



Differences in referral patterns based on race for women at high-risk for ovarian cancer in the southeast: Results from a Gynecologic Cancer Risk Assessment Clinic

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HIGHLIGHTS

- Black women were more likely referred for genetic assessment by surgical oncology or a genetic counselor than white women.
- Black women evaluated in our clinic were more than twice as likely as white women to have a *BRCA2* pathogenic variant.
- No black women were referred by primary care physicians to the genetic assessment clinic.
- Opportunities exist for improving minority referral patterns for genetic evaluation.

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ABSTRACT

Objective. To compare referral patterns, genetic testing and pathogenic variant rates in Black women (BW) and White women (WW) in a large academic Gynecologic Cancer Risk Assessment Clinic (GCRAC).

Methods. Cross sectional study of an IRB-approved prospective, cohort study from a GCRAC. Data evaluated included: age, race, referral provider specialty and indication, genetic testing frequency, as well as frequency and types of pathogenic variants.

Results. 588 WW and 57 BW were evaluated from 1/2010–12/2015. Although approximately one-third of BW and WW were referred for family history alone, referral indications varied. BW were more likely referred for a known pathogenic variant (20.0% vs. 6.2%) although less likely referred for a personal history of ovarian cancer (24.0% vs. 46.8%; $p = 0.0023$). While gynecologic oncologists referred most patients (BW 43.6% vs. WW 63.0%), BW were more likely to be referred by surgical oncologist (23.0% vs. 12.8%) or genetic counselor (12.8% vs. 5.9%) than WW ($p = 0.0234$). Referral from non-OBGYN primary care providers was <3% in both groups. Genetic testing rates were similar in both races (82.4% vs. 85.5%). Rates of *BRCA1* mutations (12.7% vs. 11.5%) were similar; however, BW had more *BRCA2* mutations (21.3% vs. 9.5%; $p = 0.0194$).

Conclusions. Since BW are more likely to be referred by surgical oncology or genetics counselor, breast clinics might be an entry point to ensure genetic counseling and testing. Continued efforts to increase awareness regarding the importance of patient referral at the primary care level may help identify the subset of women not currently undergoing counseling and testing.

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1. Introduction

It is estimated that >22,000 American women will be diagnosed with ovarian cancer in 2018. With a predicted 14,070 deaths, ovarian cancer is the most deadly gynecology malignancy in the United States and fifth for cancer deaths among women [1]. Half of ovarian cancer diagnoses are attributed to somatic mutations in the TP53 gene, and

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approximately 20% of ovarian cancer cases are attributed to pathogenic germline variants (mutations) [2]. Pathogenic germline variants are most often in the following genes: *BRCA1*, *BRCA2*, *BRIP1*, *RAD51C*, *RAD51D*, and Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), among others [3]. Genetic counseling and testing for a germline pathogenic variant in ovarian cancer patients offers prognostic information with early treatment and may assist in tailoring treatment options. The need for this information is highlighted by a clear demonstration of the benefit of olaparib for primary maintenance therapy in patients who carry a pathogenic *BRCA* variant [4]. Additionally, screening relatives via cascade testing allows the possibility for interventions to reduce cancer risk [5]. For these reasons, the National Comprehensive Cancer Network now recommends genetic evaluation and testing for all women who have an epithelial ovarian cancer.

While black women (BW) have a lower incidence of ovarian cancer than white women (WW) (10.1/100,000 vs. 14.1/100,000), BW have worse five-year survival across all ages when compared in WW [6]. This is a common trend as BW generally have the highest death rate and shortest survival in most cancer groups, with a 6% lower risk of diagnosis but 14% higher risk of death [1]. There is a paucity of data regarding ovarian cancer in BW, and they are underrepresented in published literature [7]. Previous studies have suggested that BW are underrepresented in Gynecologic Cancer Risk Assessment Clinics (GCRAC) [8]. The objective of this study was to compare referral patterns including referring provider specialty type, genetic testing, and pathogenic variant rates between BW and WW in a large southeastern GCRAC.

