Uptake of Screening and Risk Reducing Recommendations Among Women with Hereditary Breast and Ovarian Cancer Syndrome Evaluated at a Large Urban Comprehensive Cancer Center

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Abstract

Purpose: Carriers of pathogenic variants in *BRCA1*/2 have an elevated lifetime cancer risk warranting high-risk screening and risk-reducing procedures for early detection and prevention. We report on prevention practices among women with pathogenic *BRCA* variants to evaluate compliance with NCCN recommendations and to identify barriers to guideline-recommended care.

Methods: We evaluated women tested positive for pathogenic variant in *BRCA1/2* via 54-item questionnaire to measure socio-demographics, medical history, rates of cancer screening and risk-reducing surgery, disclosure of test results, and cancer worry. We reported rates of compliance with risk-reducing salpingo-oophorectomy (RRSO), risk-reducing mastectomy (RRM) and NCCN guidelines (version 3.2019). A multivariable logistic regression analyses was used to identify predictors of these outcomes.

Results: Of 129 evaluable women with pathogenic *BRCA1*/2 variants, 95 (74%) and 77 (60%) underwent RRSO and RRM, respectively, and 107 (83%) were considered adherent to NCCN guidelines. After multivariable analyses, personal history of breast or ovarian cancer was positively associated with RRM (OR = 2.81; 95% CI 1.10 – 7.44; p = 0.025). Increasing age was associated with an increased likelihood of RRSO (OR=1.05; 95% CI 1.01 – 1.09; p = 0.022) and a decreased likelihood for RRM (OR=0.96; 95%CI 0.92 – 0.99; p value = 0.013). Women who had RRM were 3 times more likely to undergo RRSO (OR = 3.28; p = 0.004). Rates of RRSO or RRM were not impacted by participant race, education, annual household income, marital status, or family history. There was near universal (127/129) disclosure of genetic test results to family members resulting in the discovery of 1 relative with a pathogenic variant (range = 0-8) through cascade testing.

Conclusion: Long term follow up of a cohort of women with pathogenic variants in *BRCA1*/2 revealed high rates of compliance with screening and risk reducing recommendations. Further efforts should focus on increasing compliance among unaffected carriers especially for RRSO.

Introduction

Women who carry pathogenic variants in *BRCA1* or *BRCA2* have an estimated cumulative risk of breast cancer by age 80 of up to 72% and of ovarian cancer of up to 44% [1]. To facilitate early detection and risk reduction, National Comprehensive Cancer Network (NCCN) guidelines (version 3.2019) recommend screening mammogram with consideration of tomosynthesis alternating with breast MRI with contrast, consideration of risk reducing mastectomy (RRM), and risk-reducing salpingo-oophorectomy (RRSO). RRSO confers both an 80% reduction in ovarian cancer risk and a 50% reduction in breast cancer risk among pre-menopausal women, improving cancer specific and overall mortality [2, 3]. For carriers who decline RRSO or are still in child-bearing years, NCCN guidelines recommend screening by transvaginal ultrasound (TVUS) and CA-125 every 6-12 months, beginning at the age of 30-35. [4].

In North America, studies of women with pathogenic *BRCA1/2* variants have reported uptake of RRSO ranging from 36–89% and RRM from 21–96% [5–13]. In one study evaluating racial differences in

preventative surgery, the rates of RRSO and RRM among Black carriers was 28.1% and 68.8%, respectively compared to 76.6% and 95.7%, respectively for White women [7]. Given possible racial disparity in uptake of risk-reducing measures and the potential life-saving outcomes associated with early detection and prophylactic surgery, it is important to assess uptake of preventative and risk-reducing strategies among high-risk women from diverse race and ethnic backgrounds. We present results of a survey designed to assess use of NCCN recommended screening and risk-reducing procedures among women with pathogenic *BRCA1/2* variants evaluated at a large, urban comprehensive cancer center in Detroit, Michigan. Predictors of uptake of screening and prevention guidelines such as personal and family history of cancer, participant demographics, and cancer worry were examined. We also studied disclosure of genetic test results and cascade testing of family members.

Methods

Study Population

Women who tested positive for pathogenic variants in the *BRCA1* or *BRCA2* genes between January 1, 2000, and December 31, 2017 were identified through the Cancer Genetic Counseling Service (CGCS) database at the Karmanos Cancer Institute (KCI). Since January 1, 2000, the CGCS has provided comprehensive pre and post-test genetic counseling at 2 sites in Metropolitan Detroit, and since 2018, at 7 other community locations throughout Michigan. Potentially eligible participants were mailed information letters about a survey of practice patterns after genetic testing and were also provided the option to opt out of the study. Those who did not opt out, were mailed a 54-item questionnaire and return of the completed questionnaire was considered as consent. After at least two weeks, participants who did not return the questionnaire were contacted to request participation in a phone-based interview. Each woman was called at least three times before being designated a non-responder.

