Published in final edited form as:

Breast Cancer Res Treat. 2015 August ; 153(1): 201–209. doi:10.1007/s10549-015-3527-8.

Deleterious *BRCA1/2* mutations in an urban population of Black women

Filipa Lynce¹, Karen Lisa Smith², Julie Stein³, Tiffani DeMarco⁴, Yiru Wang⁵, Hongkun Wang⁵, Melissa Fries⁶, Beth N. Peshkin⁷, and Claudine Isaacs⁷

¹Division of Hematology/Oncology, Lombardi Comprehensive Cancer Center, MedStar Georgetown University Hospital, 3800 Reservoir Rd NW Podium C, Washington, DC 20007, USA

²Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA

³George Washington University, Washington, DC, USA

⁴Inova Fairfax Hospital, Falls Church, VA, USA

⁵Department of Biostatistics, Bioinformatics and Biomathematics, Georgetown University, Washington, DC, USA

⁶MedStar Washington Hospital Center, Washington, DC, USA

⁷Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA

Abstract

Information on the prevalence of deleterious *BRCA1* and *BRCA2* (*BRCA1/2*) mutations in clinic-based populations of Black women is limited. In order to address this gap, we performed a retrospective study to determine the prevalence of deleterious *BRCA1/2* mutations, predictors of having a mutation, and acceptance of risk-reducing surgeries in Black women. In an urban unselected clinic-based population, we evaluated 211 self-identified Black women who underwent genetic counseling for hereditary breast–ovarian cancer syndrome. *BRCA1/2* mutations were identified in 13.4 % of the participants who received genetic testing. Younger age at diagnosis, higher BRCA-PRO score, significant family history, and diagnosis of triple-negative breast cancer were associated with identification of a *BRCA1/2* mutation. Of the affected patients found to have a deleterious mutation, almost half underwent prophylactic measures. In our study population, 1 in 7 Black women who underwent genetic testing harbored a deleterious *BRCA1/2* mutation independent of age at diagnosis or family history.

Keywords

Genetic testing; *BRCA* mutations; Black women; Breast cancer

Correspondence to: Filipa Lynce.

Presented at San Antonio Breast Cancer Symposium 2013.

Conflict of interest The authors declare that they have no conflict of interest.

Introduction

The prevalence of deleterious *BRCA1* and *BRCA2* (*BRCA1/2*) mutations in minority groups other than the Ashkenazi Jewish population has not been well studied. Population-based studies have reported that Black women are approximately two to three times more likely to have triple-negative breast cancer (TNBC) than White women [1, 2] and this clinical subtype of breast cancer has been associated with germline *BRCA1* mutations [3–5]. Even among patients unselected for family history of breast cancer, women with TNBC are more likely to have *BRCA1/2* mutations, and these patients are often diagnosed at an earlier age and have higher grade tumors than those without mutations [6]. Given the high rate of early onset breast cancer and TNBC in Black women, it is important to determine the prevalence of *BRCA1/2* mutations in this population [7].

To date, most data regarding *BRCA1/2* mutations in Black women arise from population-based studies or from cohorts comprised highly selected families [8–12]. Two population-based series of female breast cancer patients found that Black women and non-Hispanic White patients had a similar prevalence of *BRCA1* mutations, with estimates of *BRCA1* mutation prevalence between 1.3 and 2.9 % [9, 10]. In a different setting where individuals were referred for genetic testing, estimates of *BRCA1/2* prevalence in women of African ancestry ranged from 12.1 to 15.6 % and were significantly higher than in women of Western European ancestry (ranged from 7.5 to 12.1 %) [13, 14].

The literature consistently supports the fact that Black women have a higher incidence of variants of unknown significance (VUS) compared with other ethnic groups. In a comparative analysis of families with 2 or more cases of breast and/or ovarian cancer among first- and second-degree relatives, African Americans were reported to have a significantly higher prevalence of VUS (44.2 %) compared with non-Hispanic, non-Jewish whites (11.5 %) [12]. However, the incidence of VUS in *BRCA1/2* has decreased over time, particularly among women of African ancestry [13].

The purpose of this study was to determine the prevalence of deleterious *BRCA1/2* mutations and VUS in an unselected urban clinic-based population of Black women with varied ancestry referred for genetic counseling for hereditary breast–ovarian cancer (HBOC) syndrome. We also describe predictors of deleterious *BRCA1/2* mutations and risk-reducing measures taken after receipt of *BRCA1/2* test results. Understanding the prevalence of *BRCA1/2* mutations in this clinically representative population can inform physicians involved in the care of Black women in whom testing for HBOC syndrome may be considered.