2. Materials and methods

We performed a cross sectional study of an IRB-approved prospective, cohort study of patients from a GCRAC embedded within our NCI designated Comprehensive Cancer Center. This multidisciplinary clinic is composed of a board-certified gynecologic oncologist, a nurse practitioner, and cancer genetic counselors. Detailed genetic evaluation, including counseling and testing, is performed for high-risk individuals. Patients are referred to this clinic for four general indications: [1] women with a personal history of ovarian or other gynecologic cancers, [2] unaffected women with a strong family history of cancer, [3] women with a first, or less commonly, a second degree relative with a positive germline test who have not themselves undergone germline testing and [4] women who have undergone germline testing at an outside institution, were found to have a pathogenic germline variant, and need either surveillance and/or prophylactic surgical recommendations. This study was conducted in a state where African Americans comprise about a quarter of the population and Caucasians comprise approximately two-thirds. For the current study, we limited our analysis to WW and BW evaluated from 1/2010–12/2015. Data evaluated included: age, race, frequency of genetic testing, referral provider specialty and indication, as well as frequency and types of pathogenic variants. When questions arose regarding genetic test results, ClinVar (www.clinvar.com) was utilized for categorizing genetic test results as pathogenic or not. Women reporting Hispanic or Jewish ethnicity as well as Asian, Native American or Pacific Islander race were excluded. Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary NC) to compare means with standard deviations and frequencies of categorical variables between the two groups.

3. Results

588 (91.2%) WW and 57 (8.8%) BW were evaluated in our GCRAC. The mean age of BW was younger (49.3 ± 12.5 years) than WW (54.2 ± 14.8 years) ($p = 0.016$). Although approximately one third of both BW (36.0%) and WW (32.6%) were referred for family history alone, BW were more likely to be referred for a known pre-existing pathogenic variant (20.0% vs. 6.2%) and less likely to be referred for a personal

history of ovarian cancer (24.0% vs. 46.8%; $p = 0.0023$). Other referral indications are depicted in Table 1. While both groups were most likely referred by a gynecologic oncologist (BW 43.6% vs. WW 63.0%), BW were more likely to be referred by surgical oncologist (23.0% vs. 12.8%) or genetic counselor (12.8% vs. 5.9%) than WW ($p = 0.02$) (Fig. 1). Referral rates from primary OBGYNs were similar (BW 15.3% vs. WW 12.8%), while referral from other primary care providers was low in both groups (BW 0% vs. WW 2.9%).

Overall 556 of 645 (86.2%) of WW and BW evaluated underwent genetic testing following genetic counseling. The rates of genetic testing were similar for both groups (BW 82.4% vs. WW 85.5%; $p = 0.5563$). WW and BW had similar rates of pathogenic *BRCA1* variants (12.7% vs. 11.5%); however, BW were more likely to have pathogenic *BRCA2* variants (21.3% vs. 9.5%; $p = 0.02$) (Fig. 2). Findings of other pathogenic variants and variants of uncertain significance results were similar and are depicted in Table 2.

4. Discussion

Our prior study in gynecologic risk assessment demonstrated that the proportion of BW represented in risk assessment clinics is low and was similar to what was seen in the current study [8]. Most data regarding BW and *BRCA* genetic testing has been studied in breast cancer patients [9–11] and has noted that BW women with a history of breast or ovarian cancer were less likely than WW to undergo genetic testing [12]. Overall, the number of BW women represented in our study was low. BW were more likely than WW to be referred for a known pathogenic variant and were more likely to have pathogenic *BRCA2* variants than WW (Table 1). Previous research has shown that ethnically diverse populations have a higher proportion of pathogenic *BRCA2* variants compared to more homogeneously white samples [13].

Given ovarian cancer is the leading cause of death from gynecologic cancers and has an associated hereditary risk, it is imperative that at-risk patients be appropriately evaluated via genetic counseling, and when appropriate, with genetic testing. Genetic risk assessments provide patients with the ability to understand hereditary risks and aid in management. Our current research shows that women are most likely to be referred based on family history (BW 36.0% vs. WW 32.6%) or a personal history of ovarian cancer (BW 24.0% vs. WW 46.8%). Interestingly, 20% of BW were referred to our clinic for a known pathogenic variant. It has also been presented that BW with greater perceived benefit of genetic testing, higher income, and higher risk of pathogenic *BRCA* variants are more likely to undergo testing [14]. It has been recommended that all women with high-grade epithelial tumors should have genetic testing, and current NCCN guidelines endorse that all

Table 1

Characteristics of white and black women evaluated at a gynecologic cancer risk assessment clinic.

