Published in final edited form as:

Fam Cancer. 2013 March ; 12(1): 83–87. doi:10.1007/s10689-012-9581-z.

An Unusual *BRCA* Mutation Distribution in a High Risk Cancer Genetics Clinic

Anna C. Nelson-Moseke, MD¹, Joanne M. Jeter, MD^{2,3}, Haiyan Cui, PhD³, Denise J. Roe, DrPH^{3,4}, Setsuko K. Chambers, MD^{1,3}, and Christina M. Laukaitis, MD, PhD^{3,5,6}

¹Department of Obstetrics and Gynecology, University of Arizona

²Division of Oncology, Department of Medicine, University of Arizona

³University of Arizona Cancer Center, University of Arizona

⁴Division of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona

⁵Division of Geriatrics, General and Palliative Medicine, University of Arizona

Abstract

The Database of Individuals at High Risk for Breast, Ovarian, or Other Hereditary Cancers at the Arizona Cancer Center in Tucson, Arizona, assesses cancer risk factors and outcomes in patients with a family history of cancer or a known genetic mutation. We analyzed the subset of clinic probands who carry deleterious *BRCA* gene mutations to identify factors that could explain why mutations in *BRCA2* outnumber those in *BRCA1*. Medical, family, social, ethnic and genetic mutation histories were collected from consenting patients' electronic medical records. Differences between *BRCA1* and *BRCA2* probands from this database were analyzed for statistical significance and compared to published analyses. A significantly higher proportion of our clinic probands carry mutations in *BRCA2* than *BRCA1*, compared with previous reports of mutation prevalence. This also holds true for the Hispanic sub-group. Probands with *BRCA2* mutations were significantly more likely than their *BRCA1* counterparts to present to the high risk clinic without diagnosis of cancer. Other differences between the groups were not significant. Six previously unreported *BRCA2* mutations appear in our clinic population. The increased proportion of probands carrying deleterious *BRCA2* mutations is likely multifactorial, but may reflect aspects of Southern Arizona's unique ethnic heritage.

Keywords

BRCA1; *BRCA2*; breast cancer; hereditary cancer syndromes; ovarian cancer

INTRODUCTION

BRCA1 and *BRCA2* mutations have been found in women from a broad range of racial and ethnic backgrounds [1, 2]. These genetic mutations are inherited in an autosomal dominant fashion and significantly increase risk of both breast and epithelial ovarian cancer. Women with a *BRCA1* mutation have a lifetime probability of developing breast cancer of 65–81% and epithelial ovarian cancer of up to 35–60%, while women carrying a *BRCA2* mutation

⁶Author for correspondence: PO Box 245024, 1515 N. Campbell Ave., Tucson, AZ 85724. Phone: (520)626-5845, Fax: (520)626-9088, claukaitis@azcc.arizona.edu.

CONFLICTS OF INTEREST: The authors report no conflicts of interest.

have a 45–85% chance of developing breast cancer and a 10–27% chance of developing epithelial ovarian cancer [3]. *BRCA* mutations also predispose to melanoma, prostate and pancreatic cancers [4]. While *BRCA1* and *BRCA2* mutations are responsible for a minority of breast and ovarian cancers, they are found in as many as 5–10% of patients with breast and epithelial ovarian cancers [5, 6]. Chemoprevention and prophylactic surgery (bilateral mastectomy and bilateral salpingo-oophorectomy) can decrease cancer risk in carriers of *BRCA1* and *BRCA2* mutations [7–12]. These mutations continue to be a focus of intense investigation for development of better prevention strategies and treatment modalities.