Materials and methods

Participants

Participants were Black women (defined as women who self-identified as Black, African, or African-American) who underwent genetic counseling for HBOC syndrome, with or without testing for *BRCA1/2* mutations, at two genetic counseling clinics at hospitals in Washington, DC between 2006 and 2012. Self-reported race was the only inclusion criterion. Eligible

women were identified through review of electronic medical records, paper records when available, and the Familial Cancer Registry (FCR). The FCR is an integrated and comprehensive registry of individuals at high genetic risk for cancer developed at Georgetown University that includes detailed demographic data, family history, medical history, and cancer risk factors, in addition to biospecimens. Our study protocol was approved by the Oncology Institutional Review Board at MedStar Health Research Institute, Georgetown University. Informed consent was not required due to the de-identified nature of the study data.

Genetic counseling and testing

Women were self-referred or provider-referred to the genetic counseling programs at MedStar Washington Hospital Center (MWHC) and Lombardi Comprehensive Cancer Center (LCCC). At MWHC, participants were seen by a physician geneticist and a genetic counselor (GC) and the visit was billed to the patient's insurance. At LCCC, counseling was performed by a GC only at no charge to the patient. Genetic testing was performed on blood or saliva at Myriad Genetic Laboratories (Salt Lake City, UT). Women could provide a DNA sample at the conclusion of their genetic counseling session or at any time subsequently. Genetic testing was billed to the patient's insurance or was supported by a pharmaceutical grant from Genentech (City, State). Women who were underinsured or uninsured were eligible for grant funding.

Measures

In this retrospective study, we performed a review of the clinical charts from genetic counseling sessions. Data abstracted included socio-demographic variables; referral source; insurance status; family history of cancer; personal history of breast, ovarian, or fallopian cancer; BRCAPRO pre-test *BRCA1/2* mutation probability; *BRCA1/2* test results; and risk-reducing surgeries after receipt of test results.

Family history was based on information obtained by patient report. We defined significant family history as the presence of first-degree relatives (FDR) or second-degree relatives (SDR) affected with breast cancer diagnosed before age 50 or with ovarian cancer at any age. For women with a personal history of breast cancer, triple-negative phenotype was defined based on estrogen receptor (ER), progesterone receptor (PR), and HER2 available from pathology reports. Ten percent or more staining of ER and PR based on routine immunohistochemistry was reported as positive. HER2 was analyzed by IHC and, in the presence of equivocal results, by fluorescence in situ hybridization. Results regarding receptor status were not available for 8.7 % of patients.

BRCA1/2 status was recorded based on test results and interpretation provided by Myriad Genetic Laboratories. Four test results were possible: positive (when a deleterious mutation was detected), VUS (genetic mutation detected but unclear if it is associated with an increased risk for cancer), inconclusive negative test (no known deleterious mutations in relatives and none detected in the patient), or true negative result (if there is a known confirmed deleterious mutation in relatives and none detected in the patient). For patients in whom VUS were reported at initial testing, amended reports were issued over time if the

VUS was reclassified after the initial post-test genetic counseling session. In such instances, the GC received an amended report, and all patients were contacted with new information and any change in interpretation. For the current study, the data on reclassification of VUS reflect updates received from Myriad as of March 31, 2013.

Participants with breast cancer who had contralateral mastectomy for prevention and unaffected women or those affected with ovarian cancer who had bilateral mastectomy for prevention were classified as having risk-reducing mastectomy (RRM). Participants who had both ovaries and fallopian tubes removed for prevention were classified as having had risk-reducing bilateral salpingo-oophorectomy (RRSO). For the purposes of this study, women were considered to have undergone RRM and RRSO only if one or both surgeries were performed after post-test genetic counseling.

Statistical analysis

Demographic and clinical variables were summarized using descriptive statistics including means, standard deviations, and frequencies. *BRCA1/2* mutation prevalence was calculated in our population as well as in various subgroups of interest. Further exploratory analysis was performed to evaluate the association of *BRCA1/2* mutations with demographic and clinical variables. All variables were analyzed as possible predictive factors for having a deleterious mutation. The two-sample *t* test or the nonparametric Wilcoxon-Mann-Whitney test was used for comparing the group means when appropriate. χ^2 test or Fisher's Exact test was used to compare categorical data. The effect of each variable was evaluated using logistic regression models in the univariate as well as multivariate setting. Data were entered into the Research Electronic Data Capture (RedCap) database. If a pre-test BRCAPRO score was not documented in the GC's chart, we calculated it using the software available online at <http://www.utsouthwestern.edu/cancergene/>, version 6.0. SAS software version 9.3 (SAS Inc. NC) was used for all statistical analysis. A *p* value < 0.05 was considered statistically significant.

