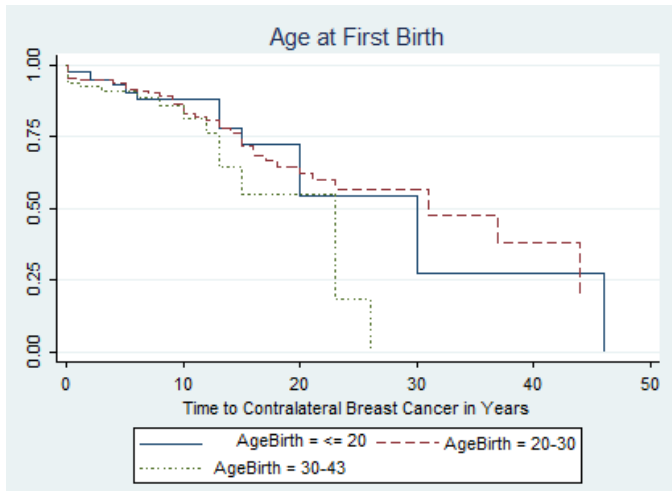
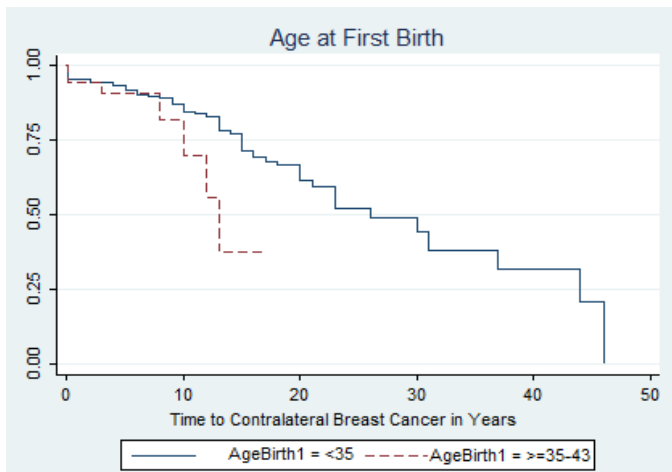


Figure 8A shows the Kaplan-Meier curve for age at first live birth when divided into three groups. Group one is women who had their first live birth under the age of 20 years old. Group two is women who had their first live birth between the ages of 20 and 30 and group three is women who had their first live birth between the ages of 30 and 43. The p-value for this curve was 0.18. Figure 8B shows the Kaplan-Meier curve for age at first birth when divided into two groups. Group one is women who had their first live birth under the age of 35 and group two is women who had their first live birth over the age of 35. The p-value for this curve was 0.12.

Figure 8: Kaplan-Meier Curves for Age at First Birth in Different Subgroups



A: Log-Rank P-Value = 0.18



B: Log-Rank P-Value = 0.12

Figure 9 shows the Kaplan-Meier curve for whether a woman ever used oral contraceptive pills or not. The p-value for this curve was 0.07.

Figure 9: Kaplan-Meier Curve for Oral Contraceptive Use

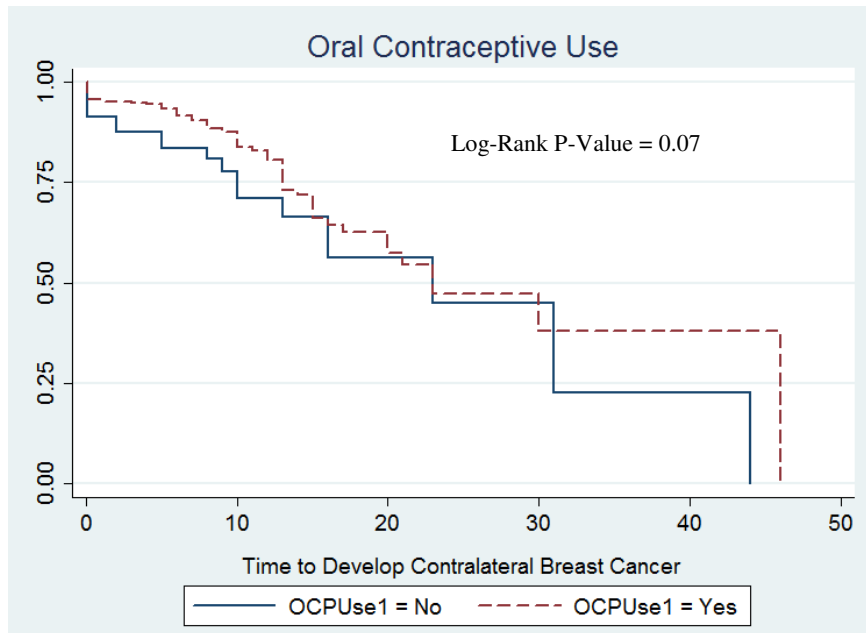
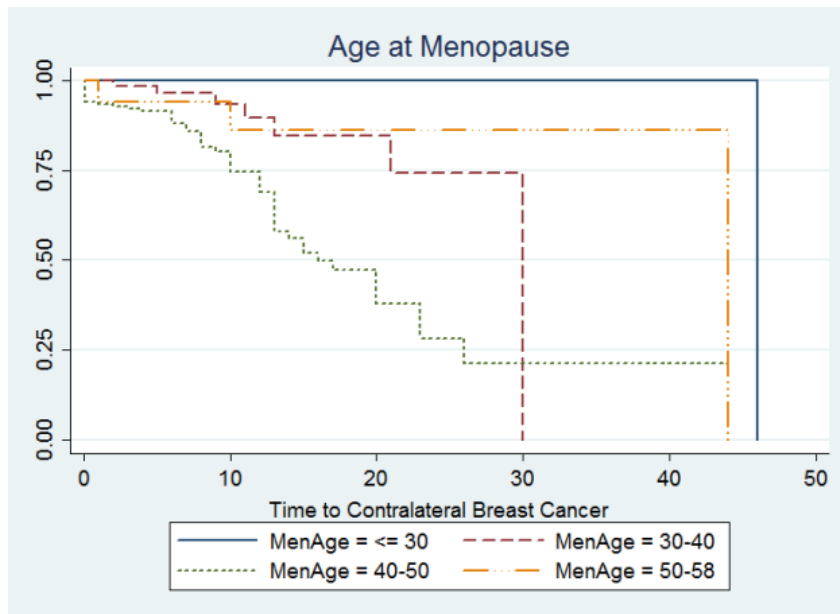
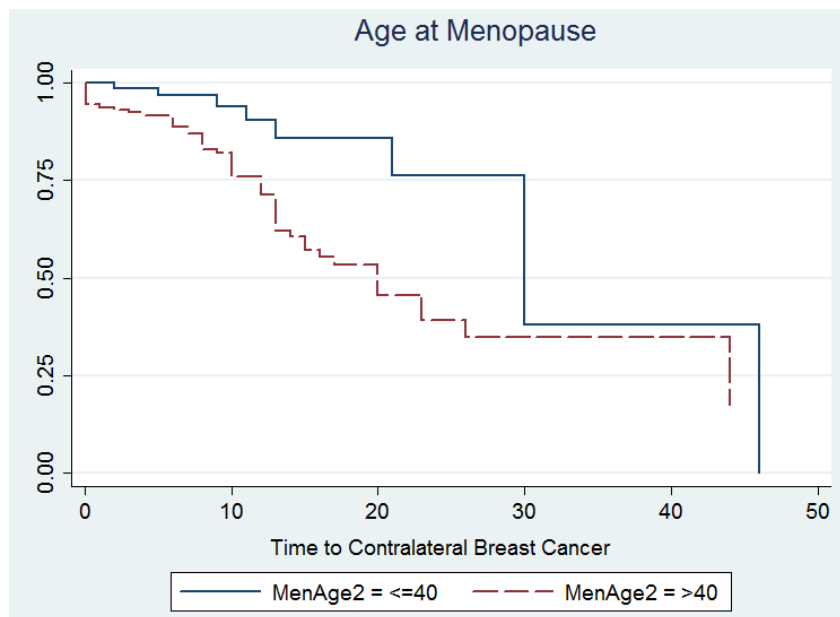


Figure 10A shows the Kaplan-Meier curve for age at which menopause occurred when divided into four groups. Group one is women who experienced menopause under the age of 30. Group two is women who experienced menopause between the ages of 30 and 40. Group three is women who experienced menopause between the ages of 40 and 50. Group four is women who experienced menopause between the ages of 50 and 58. The p-value for this curve was 0.0005. Figure 10B shows the Kaplan-Meier curve for age at which menopause occurred when divided into two groups. Group one is women who experienced menopause under the age of 40 and group two is women who experienced menopause over the age of 40. The p-value for this curve was 0.0020.