In studies reporting other high risk clinic databases, *BRCA1* mutations are uniformly more frequent than *BRCA2* mutations [1, 2, 13, 14]. The largest published analysis of genetic test results of commercially-tested patients found that among 46,276 patients tested, 5,795 harbored a deleterious *BRCA* gene mutation [2]. Of these, 7.2% carried a deleterious *BRCA1* mutation and 5.3% of patients carried a deleterious *BRCA2* mutation. Thus 42% of mutations were in *BRCA2*, while 58% affected *BRCA1*. We analyzed the Hispanic patients reported by Hall [2] and found that 36% (from a total of 290 patients) carried a deleterious *BRCA2* mutation.

The University of Arizona Cancer Center (UACC) established a high risk clinic in 2004 and it has grown steadily since. As of January 2012, 251 patients were enrolled in a database to collect information about the clinical course of high risk patients. Unexpectedly, we observed that *BRCA2* mutations are more common than *BRCA1* mutations in our clinic population. This is, to our knowledge, a unique finding. We considered three hypotheses to explain this phenomenon: 1) a previously unrecognized mutation may be present in this population; 2) the unique ethnic composition of our community might have allowed maintenance of unique allele frequencies; or 3) by virtue of being a high risk clinic, we attract patients by marketing aimed at providers and/or the community and might have captured a unique population of patients who differ from those previously reported from high risk clinics. To address the first two hypotheses, we asked whether the *BRCA1/BRCA2* ratio is skewed in probands who self-identify as Hispanic or Ashkenazi Jewish. We also asked whether any specific mutations are over-represented in our probands. Some data suggest that *BRCA2* carriers develop cancer at an older age than their *BRCA1* counterparts [15, 16]. Thus, we analyzed the age at which probands presented to initiate preventative care, their prior cancer diagnoses and the burden of cancer in their pedigrees to address the third hypothesis.

METHODS

The Database of Individuals at High Risk for Breast, Ovarian, or Other Hereditary Cancers [BIO # A06-028 (06-0477-04)] at the UACC in Tucson, AZ is a collection of data from consented patients with known genetic predisposition to cancers or a significant personal and/or family history for cancers that suggests an inherited cancer predisposition. Between January 2006 and January 31, 2012, 251 patients were consented. Data regarding the medical, family, social, and genetic mutation history from this cohort were collected from the patients' electronic medical records. For the purposes of this study, we analyzed patients who have known *BRCA1* or *BRCA2* mutations, excluded patients carrying mutations classified as variants of uncertain significance, and included only the proband from each family. We re-analyzed pedigrees from individuals with the same mutation to exclude relatedness and were left with 52 probands. Information about specific *BRCA* mutations, personal and family cancer history, ages at presentation and diagnosis, whether the proband had been diagnosed with cancer when she presented to the clinic, and self-reported ethnic background were collected from a chart review for further analysis.

A binomial exact test was used to compare the proportion of *BRCA1:BRCA2* mutations in different populations. Frequencies of *BRCA1* to *BRCA2* mutations in subgroups of probands with shared ethnicity, a previous diagnosis of cancer, or varying numbers of relatives with cancer were compared using the Fisher Exact test or a chi-squared test, when appropriate. Finally, the t-test was employed to compare ages at presentation to the clinic between *BRCA1* and *BRCA2* carriers. All analyses were performed using the SAS and Minitab 15 programs.

RESULTS

Analysis of the mutations carried by probands in our high-risk clinic database revealed that 21 women carry mutations in *BRCA1*, while 31 carry *BRCA2* mutations (Table 1), which differs significantly from previous reports ($p=0.01$;[1]).

We analyzed the self-reported ethnic background of mutation carriers. In the 2010 U.S. Census, 34.6% of Pima County, AZ residents reported being of “Hispanic or Latino origin” compared to 29.6% of all Arizonans and 16.3% of all Americans [17]. In our registry, 15 probands report Mexican or Hispanic ancestry (28.8%). Five of these women carry *BRCA1* mutations, while 10 carry *BRCA2* mutations, which differs significantly from previous reports ($p=0.01$; Table 1; [2]). In Pima County, AZ 2.4% of residents report Ashkenazi Jewish ancestry [18], compared with 11% of clinic probands. Despite under-representation of one group and over-representation of the other, there is no significant difference between the representations of Ashkenazi Jewish or Hispanic ancestry between *BRCA1* and *BRCA2* carriers.