Results

Description of the study population

Two hundred and eleven Black women received genetic counseling for HBOC syndrome from 2006 to 2012 at two hospitals in Washington DC: 85.8 % at MedStar Washington Hospital Center and 14.2 % at MedStar Georgetown University Hospital. The mean age at the time of initial genetic counseling was 49 years. One hundred and ninety-two patients (91 %) were probands. One hundred and fifty-five patients (73.5 %) who underwent genetic counseling were affected: 149 with breast cancer and 6 with ovarian cancer (Table 1). Five of these patients were non-probands. Out of 56 unaffected women who underwent genetic counseling, 42 were probands and the other 14 were relatives of individuals that tested positive for a deleterious mutation. Of these 14 non-probands, only 2 were found to be a true positive. The majority of women who received genetic counseling (*N* = 149; 70.6 %) underwent *BRCA1/2* testing (Fig. 1). Of those, 120 women had breast cancer, 6 had ovarian cancer, and 23 were unaffected with either cancer.

The mean age at counseling was 49 ± 11 (SD) years. An oncologist or a surgeon referred most of the patients. The majority of the patients who presented for genetic counseling (62.1 %) had at least one first- or second-degree relative with breast cancer diagnosed before the age of 50 or with ovarian cancer (Table 1). Most of unaffected participants (55.3 %) received genetic counseling after 2009. Participants who underwent genetic testing were younger (47.6 vs. 50.9 years, $p < 0.05$), more often referred by an oncologist (42 vs. 21 %, $p < 0.01$), and had a diagnosis of breast or ovarian cancer compared to women who were not tested (85.5 vs. 47 %, $p < 0.01$).

Test results

Deleterious *BRCA1/2* mutations were identified in 20 (13.4 %) women (Table 3). Of the deleterious mutations, 55 % were identified in the *BRCA1* gene (Table 2). Five (35.7 %) of the 14 identified mutations were identified in more than one study participant, and 3 of these recurrent mutations were identified in more than one non-related study participant (5804del4, IVS13 + IG, IVS16 + 6T) (Table 2). All such carriers had a significant family history. VUS were initially identified in 14 (9.4 %) women, most in the *BRCA2* gene. Nine (64.3 %) VUS were reclassified, all as benign polymorphisms except for one (Fig. 1). Of the Black women tested in 2006–2009, 15.2 % had VUS compared to 4.9 % of Black women tested in 2010–2012. BRACAnalysis Large Rearrangement Test (BART), a multiplexed quantitative endpoint polymerase chain reaction assay to detect additional large genomic rearrangements in both *BRCA1* and *BRCA2*, was performed in 31 (20.8 %) participants but did not identify any mutations.

Triple-negative breast cancer

Among patients with breast cancer who underwent genetic testing, 23 of 120 (19.2 %) had TNBC. Of those, 6 (21.4 %) had a deleterious mutation, 4 in the *BRCA1* gene and 2 in the *BRCA2* gene (Table 3). Patients with TNBC found to have a deleterious *BRCA1/2* mutation were younger (mean age 41.6 vs. 51.4 years), more likely to have significant family history (83.3 vs. 47.1 %) and to undergo risk-reducing measures (33.3 vs. 11.8 % for RRSO and 66.7 vs. 17.6 % for RRM) than non-carriers with TNBC. Deleterious *BRCA1/2* mutations were identified in 35 % (6 out of 17) of Black women diagnosed with TNBC at the age of 50 or younger, in 30 % (6 out of 20) of Black women diagnosed with TNBC at the age of 60 or younger, and in 56 % (5 out of 9) of Black women with TNBC diagnosed at or before the age of 50 who also had a significant family history.

Predictors of BRCA1/2 mutations in women with breast cancer

Among patients who underwent genetic testing, those found to have a deleterious mutation were younger, more likely to have significant family history or to be affected with TNBC (Table 4). Patients who had VUS that had not been reclassified at the time of this analysis ($n = 5$) were included in the category “genetic testing and no deleterious mutation.”

Among patients with a history of breast cancer, higher BRCAPRO score, younger age at diagnosis, presence of significant family history, and being diagnosed with TNBC or hormone negative BC were found to predict the presence of a deleterious *BRCA1/2* mutation in univariate analysis (Table 5). However, in multivariate analysis, only BRCAPRO

score remained statistically significant factor predictive of having a deleterious *BRCA1/2* mutation in women with a history of breast cancer (Table 5).

Risk-reducing surgeries after genetic testing

Data on RRSO were available for 87.5 % (105 of 120) of the patients with breast cancer. Data on RRM were available for 84.9 % (107 of 126) of the patients diagnosed with breast or ovarian cancer. In addition, 47.8 % (11 of 23) of the unaffected women had available data regarding risk-reducing surgeries.

