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Cancer Incidence in First and Second Degree Relatives of BRCA1 and BRCA2 Mutation Carriers

Haley Streff

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CANCER INCIDENCE IN FIRST AND SECOND DEGREE RELATIVES OF
BRCA1 AND BRCA2 MUTATION CARRIERS

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A

THESIS

Presented to the Faculty of
The University of Texas
Health Science Center at Houston
and
The University of Texas
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in Partial Fulfillment

of the Requirements

for the Degree of

MASTER OF SCIENCE

by

Haley Streff, BS
Houston, Texas

May, 2015

Dedication

High Five Buddy!

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CANCER INCIDENCE IN FIRST AND SECOND DEGREE RELATIVES OF
BRCA1 AND BRCA2 MUTATION CARRIERS

Haley Streff, BS

Advisory Professor: Jennifer Litton, M.D.

Mutations in the *BRCA1* or *BRCA2* genes are associated with increased risks for breast, ovarian, and several other cancers. The purpose of this study was to evaluate the incidence of cancers in first and second degree relatives of *BRCA* mutation carriers compared to the general population. A total of 1086 pedigrees of *BRCA* mutation carriers were obtained from a prospectively maintained, internal review board approved study of persons referred for clinical genetic counseling at The University of Texas MD Anderson Cancer Center. We identified 9032 first and second degree relatives from 784 pedigrees which demonstrated a clear indication of parental origin of mutation. Standardized incidence ratios (SIRs) were used to compare the observed incidence of 20 primary cancer sites to the expected incidence of each cancer based on calculated risk estimates according to a subject's age.

BRCA1 families had increased SIRs for breast and ovarian cancer ($p < 0.001$) and decreased SIRs for kidney, lung, Non-Hodgkin's lymphoma, prostate, and thyroid cancer ($p < 0.001$). *BRCA2* families had increased SIRs for breast, ovarian, and pancreatic cancer ($p < 0.001$) and decreased SIRs for kidney, lung, Non-Hodgkin's lymphoma, thyroid, and uterine cancer ($p < 0.0025$). Analysis of only first degree relatives ($n = 4099$) identified no decreased SIRs and agreed with the increased SIRs observed in the overall study population. We confirmed previous reports of an association between breast, ovarian, and pancreatic cancers with *BRCA* mutations. Additional research to quantify the relative risks of these cancers for *BRCA* mutation carriers can help tailor recommendations for risk reduction.

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Introduction

Hereditary breast and ovarian cancer (HBOC) is caused by germline mutations in the *BRCA1* and *BRCA2* genes which are autosomal dominant tumor suppressor genes that help ensure DNA damage in the cell is repaired prior to cell replication. Since the discovery of the *BRCA1* and *BRCA2* genes in 1994 and 1995, respectively, considerable research has been completed to analyze the cancer risks associated with these genes (Miki et al., 1994; Wooster et al., 1995). Individuals with a *BRCA1* or *BRCA2* mutation have up to an 84% lifetime risk to develop breast cancer and up to a 27% or 45% lifetime risk to develop ovarian cancer, respectively (Ford et al., 1998). However, lifetime risks for cancers other than breast and ovarian cancer remain debated.

The National Comprehensive Cancer Network (NCCN) has compiled well-established screening and surveillance guidelines for *BRCA* mutation carriers. Recommendations to reduce risks for breast cancer in women include clinical breast exams beginning at age 25, annual breast MRI, or mammogram if MRI is unavailable, beginning at 25-29 years of age or based on family history, annual mammogram and breast MRI for women ages 30-75, and discussion of risk-reducing mastectomies (NCCN, 2015). Recommendations for women over age 75 should be considered on an individual basis (NCCN, 2015). For ovarian cancer risk-reduction, recommendations should be given for a bilateral salpingo-oophorectomy between ages 35 and 40 and upon completion of child bearing (NCCN, 2015). The NCCN recommends male *BRCA* carriers complete breast self-exams and clinical breast exams every 12 months beginning at age 35 (NCCN, 2015). The guidelines also advise male *BRCA2* carriers to begin, and *BRCA1* carriers to consider, prostate cancer screening at age 40 (NCCN, 2015). No specific guidelines exist for pancreatic cancer and melanoma which have an established association with *BRCA* mutations.