Figure 10: Kaplan-Meier Curves for Age at Menopause in Different Subgroups



A: Log-Rank P-Value = 0.0005



B: Log-Rank P-Value = 0.0020

Figure 11 shows the Kaplan-Meier curve for women who had a total abdominal hysterectomy and women who did not have a total abdominal hysterectomy. The p-value for this curve was 0.08.

Figure 11: Kaplan-Meier Curve for Total Abdominal Hysterectomy

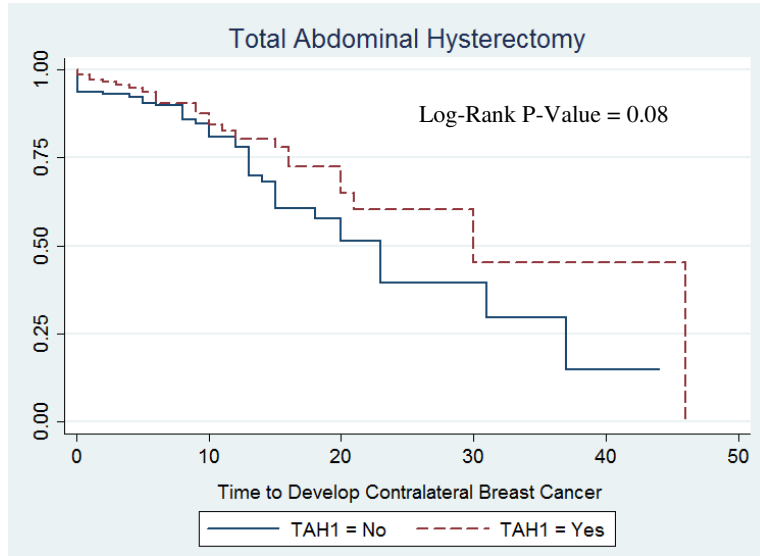


Figure 12 shows the Kaplan-Meier curve for whether the estrogen receptor status was positive or negative. The p-value for this curve was 0.09.

Figure 12: Kaplan-Meier Curve for ER Status

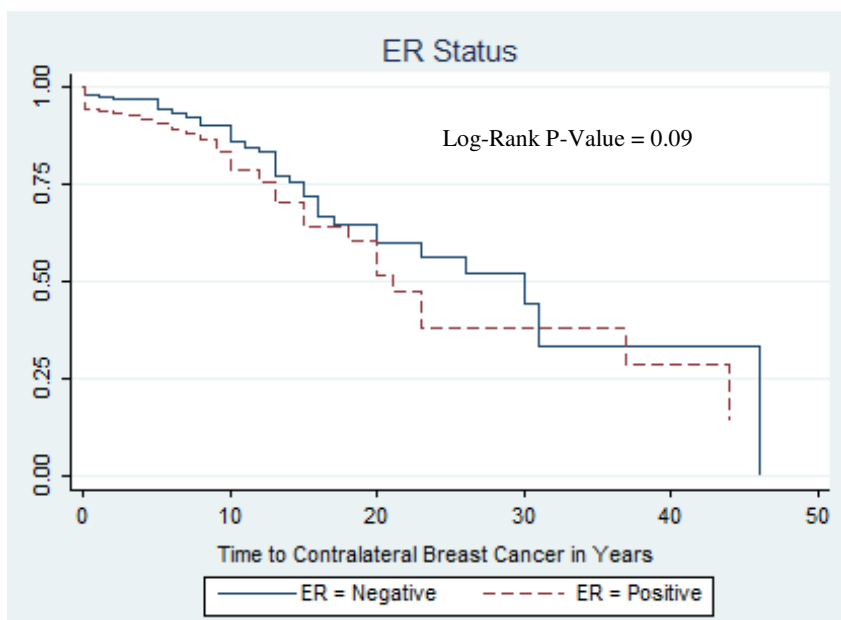


Figure 13 shows the Kaplan-Meier curve for whether the progesterone status of the primary tumor was positive or negative. The p-value for this curve was 0.06.

Figure 13: Kaplan-Meier Curve for PR Status

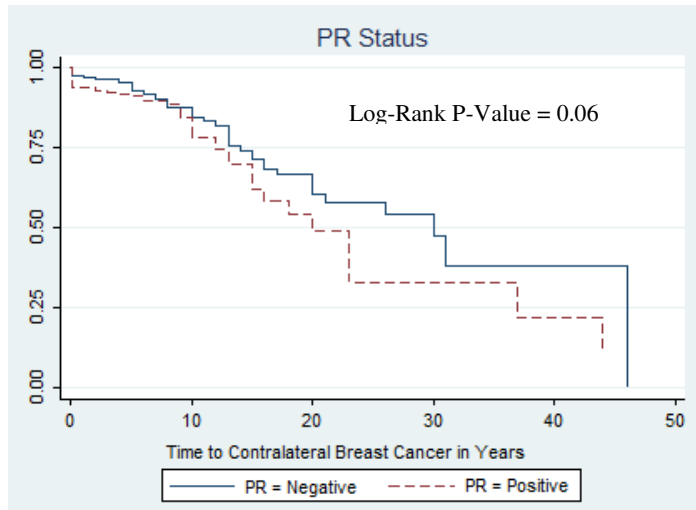


Figure 14 shows the Kaplan-Meier curve for whether a woman had a previous biopsy or not. The p-value of this curve is 0.18.

Figure 14: Kaplan-Meier Curve for Previous Biopsy

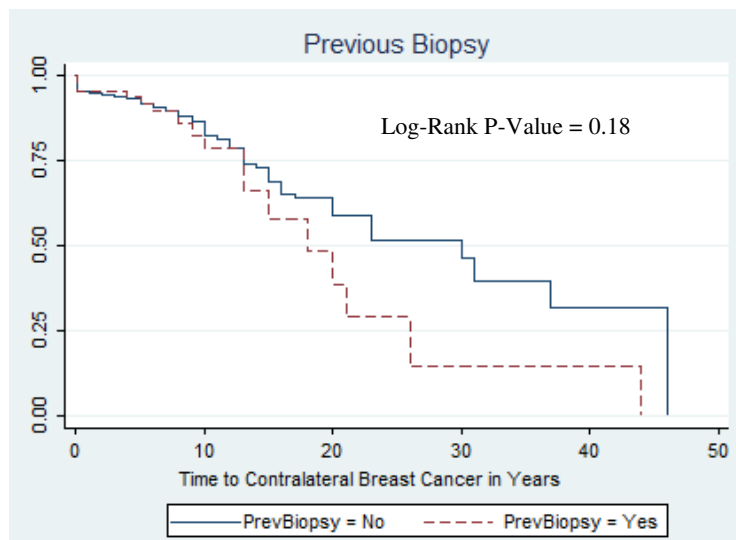


Figure 15 shows the Kaplan-Meier curve for whether the patient received radiation therapy as part of the treatment for their primary breast cancer. The p-value for this curve is 0.049.