Of the affected patients with a deleterious mutation, 42.9 % underwent RRSO and 41.7 % underwent RRM. Affected women with breast cancer and deleterious mutations were significantly more likely to undergo RRSO than affected women found not to have deleterious mutations (42.9 vs. 4.5 %, $p < 0.01$). Affected women with breast or ovarian cancer and deleterious mutations were significantly more likely to undergo RRM than affected women found not to have deleterious mutations (41.7 vs. 9.9 %, $p < 0.01$).

Insurance coverage for testing

Sixty-three (29.9 %) women who received genetic counseling and one-quarter of women who underwent genetic testing were underinsured (Medicare, Medicaid, or noninsured). Eleven (7.4 %) women who underwent genetic testing were able to receive testing only under grant support. Of those, 2 were found to have a deleterious *BRCA1/2* mutation.

Discussion

In our study, we identified *BRCA* mutations in 13.4 % in an unselected clinic-based urban population of Black women who presented for genetic counseling for HBOC syndrome. Our results are consistent with previous findings described by Hall et al. [13] in a cross-sectional analysis of 46,276 women who underwent DNA full sequence analysis of *BRCA1/2* genes and reported 15.6 % of women of African ancestry with deleterious mutations. However, we report a higher prevalence than what was previously described in cohorts of Black women diagnosed with early onset breast cancer: Pal et al. [8] reported a prevalence of 6.5 % in Black women diagnosed with breast cancer before the age of 50 and John et al. [9] found a prevalence of 16.7 % if women were younger than 35 years old at diagnosis. Contrary to these studies, our study participants were older with a mean age of 47.6 years.

In univariate analysis, the identification of a deleterious mutation in the participants of this study who were affected with breast cancer was associated with higher BRCAPRO score, younger age at diagnosis, diagnosis of hormone negative breast cancer, and significant family history. The small numbers of our cohort may explain why only the first factor was statistically significant in the multivariate analysis.

In evaluating the impact of having a diagnosis of TNBC in Black women, our data confirm that this is a significant predictor for detecting a deleterious *BRCA1/2* mutation. Greenup et al. [15] have recently reported similar results in a retrospective review of 469 patients with TNBC referred for genetic counseling. In our population, more than 1 in every 5 Black women diagnosed with TNBC at any age harbored a deleterious mutation. If age and family

history are taken into consideration, these numbers increase: more than 1 in every 3 Black women diagnosed with TNBC before the age of 50 was found to have a deleterious mutation and more than 1 in every 2 Black women diagnosed with TNBC with a significant family history had a deleterious mutation. Although numbers are small, these are compelling data that may have an important impact on clinical practice.

Current indications for *BRCA1/2* testing do not vary by race or ethnicity except for Ashkenazi Jewish individuals. Current guidelines from the National Comprehensive Cancer Network (NCCN) [16] recommend that patients diagnosed with TNBC before or at the age of 60 meet testing criteria for hereditary breast and/or ovarian cancer syndrome. Therefore, our finding that 30 % of women diagnosed with TNBC in this age group had a deleterious *BRCA 1/2* mutation is not surprising. In clinical practice, available literature suggests that genetic counseling and testing is being underutilized in women who meet NCCN referral guidelines [17] but the magnitude to which counseling and testing is underperformed in minority populations has not been well investigated and is not addressed with this study.

In our population, no women had large rearrangement mutations, although only 20 % of the patients underwent more extensive large rearrangement analysis (BART). In the literature, the prevalence of *BRCA* large rearrangements in Black women has been reported as 2.4 % in published data from Myriad Genetics that included highrisk African-American women [14] and 7.6 % in a small cohort of young Black women recruited through a cancer registry [18]. Therefore, it is possible that the rate of deleterious mutations in our population could be slightly underestimated.

Not surprisingly, the spectrum of mutations observed in our cohort is different from what has been reported in individuals of European descent. Some of the mutations identified were previously reported in the published literature and have been traced back to specific geographic origins. For example, the 943ins10 *BRCA1* founder mutation has been traced back to its ancient origin in the Ivory Coast in West Africa [19]. Interestingly, the 5804del4 *BRCA2* mutation that was identified in three participants of our cohort has been described in almost half of the carriers of deleterious mutations in a cohort of Arabic-American women [20].

Historically, higher rates of VUS are seen in Black women than women from other ethnic groups [11, 12], which makes risk assessment and genetic test result interpretation complex. Compared to older studies [12], the rate of VUS in our cohort was lower and importantly the vast majority has since been reclassified. In fact, women of African descent have experienced the largest decline in rate of VUS in *BRCA1/2* among all ethnicities, with an 87 % decline between 2002 and 2012 [21]. As more minority individuals obtain genetic testing, we would expect the frequency of VUS within these groups to continue to decline. However, the rapid integration of multi-gene testing for HBOC syndrome into clinical practice has resulted in more women who obtain VUS when tested for genes other than *BRCA1/2* [22–24]. As such, it remains crucial to prioritize research about VUS reclassification, particularly in minority groups.