Prior studies investigating cancer risks other than breast and ovarian in *BRCA1* and *BRCA2* mutation carriers have reported inconsistent results and have been largely gathered from small, familial studies. One of the larger studies to date completed by The Breast Cancer Linkage

Consortium (BCLC) in 1999 found *BRCA2* mutation carriers have an increased risk for prostate and pancreatic cancer and a statistically significant increased risk for buccal cavity, pharynx, stomach, melanoma of the skin, gallbladder, and bile duct cancers (BCLC, 1999). The increased risk for prostate and pancreatic cancer has been replicated by numerous other studies and the association between *BRCA2* mutations and these cancers is accepted in clinical practice (BCLC, 1999; Iqbal et al., 2012; Johannsson et al., 1999; Lorenzo Bermejo & Hemminki, 2004; Mersch et al., 2014; Moran et al., 2012; van Asperen et al., 2005).

Other studies describing increased risks for cancers other than breast and ovarian are conflicting. Numerous reports debate whether an increased lifetime risk for any cancer beyond breast and ovarian cancer even exists across both sexes and genes (Moran et al., 2012; Thompson & Easton, 2002). Multiple studies have agreed upon a significantly increased risk for pancreatic, prostate, and stomach cancers in all *BRCA* mutation carriers, but a consensus of the lifetime risks for these cancers continues to be debated and researched (BCLC, 1999; Brose, 2002; Johannsson et al., 1999; Noh et al., 2012). An increased risk for colon cancer in *BRCA* mutation carriers has been described citing relative risks ranging from 0.82-4.8 in mutation carriers (Phelan et al., 2014; Sopik, Phelan, Cybulski, & Narod, 2014). In 2014, Mersch, et al. completed one of the largest single institution studies of the incidence of non-breast and ovarian cancers in over 1,000 *BRCA* mutation carriers (Mersch et al., 2014). An increased incidence of pancreatic and prostate cancer in *BRCA2* mutation carriers as well as increased occurrence of melanoma in *BRCA1* carriers and cervical cancer in *BRCA2* carriers was observed (Mersch et al., 2014). Various other studies have reported an increased risk for melanoma of the skin, cervix, gallbladder, stomach, and uterine cancers; however, these have ranged from 1- to 4- fold increases, vary between *BRCA1* and *BRCA2* mutations, and are inconsistently reported (BCLC, 1999; Johannsson et al., 1999; Moran et al., 2012; Thompson & Easton, 2002; van Asperen et al., 2005).

Current literature demonstrates inconsistencies with regards to risks for non-breast and ovarian cancers, and this study aims to further clarify and characterize the spectrum of cancer risks evident in families with a known *BRCA1* or *BRCA2* mutation. It is essential to more clearly define the lifetime risks for non-breast and ovarian cancers associated with HBOC as they may inform the development of more comprehensive surveillance guidelines and improve the accuracy of risk assessment. This study sought to determine whether the incidence of cancers was higher in families with a *BRCA* mutation than the general population. We evaluated first degree relatives (FDR) and second degree relatives (SDR) of *BRCA* mutation carriers to describe the incidence of cancers in families with a *BRCA* mutation. To our knowledge this is the largest study to be completed on a cohort of families with a *BRCA* mutation.

Methods

This study was approved by the Institutional Review Board of the University of Texas MD Anderson Cancer Center (MDACC) (IRB #PA13-0650) and by the committee for the protection of human subjects of The University of Texas Health Science Center at Houston (IRB #HSC-GSBS-14-0581). Family histories of individuals who underwent genetic counseling at MDACC between 1997 and 2014 with a confirmed deleterious *BRCA1* or *BRCA2* mutation were eligible for this analysis. Family histories included the sex, relation to proband, age, vital status, and cancer history for all FDR and SDR on the affected parental side of the proband. Familial ethnicity and country of origin was provided by the proband when available. For purposes of this study, if only an age decade was identified for a relative in the family history, the individual's age was recorded as the middle age for that decade; for example, if 50s was reported as an individual's age, the age was recorded as 55 years old.

A retrospective chart review of the pedigrees previously collected during genetic counseling visits with confirmed deleterious *BRCA1* or *BRCA2* mutations were completed for this study. Parental origin of the mutation was determined by the presence of a breast and/or ovarian cancer in a female first or second degree relative diagnosed before age 60 or a male first or second degree relative diagnosed with breast cancer at any age. Pedigrees that did not meet these criteria or had breast and/or ovarian cancers in both paternal and maternal family histories were reviewed by 3 authors (JP, JL, DN). If a consensus of the parental origin of the mutation could not be determined, the pedigree was excluded from the study. All FDR and SDR of the proband on the affected parental side were included in this analysis. Relatives with no reported age or no reported age of cancer diagnosis were excluded in order to accurately account for an individual's contribution of cancer risk to the study population which was calculated according to 5 year age intervals.