Figure 15: Kaplan-Meier Curve for Radiation Exposure

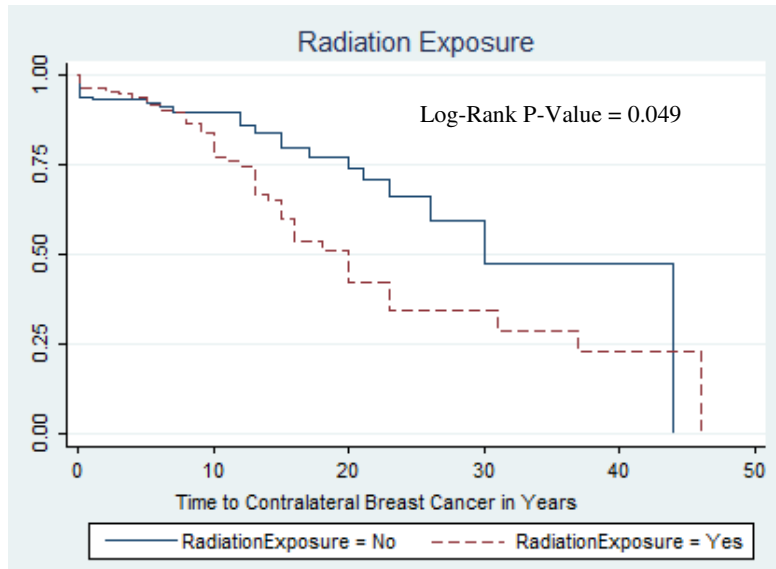
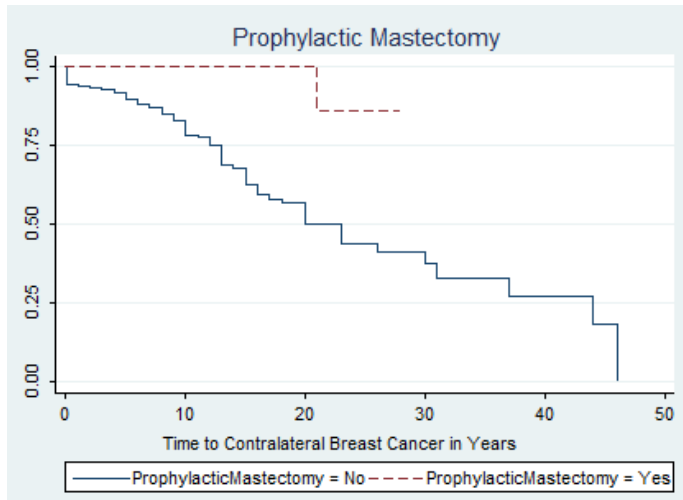


Figure 16 shows the Kaplan-Meier curve for whether a woman had a prophylactic mastectomy or not. The p-value for this curve was <0.0001.

Figure 16: Kaplan-Meier Curve for Prophylactic Mastectomy



Log-Rank P-Value = <0.0001

Figure 17 shows the Kaplan-Meier curve for whether the woman had lymphovascular invasion at the time of her primary breast cancer diagnosis or not. The p-value for this curve was 0.06.

Figure 17: Kaplan-Meier Curve for Lymphovascular Invasion

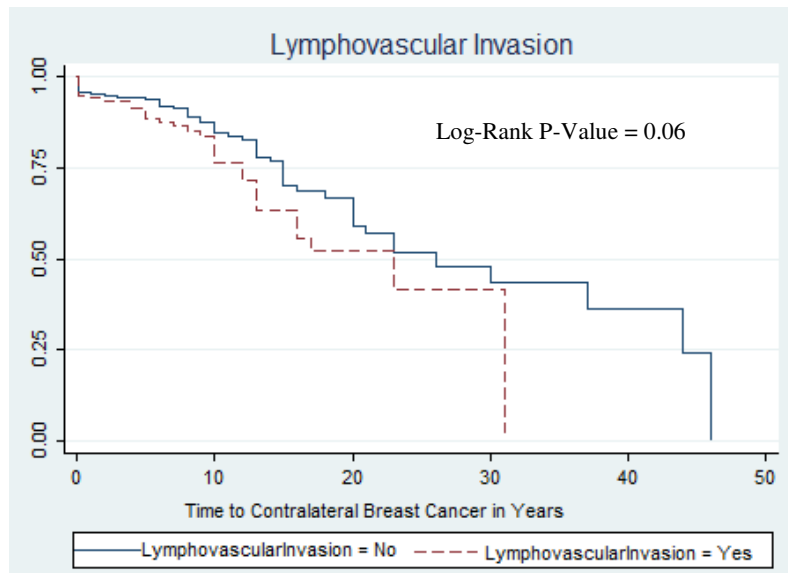
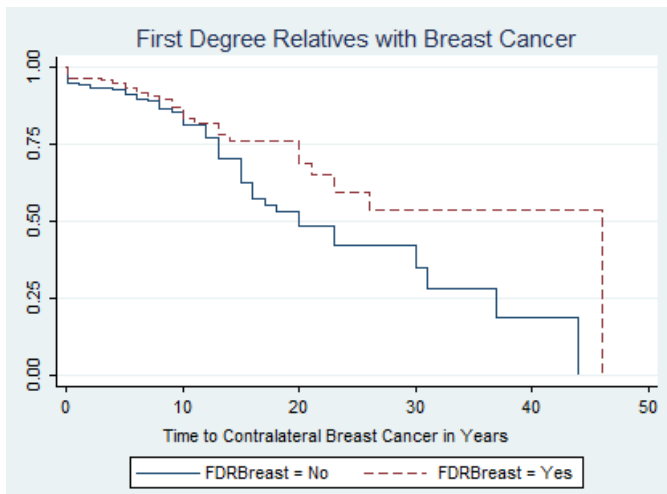
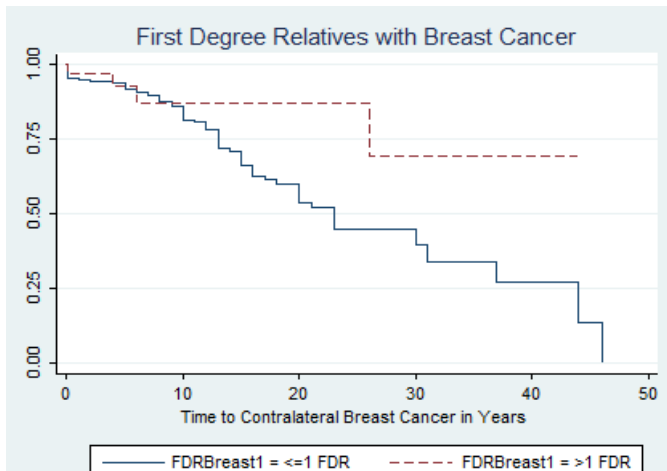


Figure 18A shows the Kaplan-Meier curve for the number of first degree relatives a woman had when divided into two groups. Group one is women who had no first degree relatives with breast cancer and group two is women who had first degree relatives with breast cancer. The p-value for this curve is 0.028. Figure 18B shows the Kaplan-Meier curve for the number of first degree relatives a woman had when divided into two different groups. Group one is women who had one or less than one first degree relative with breast cancer and group two is women who had greater than one first degree relative with breast cancer. The p-value for this curve was 0.08.