Race	White	Black	P value
N, (%)	588 (91.2)	57 (8.8)	
Age (years) – mean \pm St. dev	54.2 \pm 14.8	49.3 \pm 12.5	0.016
Referral indication	N (%)	N (%)	
BRCA + relative	33 (5.9)	4 (8.0)	
Personal history of breast cancer ^a	27 (4.8)	4 (8.0)	
Personal history of ovarian cancer	263 (46.8)	12 (24.0)	0.0023
Family history of cancer	183 (36.0)	18 (32.6)	
Known pathologic mutation	35 (6.2)	10 (20.0)	
Referring provider specialty	N (%)	N (%)	
Gynecologic oncologist	310 (63.0)	17 (43.6)	
Surgical oncologist	68 (13.8)	9 (23.1)	
OBGYN	63 (12.8)	6 (15.4)	
Genetic counselor/medical geneticist	29 (5.9)	5 (12.8)	0.0234
Internal medicine	14 (2.9)	0 (0.0)	
Medical oncologist	3 (0.6)	2 (5.1)	
Other	5 (1.0)	0 (0.0)	

^a With other high-risk feature (relative with ovarian cancer, age < 40, founder population, etc.).

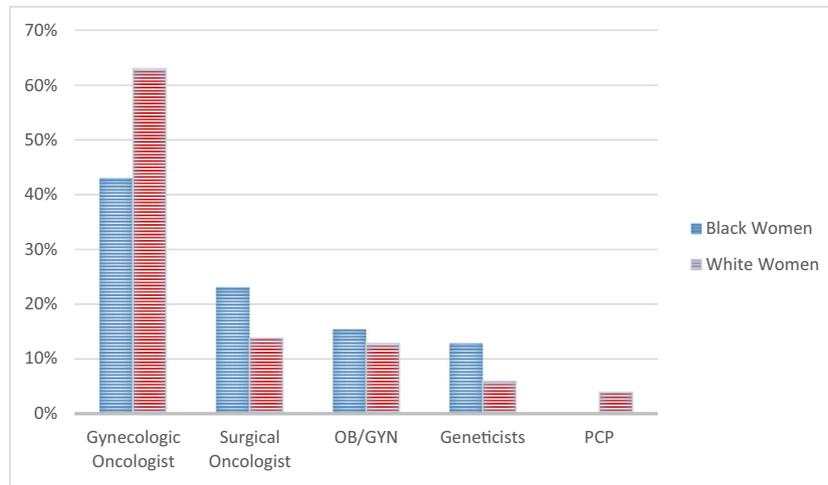


Fig. 1. Type of referring provider for women evaluated in GCRAC*.

women with ovarian cancer be offered genetic testing [15–17]. The Society of Gynecologic Oncology (SGO) also put forth recommendations for referral for genetic testing including (but not limited to): high-grade epithelial ovarian or peritoneal cancer, breast cancer less than or equal to 45 years old, breast cancer with greater than or equal to 2 close relatives with breast cancer, a close relative with a pathogenic *BRCA 1* or 2 variant [18].

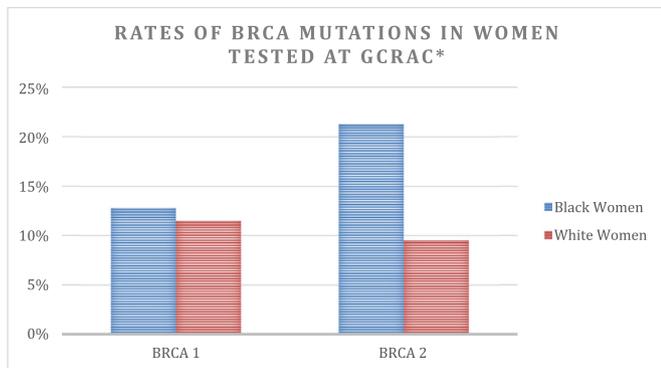
Our study demonstrated that BW and WW were most likely to be referred by a gynecologist oncologist and least likely by a primary care providers (PCP). Referral rates from OBGYNs were similar (BW 15.3% vs. WW 12.8%), while referral from other primary care providers was low in both groups (BW 0% vs. WW 2.9%). In fact, no BW were referred by a PCP to the genetic clinic (Table 1). Primary care providers can be instrumental in discovering patients who need genetic evaluation. Hamilton et al. performed a literature review evaluating breast and colorectal cancer genetic referral patterns [19]. Their results suggested that PCPs have limited knowledge about genetic testing options, and furthermore, PCPs expressed ethical, legal, and social concerns about testing. ACOG recommends that all women with a familial or personal history of ovarian or breast cancer be referred for genetic counseling to evaluate if genetic testing is warranted. It is apparent that further research, resources, and interventions need to be utilized in order to increase PCP knowledge and communication with gynecologic genetic referral centers.