The incidence of cancers found in the study population was compared to the general population incidence of cancers as reported by the United States Cancer Statistics: 1999-2011

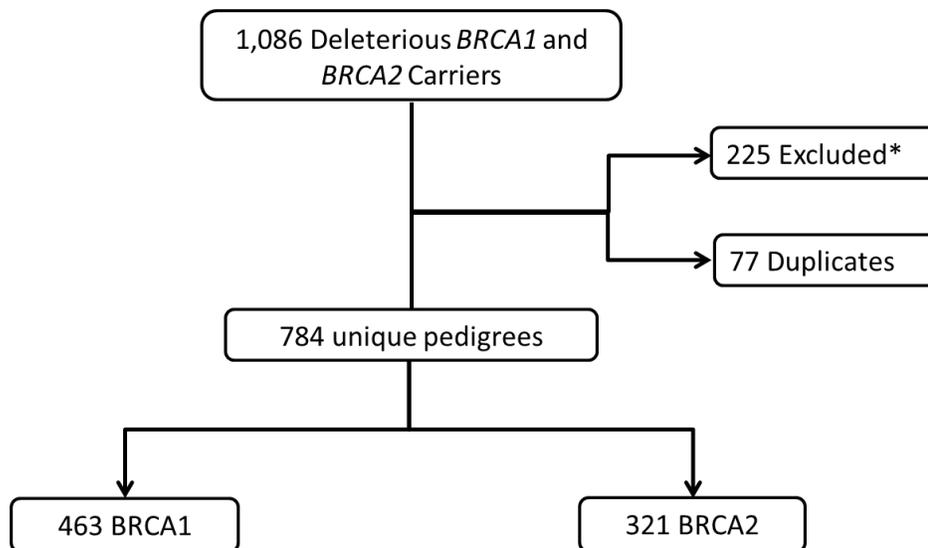
Incidence and Mortality Web-based Report (USCS). The defined reference time frame for age-specific incidence rates in the USCS report was 2007-2011. This report combines cancer registry data from the Centers for Disease Control and Prevention National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology and End Results Program. There were 50 different cancers reported in the study population, but similar or related cancers were grouped together. For example, gum, lip, oral, and throat cancer were grouped into oral cavity cancer and fallopian tube and primary peritoneal cancer were grouped with ovarian cancer. This resulted in 42 cancer types in the study population. The USCS report included 20 of the 42 cancer types (USCS, 2014). Cancers not included in the USCS report were excluded from the analysis.

Observed number of cases for each cancer type was calculated based on the study population. Expected number of cases was calculated by multiplying age, gender, ethnicity, and period specific person-years at risk by the corresponding general population cancer incidence rates. Expected number of cases for each cancer type is the sum of expected numbers by age, gender, and ethnicity group. Standardized incidence ratios (SIR) for each cancer type and its corresponding 95% confidence intervals (CIs) were calculated to compare the observed number of cases with the expected number of cases. We also calculated the SIR stratifying by *BRCA1* and *BRCA2* mutation and by first and second degree relative status. To adjust for multiple comparisons due to testing 20 cancer sites, a p value of <0.0025 ($=0.05/20$) was considered statistically significant.

Results

We identified 1,086 individuals with a deleterious *BRCA1* or *BRCA2* mutation from 1997-2014. In 164 of the pedigrees, the parental origin of the mutation could not be determined and were excluded. Sixty-one other pedigrees were eliminated from the study for numerous reasons: 15 of the known mutation carriers did not have a pedigree available; 41 pedigrees lacked a comprehensive family history and did not include three generations; 2 pedigrees had the presence of another genetic conditions in the family (hereditary retinoblastoma and neurofibromatosis type 1); and 3 pedigrees had both a *BRCA1* and *BRCA2* mutation in the family. Seventy-seven of the reviewed pedigrees were determined to be duplicates due to another individual in the same family seeking site-specific testing. In these cases, the proband of a given pedigree was considered to be the individual who presented to clinic first and only the most recent version of a family's pedigree in the database was included in the analysis. In total, 784 unique pedigrees were analyzed (Figure 1).

Figure 1: Positive *BRCA1* and *BRCA2* mutation carriers seen at MDACC



*164 undetermined inheritance, 15 missing pedigrees, 2 other genetic conditions, 3 *BRCA1* and *BRCA2* mutations, 41 incomplete

In 784 pedigrees, 11,462 FDR and SDR were reported, but 2,089 individuals did not have an age reported and 439 individuals did not have an age of cancer diagnosis reported and were thus eliminated from the study. A total of 9,032 relatives were included in this analysis. Demographic characteristics including familial gene, sex, degree of relationship to the proband, and ethnicity are reported in Table 1. The age of the study population followed a normal distribution curve with an average age of 45.2 years old and a range of 1-104 years old. Majority of the population was living at the time the pedigree was collected (6,545, 72%).