Analysis of specific deleterious mutations reveals several points: (1) all three of the Ashkenazi Jewish founder mutations are present (*BRCA1* 187 delAG, *BRCA1* 5385 insC, and *BRCA2* 6174 delT); (2) the *BRCA2* 886 delGT mutation is found in four probands, who are believed to be unrelated based on careful comparison of known family relationships and pedigrees; (3) there are six deleterious *BRCA2* mutations that have not been previously reported, one of which (8822 insT) is found in two apparently unrelated probands.

The 886 delGT mutation has been reported 37 times in the National Human Genome Research Institute database containing 14,780 *BRCA2* mutations [19]. Finding this mutation in four apparently non-related probands is statistically significant ($p<0.0001$; binomial exact test). These four probands all self-identify as Hispanic and one has a personal history of cancer. Three of the four probands report having more than seven cancer-affected family members (range 8–10). All probands have family members affected by breast cancer; two have a family history of ovarian cancer. Family histories of pancreatic, testicular, stomach, and liver cancers as well as leukemia were also reported. The age of presentation to the high risk clinic varies from 26 to 49 years.

Among the seven probands who carry previously unidentified mutations, two report Mexican ancestry, two Native American ancestry, two Asian or Pacific Islander heritage, and one proband reports Caucasian ancestry. Three of the probands carrying previously unreported mutations have diagnoses of cancer: two have had breast cancer (diagnosed at ages 39 and 42 years) and one has ovarian cancer (diagnosed at age 64 years, found during her evaluation for prophylactic oophorectomy).

In order to evaluate our hypothesis that *BRCA2* over-representation could be expected in high risk clinic recruiting from healthy community members, we asked whether probands presented to the clinic as a result of a cancer diagnosis or because of high risk status (known *BRCA* mutation or suspicious family history). *BRCA1* carriers were significantly more

likely to present as a result of cancer diagnosis, while *BRCA2* carriers more often presented as a result of high risk status (Table 2; $p=0.04$).

The difference in the proportion of probands with a new or previous cancer diagnosis at the time of presentation could be attributed to the previously reported difference in the age of cancer diagnosis between *BRCA1* and *BRCA2* mutation carriers [15, 16]. To explore this, we examined the ages at which probands presented to the high risk clinic and the age at which they were diagnosed with their first incidence of cancer (some probands have > 1 cancer diagnosis). The average age of initial presentation to high risk clinic ranges from 27 to 69 years for *BRCA1* probands and 19 to 69 years for *BRCA2* probands. Neither age of first presentation nor age of first cancer diagnosis was significantly different between *BRCA1* and *BRCA2* mutation carriers.

We evaluated the total percentage of probands with cancer diagnoses (either before or after initial presentation to care) and found no statistically significant difference between *BRCA1* and *BRCA2* carriers. Sub-analysis of probands with either breast or epithelial ovarian/primary peritoneal cancers also revealed no significant difference in the percentage of probands with *BRCA1* and *BRCA2*. One proband in the *BRCA1* group and two in the *BRCA2* group were diagnosed with both breast and epithelial ovarian/primary peritoneal cancers. Two probands in the *BRCA1* group had non-breast, non-epithelial ovarian cancer as did three probands in the *BRCA2* group.

In order to further evaluate the hypothesis that *BRCA2* carriers would present to clinic because of multiple affected relatives, we examined the pedigrees of each proband for the number of first- and second-degree relatives with cancer. We analyzed *BRCA*-associated cancers, cancers not traditionally associated with *BRCA* mutations, and the total number of relatives in the proband's pedigree with any type of cancer. Comparison of *BRCA1* to *BRCA2* carriers did not yield statistically significant differences in any of these analyses.

