5-2021

Breast Cancer Risk for Female Relatives of Male Breast Cancer Patients with Negative BRCA1/2 Testing

Emily Martin

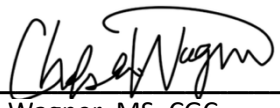
Breast Cancer Risk for Female Relatives of Male Breast Cancer

Patients with Negative BRCA1/2 Testing

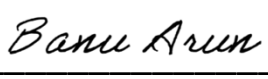
by

Emily Martin, BS

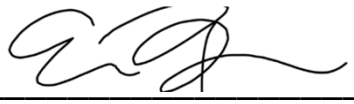
APPROVED:



Chelsea Wagner, MS, CGC
Advisory Professor



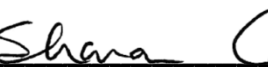
Banu Arun, MD



Erica Bednar, MS, MPH, CGC

Leslie Dunnington, MS, CGC

Rachel Bluebond, MMSc, CGC



Sharon Giordano, MD, MPH, FASCO

APPROVED:

Dean, The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences

Breast Cancer Risk for Female Relatives of Male Breast Cancer Patients with Negative *BRCA1/2* Testing

A

Thesis

Presented to the Faculty of

The University of Texas

MD Anderson Cancer Center UTHealth

Graduate School of Biomedical Sciences

in Partial Fulfillment

of the Requirements

for the Degree of

Master of Science

by

Emily Martin, BS

Houston, Texas

May, 2021

Breast Cancer Risk for Female Relatives of Male Breast Cancer Patients

with Negative *BRCA1/2* Testing

Emily Martin, BS

Advisory Professor: Chelsea Wagner, MS, CGC

Abstract

Risk models exist to estimate a female's lifetime risk of breast cancer in the absence of a hereditary predisposition to cancer, namely Hereditary Breast and Ovarian Cancer syndrome. These risk models consider various factors such as reproductive history and family history, but few models take a family history of male breast cancer into account. This study aims to evaluate if prevalence of breast cancer among female relatives is higher when there is a family history of male breast cancer in the context of uninformative *BRCA1* and *BRCA2* testing. This information may aid in the process of risk assessments for patients and their families following uninformative germline genetic testing.

A retrospective chart review was performed to compare the family histories of males with breast cancer (the case group) and males with prostate cancer (the comparison group) following uninformative *BRCA1* and *BRCA2* germline genetic testing. Univariate logistic regression was performed to calculate odds ratios for first- and second-degree relatives with statistical significance assumed at $p < 0.05$.

Our data showed a statistically significant difference in odds ratio for first-degree relatives, however the comparison group may have had a selection bias. There was no statistically significant difference in odds ratios for maternal and paternal second-degree relatives. These results support current clinical recommendations for female relatives of male breast cancer patients following uninformative *BRCA1* and *BRCA2* testing, however further research is needed to better characterize the risk to female family members of males with breast cancer.

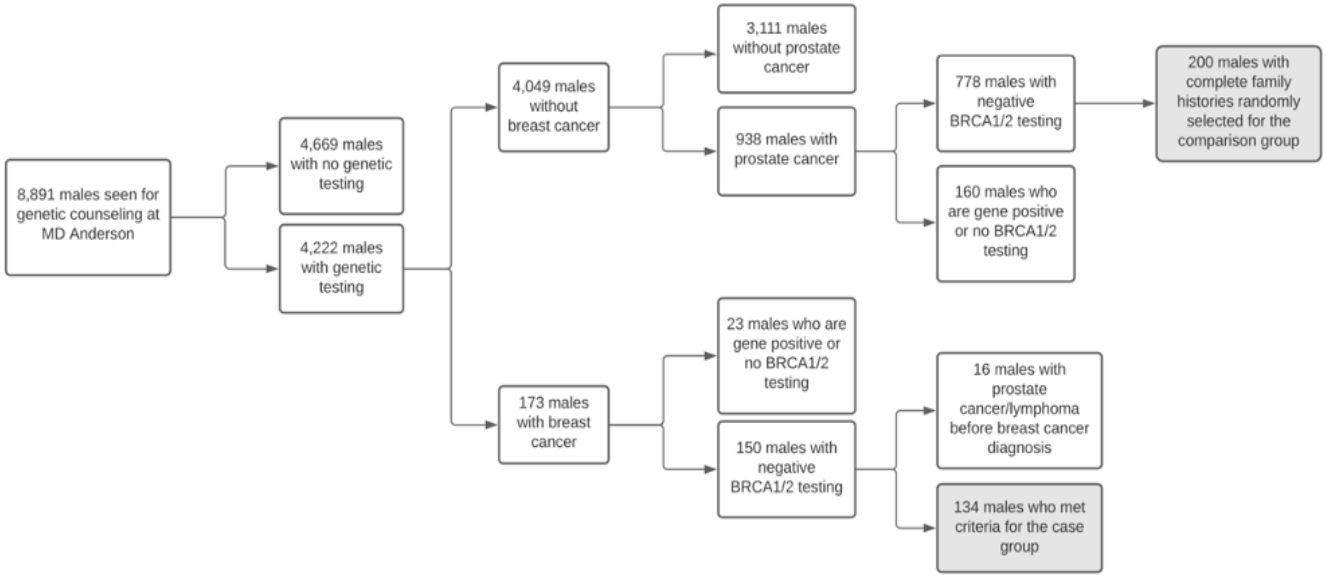
TABLE OF CONTENTS

PRELIMINARY PAGES

MANUSCRIPT

Illustrations

Figure 1: Flowchart depicting the process by which the case and comparison groups were selected from MD Anderson clinical cancer genetics database.