Table 1: Demographics of study population (n=9,032)

| | BRCA1 | BRCA2 | Total |
|---------------------------|--------------|--------------|--------------|
| Total (n = 9,032) | 5,237 (58%) | 3,795 (42%) | 9,032 (100%) |
| Sex | | | |
| Male | 2,401 (46%) | 1,802 (47%) | 4,203 (47%) |
| Female | 2,836 (54%) | 1,993 (53%) | 4,829 (53%) |
| Degree of Relation | | | |
| FDR | 2,430 (46%) | 1,669 (44%) | 4,099 (45%) |
| SDR | 2,807 (54%) | 2,126 (56%) | 4,933 (55%) |
| Ethnicity | | | |
| White | 3,679 (70%) | 2,952 (78%) | 6,631 (73%) |
| Hispanic | 912 (17%) | 348 (9%) | 1,260 (14%) |
| Black | 462 (9%) | 306 (8%) | 768 (9%) |
| Asian/Pacific Islander | 163 (3%) | 134 (4%) | 297 (3%) |
| Am Indian/Native American | 21 (1%) | 55 (1%) | 76 (1%) |

Male breast cancer, which has a well-described association with *BRCA* mutations, was not analyzed as it was not included in the USCS report due to its low prevalence in the general population. However, 24 cases of male breast cancer were identified in the study population; 12 were of *BRCA1* families and 12 were of *BRCA2* families. The average age of diagnosis of male breast cancer in *BRCA1* families was 48 years (27-75 years) and 64 years (47-75 years) in *BRCA2* families.

We found multiple increased and decreased SIRs among *BRCA1* and *BRCA2* families described in Tables 2 and 3. We observed an increased SIR in *BRCA1* families for breast cancer (SIR 3.37, 95% CI 3.09-3.67, $p < 0.0001$) and ovarian cancer (SIR 14.31, 95% CI 12.28-16.58, $p < 0.0001$). A trend of increasing incidence of pancreatic cancer (SIR 1.84, 95% CI 1.24-2.62, $p = 0.0030$) was also observed in the *BRCA1* population. The average age of diagnosis of breast cancer was 46.1 years old (24-95 years), ovarian cancer was 53.0 years old (25-88 years), and pancreatic cancer was 58.9 years old (24-88 years). In *BRCA2* families, breast (SIR 3.44, 95% CI 3.13-3.79, $p < 0.0001$), ovarian (SIR 9.70, 95% CI 7.77-11.96, $p < 0.0001$), and pancreatic (SIR 2.02, 95% CI 1.33-2.95, $p = 0.0013$) cancer had an increased SIR. Average age of diagnosis of breast cancer was 49.8 years (20-97), ovarian cancer was 57.1 years (23-80 years), and pancreatic cancer was 62.0 years (29-86 years). When stratifying the study population by sex, we found an increased SIR for pancreatic cancer (SIR 2.61, 95% CI 1.87-3.56, $p < 0.0001$) when considering both *BRCA1* and *BRCA2* mutations in men. Women, though, had an increased SIR for only breast (SIR 3.41, 95% CI 3.19-3.63, $p < 0.0001$) and ovarian (SIR 12.37, 95% CI 10.92-13.96, $p < 0.0001$) cancer.

Table 2: Cancer sites with significantly increased SIRs ($p < 0.0025$)

| Cancer Site | Gene | Observed | Expected | SIR | 95% CI | P value |
|-------------|-------|----------|----------|-------|-------------|---------|
| Breast | BRCA1 | 534 | 158.4 | 3.37 | 3.09-3.67 | <0.0001 |
| Breast | BRCA2 | 435 | 126.1 | 3.45 | 3.13-3.79 | <0.0001 |
| Ovarian | BRCA1 | 177 | 12.4 | 14.31 | 12.28-16.58 | <0.0001 |
| Ovarian | BRCA2 | 87 | 9.0 | 9.70 | 7.77-11.96 | <0.0001 |
| Pancreas* | BRCA1 | 30 | 16.3 | 1.84 | 1.24-2.62 | 0.0030 |
| Pancreas | BRCA2 | 27 | 13.3 | 2.02 | 1.33-2.95 | 0.0013 |

*Trending ($p < 0.007$)

Several cancers were also observed to have a decreased SIR ($p < 0.0025$); in *BRCA1* families there was a decreased SIR for kidney, lung, Non-Hodgkin's lymphoma, prostate, and thyroid cancer. In *BRCA2* families a decreased SIR for kidney, lung, Non-Hodgkin's lymphoma, thyroid, and uterine cancer was observed. Men in the *BRCA1* population had a decreased SIR for kidney, lung, Non-Hodgkin's lymphoma, oral cavity, and prostate cancer and men in *BRCA2* families had a decreased SIR for Non-Hodgkin's lymphoma. Women of *BRCA1* families had a decreased SIR for lung, Non-Hodgkin's lymphoma, and thyroid cancer while women of *BRCA2* families had a decreased SIR for lung, melanoma, thyroid, and uterine cancer.