Figure 18: Kaplan-Meier Curves for Number of First Degree Relatives with Breast Cancer



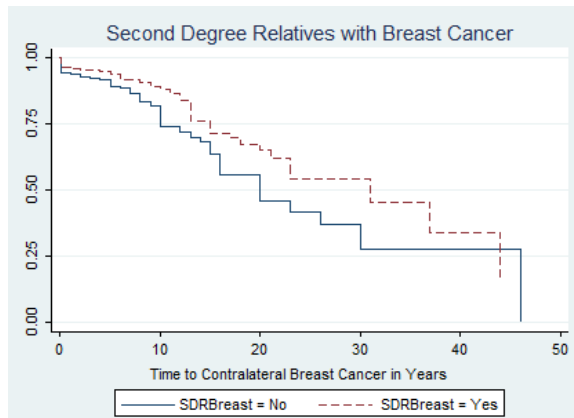
A: Log-Rank P-Value = 0.028



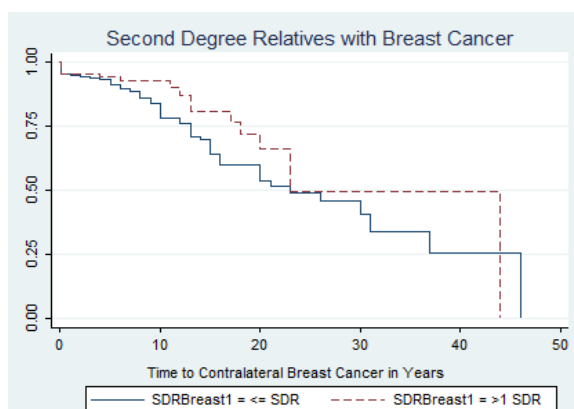
B: Log-Rank P-Value = 0.08

Figure 19A shows the Kaplan-Meier curve for the number of second degree relatives a woman had with breast cancer divided into two groups. Group one is women who had no second degree relatives with breast cancer and group two is women who had at least one second degree relative with breast cancer. The p-value for this curve was 0.0264. Figure 19B shows the Kaplan-Meier curve for the number of second degree relatives with breast cancer a woman had when divided into two different groups. Group one is women who had one or less than one second degree relative with breast cancer and group two is women who had more than one second degree relative with breast cancer. The p-value for this curve was 0.11.

Figure 19: Kaplan-Meier Curves for Number of Second Degree Relatives with Breast Cancer



A: Log-Rank P-Value = 0.0264



B: Log-Rank P-Value = 0.11

After the multivariable Cox Proportional Hazard model was ran, recursive partitioning was performed using predictive covariables that classified the women by whether or not they developed contralateral breast cancer by creating a decision tree. A Kaplan-Meier curve was then used to determine which women were at a low risk to develop contralateral breast cancer, which women were at a medium risk to develop contralateral breast cancer, and which women were at a high risk to develop contralateral breast cancer. When the RPART model was run, it was determined that the estrogen receptor status of the primary tumor was confounding with another statistically significant variable and therefore was not included in the final RPART tree. The most statistically significant covariable was prophylactic mastectomy. There was one woman who developed contralateral breast cancer after having a prophylactic mastectomy out of 115 women who had prophylactic mastectomies. Their estimated rate to develop contralateral breast cancer relative to our study population was 0.12. If the woman did not have a prophylactic mastectomy and she had at least one first degree relative with breast cancer, her estimated risk to develop contralateral breast cancer relative to our study population was 0.823. This applied to 30 women out of 170 women who had at least one first degree relative with breast cancer. If the woman did not have a prophylactic mastectomy, did not have any first degree relatives with breast cancer and was diagnosed with her primary breast cancer over the age of 46 years, her estimated rate to develop contralateral breast cancer relative to our study population was 2.7. This applied to 18 out of 54 women. If the woman did not have a prophylactic mastectomy, did not have any first degree relatives with breast cancer, was diagnosed with her first primary before the age of 46 and had a second degree relative with breast cancer, her estimated rate to develop contralateral breast cancer relative to our study population was

0.86 and if she did not have a second degree relative with breast cancer her estimated rate was 1.9.

Figure 20: RPART model

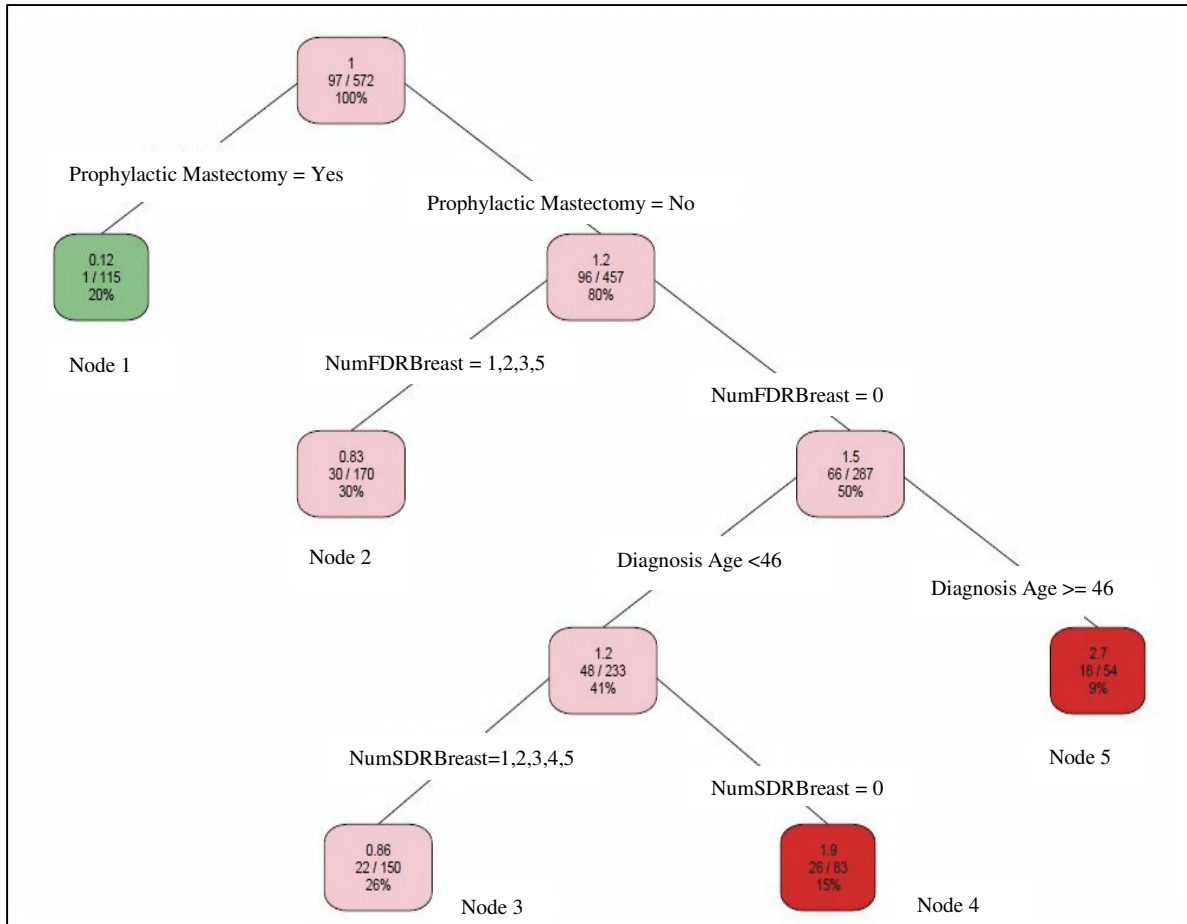


Figure 20: The top node of the decision tree begins with all 97 women with contralateral breast cancer out of the 572 women in the cohort. The 97 women have an estimated rate of 1 to develop contralateral breast cancer relative to the study population. Node 1 had the one woman who had a prophylactic mastectomy and developed contralateral breast cancer with an estimated rate to develop CBC of 0.12 relative to the study population. Node 2 shows that this group of women has a 0.83 estimated rate to develop CBC relative to the study population. Node 3 shows that this group of women has a 0.86 estimated rate to develop CBC relative to the study population. Node 4 shows that this group of women has a 1.9 estimated rate to develop CBC relative to the study population. Node 5 shows that this group of women has 2.7 estimated rate to develop CBC relative to the study population.