Questionnaire

The questionnaire was adopted from an instrument used for a similar study of practice patterns conducted by the State of Michigan [5] and contained 46 multiple choice and 8 Likert style items divided into the following seven sections: 1) genetic history and disclosure of results, 2) prophylactic surgery, 3) screening and surveillance, 4) other cancer prevention methods, 5) demographics and lifestyle, 6) cancer history and 7) a cancer worry scale (validated by Jose A E Custers et. al [14]). Responses to open ended questions were reviewed by investigators and presented as descriptive data. The questionnaire was reviewed to ensure item clarity and respondent comprehension through expert review, community engagement, and cognitive interviewing of local community stakeholders.

Outcome Variables

The outcomes of interest included completion of RRSO, RRM and adherence to NCCN guidelines for prevention and early detection in carriers of *BRCA* pathogenic variants. According to NCCN (version 3.2019) recommendations, RRSO should be completed by age 40 for *BRCA1* pathogenic carriers, and by age 45 for *BRCA2* carriers. Since the survey did not include a question about the date of surgery, we considered a participant to have completed RRSO if they had no previous history of ovarian cancer and reported RRSO. Subjects were considered to have completed RRM if they reported RRM at any age. Subjects with a history of unilateral breast cancer were considered to have had RRM if they underwent mastectomy on the contralateral, unaffected side. Subjects were considered to have met the endpoint of NCCN guideline adherence if they: A) underwent RRSO by age 45 and RRM at any age, B) if they were less than 45 years old and received at least one TVUS and one CA-125 blood measurement in the past 12 months, and either underwent RRM or received at least one mammogram and one breast MRI in the past 12 months, C) Underwent RRSO and either RRM or received at least one mammogram and one breast MRI in the past 12 months. For subjects between the ages of 25 and 30, only breast MRI was required per NCCN guidelines. Subjects over the age of 45 who did not have RRSO were not considered to have met NCCN guideline adherence endpoints regardless of screening practices.

Other Predictor Variables

Information was collected on socio-demographic variables including race, health insurance, annual household income, education level and marital status. Race was categorized as White or Black and ethnicity was categorized based on how it was collected by cancer genetic counseling service as Hispanic, Arab, Asian, Native American, or other (which included mixed race and Indian). Information was also collected on history of Ashkenazi Jewish ancestry. Insurance status was dichotomized as private insurance with or without Medicare/Medicaid or government insurance alone.

Participants answered questions regarding whether they disclosed genetic test results, the number of family members to whom the results were disclosed and cascade testing of family members as well as knowledge of a prior pathogenic *BRCA* mutation in the family. The number of women who disclosed their diagnosis of Hereditary Breast and Ovarian Cancer Syndrome (HBOC) and the reasons they may have kept the information private are presented as descriptive data. Participants also completed a cancer worry scale [14] which consisted of Likert style questions to indicate whether anxiety about cancer affects their daily lives. We analyzed the average score on the cancer worry scale for each endpoint of RRSO, RRM, and NCCN guideline adherence (Table 6).

Statistical Analysis

Adherence to recommended risk management, a dichotomous variable, was calculated separately for each endpoint; RRSO, RRM, and compliance with NCCN recommendations. We calculated descriptive statistics for demographic factors (e.g., age, self-reported race, ethnicity, education, type of health insurance), cancer family history, personal cancer history, and cancer-related worry. Univariable and

multivariable logistic regression models were used to assess associations between participant characteristics and adherence to risk management guidelines separately for each outcome. The final multivariable model was selected using backwards stepwise selection, starting with a model that included all variables significant at $p < 0.05$ in univariate analysis. We included race, insurance status, education, personal history of cancer, and family history of breast or ovarian cancer in multivariate models to reduce the chance of excluding a potentially significant variable from the final model. Due to small numbers, “other” race in the multivariable model included Arab, Hispanic, Native American and mixed race. OR and *p*-values were calculated for final multivariable models.

Results

From October 1, 2019, to May 30, 2020, a total of 374 information letters were mailed to female *BRCA1/2* carriers identified in the CGCS database. After 11 women opted out, 363 surveys were mailed, of which 76 (21%) were completed and returned. Of the remaining 287 surveys, 54 (19%) women were reached by phone at which time the survey was completed for a total response rate of 130/363 (36%). Of the 233 individuals who did not complete a survey, there were 110 subjects who did not answer any of at least three phone calls, 22 who answered but declined to participate, 91 who were unable to be reached due to phone or address change, 7 who were deceased and 3 who were males (Figure 1). One survey was excluded due to inconsistent clinical responses, reporting both RRM and RRSO and a history of breast and ovarian cancer that investigators were unable to reconcile.