Table 3: Cancer sites with significantly decreased SIRs ($p < 0.0025$)

| Cancer Site | Gene | Observed | Expected | SIR | 95% CI | P value |
|---------------|-------|----------|----------|------|-----------|---------|
| Kidney | BRCA1 | 5 | 23.9 | 0.21 | 0.07-0.49 | <0.0001 |
| Kidney | BRCA2 | 6 | 19.2 | 0.31 | 0.11-0.68 | 0.0009 |
| Lung | BRCA1 | 33 | 83.8 | 0.40 | 0.27-0.55 | <0.0001 |
| Lung | BRCA2 | 30 | 70.8 | 0.42 | 0.29-0.61 | <0.0001 |
| Non-Hodgkin's | BRCA1 | 8 | 27.8 | 0.29 | 0.12-0.57 | <0.0001 |
| Non-Hodgkin's | BRCA2 | 4 | 22.4 | 0.18 | 0.08-0.46 | <0.0001 |
| Prostate | BRCA1 | 53 | 91.7 | 0.58 | 0.43-0.76 | <0.0001 |
| Thyroid | BRCA1 | 8 | 24.9 | 0.32 | 0.14-0.63 | 0.0002 |
| Thyroid | BRCA2 | 7 | 19.3 | 0.36 | 0.15-0.75 | 0.0025 |
| Uterine | BRCA2 | 4 | 16.8 | 0.24 | 0.06-0.61 | 0.0004 |

When considering only FDR, no decreased SIRs were identified. We observed FDR of *BRCA1* families had an increased SIR for breast (SIR 4.37, 95% CI 3.86-4.93, $p < 0.0001$), ovarian (SIR 21.9, 95% CI 17.59-26.95, $p < 0.0001$), and pancreatic (SIR 3.53, 95% CI 1.88-6.04, $p < 0.0003$) cancer. Similarly, FDR of *BRCA2* families had an increased SIR for breast (SIR 4.57, 95% CI 3.98-5.22, $p < 0.0001$), ovarian (SIR 12.61, 95% CI 9.98-19.53, $p < 0.0001$), and pancreatic (SIR 3.77, 95% CI 1.95-6.58, $p < 0.0001$) cancer which agrees with the previously reported data when SDR are included as well as established cancer risks in HBOC. Additionally, a trend for an increased incidence of prostate cancer was observed in *BRCA2* families (SIR 1.63, 95% CI 1.15-2.23, $p = 0.0067$).

Discussion

This study aimed to further define the cancers associated with *BRCA* mutations through analysis of the incidence of cancers in first and second degree relatives of known *BRCA1* and *BRCA2* mutation carriers. The results confirm the recognized increased incidence of breast and ovarian cancer in females with a *BRCA* mutation. Additionally, this study confirms an association between *BRCA* mutations and pancreatic cancer based on the increased incidence of pancreatic cancer in *BRCA2* families and the trending increased incidence of pancreatic cancer in *BRCA1* families. The increased SIRs for breast and ovarian cancer in both *BRCA1* and *BRCA2* families and for pancreatic cancer in *BRCA2* families are consistent with results from Mersch, et al. who examined the incidence of non-breast and ovarian cancers in the *BRCA* mutation-positive probands of this current study (Mersch et al., 2014). The increased incidence of prostate cancer in *BRCA2* mutation carriers found by Mersch, et al. is also supported by this study when analyzing only FDR in the study population.

Several studies have investigated the cancer risks for HBOC in cohorts of individuals without confirmed *BRCA1* or *BRCA2* mutations similar to this study population. In studies regarding *BRCA1*, increased risks for pancreatic, prostate, and uterine body/cervical cancer have been reported in cohorts of individuals with unknown *BRCA* mutation carrier status (Thompson & Easton, 2002). Our results are consistent with the increased incidence of pancreatic cancer, but failed to find an association with prostate cancer or uterine body/cervical cancer. In *BRCA2* research, increased risks for breast, ovarian, pancreatic, prostate, bone, and pharynx cancer, and uveal melanoma have been reported in populations which include unconfirmed *BRCA* mutation carriers (Moran et al., 2012; van Asperen et al., 2005). Melanoma, breast, ovarian, pancreatic, and prostate cancers are all mentioned in the NCCN guidelines for HBOC (NCCN, 2015). Excluding melanoma, these findings were replicated when considering just FDR. The increased risks for bone and pharynx cancer identified by Van Asperan, et al. have not been replicated to our knowledge

(van Asperen et al., 2005). This study did not analyze bone cancer and found no significant incidence of pharynx cancer.