Found on page 5

Tables

Table 1: Demographic Information and Cancer History for the Case and Comparison Groups

	Case (N = 134)		Comparison (N = 134)		P Value
	N	%	N	%	
Mean Current Age/Age at Death (Years)	67.48		68.08		0.64
Ethnicity/Race					0.91
White/Not Hispanic or Latino	107	79.85%	107	79.95%	
Black/African American	13	9.70%	13	9.70%	
Hispanic/Latino	10	7.46%	12	8.96%	
Asian	3	2.24%	1	0.75%	
Other	1	0.75%	1	0.75%	
Cancer History					
Mean Age of Dx (Years)	59.24		61.05		0.29
Multiple Primary Cancer	33	24.63%	1	0.75%	< 0.01
Mean # of Primary Cancers	1.52		1		

Dx, diagnosis

Found on page 6

Table 2: Family History of Female Breast Cancer Among First- and Second-Degree Relatives Age ≥ 30 Years for Case and Comparison Groups

		Case (N = 134)		Comparison (N = 134)		P Value
		N	%	N	%	
FDRs	Mean # of Relatives	3.15		3.49		0.21
	Positive Family History of BC	35	26.12%	49	36.57%	0.06
	Mean # of Relatives with BC	1.06		1.22		
	Mean Age of Dx of BC (Years)	59.08		56.53		0.32
	No Family History Available	4	2.99%			
pSDRs	Mean # of Relatives	2.75		2.50		0.22
	Positive Family History of BC	21	15.67%	13	9.70%	0.08
	Mean # of Relatives with BC	1.24		1.38		
	Mean Age of Dx of BC (Years)	61.62		53.63		0.06
	No Family History Available	12	8.96%			
mSDRs	Mean # of Relatives	2.83		2.63		0.08
	Positive Family History of BC	21	16.80%	13	9.70%	0.10
	Mean # of Relatives with BC	1.05		1.08		
	Mean Age of Dx of BC (Years)	57.63		57.27		0.73
	No Family History Available	9	6.72%			

BC, breast cancer; Dx, diagnosis; FDRs, first-degree relatives; pSDRs, paternal second-degree relatives; mSDRs, maternal second-degree relatives

Found on page 9

Table 3: Pooled Prevalence of Female Breast Cancer Among First- and Second-Degree Relatives Between the Case and Comparison Groups

	Case (N = 134)	Comparison (N = 134)	P Value
FDRs	9.02%	12.82%	0.09
pSDRs	7.74%	5.37%	0.28
mSDRs	6.17%	3.98%	0.24

FDRs, first-degree relatives; pSDRs, paternal second-degree relatives; mSDRs, maternal second-degree relatives

Found on page 9

Abbreviations

HBOC: Hereditary Breast and Ovarian Cancer syndrome

NCCN: National Comprehensive Cancer Network

VUS: Variant of Uncertain Significance

OR: Odds Ratio

CI: Confidence Interval

FDR: First-degree Relative

pSDR: Paternal Second-Degree Relative

mSDR: Maternal Second-Degree Relative

SEER: Surveillance, Epidemiology, and End Results

1.0 Introduction

Breast cancer is the leading non-skin cancer diagnosed among females, and the second leading cause of cancer death.[1] It is estimated that a female's lifetime risk for developing breast cancer is currently 12.9%.[2] Males are less frequently affected with an estimated lifetime risk for developing breast cancer of 0.1%.[3]

Several risk factors contribute to an individual's risk of developing breast cancer. For males, hormonal imbalances and radiation exposure incurred in the treatment of prostate cancer and lymphoma have been linked to an increased risk of developing male breast cancer.[4,5] A female's reproductive history, hormonal medications, and lifestyle factors contribute to her lifetime risk.[1,6,7] While most breast cancer cases are considered sporadic, about 5-10% of all breast cancers develop due to a pathogenic variant in *BRCA1* or *BRCA2*, associated with Hereditary Breast and Ovarian Cancer syndrome (HBOC).[8] Males with HBOC have up to a 7% lifetime risk of developing breast cancer.[4] Currently, any male diagnosed with breast cancer meets the National Comprehensive Cancer Network's (NCCN) guidelines for *BRCA1* and *BRCA2* germline genetic testing.[9]

In the absence of a known hereditary predisposition, about 20% of breast cancer cases are familial.[8] A positive family history of breast cancer is a risk factor for both male and female breast cancer.[4,5,6,10] Previous studies have shown that a positive family history of female breast cancer incurs a relative risk of 1.76 for male breast cancer when there is one affected first degree relative, and 2.28 when there are two affected first degree relatives.[11] Conversely, these studies have reported a relative risk of 1.90 for female breast cancer when there is one affected first degree relative with male breast cancer, but these studies do not rule out a hereditary predisposition to breast cancer.[11]

Awareness of an individual's pertinent risk factors can aid in making tailored cancer screening recommendations in the absence of an identifiable hereditary predisposition to cancer. Risk models such as the Gail model and Tyrer-Cuzick Model estimate a female's lifetime risk of breast cancer in the absence of HBOC.[7,12] These types of models consider factors such as personal reproductive history or

family history of breast cancer among females, but few models take a family history of male breast cancer into account as sufficient data on the risk is not yet available. There is limited data for breast cancer risk for female relatives of males with breast cancer in the absence of HBOC.