Based on the RPART model, the five terminal nodes were divided into three different subgroups. Subgroup 1 contains node 1, which contains the one woman who developed contralateral breast cancer after undergoing a prophylactic mastectomy. Subgroup 2 contains nodes 2 and 3. Node 2 is the women who did not have a prophylactic mastectomy and had at least one first degree relative with breast cancer. Node 3 is the women who did not have a prophylactic mastectomy, had no first degree relatives with breast cancer, were diagnosed with their primary breast cancer under the age of 46 and had at least one second degree relative with breast cancer. Subgroup 3 is nodes 4 and 5. Node 4 is the women who did not have a prophylactic mastectomy, had no first degree relatives with breast cancer, were diagnosed with their primary breast cancer under the age of 46, and had no second degree relatives with breast cancer. Node 5 is the women who did not have a prophylactic mastectomy, had no first degree relatives with breast cancer, and were diagnosed with their first primary breast cancer over the age of 46. The average time to contralateral breast cancer diagnosis for subgroup two is 31 years after the primary breast cancer diagnosis. The average time to contralateral breast cancer diagnosis for subgroup three is 15 years after the primary breast cancer diagnosis. The Kaplan-Meier curve based on the RPART model shows that subgroup one had a low risk to develop contralateral breast cancer. Subgroup two had a medium risk to develop contralateral breast cancer and subgroup three had a high risk to develop contralateral breast cancer.

Figure 21: Kaplan-Meier Curve Based on RPART with Nodes Divided into 3 Subgroups

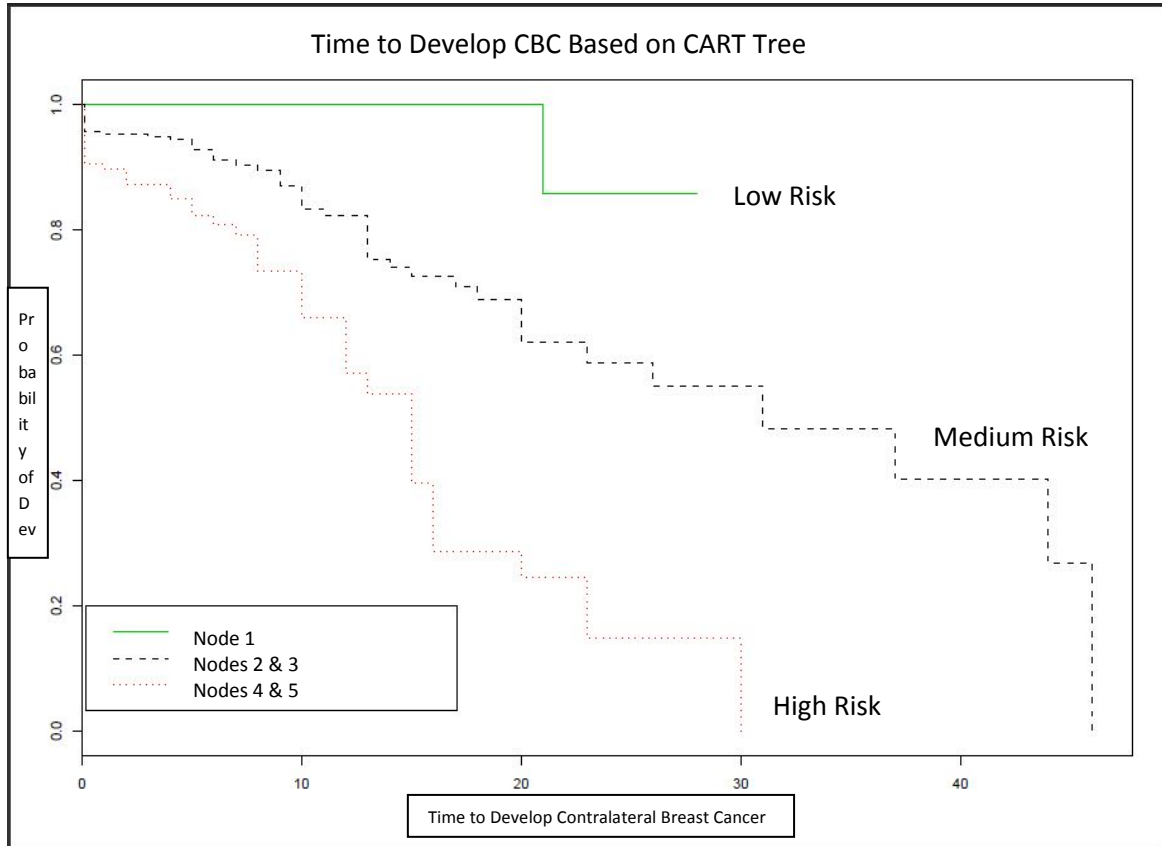


Figure 21: The low risk group contains node 1 from the RPART tree which contains the one woman who developed contralateral breast cancer after having a prophylactic mastectomy. The medium risk group contains nodes 2 & 3. Node 2 is women who did not have a prophylactic mastectomy and had at least one first degree relative with breast cancer. Node 3 is women who did not have a prophylactic mastectomy, had no first degree relatives with breast cancer, were diagnosed under the age of 46 years old, and had at least one second degree relative with breast cancer. The high risk group contains nodes 4 & 5. Node 4 is women who did not have a prophylactic mastectomy, had no first degree relatives with breast cancer, were diagnosed under the age of 46 years old, and had no second degree relatives with breast cancer. Node 5 is women who did not have a prophylactic mastectomy, had no first degree relatives with breast cancer, and were diagnosed over the age of 46 years old.

DISCUSSION

After an extensive literature review, we have not discovered any research that focused on a *BRCA* negative woman's risk to develop a second primary breast cancer after being diagnosed with a primary breast cancer under the age of 50 when they have a strong family history of breast and/or ovarian cancer. One of the aims of this study was to identify the incidence of contralateral breast cancer in a population of women who had a previous primary invasive breast cancer diagnosed under the age of 50, a BRCAPro risk assessment model of greater than 10%, and who tested negative for a mutation in the *BRCA1* and *BRCA2* genes. A second aim of this study was to identify predictors of contralateral breast cancer in this population of women. There have been numerous other studies that have identified predictors of contralateral breast cancer in women with a primary breast cancer who have not been tested for a *BRCA1/2* mutation. There have been many other studies that have identified predictors of contralateral breast cancer in women with a *BRCA1* or *BRCA2* mutation. There have been no studies looking at predictors of contralateral breast cancer in our patient population. The goal of this study was to identify the predictors of contralateral breast cancer in our specific cohort as well as to identify the incidence of contralateral breast cancer in the cohort.

This study population had an incidence of contralateral breast cancer of 17%. Approximately 30% of the contralateral breast cancer subpopulation had synchronous contralateral breast cancer and 70% had metachronous contralateral breast cancer.

DEMOGRAPHIC AND LIFESTYLE COVARIABLES

Ethnicity

Ethnicity of the women in our cohort did not have statistical significance when determining predictors of contralateral breast cancer. Our study population was mostly Non-Hispanic White, which skews the data and makes it less significant. Several other studies also had a higher number of Non-Hispanic Whites in their population and also found ethnicity to not be statistically significant when looking at the risk of contralateral breast cancer in women who have a *BRCA1* or *BRCA2* mutation as well as in cohorts where genetic testing was not performed [2,18,28,35]. However, Gao et al. (2003) found that being African-American increased one's risk to develop contralateral breast cancer [1]. Gao's study contained 6% African-American women while our study contained 9% and we did not see the same trend that being of African-American ethnicity increased a woman's risk to develop contralateral breast cancer. More studies are needed to determine if being African-American increases a woman's risk to develop contralateral breast cancer.