No previously unreported associations of specific cancers with *BRCA* mutations were identified in this study and relatively few cancers had a significantly increased SIR when compared to other reports. However, many of these studies were based on analysis of confirmed *BRCA1* and *BRCA2* mutation carriers (Brose, 2002; Iqbal et al., 2012; Johannsson et al., 1999; Mersch et al., 2014; Noh et al., 2012; Phelan et al., 2014). Because only half of our study population is assumed to have a *BRCA* mutation, we expected that cancers associated with *BRCA* mutations would not have as high an incidence as they would in a population comprised solely of known mutation carriers. Still, the outcomes of the present study may be more helpful in the development and review of screening protocols for HBOC because individuals seeking surveillance may be at risk for a known familial mutation but be untested.

Focusing on only FDR in the study population is beneficial to account for patient-reported family histories and should provide the most precise and accurate interpretation of results. This study relies on the accuracy of reported family histories which has been shown to be reduced in distant relatives. Studies examining the accuracy of patient-reported family histories indicate that the site of a cancer diagnosis in FDR and SDR is correctly reported in 78-95% and 53-67% of cases, respectively (Love, Evans, & Josten, 1985; Schneider et al., 2004; Ziogas & Anton-Culver, 2003). When considering only FDR, the incidences of cancers in the study population align almost completely with the previously established cancer associations for *BRCA* mutations. FDR of *BRCA1* mutation carriers demonstrated an increased SIR for breast, ovarian, and pancreatic cancer and the FDR of *BRCA2* carriers likewise revealed an increased SIR for breast, ovarian, and pancreatic cancer in addition to a trending increased SIR for prostate cancer. These cancer associations are all reported by the NCCN and information regarding risk reduction and surveillance recommendations

for these cancers are addressed in the guidelines for HBOC (NCCN, 2015). Furthermore, no decreased SIRs were observed in the population of only FDR.

Studies suggest that underreporting of cancer is more common than over reporting of cancers in family histories (Love et al., 1985; Ozanne et al., 2012; Quillin et al., 2006; Ziogas & Anton-Culver, 2003). The overall accuracy of patient-reported family history is dependent on age, education, sex, degree of relation, and socioeconomic status of the patient or historian (Ozanne et al., 2012; Quillin et al., 2006; Schneider et al., 2004). Family structure and dynamics, social stigma, and communication barriers may likewise contribute to an underreporting bias in a family history. Also, for individuals of older generations, cancers may have gone undiagnosed as cancer detection and prevention measures improve with time and new technology (Singh, Sethi, Raber, & Petersen, 2007). Moreover, pedigrees in which a complete family history was not reported (i.e. no paternal history known) were eliminated from the study if the parental origin of the mutation was not confirmed or could not be inferred. The influence of these factors may be reduced in the FDR population and may also provide explanations for the number of decreased SIRs observed in the overall study population when SDR were included in the analysis.

The average age of diagnosis of breast and ovarian cancer in individuals with *BRCA* mutations is expected to be lower than an individual without a mutation in the general population (Litton et al., 2012; Panchal et al., 2010). The average age of diagnosis for breast and ovarian cancer in the general population is 61 years old and 63 years old, respectively (Howlader N, 2014). The average age of breast cancer diagnosis in the study population was 47.8 years old and 54.4 years old for ovarian cancer. This data generally agrees with recommendations of the NCCN to begin breast imaging in mutation carriers at 25 years of age as only 6 of the 968 (0.62%) reported cases of breast cancer were diagnosed prior to age 25. The NCCN guidelines do account for the use of family history information for making individualized screening recommendations (NCCN, 2015). Therefore some of these individuals may have begun screening before age 25 based on family

history. The NCCN also recommends prophylactic bilateral salpingo-oophorectomy at 35-40 years and upon completion of child-bearing (NCCN, 2015). Fourteen of the 166 (8.4%) cases of ovarian cancer were diagnosed prior to age 35 and 28 (16.9%) cases were diagnosed prior to age 40. Again, the NCCN guidelines advise that clinicians consider personal and family history information when making recommendations.