This study aims to evaluate the prevalence of female breast cancer when there is a family history of male breast cancer in the setting of uninformative *BRCA1* and *BRCA2* germline genetic testing. This information may aid in the process of risk assessments for patients and their families following uninformative germline genetic testing.

2.0 Methods

This study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center (2020-0543) and The University of Texas Health Science Center at Houston (HSC-DB-20-0869). A waiver of informed consent was approved by the institutional review board.

2.1 Subjects

This study is a retrospective chart review involving a case group and a comparison group. Study participants in the case group included adult males with a diagnosis of breast cancer who completed a genetic counseling consultation and germline genetic testing at MD Anderson Cancer Center in Houston, Texas between May 1, 1994 to June 30, 2020 and who had uninformative *BRCA1* and *BRCA2* germline genetic testing (defined as a negative result or a result with a variant of uncertain significance [VUS]). Males were excluded if they were found to have a pathogenic variant in a gene related to hereditary breast cancer, if there was a reported family history of a pathogenic variant in a gene related to hereditary breast cancer, or if they had a history of lymphoma or prostate cancer prior to their diagnosis of breast cancer.

The comparison group included males with a diagnosis of prostate cancer who met the same inclusion criteria as the case group. Subjects were excluded if there was a pathogenic variant in a gene related to hereditary breast cancer, if there was a reported family history of a pathogenic variant in a

gene related to hereditary breast cancer, if they had a personal history of breast cancer, or if there was an incomplete family history in their medical record. Of note, males who present to MD Anderson Cancer Center with metastatic prostate cancer receive either pre-test counseling via a pre-recorded video or a full in-person genetic counseling session if their family histories warrant a more extensive risk assessment.

2.2 Data Collection

Data was extracted from MD Anderson's Clinical Cancer Genetics database between September 1, 2020 and December 31, 2020.

Data was de-identified and stored in a Microsoft Excel file on a secure cloud-based drive. For males with breast cancer, the age at breast cancer diagnosis, pathology of the breast cancer (categorized as invasive ductal carcinoma, ductal carcinoma in situ, invasive ductal carcinoma with a ductal carcinoma in situ component, or other), and hormone receptor status was recorded. For males with prostate cancer, information about whether the prostate cancer was metastatic or had a Gleason score of ≥ 7 was recorded. The following data points were collected for all subjects: age; ethnicity/race (categorized as White/Not Hispanic or Latino, Black/African American, Hispanic/Latino, Asian, or Other); any known Ashkenazi Jewish ancestry; any additional cancer diagnoses including cancer type; the genetic test performed (categorized as panel testing or *BRCA1* and *BRCA2* testing), and for panel testing, the type of panel ordered (categorized as an indication-based panel or expanded multi-gene panel); the result of the genetic test (categorized as negative or VUS); the total number of female first-degree relatives age ≥ 30 years at the time of data collection, and of those, the number with a diagnosis of breast cancer; the total number of female maternal and paternal second-degree relatives age ≥ 30 years at the time of data collection, and of those, the number with a diagnosis of breast cancer; and the ages of breast cancer diagnosis for all first- and second-degree relatives. If a subject had an incomplete family history, it was noted and the family history that was available was collected.

2.3 Data Analysis

Case subjects were matched with a comparison subject using the R programming language in a 1:1 ratio based on ethnicity/race, current age, and family size (defined as the total number of first- and second-degree female relatives age ≥ 30 years). If a case subject did not have a complete family history available, family size was not considered as part of the matching process and they were matched to a comparison subject based on ethnicity/race and current age only. An excess of comparison subjects were included in data collection to facilitate more accurate matching between the two groups.

Data was analyzed with STATA (version 13.1) and R (version 3.6.3) programming software and statistical significance was assumed at $p < 0.05$. Means and frequencies were reported for demographic information for the case and comparison groups. $\chi 2$ and Fisher's exact analyses were used to compare categorical variables and Wilcoxon rank sum tests were used to compare numerical and continuous variables between case and comparison subjects where p-values were estimated. Univariate logistic regression adjusted for the covariates of current age, ethnicity/race, and family size was performed with case/comparison status as the response variable, and prevalence of breast cancer among female relatives age ≥ 30 years as the predictor. First-degree relatives, paternal second-degree relatives, and maternal second-degree relatives were analyzed both independently and together using this method. These analyses produced odds ratios (ORs) with a corresponding 95% confidence interval (CI). Pooled prevalence of breast cancer among female relatives age ≥ 30 years was calculated by averaging the number of affected females across all subjects and dividing by the total number of female relatives across all subjects. This was done to reduce skewed values among families with a positive family history of breast cancer.