Age at Primary Diagnosis

The age at the primary breast cancer diagnosis was found to be statistically significant and a predictor of contralateral breast cancer, with a p-value of 0.004. In our study, being over the age of 46 at the time of the first diagnosis, places a woman in the high risk category to develop contralateral breast cancer. This is consistent with some published literature regarding age at the primary breast cancer diagnosis and the risk to develop contralateral breast cancer. Several studies have shown that being younger at the age of the first primary, defined as before 50 years of age, increased a woman's risk to develop

contralateral breast cancer [8,15,17,18,19,20,21,24,28]. This was also found in women who tested positive for a *BRCA1* or *BRCA2* mutation [2,23,25].

BRCAPro Risk Assessment Number

The BRCAPro risk assessment number was not found to be a statistically significant predictor of contralateral breast cancer in our study population. There have not been many studies that used the BRCAPro risk assessment number as a covariable in determining risk for breast cancer or for contralateral breast cancer risk. Ready et al. (2009) looked at the BRCAPro model and found that it overestimates the risk to carry a mutation in women who have bilateral breast cancer, especially if these women were diagnosed over the age of 40 years [33]. However, this study did not look at the BRCAPro risk assessment number as a predictor of contralateral breast cancer as our study did. More studies are needed to determine if having a high BRCAPro risk assessment number is a predictor of contralateral breast cancer.

Ashkenazi Jewish Ancestry

Ashkenazi Jewish ancestry was not found to be a significant predictor of contralateral breast cancer in our study cohort. Malone et al. (2010) also found that being of Jewish ancestry did not influence the risk of developing a contralateral breast cancer [2]. Malone's study had a large cohort of 52, 536 women of which 162 were of Jewish ancestry, which is approximately 0.31% of their population. Our cohort had 70 out of 572 women who were of Ashkenazi Jewish ancestry, which computes to approximately 12.24% of the population. Because of the small number of Ashkenazi Jewish women in both Malone's study and our study, it is difficult to determine if being of Ashkenazi Jewish ancestry does increase one's risk to develop contralateral breast cancer or not. In the future, more studies

should look at Ashkenazi Jewish ancestry to determine if it is a predictor of contralateral breast cancer.

Smoker/Smoking Length

Our study did not find a statistically significant risk to develop contralateral breast cancer when looking at whether a woman ever smoked or not. This was consistent with other published studies which also did not find smoking to increase the risk to develop contralateral breast cancer. Bernstein et al. (2002) and Li et al. (2011) found smoking to not be a statistically significant predictor of contralateral breast cancer [20,28]. Knight et al. (2009) researched the effect of smoking and alcohol on the risk to develop contralateral breast cancer and found that a history of smoking did not increase a woman's risk to develop contralateral breast cancer [27]. They also found that the length of time a woman smoked did not increase a woman's risk to develop contralateral breast cancer either [27]. In our study, the length of time a woman smoked was also found to not be a predictor of contralateral breast cancer, consistent with Knight et al.'s (2009) findings.

Alcohol Use

Whether a woman ever drank alcohol was not a statistically significant predictor of contralateral breast cancer in our cohort population. This was inconsistent with the one published study that looked at the relationship between alcohol consumption and contralateral breast cancer risk. Knight et al. (2009) found that drinking alcohol increases the risk to develop contralateral breast cancer [27]; however, there have not been many other studies that have looked at the risk of contralateral breast cancer in women who consume alcohol. Knight's study looked at 2,107 women of whom 708 had contralateral breast cancer. Of the 2,107 total population, 1,277 women reported drinking, which is approximately

60.61% of the total population. Our study had 350 of 572 women, who reported drinking, which is approximately 61.19% of the total population. Both studies had almost identical percentages of women who reported drinking alcohol, but two statistically different outcomes. Therefore, we propose that more research needs to be done on the effect of drinking alcohol and the risk to develop contralateral breast cancer.

Body Mass Index (BMI)

In our cohort, body mass index at the time of the primary diagnosis was not found to increase a woman's risk to develop contralateral breast cancer. This is consistent with the published literature studying the effects of body mass index on the risk to develop contralateral breast cancer. Brooks et al. (2011) found that a woman's body mass index at the time of diagnosis of the first primary was not a predictor of contralateral breast cancer diagnosis [29]. Because of the small number of studies looking at body mass index and the risk to develop contralateral breast cancer, future studies should also look at this variable to determine if it is a predictor of contralateral breast cancer or not, although the current trend indicates that this is not a significant predictor.

REPRODUCTIVE RISK FACTORS

Age at Menarche

The age at which a woman experienced menarche was not a significant predictor of contralateral breast cancer in our population. This was not consistent with the published literature regarding age at menarche and contralateral breast cancer risk. Poynter et al. (2010) and Largent et al. (2007) found that a younger age at menarche, defined as before 13 years of age, increased a woman's risk to develop contralateral breast cancer [5,30]. Both of

these studies had significantly larger cohort's than our study had, making it more likely that a younger age of menarche does, in fact, increase a woman's risk to develop contralateral breast cancer even though our study did not have similar findings. More studies are needed to confirm or dispute if the age of menarche is a predictor of contralateral breast cancer in a patient population similar to ours.

Parity/Age at First Full Term Birth

We did not find an increased risk for contralateral breast cancer based on whether a woman had ever had a full term birth or not; however, we did find that the age at which a woman had her first full term birth was a significant predictor of contralateral breast cancer in univariable analysis, but not in multivariable analysis. This is inconsistent with the published literature. Poynter et al. (2010) and Largent et al. (2007) did not find the age at first full term birth to increase the risk of contralateral breast cancer, but they did find that a higher number of full term births decreased a woman's risk [5,30]. This is opposite of our study's findings. The cohorts in the two previously published studies were larger than our cohort and therefore could carry more statistical significance. These variables should be studied in future cohorts with a similar patient population that have a larger population of women to determine the clinical validity of the findings.

Experienced Menopause/Age at Menopause

Whether a woman had ever experienced menopause was not found to be a predictor of contralateral breast cancer; however, the age at which a woman experienced menopause was found to be statistically interesting in the univariable analysis. This was then determined to not achieve statistical significance in the multivariable analysis due to missing information regarding the age at which women were experiencing menopause. The final

results are consistent with the current literature. Largent et al. (2007) also found that age at the time of menopause did not increase a woman's risk to develop contralateral breast cancer [30]. Poynter et al. (2010) found that experiencing menopause did not increase or decrease a woman's risk to develop contralateral breast cancer [5]. Both studies are consistent with our findings that experiencing menopause and the age at which a woman experiences menopause are not significant predictors of contralateral breast cancer.

Hormone Replacement Use/Length of Use of Hormone Replacement

The length of use of hormone replacement therapy and if a woman ever took hormone replacement therapy drugs was not found to increase her risk to develop contralateral breast cancer. This was consistent with the limited research regarding hormone replacement therapy and the risk for contralateral breast cancer. Figueiredo et al. (2010) also found that using hormone replacement therapy does not increase the risk to develop contralateral breast cancer [31]; however, there are not many studies that look at hormone replacement therapy as a predictor of contralateral breast cancer. Future research should study the effect of hormone use on the risk to develop contralateral breast cancer, as this variable has not been studied much when looking at predictors of contralateral breast cancer.