While this study allowed for analysis of a large number of relatives, the data is limited to one time point, as this was a retrospective data collection, so instances of cancer diagnosed after the date the pedigree was last updated are not included. For example, when interpreting the current results for prostate cancer, previous literature and the NCCN report an increased risk for prostate cancer in male *BRCA2* mutation carriers and a likely increased risk in *BRCA1* mutation carriers. Therefore we expect an increased SIR for prostate cancer in the study population. However, the results of this study found a decreased SIR for *BRCA1* mutation families. The average age of men in the *BRCA1* population was 43.8 years old (1-104 years) and the average age of prostate cancer diagnosis is 66 years old in the general population with *BRCA* carriers under age 65 having an increased relative risk for prostate cancer of 1.44-3.75 (Howlader N, 2014; Leongamornlert et al., 2012; Thompson & Easton, 2002). Therefore, more of the men in the *BRCA1* study cohort may develop prostate cancer in their lifetime which would increase the incidence in the study population and alter results.

Given that family history of cancer can evolve over time, the statistical analysis did account for each individual's contribution to the cancer risk of the study population based on ethnicity, sex, and age in 5-year intervals. Similarly, the pedigrees in the analysis were prospectively updated if the proband proactively provided new family history information or clarifications. However, this additional information may be more likely to only include clarifications regarding diagnoses of previously defined *BRCA*-associated cancers and not other cancer diagnoses which may induce a collection bias. A prospective study may help reduce this bias and could possibly obtain more

accurate current ages, ages of cancer diagnoses, environmental exposures, surgical histories, and health histories, but knowledge of family history information may remain vague or ambiguous regardless of study design.

This study has limitations that should be considered when interpreting data. First, multiple cancers included in this analysis have known environmental risk factors and lifestyle choices like a history of tobacco use, obesity, sun exposure, or completion of surgeries or procedures, that increase or decrease an individual's risk for cancer ("American Cancer Society: What Causes Cancer?," 2015). Environmental exposures and/or surgical decisions in family members are not consistently reported during a family history intake; therefore we are unable to comment on their influence on the results. Also, because the majority of pedigrees were obtained in a clinical setting, a collection bias in the population may be present. A genetic counselor may ask more detailed questions to clarify reports of cancers only related to the syndrome of interest (i.e. breast, ovarian, pancreatic cancer in HBOC) and not explore cancers without an association with a hereditary cancer syndrome as thoroughly. If a specific age or cancer diagnosis was not clarified and reported on the pedigree, then that individual would have been excluded from this study consequently decreasing the incidence of that cancer in the study population. Therefore, cancers without a previous association to HBOC or a hereditary cancer syndrome may be underreported in the study population. Finally, the data cannot be generalized to individuals of all ethnicities given that the study population is predominantly Caucasian.

Moving forward, studies may wish to focus on non-Caucasian ethnicity specific cancer risks in HBOC because to our knowledge, most other studies on *BRCA* mutation carriers are based on a majority Caucasian population. Further investigation to obtain more specific lifetime relative risks for the cancers associated with HBOC should also be completed. Cohorts of known *BRCA* mutation carriers with their at-risk family members can be used as an unbiased population to better determine these risks and define age-specific incidence rates for more appropriate risk

assessments for *BRCA* families. Additionally, more work to enhance screening and surveillance guidelines for mutation carriers is indicated as pancreatic cancer currently does not have well-established surveillance methods and recommendations for prostate cancer screenings are vague. Screening guidelines from the NCCN acknowledge all of the cancer associations of *BRCA* mutations identified in this study, but risk reduction data and strategies may still be evolving.

Conclusion

The utilization of a cohort of individuals with an unknown *BRCA* mutation status from families with a known *BRCA* mutation allowed for a large sample size that demonstrated a comprehensive analysis of cancer incidence in HBOC. This study supports previous reports of an association between *BRCA1* and *BRCA2* mutations and breast cancer, ovarian cancer, and pancreatic cancer. Analysis of only FDR similarly confirmed an association between *BRCA1* mutations with breast, ovarian, and pancreatic cancers and *BRCA2* mutations with breast, ovarian, pancreatic, and prostate cancers. This study did not find any cancers to be associated with *BRCA* mutations that have not been addressed in the NCCN guidelines or have not had a previously well-established and accepted association with HBOC. Results of this study indicate the spectrum of cancers associated with *BRCA1* and *BRCA2* mutations seems to be fairly well-defined at this time.