3.0 Results

In total, data was collected on 134 men with breast cancer and 200 men with prostate cancer. After matching, 278 participants were included in data analysis: 134 men with breast cancer and 134 men with prostate cancer (Figure 1).

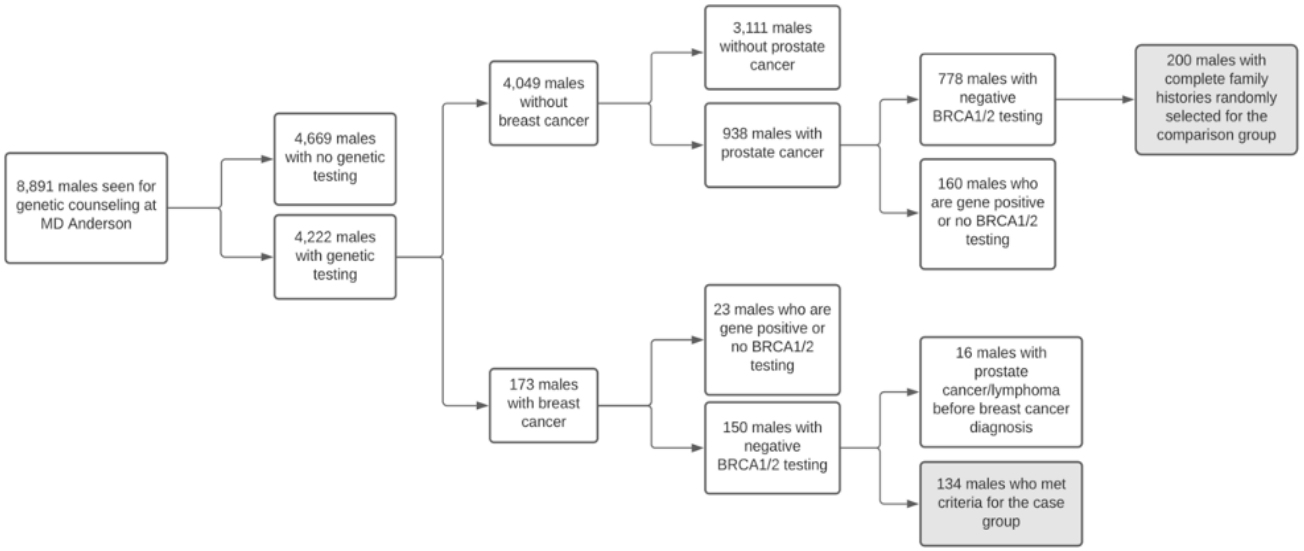


Figure 1: Flowchart depicting the process by which the case and comparison groups were selected from MD Anderson clinical cancer genetics database.

3.1 Demographics

Demographic information for the case and comparison groups is summarized in Table 1. There were no significant differences between the case and comparison groups by current age at the time of data collection, race/ethnicity, and age of cancer diagnosis ($p = 0.64$, $p = 0.91$, $p = 0.29$, respectively). There was a significant difference between the number of subjects with multiple primaries between the case and comparison groups ($p < 0.01$), with 24.63% the males in the case group reporting multiple primaries and 0.75% of males in the comparison group reporting multiple primaries. Among males in the case group who reported multiple primary cancers, 9.10% (3/33) reported two breast primaries.

Table 1: Demographic Information and Cancer History for the Case and Comparison Groups

	Case (N = 134)		Comparison (N = 134)		P Value
	N	%	N	%	
Mean Current Age/Age at Death (Years)	67.48		68.08		0.64
Ethnicity/Race					0.91
White/Not Hispanic or Latino	107	79.85%	107	79.95%	
Black/African American	13	9.70%	13	9.70%	
Hispanic/Latino	10	7.46%	12	8.96%	
Asian	3	2.24%	1	0.75%	
Other	1	0.75%	1	0.75%	
Cancer History					
Mean Age of Dx (Years)	59.24		61.05		0.29
Multiple Primary Cancer	33	24.63%	1	0.75%	< 0.01
Mean # of Primary Cancers	1.52		1		

Dx, diagnosis

3.2 Cancer Pathology

For subjects diagnosed with breast cancer, 77.61% (104/134) of tumors were described as invasive ductal carcinoma, 8.21% (11/134) of tumors were described as invasive ductal carcinoma with a ductal carcinoma in situ component, 6.72% (9/134) were described as ductal carcinoma in situ, and 7.46% (10/134) of tumors were described as an other tumor type. These included invasive lobular carcinoma, mucinous tumors, papillary tumors, and tumors with unknown pathology. 90.30% (121/134) of tumors were ER/PR positive, 4.48% (6/134) of tumors were ER/PR negative, and 5.22% (7/134) of tumors did not report on ER/PR receptor status. 78.36% (105/134) of tumors were HER-2 negative, 3.73% (5/134) of tumors were HER-2 positive, 4.48% (6/134) of tumors were HER-2 equivocal, and 13.43% (18/134) of tumors did not report on HER-2 receptor status.