Oral Contraceptive Pills Use/Length of Use of Oral Contraceptive Pills

If a woman ever used oral contraceptive pills was found to be statistically interesting in the univariable analysis, but this was not found to be statistically significant in the multivariable analysis. The length of time that the women took oral contraceptive pills was not found to cause an increase the risk to develop contralateral breast cancer in our cohort. This is consistent with the published literature. Figueiredo et al. (2010) looked specifically at oral contraceptive use and the risk of contralateral breast cancer and did not find an

increased risk for contralateral breast cancer after using oral contraceptive pills [31]. This same study also looked at the length of time that oral contraceptive pills were used and found no increase in contralateral breast cancer risk with longer length of use [31]. More studies are needed to determine if oral contraceptive pill use is in fact not correlated to an increased risk for contralateral breast cancer.

RISK REDUCING SURGERIES

Prophylactic Mastectomy

Having a prophylactic mastectomy significantly reduced our cohorts risk to develop contralateral breast cancer with a p-value of 0.003; however, one woman in our cohort did develop contralateral breast cancer after having a prophylactic mastectomy. This is consistent with the published literature regarding the risk of contralateral breast cancer after undergoing a prophylactic mastectomy [7,17,18,23,36]. As prophylactic mastectomy was our most statistically significant variable, this shows how significant a prophylactic mastectomy is in reducing a woman's risk to develop contralateral breast cancer.

Bilateral Salpingo-Oophorectomy/Age at Bilateral Salpingo-Oophorectomy

Having a bilateral salpingo-oophorectomy was not found to be a predictor of contralateral breast cancer in our patient population. The age at which a woman underwent a bilateral salpingo-oophorectomy also did not influence her risk to develop contralateral breast cancer. This is inconsistent with the published research regarding the risk to develop contralateral breast cancer after undergoing a bilateral salpingo-oophorectomy. Metcalfe et al. (2011) and van Sprundel et al. (2005) found a decrease in risk for contralateral breast cancer after having a bilateral salpingo-oophorectomy [24,36]. Both of these studies

researched the effect of having a bilateral salpingo-oophorectomy on the risk of contralateral breast cancer in a population of women who had tested positive for a *BRCA1* or *BRCA2* mutation. Our population contained only *BRCA1/2* negative women. This could explain the differences in our findings. More studies of *BRCA1/2* negative women are needed to confirm or reject our findings that showed that bilateral salpingo-oophorectomy was not a predictor of contralateral breast cancer.

Total Abdominal Hysterectomy/Age at Total Abdominal Hysterectomy

Having a total abdominal hysterectomy was found to be a predictor of contralateral breast cancer in our patient population using univariable analysis; however, this was found to not be statistically significant in the multivariable analysis. The age at which a woman had a total abdominal hysterectomy was not found to be a risk factor to develop contralateral breast cancer in our patient population. To our knowledge, there are no other studies looking specifically at the risk of contralateral breast cancer in relation to a woman having a total abdominal hysterectomy. The published studies look at the interaction between bilateral salpingo-oophorectomy and contralateral breast cancer, but not total abdominal hysterectomy. More studies need to be performed looking at this variable to determine if it is, in fact, not a predictor of contralateral breast cancer.

FAMILY HISTORY

Number of First Degree Relatives with Breast Cancer

The number of first degree relatives with breast cancer that a woman has does influence her risk to develop contralateral breast cancer. This was found to be a statistically significant predictor of contralateral breast cancer in the univariable and multivariable Cox

Proportional Hazard model, with a p-value of 0.002. Several other studies also found an increase in contralateral breast cancer risk when a patient has a family history of breast cancer, whether or not the patient also had a *BRCA1* or *BRCA2* mutation [2,8,19,21,24,25]. These studies are consistent with our findings that having a family history of breast cancer is a predictor of contralateral breast cancer.

Number of Second Degree Relatives with Breast Cancer

The number of second degree relatives with breast cancer that a patient in our cohort does influence her risk to develop contralateral breast cancer. This was found to be a statistically significant factor for developing contralateral breast cancer after the univariable and the multivariable Cox Proportional Hazard models were run, with a p-value of 0.005. Several other studies found that having a family history of breast cancer increased a patient's risk to develop a contralateral breast cancer, regardless of whether the patient had a mutation in *BRCA1* or *BRCA2* [8,19,21,24,25]. The findings of these studies are consistent with our results in our patient population as well.

Number of First and Second Degree Relatives with Ovarian Cancer

The number of first and second degree relatives with ovarian cancer that a woman had was not found to increase or decrease her risk to develop contralateral breast cancer in our cohort. There were no other studies that looked into a family history of ovarian cancer as a predictor of contralateral breast cancer. Future studies should look at the interaction between a family history of ovarian cancer and the risk to develop contralateral breast cancer to help determine the significance of the results in our study.

PRIMARY TUMOR CHARACTERISTICS

Estrogen Receptor Status

Having a positive estrogen receptor status of the primary tumor was found to be a predictor of contralateral breast cancer in our patient population. This was also found to be statistically significant in the multivariable analysis with a p-value of 0.038. This is not consistent with the current research regarding estrogen receptor status as a predictor of contralateral breast cancer. Kollias et al. (1999) and Metcalfe et al. (2011) did not find estrogen receptor status to be a predictor of contralateral breast cancer [19,24]. Both previous studies had large cohorts compared to our population size. Metcalfe et al. (2011) studied only women with a *BRCA1/2* mutation, while Kollias et al. (1999) studied all women regardless of *BRCA1/2* mutation status. Future studies with a larger cohort should re-evaluate the effect of estrogen receptor status on contralateral breast cancer risk in a similar patient population to ours.

Progesterone Receptor Status

Having a positive progesterone receptor status of the primary tumor was found to be a predictor of contralateral breast cancer in our cohort in univariable analysis; however, this was not found to be statistically significant using the multivariable analysis model. This was found to be consistent with the published literature. Kollias et al. (1999) and Metcalfe et al. (2011) also found the progesterone status of the primary tumor to not be a predictor of contralateral breast cancer [19,24]. These two studies had larger patient populations than our study. They also looked at different subsets of patients. Kollias et al. (1999) looked at women who had not had genetic testing while Metcalfe et al. (2011) studied women who were *BRCA1/2* positive [19,24]. Due to the differing nature of our cohort and these two

cohorts, future studies should look at progesterone receptor status in different patient populations to identify if it is a predictor of contralateral breast cancer or not.

Her2/neu Status

The Her2/neu status of the primary tumor was not found to influence the risk of a woman developing contralateral breast cancer in our patient population. No other studies looked at Her2/neu as a predictor of contralateral breast cancer. Future studies should look at this predictor to see if it increases the risk of contralateral breast cancer in a similar patient population.

Pathology of Tumor

The pathology of the primary tumor was not found to be a predictor of contralateral breast cancer in our patient population. This is mostly consistent with the published research. Three other studies also found that the pathology subtype of the primary tumor did not increase the risk to develop contralateral breast cancer [8,17,20]. However, Yi et al. (2009) and Kollias et al. (1999) found an increase in contralateral breast cancer risk when the pathology of the primary tumor was invasive lobular carcinoma [18,19]. Yi et al. (2009) looked at a similar cohort size and Kollias et al. (1999) had a larger cohort size, but neither study looked at their cohort's *BRCA1/2* mutation status. Because of the difference in the patient populations of these studies, more research should study the pathology of the primary breast cancer tumor to determine if invasive lobular carcinoma, or other pathology types, increases a woman's risk to develop contralateral breast cancer.