DISCUSSION

Analysis of our database demonstrates that we have a significantly greater representation of deleterious *BRCA2* mutations than would be expected based on the published analysis of *BRCA* mutations [2]. Detailed, retrospective analysis of our patient records for identity of specific mutations, reported ethnicity, timing of presentation to care, timing of cancer diagnoses, and personal and family history of cancer reveals some patterns and even more questions.

The higher proportion of *BRCA2* carriers is likely due in part to finding the *BRCA2* 886 delGT mutation in four probands, as well as six previously unreported *BRCA2* mutations (8822 insT, 2121 delT, 4075 delAG, 4363 delC, 5103 delAA, and 6873 delC). All four of probands carrying *BRCA2* 886 delGT and the one carrying 8822 insT report Hispanic ancestry. Five other new mutations were found in women who did not report Hispanic ancestry. While our sample size is low, the excess of newly identified or rare mutations in people reporting Hispanic ancestry suggests that the mutation complement in our community differs from previously studied Hispanic communities [2, 20]. The haplo types on which the 886 delGT resides should be analyzed for common haplo types suggestive of a founder effect [20] and interrelationships between families further probed.

We hypothesized that *BRCA2* carriers are more likely than *BRCA1* carriers to be referred to the "high risk" clinic because they are identified as being high risk prior to a diagnosis of cancer, based on a combination of later age at diagnosis of cancer and more complicated pedigrees. In order to test this hypothesis, we asked whether probands had a cancer diagnosis at time of presentation to care, and we compared the age of cancer diagnosis as

well as the number of family members with cancer in *BRCA1* and *BRCA2* mutation carriers. There was no difference between the numbers of first, second, or total relatives with cancer between the two groups or in the age of cancer diagnosis between *BRCA1* and *BRCA2* carriers in our population. We did find, however, that *BRCA2* probands were significantly more likely to present for cancer prevention efforts before a diagnosis of cancer. Thus, the later age of cancer diagnosis in *BRCA2* carriers might provide a longer window of opportunity to establish a preventative care regimen; however the lack of a difference in age at subsequent cancer diagnosis remains confusing. Closer analysis suggests, also, that patients initially diagnosed with breast cancer remain with their oncologist, instead of transferring to the high-risk cancer prevention clinic. Thus, earlier-diagnosed patients, who might be enriched for *BRCA1* mutations, may simply not be enrolling in our clinic. If this is true, then it is not clear how at-risk relatives are being identified, counseled or monitored?

Our database provides an opportunity to gain a better understanding of patients with *BRCA* mutations and of our clinic population. The factors leading to our excess of *BRCA2* mutations are likely complex and may have biological, epidemiological, and financial roots. Exploring the unique aspects of our high-risk clinic has identified issues that might be preventing optimal care for all community members.

Acknowledgments

The authors would like to thank Christina Kim, MD for establishing the high-risk clinic database. Corina Mauss performed database entry, Jessica Ray, MS, CGC, Gail Martino, MS, CGC and Zoe Powis, MS, CGC identified, counseled and consented patients and Sam Pinkerton, RN and Stephanie Taylor, RN helped with patient recruitment. This work was supported in part by the Arizona Cancer Center Better Than Ever Program (SKC, ANM), P50CA95060 (CML), U54 CA143924 (CML), P30CA023074 (CML, HC, DJR, JMJ), R25TCA078447 (JMJ) and an unlimited use gift from Barry and PatYellen (CML).