For the comparison group, 94.03% (126/134) of subjects had a prostate cancer diagnosis that was considered metastatic or had a Gleason score ≥ 7. 5.97% (8/134) of subjects had a prostate cancer diagnosis that was considered non-metastatic or with a Gleason score of < 7.

3.3 Genetic Testing

62.69% (84/134) of case subjects received *BRCA1* and *BRCA2* germline genetic testing and 37.31% (50/134) of case subjects received panel genetic testing which included *BRCA1* and *BRCA2*. For

case subjects who underwent panel testing, a hereditary breast cancer panel was the most commonly ordered test. While the genes included on hereditary breast cancer panels varied by lab and ordering provider, these panels generally analyzed well-established genes associated with hereditary breast cancer. 5.22% (7/134) of comparison subjects received *BRCA1* and *BRCA2* genetic testing only and 94.78% (127/134) of comparison subjects received panel genetic testing which included *BRCA1* and *BRCA2*. For comparison subjects who underwent panel testing, a hereditary prostate cancer panel was the most commonly ordered test. Similar to the hereditary breast cancer panel, these panels varied by lab and ordering provider, but included well-established genes associated with hereditary prostate cancer. There was a statistically significant difference for the type of genetic testing performed between the case group and comparison group ($p < 0.001$).

90.30% (121/134) of case subjects received a negative genetic test result and 9.70% (13/134) of case subjects were found to have at least one VUS. Comparatively, 88.81% (119/134) of comparison subjects received a negative genetic test result and 11.19% (15/134) of comparison subjects were found to have at least one VUS. There was no statistically significant difference for genetic test results between the case and comparison groups ($p = 0.69$).

3.4 Family History

Family history data for first- and second-degree female relatives is summarized in Table 2. There was no statistically significant difference between case and comparison groups for total number of female first degree relatives (FDRs) age ≥ 30 years ($p = 0.21$) or for total number of female FDRs age ≥ 30 years with breast cancer ($p = 0.06$). Using univariate logistic regression, an OR for the case group was 0.62 (95% CI 0.40-0.95) based on family history of breast cancer among female FDRs age ≥ 30 years. There was no statistically significant difference between ORs when calculated for each reported ethnicity/race. Of note, one comparison subject reported a male FDR with a history of breast cancer, but this diagnosis was not included in data analysis.

There was no statistically significant difference between case and comparison groups for the total number of female paternal second-degree relatives (pSDR) age ≥ 30 years ($p = 0.22$) or female pSDRs age ≥ 30 years with breast cancer ($p = 0.08$). There was no statistically significant difference between case and comparison groups for the total number of female maternal second-degree relatives (mSDR) age ≥ 30 years ($p = 0.08$) or female mSDRs age ≥ 30 years with breast cancer ($p = 0.10$). The ORs for pSDRs and mSDRs among the case group was not statistically significant. The OR for pSDRs was calculated to be 0.74 (95% CI 0.13-4.20) and the OR for mSDRs was calculated to be 1.00 (95% CI 0.19-5.34). There was no statistically significant difference between ORs when calculated for each reported ethnicity/race.

An OR was calculated for total family size by combining FDR, pSDR, and mSDR family histories and adjusting for the covariates of age, race/ethnicity, and family size. This value was not found to be statistically significant at 1.01 (95% CI 0.17-5.80).

The pooled prevalence of breast cancer among female FDRs and SDRs age ≥ 30 years is summarized in Table 3. There was no statistically significant difference in pooled prevalence of breast cancer between the case and comparison groups.

Table 2: Family History of Female Breast Cancer Among First- and Second-Degree Relatives Age ≥ 30 Years for Case and Comparison Groups

		Case (N = 134)		Comparison (N = 134)		P Value
		N	%	N	%	
FDRs	Mean # of Relatives	3.15		3.49		0.21
	Positive Family History of BC	35	26.12%	49	36.57%	0.06
	Mean # of Relatives with BC	1.06		1.22		
	Mean Age of Dx of BC (Years)	59.08		56.53		0.32
	No Family History Available	4	2.99%			
pSDRs	Mean # of Relatives	2.75		2.50		0.22
	Positive Family History of BC	21	15.67%	13	9.70%	0.08
	Mean # of Relatives with BC	1.24		1.38		
	Mean Age of Dx of BC (Years)	61.62		53.63		0.06
	No Family History Available	12	8.96%			
mSDRs	Mean # of Relatives	2.83		2.63		0.08
	Positive Family History of BC	21	16.80%	13	9.70%	0.10
	Mean # of Relatives with BC	1.05		1.08		
	Mean Age of Dx of BC (Years)	57.63		57.27		0.73
	No Family History Available	9	6.72%			

BC, breast cancer; Dx, diagnosis; FDRs, first-degree relatives; pSDRs, paternal second-degree relatives; mSDRs, maternal second-degree relatives

Table 3: Pooled Prevalence of Female Breast Cancer Among First- and Second-Degree Relatives Between the Case and Comparison Groups