Previous Biopsy/Previous Biopsy Number

Whether or not a woman had a previous biopsy was found to be a predictor of contralateral breast cancer using univariable analysis; however, this was not found to

achieve statistical significance in the multivariable analysis. The number of previous biopsies that a woman had was not found to be a predictor of contralateral breast cancer. Having a previous biopsy was not used as a covariable in any other studies predicting risk factors for contralateral breast cancer. More studies are needed to determine if having previous biopsies increases a woman's risk to develop contralateral breast cancer.

Tumor Size

The size of the primary tumor was not found to be a predictor of contralateral breast cancer in our patient population. This was consistent with the published literature. Kollias et al. (1999) also did not find the size of the primary breast cancer tumor to be a predictor of contralateral breast cancer [19]. This study looked at women who had not undergone *BRCA1/2* testing and therefore had a different patient population than our study. More studies are needed to determine if the size of the primary breast cancer tumor is a predictor of contralateral breast cancer in patient populations similar to ours.

Grade of Tumor

The grade of the primary tumor was not found to be a predictor of contralateral breast cancer in this cohort. This is mostly consistent with the published research. Kollias et al. (1999) did find an increase in contralateral breast cancer risk when the grade of the primary breast cancer was one or two, but this did not reach statistical significance in their study [19]. Metcalfe et al. (2011) did not find an increase in contralateral breast cancer risk with the grade of the primary tumor [24]. More studies are needed to determine if the grade of the primary breast cancer tumor is a predictor of contralateral breast cancer, especially in a patient population similar to ours.

Lymphovascular Invasion

Lymphovascular invasion was found to be a predictor of contralateral breast cancer in our cohort; however, this was not found to be statistically significant in the multivariable Cox Proportional Hazard model. The current published literature regarding lymphovascular invasion as a risk factor for contralateral breast cancer has found lymphovascular invasion to be a risk factor as well as it to not be a risk factor. Metcalfe et al. (2011) and Kirova et al. (2005) found that lymphovascular invasion was a predictor of contralateral breast cancer in their population [24,25]. Both of these studies looked at lymphovascular invasion as a predictor of contralateral breast cancer in women who tested positive for a *BRCA1/2* mutation, unlike our cohort which had *BRCA1/2* negative women. Kollias et al. (1999) and Vichapat et al. (2011) did not find lymphovascular invasion to be a predictor of contralateral breast cancer [19,21]. These two studies did not look at a woman's *BRCA1/2* mutation status and found similar results to ours. Future studies are needed to determine which patient populations are at an increased risk to develop contralateral breast cancer after having lymphovascular invasion with the primary breast cancer diagnosis.

TREATMENT

Radiation Therapy

Radiation exposure during the treatment for the primary breast cancer was found to be a predictor of contralateral breast cancer; however, this did not achieve statistical significance in the multivariable analysis. This is mostly consistent with the current published literature. Three different studies also did not find radiation treatment to be a risk factor for contralateral breast cancer [20,24,25]. Rubino et al. (2010) and Kollias et al.

(1999) found an increase in contralateral breast cancer risk after radiation therapy, but neither reached statistical significance [17,19]. Gao et al. studied the risk to develop contralateral breast cancer after receiving radiation therapy for the first primary. They found that radiation therapy was associated with an increase of contralateral breast cancer being diagnosed more than five years after the first primary diagnosis [1]. Our study did not look at the relationship between radiation exposure and how it was related to the time to contralateral breast cancer development. Future studies are needed to determine if radiation therapy for the primary breast cancer increases a woman's risk to develop contralateral breast cancer.

Chemotherapy

Chemotherapy to treat the primary breast cancer was not found to be a predictor of contralateral breast cancer in our patient population. This is consistent with the published literature. Kollias et al. (1999) and Metcalfe et al. (2011) also did not find an increase in contralateral breast cancer risk after receiving chemotherapy for the primary breast cancer [19,24]. Reding et al. (2010) found a decrease in contralateral breast cancer risk after chemotherapy for the first primary breast cancer [37]. Kollias et al. (1999) and Metcalfe et al. (2011) results are consistent with our findings.

Tamoxifen Use/Tamoxifen Length of Use

The use of Tamoxifen as chemoprevention was not found to be a predictor of contralateral breast cancer. The length of time a patient took Tamoxifen was also not found to be a predictor of contralateral breast cancer in our patient population. This is consistent with the currently published literature regarding contralateral breast cancer risk after a

woman takes Tamoxifen. Kollias et al. (1999) and Metcalfe et al. (2011) also did not find an increase in contralateral breast cancer risk after the patients took Tamoxifen [19,24].

SUMMARY

Our study found three different groups that had a low, medium, or high risk to develop contralateral breast cancer. We found that having a prophylactic mastectomy gives a woman a low risk to develop contralateral breast cancer. Women who did not have a prophylactic mastectomy and had at least one first degree relative with breast cancer had a medium risk to develop contralateral breast cancer. The medium risk group also included women who had not had a prophylactic mastectomy, had no first degree relatives with breast cancer, were diagnosed with their primary under the age of 46 and had at least one second degree relative with breast cancer. The high risk group included women who had not had a prophylactic mastectomy, had no first degree relatives with breast cancer, were diagnosed under the age of 46 with their first primary breast cancer and had no second degree relatives with breast cancer. The high risk group also included women who did not have a prophylactic mastectomy, had no first degree relatives with breast cancer, and were diagnosed over with their first primary over the age of 46.

We looked at a number of other variables, but none of them were statistically significant enough to be thought of as predictors of contralateral breast cancer. Surprisingly, having a high body mass index did not increase a woman's risk to develop contralateral breast cancer and undergoing a bilateral salpingo-oophorectomy did not decrease a woman's risk to develop contralateral breast cancer, as found in previous studies. Several other risk factors that have previously been found to be predictors of contralateral breast cancer were

not found to be significant in our study, including: progesterone receptor status, lymphovascular invasion of the primary tumor and radiation treatment of the primary tumor. Our study found the most significant risk factors to increase the risk for contralateral breast cancer to be having a family history of breast cancer, having a young age at diagnosis of the primary breast cancer, and having a positive estrogen receptor status of the primary breast cancer. Undergoing a prophylactic mastectomy was found to decrease the risk for contralateral breast cancer.

STUDY LIMITATIONS

There are several limitations of this study. The BRCAPro risk assessment probability, used to exclude patients from the study, was run using the CancerGene software. This software was updated several times during the time period where our patient population was receiving genetic testing. The BRCAPro risk assessment numbers were not all performed on the same version of CancerGene and therefore, the numbers could be off if recalculated using the newest version of CancerGene.

There is also a significant ascertainment bias in our population. The entire study population consisted of patients who were seen MD Anderson Cancer Center, which has a patient population consisting of mostly Non-Hispanic Whites in the upper and middle classes. This skews the data to be more representative of this population and not of the general population.

Since the study was a retrospective chart review, there was information missing in several of the electronic medical records. Having complete medical histories on all of the

women might have given different significant predictors of contralateral breast cancer. A prospective study looking at a similar cohort might also yield different results.

Another limitation to our study is that the follow-up time was not the same for all of the patients. Some patients had long follow-up times while others had very short follow-up times. Because of the varying follow-up times, we do not know if some of the unilateral breast cancer patients will develop contralateral breast cancer in the future if we followed them for long enough.

CONCLUSION

Based on our research, there should be more studies looking at the predictors of contralateral breast cancer in this patient population. Our population had a contralateral breast cancer incidence of 17%, which is higher than the general population's risk to develop a primary breast cancer of 12%. Because of this, identifying predictors of contralateral breast cancer is important in this population so that clinicians can follow those women who are at a higher risk to develop contralateral breast cancer more closely and offer them prophylactic mastectomies to reduce their risk. Clinicians should pay special attention to those women who have family histories of breast cancer as well as those diagnosed at younger ages and with positive estrogen receptor tumors and monitor them closely for contralateral breast cancer occurrence.

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