The acceptability of RRM and RRSO among Black women found to carry deleterious mutations is unknown. In a prospective evaluation of 465 participants who underwent *BRCA1/2* testing, mainly Caucasians, more than 80 % of carriers had obtained either RRM or RRSO [25]. In a smaller study of 88 *BRCA1/2* mutation carriers, RRSO was associated with being White, but minorities constituted only 11 % of the cohort [26]. Other studies have suggested that African-American women at high risk for breast cancer prefer to pursue surveillance instead of risk-reducing surgeries [27, 28]. In our study, almost half of the carriers underwent risk-reducing surgeries. However, the vast majority of our patients were affected and our study was not powered to address this question.

Interestingly, most participants in our study were affected, which is not surprising given that the majority of women were referred by oncologists. Affected high-risk women are appropriate probands, and it is recommended to test such women before testing at-risk relatives [16]. However, it is important to understand patterns of referral for genetic counseling in Black women among other providers such as obstetrician gynecologists, primary care doctors, and surgeons. Previous literature has suggested that physician recommendation of genetic counseling in high-risk unaffected black women based on family history is low [29, 30]. These findings highlight the need for further research on the patterns of referral for genetic counseling among minority groups.

Among many factors that have been identified as barriers to genetic testing in Black women [31–33], inadequate insurance coverage is a significant concern. In our population, 1 in every 10 *BRCA1/2* mutation carriers would have remained unidentified without grant support. Health care policy decisions about coverage of genetic testing may influence identification of carriers and also uptake of genetic testing among Black women [34]. Under the Affordable Care Act, and based on current United States Preventive Services Task Force recommendations, genetic counseling and *BRCA1/2* testing should be made available as a preventive service for appropriate individuals and without cost-sharing [35]. However, this only applies to unaffected women at high risk for breast and/or ovarian cancer and would not comprise the majority of our study participants.

The strength of this study lies in the inclusion of all individuals who underwent genetic counseling regardless of personal or family history. Moreover, through chart review, we had access to clinical information that allowed the detailed study of patients with TNBC and descriptive analysis of measures taken after receipt of test results. Most of the limitations of our study are related to its retrospective nature. While it was not possible to ascertain barriers to testing, we believe that a 70 % uptake of genetic testing in our study population is acceptable. Another limitation of our study is the lack of a comparative group of non-Black women who were seen for genetic counseling at these sites.

For most of the participants in our study, genetic testing was limited to *BRCA1* and *BRCA2* mutations. Recent data found that among high-risk African-American women diagnosed with breast cancer, 22 % tested positive for a gene mutation, 80 % of whom had mutations in the *BRCA1/2* genes, while 20 % had mutations in *PALB2*, *CHEK2*, *BARD1*, *ATM*, *PTEN*, or *TP53* [36]. Interestingly, two studies [37, 38] reported an association between *PALB2* mutations and higher incidence of TNBC (30–54 %). For these reasons, it is of critical

importance that Black women have access to genetic counseling not only to discuss the option of proceeding with multi-gene testing but also to have appropriate expertise in the understanding of mutation profiles.

Our findings are consistent with the limited body of literature available regarding Black women with *BRCA1/2* mutations and underscore the importance of referring these patients for genetic counseling and testing, in particular, if younger at diagnosis, with a significant family history or found to have TNBC.

Acknowledgments

We thank the following genetic counselors who saw the patients who participated in this study (besides TD and BNP): Rachel Nusbaum MS, CGC, Gillian Hooker PhD, MS, and Morgan Similuk, MGC, CGC. We thank the endowed Jess and Mildred Fisher Center for Hereditary Cancer and Clinical Genomics Research, and Genentech for the grant received for genetic counseling and testing.

Funding This study was supported by the Familial Cancer Registry and Nontherapeutic Subject Registry Shared Resource at Lombardi Comprehensive Cancer Center, and was partially supported by the National Institutes of Health Grant P30-CA-51008. Study data were collected and managed using REDCap electronic data capture tools hosted at Georgetown University Medical Center. Ms. Peshkin and Dr. Isaacs received support from the endowed Jess and Mildred Fisher Center for Hereditary Cancer and Clinical Genomics Research.