	Case (N = 134)	Comparison (N = 134)	P Value
FDRs	9.02%	12.82%	0.09
pSDRs	7.74%	5.37%	0.28
mSDRs	6.17%	3.98%	0.24

FDRs, first-degree relatives; pSDRs, paternal second-degree relatives; mSDRs, maternal second-degree relatives

4.0 Discussion

The results of our study suggest that there is no significant difference in the family histories of breast cancer among female relatives age ≥ 30 years when comparing subjects with male breast cancer (case) to subjects with prostate cancer (comparison) in the context of uninformative *BRCA1* and *BRCA2* germline genetic testing. Previous research has demonstrated that male breast cancer is associated with an increased risk of breast cancer for unaffected female relatives, but limited data exists to characterize the risk to unaffected female relatives in the absence of a hereditary predisposition to breast cancer, namely HBOC.[4,10,11] Our data suggests that in the absence of a hereditary predisposition to breast cancer, a family history of male breast cancer may not impact a female relative's risk.

The comparison groups suggest that they are similar in age ($p = 0.64$), reported ethnicity/race ($p = 0.91$), and family size (FDRs $p = 0.21$; pSDRs $p = 0.22$; mSDRs $p = 0.08$). This implies that matching between the two groups produced a uniform cohort when accounting for the covariates of age, reported ethnicity/race, and family size, and this reduces differences of several variables that contribute towards a female relative's breast cancer risk.[6,13]

The mean age of diagnosis of male breast cancer was 59.24 years which is younger than the median age of diagnosis of 67 years that has been previously reported.[14,15] Males with breast cancer were more likely to have multiple primaries compared to the comparison group ($p < 0.01$). Outside of prostate cancer and lymphoma, cancer history was not selected against for the case group. The high proportion of males with breast cancer who reported additional cancer primaries suggests either that additional cancer history could be a risk factor to develop male breast cancer or that a history of male breast cancer could incur a risk to develop subsequent cancers later in life. This was not the focus of our study but could be an area of interest for future research. A large proportion of male breast cancer tumors were IDC, hormone receptor positive, and HER-2 negative, consistent with tumor demographics previously reported in the literature.[14,15]

There was a significant difference between the type of genetic testing ordered for the case and comparison groups, with males with a diagnosis of breast cancer more likely to have undergone *BRCA1* and *BRCA2* testing only vs. panel testing ($p < 0.001$). This difference can be attributed to several factors, including data available on hereditary predispositions to male breast cancer compared to male prostate cancer. *BRCA1* and *BRCA2* were the first genes to be associated with an increased risk of male breast cancer.[15] Since then, other genes such as *CHEK2* and *PALB2* have been associated with male breast cancer, but their risks are still not well quantified.[4,15,16] Similarly, *BRCA1* and *BRCA2* were identified as genes associated with an increased risk of prostate cancer. Additional genes including those associated with Lynch syndrome, *ATM,* and *PALB2* have been associated with prostate cancer, and these risks are now well-established. [17,18] Updates to the NCCN guidelines reflect the expansion of knowledge about

hereditary prostate cancer coming out of more recent publications, whereas male breast cancer has been included in these guidelines for much longer.

VUS rates were similar between the case and comparison groups, despite the difference in rates of panel testing. Most panels selected only included well-established genes relevant to the patient's personal and family history, thereby resulting in lower VUS rates when compared to larger panels.

When evaluating family histories, our study shows no significant difference between the family histories of breast cancer among FDRs, SDRs, or pooled prevalence for the case and comparison groups. Our data shows a higher prevalence of breast cancer among FDRs in the comparison group and a higher prevalence of breast cancer among SDRs in the case group. None of these differences are statistically significant, although the difference between FDRs trended towards significance with a p-value of < 0.10, highlighting the need for larger studies. These differences in family history could be due in part to a selection bias in the comparison group.

Males with prostate cancer who received pre-test genetic counseling from a genetic counselor were more likely to have a complete family history in the cancer genetics database compared to males who received pre-test counseling by video. Because a complete family history was required in order to be included in the comparison group, it is possible that males who received a full genetic counseling session and therefore had more extensive family histories of cancer were more likely to be selected for the comparison group.

The pooled prevalence of breast cancer among female FDRs age ≥ 30 years was greater than the prevalence of breast cancer among female SDRs age ≥ 30 years. Previous research has shown that individuals are more likely to report a positive family history among FDRs than among SDRs.[19] Interestingly, previous research has also demonstrated that paternal family history is underreported when compared to maternal family history.[19] Underreporting of paternal family history was not seen in

our data, which may be attributed to our study only analyzing data when there was a complete paternal family history reported.

Using the Surveillance, Epidemiology, and End Results (SEER) Cancer Query System, the estimated complete prevalence of breast cancer among females age ≥ 30 years is 3.50%.[2] This number does not reflect females who were diagnosed and subsequently died and therefore is likely a conservative estimate. Along with a female's lifetime risk of 12.9% to develop breast cancer, we can use these two estimates as a range to interpret the prevalence of female breast cancer among female relatives age ≥ 30 years in our data. [2] All pooled prevalence values were between 3.50% and 12.9% which falls within the range of prevalence values from the SEER data. This suggests a nonsignificant result and that our comparison group may have similar breast cancer rates to the general population.