Appendix 1: SIRs for all cancer sites for *BRCA1* and *BRCA2*

| Cancer Site | Gene | Observed | Expected | SIR | 95% CI | P value |
|--------------------|-------------|-----------------|-----------------|------------|---------------|----------------|
| Bladder | BRCA1 | 12 | 25.3 | 0.47 | 0.25-0.83 | 0.0052 |
| Bladder | BRCA2 | 13 | 21.4 | 0.61 | 0.32-1.04 | 0.0744 |
| Brain | BRCA1 | 9 | 12.3 | 0.73 | 0.33-1.39 | 0.4278 |
| Brain | BRCA2 | 6 | 9.8 | 0.61 | 0.23-1.34 | 0.2923 |
| Breast | BRCA1 | 534 | 158.4 | 3.37 | 3.09-3.67 | <0.0001 |
| Breast | BRCA2 | 435 | 126.1 | 3.45 | 3.13-3.79 | <0.0001 |
| Colorectal | BRCA1 | 43 | 59.6 | 0.72 | 0.52-0.97 | 0.0302 |
| Colorectal | BRCA2 | 29 | 48.4 | 0.60 | 0.40-0.86 | 0.0036 |
| Cervical | BRCA1 | 6 | 8.2 | 0.73 | 0.27-1.59 | 0.5714 |
| Cervical | BRCA2 | 6 | 6.0 | 0.99 | 0.36-2.16 | 1.0000 |
| Esophageal | BRCA1 | 11 | 6.3 | 1.74 | 0.87-3.11 | 0.1155 |
| Esophageal | BRCA2 | 10 | 5.3 | 1.89 | 0.91-3.48 | 0.0866 |
| Hodgkin's | BRCA1 | 3 | 5.9 | 0.51 | 0.11-1.45 | 0.3269 |
| Hodgkin's | BRCA2 | 3 | 4.5 | 0.66 | 0.14-1.94 | 0.6779 |
| Kidney | BRCA1 | 5 | 23.9 | 0.21 | 0.07-0.49 | <0.0001 |
| Kidney | BRCA2 | 6 | 19.2 | 0.31 | 0.11-0.68 | 0.0009 |
| Leukemia | BRCA1 | 10 | 21.2 | 0.47 | 0.23-0.87 | 0.0111 |
| Leukemia | BRCA2 | 11 | 16.7 | 0.66 | 0.33-1.18 | 0.1934 |
| Lung | BRCA1 | 33 | 83.8 | 0.39 | 0.27-0.55 | <0.0001 |
| Lung | BRCA2 | 30 | 70.8 | 0.42 | 0.29-0.61 | <0.0001 |
| Melanoma | BRCA1 | 16 | 27.5 | 0.58 | 0.33-0.95 | 0.0260 |
| Melanoma | BRCA2 | 10 | 23.3 | 0.42 | 0.21-0.79 | 0.0033 |

| | | | | | | |
|----------------------|-------|-----|------|-------|-------------|---------|
| Myeloma | BRCA1 | 2 | 8.1 | 0.24 | 0.03-0.89 | 0.0255 |
| Myeloma | BRCA2 | 2 | 6.5 | 0.31 | 0.04-1.12 | 0.0885 |
| Non-Hodgkin's | BRCA1 | 8 | 27.8 | 0.29 | 0.12-0.57 | <0.0001 |
| Non-Hodgkin's | BRCA2 | 4 | 22.4 | 0.18 | 0.05-0.46 | <0.0001 |
| Oral Cavity | BRCA1 | 8 | 16.0 | 0.50 | 0.22-0.99 | 0.0450 |
| Oral Cavity | BRCA2 | 5 | 13.2 | 0.38 | 0.12-0.88 | 0.0186 |
| Ovarian | BRCA1 | 177 | 12.4 | 14.31 | 12.28-16.58 | <0.0001 |
| Ovarian | BRCA2 | 87 | 9.0 | 9.70 | 7.77-11.96 | <0.0001 |
| Pancreas | BRCA1 | 30 | 16.3 | 1.84 | 1.24-2.63 | 0.0030 |
| Pancreas | BRCA2 | 27 | 13.3 | 2.02 | 1.33-2.95 | 0.0013 |
| Prostate | BRCA1 | 53 | 91.7 | 0.58 | 0.43-0.76 | <0.0001 |
| Prostate | BRCA2 | 79 | 79.2 | 1.00 | 0.79-1.24 | 1.0000 |
| Stomach | BRCA1 | 15 | 9.9 | 1.51 | 0.85-2.49 | 0.1589 |
| Stomach | BRCA2 | 11 | 7.6 | 1.45 | 0.72-2.59 | 0.2934 |
| Thyroid | BRCA1 | 8 | 24.9 | 0.32 | 0.14-0.63 | 0.0002 |
| Thyroid | BRCA2 | 7 | 19.3 | 0.36 | 0.15-0.75 | 0.0025 |
| Uterine | BRCA1 | 12 | 21.1 | 0.57 | 0.29-0.99 | 0.0467 |
| Uterine | BRCA2 | 4 | 16.8 | 0.24 | 0.07-0.61 | 0.0004 |

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