References

1. Bauer KR, Brown M, Cress RD. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. *Cancer*. 2007; 109(9):1721–1728. [PubMed: 17387718]
2. Kwan ML, Kushi LH, Weltzien E, et al. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. *Breast Cancer Res*. 2009; 11(3):R31.doi: 10.1186/bcr2261 [PubMed: 19463150]
3. Peshkin BN, Alabek ML, Isaacs C. *BRCA1/2* mutations and triple negative breast cancers. *Breast Dis*. 2010; 32(1–2):25–33. [PubMed: 21778580]
4. Young SR, Pilarski RT, Donenberg T, et al. The prevalence of *BRCA1* mutations among young women with triple-negative breast cancer. *BMC Cancer*. 2009; 9:86.doi: 10.1186/1471-2407-9-86 [PubMed: 19298662]
5. Atchley DP, Albarracin CT, Lopez A, et al. Clinical and pathologic characteristics of patients with *BRCA*-positive and *BRCA*-negative breast cancer. *J Clin Oncol*. 2008; 26:4282–4288. [PubMed: 18779615]
6. Couch FJ, Hart SN, Sharma P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. *J Clin Oncol*. 2015; 33:304–311. [PubMed: 25452441]
7. Althuis MD, Brogan DD, Coates RJ. Breast cancers among very young premenopausal women (United States). *Cancer Causes Control*. 2003; 14(2):151–160. [PubMed: 12749720]
8. Pal T, Bonner D, Kim J, et al. Early onset Breast Cancer in a Registry-based sample of African-American women: *BRCA* mutation prevalence, and other personal and system-level clinical characteristics. *Breast J*. 2013; 19(2):189–192. [PubMed: 23320992]
9. John EM, Miron A, Gong G, et al. Prevalence of pathogenic *BRCA1* mutation carriers in 5 U.S. racial/ethnic groups. *JAMA*. 2007; 298(24):2869–2876. [PubMed: 18159056]
10. Malone KE, Daling JR, Doody DR, 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]

11. Haffty BG, Silber A, Matloff E, et al. Racial differences in the incidence of BRCA1 and BRCA2 mutations in a cohort of early onset breast cancer patients: African American compared to white women. *J Med Genet.* 2006; 43:133–137. [PubMed: 15983021]
12. Nanda R, Schumm LP, Cummings S, et al. Genetic testing in an ethnically diverse cohort of high-risk women: a comparative analysis of BRCA1 and BRCA2 mutations in American families of European and African ancestry. *JAMA.* 2005; 294(15):1925–1933. [PubMed: 16234499]
13. Hall MJ, Reid JE, Burbidge LA, 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]
14. Judkins T, Rosenthal E, Arnell C, et al. Clinical significance of large rearrangements in BRCA1 and BRCA2. *Cancer.* 2012; 118(21):5210–5216. [PubMed: 22544547]
15. Greenup R, Buchanan A, Lorizio W, et al. Prevalence of BRCA mutations among women with triple-negative breast cancer (TNBC) in a genetic counseling cohort. *Ann Surg Oncol.* 2013; 20(10):3254–3258. [PubMed: 23975317]
16. National Comprehensive Cancer Network Inc. [Accessed 8 July 2015] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 2.2015. www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf
17. Stuckey A, Febbraro T, Laprise J, et al. Adherence patterns to National Comprehensive Cancer Network Guidelines for referral of women with breast cancer to genetics professionals. *Am J Clin Oncol.* 2014; 2014 [Epub ahead of print].
18. Pal T, Bonner D, Cragun D, et al. BRCA sequencing and large rearrangement testing in young Black women with breast cancer. *J Commun Genet.* 2014; 5(2):157–165.
19. Stoppa-Lyonnet D, Laurent-Puig P, Essioux L, et al. BRCA1 sequence variations in 160 individuals referred to a breast/ovarian family cancer clinic. Institut Curie Breast Cancer Group. *Am J Hum Genet.* 1997; 60(5):1021–1030. [PubMed: 9150149]
20. Shatavi SV, Dohany L, Chisti MM, et al. Unique genetic characteristics of BRCA mutation carriers in a cohort of Arab American women. *J Clin Oncol.* 2013; 31(suppl) aabstr 1541.
21. Eggington, JM., Burbidge, LA., Roa, B., et al. American College of Medical Genetics and Genomics annual meeting. Charlotte: 2012. Current variant of uncertain significance rates in BRCA1/2 and Lynch syndrome testing (MLH1, MSH2, MSH6, PMS2, EPCAM).
22. Ricker, CN., Sturgeon, JD., Gruber, SB. Mutation and uncertain variant findings in ethnic minority patients undergoing multi-gene panel testing for cancer risk assessment at a safety-net public hospital (Abstract 3428S); Presented at the 64th Annual Meeting of the American Society of Human Genetics; on October 2014; San Diego. 2014. in
23. LaDuca H, Stuenkel AJ, Dolinsky JS, et al. Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2,000 patients. *Gene Med.* 2014; 16(11):830–837.
24. Tung N, Battelli C, Allen B, et al. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer.* 2015; 121(1):25–33. [PubMed: 25186627]
25. Schwartz MD, Isaacs C, Graves KD, et al. Long-term outcome of BRCA1/BRCA2 testing: risk reduction and surveillance. *Cancer.* 2012; 118(2):510–517. [PubMed: 21717445]
26. Bradbury AR, Comfort NI, Dignam JJ, et al. Uptake and timing of bilateral prophylactic salpingo-oophorectomy among BRCA1 and BRCA2 mutation carriers. *Genet Med.* 2008; 10:161–166. [PubMed: 18344704]
27. Kinney AY, Simonsen SE, Baty BJ. Risk reduction behaviors and provider communication following genetic counseling and BRCA1 mutation testing in an African American kindred. *J Genet Couns.* 2006; 15:293–305. [PubMed: 16865561]
28. Salant T, Ganschow PS, Olopade OI. “Why take it if you don’t have anything?” breast cancer risk perceptions and prevention choices at a public hospital. *J Gen Intern Med.* 2006; 21:779–785. [PubMed: 16808782]
29. Thompson HS, Sussner K, Schwartz MD, et al. Receipt of genetic counseling recommendations among black women at high risk for BRCA mutations. *Genet Test Molec Biomark.* 2012; 16(11):1257–1262.