4.1 Missing Data

Pedigrees documented in the medical record represent family histories of cancer at that moment in time, rather than family histories that are regularly updated. Because of this, it is possible that family members in the case or comparison groups could have developed breast cancer at a later time and these diagnoses were not included in data analysis. Having updated family history could alter the ORs as well as the pooled prevalence values for our data. Further, not all males in the case group had complete family histories on file, either because they were not reported or because they were unknown to the patient. This limits the amount of family history information available in data analysis.

4.2 Limitations

The comparison group was selected because it was necessary to compare our case subjects to a cohort who presented for genetic counseling, had a complete pedigree in the medical record, and had undergone *BRCA1* and *BRCA2* germline genetic testing. However, we acknowledge that males in the comparison group also have a personal history of cancer and this could impact familial cancer risks and thus skew the results of our data analysis. There are reports of associations between familial breast cancer and familial prostate cancer, but these studies do not rule out HBOC for participants.[20] To our

knowledge, no association between prostate cancer and female breast cancer in the absence of HBOC has been reported in the literature.

Additionally, there are pathogenic variants in genes besides *BRCA1* and *BRCA2* that have been shown to contribute to breast cancer risk in males and females.[4,5,6,13] As we learn more about the impact of other genes on male and female breast cancer risk, future studies will be needed to determine how negative genetic testing in a proband influences familial breast cancer risk.

Lastly, individuals in our study are those undergoing active treatment for a medical condition, those motivated to pursue genetic testing for familial implications, or those who report family history to a provider that resulted in a genetics referral. All of these factors can contribute to a patient that is more likely to report a positive family history related to their medical concern.[21,22,23]

5.0 Conclusion

In this study, there was no statistically significant difference in family history of female breast cancer between the case and comparison group, and both groups reported family histories of breast cancer that were within the range of the SEER database's prevalence estimates.

These results support current clinical breast screening recommendations for female family members of male breast cancer patients with uninformative *BRCA1* and *BRCA2* germline genetic testing, which include breast screening based on personal risk factors and family histories of female breast cancer. Future research evaluating how family histories of unaffected comparison subjects who have uninformative *BRCA1* and *BRCA2* germline genetic testing are now needed to confirm the findings of our study. Studies investigating how family history of cancer influences an individual's risk of cancer, like this one, have the potential to improve personalized risk assessment and better identify patients that may benefit from enhanced screening.

Bibliography

[1] American Cancer Society. Cancer Facts and Figures 2020.

[2] *SEER Cancer Statistics Review, 1975-2002.* Bethesda: National Cancer Institute; 2020.

[3] Giordano, S. H., Cohen, D. S., Buzdar, A. U., Perkins, G., & Hortobagyi, G. N. (2004). Breast carcinoma in men. *Cancer*, *101*(1), 51–57. https://doi.org/10.1002/cncr.20312.

[4] Jad, A., & Yousef, A. (2017). Male Breast Cancer: Epidemiology and Risk Factors. *Seminars in Oncology*, *44*(4), 267–272. https://doi.org/10.1053/j.seminoncol.2017.11.002.

[5] Ruddy KJ, Winer EP. Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. Ann Oncol. 2013 Jun;24(6):1434-43. doi: 10.1093/annonc/mdt025. Epub 2013 Feb 20. PMID: 23425944.

[6] Rojas K, Stuckey A. Breast Cancer Epidemiology and Risk Factors. Clin Obstet Gynecol. 2016 Dec;59(4):651-672. doi: 10.1097/GRF.0000000000000239. PMID: 27681694.

[7] Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med. 2004 Apr 15;23(7):1111-30. doi: 10.1002/sim.1668. Erratum in: Stat Med. 2005 Jan 15;24(1):156. PMID: 15057881.

[8] Ford D, Easton DF, Bishop DT, et al. Risks of cancer in BRCA1 mutation carriers. *Lancet.* 1994;343:692-695.

[9] National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (Version 2.2021). https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf.

[10] Claus, E. B., Risch, N., & Thompson, W. D. (1994). Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer*, *73*(3), 643–651. https://doi.org/10.1002/1097-0142(19940201)73:3<643::AID-CNCR2820730323>3.0.CO;2-5.

[11] Zheng, G., Yu, H., Hemminki, A., Försti, A., Sundquist, K., & Hemminki, K. (2017). Familial associations of male breast cancer with other cancers. *Breast Cancer Research and Treatment*, *166*, 897–902. https://doi.org/10.1007/s10549-017-4468-1.

[12] Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, Mulvihill JJ. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989 Dec 20;81(24):1879-86. doi: 10.1093/jnci/81.24.1879. PMID: 2593165.

[13] Eitan Amir, Orit C. Freedman, Bostjan Seruga, D. Gareth Evans, Assessing Women at High Risk of Breast Cancer: A Review of Risk Assessment Models, *JNCI: Journal of the National Cancer Institute*, Volume 102, Issue 10, 19 May 2010, Pages 680–691, https://doi.org/10.1093/jnci/djq088.