REFERENCES

1. Kurian AW. *BRCA1* and *BRCA2* mutations across race and ethnicity: distribution and clinical implications. *Curr Opin Obstet Gynecol*. 2010; 22(1):72–78. [PubMed: 19841585]
2. Hall MJ, et al. *BRCA1* and *BRCA2* mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer. *Cancer*. 2009; 115(10):2222–2233. [PubMed: 19241424]
3. Euhus DM. New insights into the prevention and treatment of familial breast cancer. *J Surg Oncol*. 2011; 103(4):294–298. [PubMed: 21337561]
4. Moran A, et al. Risk of cancer other than breast or ovarian in individuals with *BRCA1* and *BRCA2* mutations. *Fam Cancer*. 2011
5. Garber JE, Offit K, et al. Hereditary cancer predisposition syndromes. *J Clin Oncol*. 2005; 23(2): 276–292. [PubMed: 15637391]
6. Russo A, et al. Hereditary ovarian cancer. *Crit Rev Oncol Hematol*. 2009; 69(1):28–44. [PubMed: 18656380]
7. Fisher B, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 1998; 90(18):1371–1388. [PubMed: 9747868]
8. Visvanathan K, et al. American society of clinical oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. *J Clin Oncol*. 2009; 27(19):3235–3258. [PubMed: 19470930]
9. Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. *Cochrane Database Syst Rev*. 2010; (11) CD002748.
10. Kauff ND, Barakat RR. Risk-reducing salpingo-oophorectomy in patients with germline mutations in *BRCA1* or *BRCA2*. *J Clin Oncol*. 2007; 25(20):2921–2927. [PubMed: 17617523]

11. Bevers TB. The STAR trial: evidence for raloxifene as a breast cancer risk reduction agent for postmenopausal women. *J Natl Compr Canc Netw*. 2007; 5(8):719–724. [PubMed: 17927929]
12. Goss PE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med*. 2011; 364(25):2381–2391. [PubMed: 21639806]
13. Keshavarzi F, Javadi GR, Zeinali S. BRCA1 and BRCA2 germline mutations in 85 Iranian breast cancer patients. *Fam Cancer*. 2012; 11(1):57–67. [PubMed: 21918854]
14. Malone KE, et al. Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. *Cancer Res*. 2006; 66(16):8297–8308. [PubMed: 16912212]
15. Ford D, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet*. 1998; 62(3): 676–689. [PubMed: 9497246]
16. Satagopan JM, et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Clin Cancer Res*. 2002; 8(12):3776–3781. [PubMed: 12473589]
17. Census, U. Quick Facts. 2012. Available from: <http://quickfacts.census.gov/qfd/states/04/04019.html>
18. InfoGroup, o.b.t.A. Survey: Religion 2009. 2009 Available from: http://www.socialexplorer.com/pub/reportdata/docbrowser.aspx?survey=Religion_InfoUSA09&header=True.
19. BRCA1, IC. The Breast Cancer Information Core Database. 2012. Available from: <http://research.nhgri.nih.gov/bic/>
20. Weitzel JN, et al. Prevalence of BRCA mutations and founder effect in high-risk Hispanic families. *Cancer Epidemiol Biomarkers Prev*. 2005; 14(7):1666–1671. [PubMed: 16030099]

Table 1

BRCA1 vs *BRCA2* mutations in the UACC high risk clinic compared literature data [2].

Mutation carrier		n	% (95% CI)	p-value
All probands	<i>BRCA1</i>	21	40.38 (27, 55)	Ho: $p_{BRCA2}=42\%$ 0.0101
	<i>BRCA2</i>	31	59.62 (45, 73)	
Probands with Hispanic ancestry	<i>BRCA1</i>	5	33.33 (12, 7)	Ho: $p_{BRCA2}=36\%$ 0.0133
	<i>BRCA2</i>	10	66.67 (30, 88)	

Table 2

BRCA mutation type stratified by reason for presentation to the UACC high risk clinic.

<i>BRCA</i> mutation	n	Number of Probands presenting with Cancer Diagnosis (%)	Number of Probands presenting for High-Risk Status (%)	p-value
<i>BRCA1</i>	21	12 (57)	9 (43)	0.0427
<i>BRCA2</i>	31	9 (29)	22 (71)	