30. Halbert CH, Brewster K, Collier A, et al. Recruiting African American women to participate in hereditary breast cancer research. *J Clin Oncol*. 2005; 23(31):7967–7973. [PubMed: 16258097]
31. Glenn BA, Chawla N, Bastani R. Barriers to genetic testing for breast cancer risk among ethnic minority women: an exploratory study. *Ethn Dis*. 2012; 22(3):267–273. [PubMed: 22870568]
32. Susswein LR, Skrzynia C, Lange LA, et al. Increased uptake of BRCA1/2 genetic testing among African American women with a recent diagnosis of breast cancer. *J Clin Oncol*. 2008; 26:32–36. [PubMed: 18165638]
33. Sussner KM, Edwards TA, Thompson HS, et al. Ethnic, racial and cultural identity and perceived benefits and barriers related to genetic testing for breast cancer among at-risk women of African descent in New York City. *Public Health Genomics*. 2011; 14(6):356–370. [PubMed: 21540561]
34. Armstrong K, Putt M, Halbert CH, et al. The influence of health care policies and health care system disrupt on willingness to undergo genetic testing. *Med Care*. 2012; 50(5):381–387. [PubMed: 22473221]
35. [Accessed on April 15 2015] Affordable Care Act Implementation FAQs–Set 12. http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs12.html
36. Churpek JE, Walsh T, Zheng Y, et al. Inherited predisposition to breast cancer among African American women. *Breast Cancer Res Treat*. 2015; 149(1):31–39. [PubMed: 25428789]
37. Heikkinen T, Kärkkäinen H, Aaltonen K, et al. The breast cancer susceptibility mutation PALB2 1592delT is associated with an aggressive tumor phenotype. *Clin Cancer Res*. 2009; 15(9):3214–3222. [PubMed: 19383810]
38. Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med*. 2014; 371(6):497–506. [PubMed: 25099575]

Fig. 1.
Patient diagram and genetic testing results

Table 1

Characteristics of patients who underwent genetic counseling

Characteristic	N (%)
<i>BRCA1/2</i> genetic testing performed	
Yes	149 (70.6)
No	62 (29.4)
Affected with breast, ovarian, or fallopian tube cancer	
No	56 (26.6)
Breast cancer	149 (70.6)
Ovarian/fallopian tube	6 (2.8)
Proband (first person counseled in the family)	
Yes	192 (91.0)
Source of referral for genetic counseling	
Oncologist	75 (35.5)
Surgeon	85 (40.3)
Survivorship nurse practitioner	5 (2.4)
Gynecologist	13 (6.2)
Self	10 (4.7)
Others/missing	23 (10.9)
Insurance	
Medicare	28 (13.3)
Medicaid	31 (14.7)
Private	160 (75.8)
None	4 (1.9)
Missing	5 (2.4)
Significant family history	
1st or 2nd degree relative with breast cancer diagnosed <age 50	100 (47.4)
1st or 2nd degree relative with ovarian cancer	22 (10.4)
Both of the above	9 (4.3)
No significant family history	98 (46.4)

Table 2

List of identified mutations

BRCA1	BRCA2
IVS13 + IG (<i>n</i> = 2)	5804del4 (<i>n</i> = 3)
IVS16 + 6T (<i>n</i> = 2)	3237delC (<i>n</i> = 2)
C64G (309T) (<i>n</i> = 2)	1433delG
W1508X	Y600X
Q563X	3036del4
943ins10	52670 (8237C > 7)
2418delA	
IVS23 + IG	