[14] Moelans CB, de Ligt J, van der Groep P, Prins P, Besselink NJM, Hoogstraat M, Ter Hoeve ND, Lacle MM, Kornegoor R, van der Pol CC, de Leng WWJ, Barbé E, van der Vegt B, Martens J, Bult P, Smit VTHBM, Koudijs MJ, Nijman IJ, Voest EE, Selenica P, Weigelt B, Reis-Filho JS, van der Wall E, Cuppen E, van Diest PJ. The molecular genetic make-up of male breast cancer. Endocr Relat Cancer. 2019 Oct;26(10):779-794. doi: 10.1530/ERC-19-0278. PMID: 31340200; PMCID: PMC6938562.

[15] Giordano SH. Breast Cancer in Men. N Engl J Med. 2018 Jun 14;378(24):2311-2320. doi: 10.1056/NEJMra1707939. PMID: 29897847.

[16] Gucalp A, Traina TA, Eisner JR, Parker JS, Selitsky SR, Park BH, Elias AD, Baskin-Bey ES, Cardoso F. Male breast cancer: a disease distinct from female breast cancer. Breast Cancer Res Treat. 2019 Jan;173(1):37-48. doi: 10.1007/s10549-018-4921-9. Epub 2018 Sep 28. PMID: 30267249; PMCID: PMC7513797.

[17] Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, Garofalo A, Gulati R, Carreira S, Eeles R, Elemento O, Rubin MA, Robinson D, Lonigro R, Hussain M, Chinnaiyan A, Vinson J, Filipenko J, Garraway L, Taplin ME, AlDubayan S, Han GC, Beightol M, Morrissey C, Nghiem B, Cheng HH, Montgomery B, Walsh T, Casadei S, Berger M, Zhang L, Zehir A, Vijai J, Scher HI, Sawyers C, Schultz N, Kantoff PW, Solit D, Robson M, Van Allen EM, Offit K, de Bono J, Nelson PS. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N Engl J Med. 2016 Aug 4;375(5):443-53. doi: 10.1056/NEJMoa1603144. Epub 2016 Jul 6. PMID: 27433846; PMCID: PMC4986616.

[18] Pritzlaff M, Tian Y, Reineke P, Stuenkel AJ, Allen K, Gutierrez S, Jackson M, Dolinsky JS, LaDuca H, Xu J, Black MH, Helfand BT. Diagnosing hereditary cancer predisposition in men with prostate cancer. Genet Med. 2020 Sep;22(9):1517-1523. doi: 10.1038/s41436-020-0830-5. Epub 2020 May 22. PMID: 32439974; PMCID: PMC7462744.

[19] Ozanne EM, O'Connell A, Bouzan C, Bosinoff P, Rourke T, Dowd D, Drohan B, Millham F, Griffin P, Halpern EF, Semine A, Hughes KS. Bias in the reporting of family history: implications for clinical care. J Genet Couns. 2012 Aug;21(4):547-56. doi: 10.1007/s10897-011-9470-x. Epub 2012 Jan 12. PMID: 22237666.

[20] Barber L, Gerke T, Markt SC, Peisch SF, Wilson KM, Ahearn T, Giovannucci E, Parmigiani G, Mucci LA. Family History of Breast or Prostate Cancer and Prostate Cancer Risk. Clin Cancer Res. 2018 Dec 1;24(23):5910-5917. doi: 10.1158/1078-0432.CCR-18-0370. Epub 2018 Aug 6. PMID: 30082473; PMCID: PMC6279573.

[21] Suttman A, Pilarski R, Agnese DM, Senter L. "Second-Class Status?" Insight into Communication Patterns and Common Concerns Among Men with Hereditary Breast and Ovarian Cancer Syndrome. J Genet Couns. 2018 Aug;27(4):885-893. doi: 10.1007/s10897-018-0214-z. Epub 2018 Feb 5. PMID: 29404823.

[22] Leenen, C.H.M., Heijer, M.d., van der Meer, C. *et al.* Genetic testing for Lynch syndrome: family communication and motivation. *Familial Cancer* 15, 63–73 (2016). https://doi.org/10.1007/s10689-015-9842-8.

[23] Saldana TM, Moshesh M, Baird DD. Self-reported family history of leiomyoma: not a reliable marker of high risk. Ann Epidemiol. 2013 May;23(5):286-90. doi: 10.1016/j.annepidem.2013.03.003. PMID: 23621994; PMCID: PMC5384608.

Vita

Emily Elizabeth Martin was born in Bradenton, Florida. She received her Bachelor of Science from The University of Alabama in 2018, majoring in Biological Sciences and minoring in Food & Nutrition. She spent the next year working as a Genetic Counseling Assistant in clinical cancer genetics at UT Southwestern Medical Center in Dallas, Texas. In August 2019, she entered The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences to pursue a Master of Science in Genetic Counseling. Following the completion of her degree, Emily plans to begin working as a Cancer Genetic Counselor at Piedmont Healthcare in Atlanta, Georgia.

Permanent Address:

4880 Hansard Drive

Cumming, Georgia 30040