When BW are actually referred to genetic counseling, the rates of genetic testing were comparable with WW (Table 2). This testing may allow for potential preventive treatment options that are available to be discussed both for the patient and even the patient's family. Patients with pathogenic variants in the *BRCA1* or *BRCA2* genes may undergo risk

reducing or prophylactic bilateral total mastectomy and bilateral salpingo-oophorectomy and/or hysterectomy. These prophylactic surgery options are known to dramatically reduce the risk of development of breast or ovarian cancer. Undergoing a risk-reducing salpingo-oophorectomy (RRSO) for women with a pathologic variant has been associated with lower all-cause mortality along with lower breast and ovarian cancer-specific mortality [5,17,20–23]. Similarly, bilateral mastectomies have been shown to decrease the risk of developing breast cancer in at least 90% of women with known pathogenic *BRCA1* or *BRCA2* variants [24]. Another option for these women is high-risk breast cancer assessments which include an annual breast MRI starting at age 25 with annual mammograms added at age 30 for those who do not wish to undergo a mastectomy [17].

Limitations in our study include its single institutional design and limitation to two racial groups. We are also potentially missing some patients given there are three cancer institutes in our state, however, ours is the largest and only designated Comprehensive Cancer Center. In addition to the described clinic which is embedded within our Gynecologic Oncology Division, there are two similar cancer genetic counseling clinics on campus. Patients with a risk of gynecologic cancer, such as those described in our manuscript are preferentially referred to our clinic, even if they were initially referred to one of the other two clinics. In addition, a comparatively small proportion of BW were evaluated, which is largely secondary to the limited referral patterns. Nonetheless, we were able to determine referral indications based on review of referral documentation from the patient's referring provider when the patient's genetic counseling visit was scheduled. Evaluating medical providers' understanding of referral indications may assist in addressing sub-optimal referral patterns.

The current study continues to aid in the investigation of BW with hereditary cancer syndromes given the limited literature at this time. While barriers to genetic referral remain poorly defined, the strength



*GCRAC – Gynecologic Cancer Risk Assessment Clinic

Fig. 2. Rates of BRCA mutations in women tested at GCRAC* This can also be removed if needed. For both figures, the *refers to the GCRAC acronym.

Table 2

Genetic testing results for women evaluated in gynecologic cancer risk assessment clinic by race.

Race	White N (%)	Black N (%)	p-Value
Underwent genetic testing	503 (85.5)	47 (82.4)	0.5563
Results			
Negative	368 (73.2)	26 (55.3)	
<i>BRCA1</i> pathogenic variant	58 (11.5)	6 (12.8)	0.0194
<i>BRCA2</i> pathogenic variant	48 (9.5)	10 (21.3)	
Other pathologic variant	4 (0.8)	2 (4.3)	
Variant of unknown significance	18 (3.6)	3 (6.4)	
Hereditary nonpolyposis colorectal cancer	7 (1.4)	0 (0.0)	

in guidelines should assist progression in clinical translation. Given that many guidelines require knowledge regarding the patient's family history, it is important that providers elicit this information in order to evaluate if the patient needs referral. Potential future strategies for improving awareness to address poor referral patterns include: outreach services such as presentations at conferences given for primary care physicians, targeted mailing questionnaires evaluating referral patterns and providing educational information regarding indications for referrals, and working in concert with support groups to raise awareness in the general populations. Studies addressing providers' understanding of referral indications will continue to aid in addressing the gap in identifying minorities at risk for hereditary cancer syndromes. Initiatives targeting increasing primary care providers' knowledge of genetic referral indications may help to improve the identification of at-risk individuals of all races.

Author contributions

Formulation of research question: Leath, Barrington.

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Data collection: Barrington, Batra.

Statistical analysis: McGwin.

Manuscript drafting: Boitano, Barrington.

Critical revision: Leath, Straughn, Boitano, Barrington, Turner, Farmer, Brown.

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Declaration of Competing Interest

None.

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