Table 3

Characteristics of patients with deleterious *BRCA1/2* mutations

Case	Gene	Mutation	Pre-test BRCA ^{PRO} score	Cancer diagnosis	Age at testing	Number of FDR/SDR with BC <50 and/or OC	Other relevant information
3	<i>BRCA2</i>	3036del4	70.4	BC@38	38	3	Additional VUS identified in <i>BRCA2</i> gene
18	<i>BRCA1</i>	C64G (309T > G)	95.9	TNBC@35	36	2	
29	<i>BRCA1</i>	2418delA	12.1	BC@56	56	2	
40	<i>BRCA1</i>	IVS13 + 1G > A	69	TNBC@50	50	1	
43	<i>BRCA1</i>	C64G (309T > G)	N/A	TNBC@36	43	2	Sister of patient 18
45	<i>BRCA2</i>	S2670L (8237C > T)	4.8	BC@24	24	0	Classified as VUS in 2006, reclassified in 2009
62	<i>BRCA2</i>	5804del4	32	TNBC@41	43	1	First BC@33
64	<i>BRCA2</i>	3237delC	0.4	BC@46	66	1	Uterine sarcoma @64
65	<i>BRCA2</i>	3237delC	N/A	Not affected	40	1	Daughter of patient 64
99	<i>BRCA1</i>	IVS23 + 1G > A	0.9	BC@39	41	0	
115	<i>BRCA1</i>	IVS16 + 6T > C	8.4	TNBC@39	39	0	Bilateral BC
128	<i>BRCA1</i>	IVS16 + 6T > C	75.2	BC@51	52	2	
135	<i>BRCA1</i>	943ins10	15.1	OC@46	48	1	
142	<i>BRCA2</i>	Y600X (2028T > A)	84.2	BC@55	56	2	
155	<i>BRCA2</i>	5804del4	67.1	TNBC@39	39	2	
160	<i>BRCA1</i>	Q563X	26.3	Not affected	50	1	
213	<i>BRCA1</i>	W1508X (4643G > A)	4.5	BC@26	27	0	
216	<i>BRCA1</i>	IVS13 + 1G > A	100	OC@49	52	3	BC@31
221	<i>BRCA2</i>	1433delG	N/A	Not affected	37	3	Relative of known carrier
223	<i>BRCA2</i>	5804del4	N/A	BC@38	47	1	Relative of known carrier

BC breast cancer, OC ovarian cancer, N/A not applicable, FDR first-degree relatives, SDR second-degree relatives, TNBC triple-negative breast cancer

Table 4

Different characteristics between women tested found to have deleterious mutations and women tested without deleterious mutations

Characteristics	<i>BRC</i> A1/2 mutations (<i>n</i> = 15) <i>N</i> (%)	Genetic testing and no deleterious mutation (<i>n</i> = 105) <i>N</i> (%)	<i>p</i> value ^{<i>a</i>}
Age at diagnosis			
Mean	40.9	47.5	0.03
Significant family history ^{<i>b</i>}	11 (73.3)	43 (41.0)	0.02
TNBC	6 (40.0)	20 (19.0)	0.03
Hormone receptor positive	5 (25.0)	67 (63.8)	0.06

^{*a*} Comparing women tested with mutations to women tested and without a deleterious mutation

^{*b*} Defined as the presence of at least one FDR or SDR affected with breast cancer diagnosed before age 50 or with ovarian cancer at any age

Univariate and multivariate modeling for factors predictive of deleterious mutations in patients with breast cancer

Table 5

Variable	Category	Univariate analysis		Multivariate analysis	
		OR (95 % CI)	p value	OR (95 % CI)	p value
BRCAPRO score ^a	Continuous	1.04 ^a (1.02, 1.07)	<0.01	1.05 ^a (1.01, 1.10)	0.03
Age at diagnosis	>40 versus 40	0.28 (0.09, 0.85)	0.02	0.20 (0.03, 1.23)	0.08
Significant family history ^b	Yes versus No	3.97 (1.18, 13.28)	0.03	0.76 (0.08, 7.69)	0.81
TNBC	Yes versus No	4.71 (1.35, 16.37)	0.01	1.93 (0.05, 78.28)	0.73
Hormone receptor positive	Yes versus No	0.25 (0.07, 0.90)	0.03	0.60 (0.02, 22.09)	0.78

^aFor each point increase in BRCAPRO score, the likelihood of testing positive increased by 4 % in univariate analysis and by 5 % in multivariate analysis

^bDefined as the presence of at least one FDR or SDR affected with breast cancer diagnosed before age 50 or with ovarian cancer at any age