Table 1 shows demographic and clinical characteristics of participants. The average age at *BRCA1/2* testing was 48 years (range, 20-81) with an average time since *BRCA1/2* carrier diagnosis and completion of survey of 6.6 years (range, 0.21 – 20.34). The racial/ethnic distribution of participants included 89 (69%) White, 17 (13%) Black, 13 (10%) Ashkenazi Jewish, 2 (2%) Hispanic, 1 (1%) Arab, 1 (1%) Native American, 4 (3%) mixed race, and 2 (2%) unsure or declined to specify. Other races included mixed ancestry. There were 58 (45%) of the respondents had a previous pathogenic *BRCA* identified in the family, 69 (53%) with a personal history of breast cancer, 12 (9%) with a personal history of ovarian cancer, and 5 (4%) with a personal history of both breast and ovarian cancer. The participants were highly educated, with 72% having a college degree or higher, 33% reported a household income greater than $100,000 and 84% had private insurance.

Table 1
Socio-demographic and clinical characteristics of women with *BRCA1/2* pathogenic variants in the survey of practice patterns after genetic testing

Variable	N=129
Race/Ethnicity	
White	89 (69%)
Black	17 (13%)
Hispanic	2 (2%)
Arab	1 (1%)
Ashkenazi Jewish	13 (10%)
Native American	1 (1%)
Other*	4 (3%)
Not sure/Refuse to answer	2 (2%)
Age at BRCA1/2 diagnosis, year	48 (20,81)
Time between diagnosis and survey, year	6.6 (0.21,20.34)
Known BRCA Mutation in the Family	
Yes	58 (45%)
No	63 (49%)
Not Sure	8 (6%)
Personal history of BC	
Yes	69 (53%)
No	60 (47%)
Personal history of OC	
Yes	12 (9%)
No	117 (91%)
Family history of BC or OC in 1st or 2nd degree relatives	
Yes	104 (81%)
No	12 (9%)
Unknown	13 (10%)
Nulliparous	

Variable	N=129
Yes	15 (12%)
No	113 (88%)
Unknown	1 (1%)
Insurance	
Medicaid/Medicare only	21 (16%)
Private Insurance w or w/o Medicare	108 (84%)
Household income	
≤35,000	17 (13%)
35,001-100,000	51 (40%)
>100,000	42 (33%)
Not sure/Refuse to answer/Unknown	19 (15%)
Education level	
Some high school	1 (1%)
High school graduate or GED	11 (9%)
Some college	24 (19%)
College degree	56 (43%)
Graduate degree	37 (29%)
Abbreviations: BC, Breast Cancer; OC, Ovarian Cancer	
Continuous variables are expressed as median (range) and categorical variables as number (percentage).	
* Mixed race (White and Native American, Native American/Irish, Dutch-Indonesian) and Indian	

Table 1
(Continued)

Variable	N=129
Married or cohabiting	
Yes	85 (66%)
No	43 (33%)
Refuse to answer	1 (1%)
RRM	
Yes	77 (60%)
No	50 (39%)
Not evaluable	2 (2%)
RRSO	
Yes	95 (74%)
No	28 (22%)
Not evaluable	6 (5%)
Mammogram past year	
None	25 (19%)
1	37 (29%)
2	4 (3%)
More than 2	2 (2%)
Not applicable	61 (47%)
Breast MRI past year	
None	36 (28%)
1	38 (29%)
2	3 (2%)
Not applicable	52 (40%)
Transvaginal Ultrasound past year	
None	45 (35%)
1	12 (9%)
2	3 (2%)

Variable	N=129
Not applicable	69 (53%)
CA-125 past year	
None	46 (36%)
1	15 (12%)
2	6 (5%)
More than 2	6 (5%)
Not applicable	53 (41%)
Not sure	3 (2%)
Prophylactic Hormonal Therapy	
Yes	12 (9%)
No	117 (91%)
Abbreviations: RRM, Risk-Reducing Mastectomy; RRSO, Risk-Reducing Salpingo-oophorectomy	
Continuous variables are expressed as median (range) and categorical variables as number (percentage).	

There were 95 women (74%) who had RRSO, however this endpoint was not evaluable for 6 women (3 had undergone hysterectomy with bilateral oophorectomy for gynecologic reasons unrelated to their *BRCA* status and 3 were under the age of 30.) There were 77 women who had RRM (60%) and 2 who were not evaluable (1 had bilateral breast cancer treated with mastectomy, the other was under the age of 25.) Regarding mammography, 43 (33%) women reported at least one mammogram in the past year, 25 (19%) did not have a mammogram within the past year, and 61 (47%) were not evaluable because of absence of breasts or being too young for screening. There were only 12 women (9%) who reported the use of prophylactic tamoxifen or raloxifene. Uptake of ovarian screening for eligible women was low (n = 31) with 12 (39%) and 3 (9.7%) having 1 or 2 TVUS in the past year, respectively. Uptake of screening CA-125 blood test was similarly low with 15/31 (48%), 6/31 (19%), and 6/31 (19%) women having one, two, or more than two CA-125 levels drawn within the past year respectively.

Completion Of Rrso

Table 2 shows the relationship between participant characteristics and completion of RRSO. Women who had RRSO versus not were more likely to be older (average age 49 (27-81) vs. 37.5 years (22 – 73) respectively) and more likely to have a personal history of breast cancer (59% vs. 39%). Women who had RRSO were less likely to have a known pathogenic variant in the family (40% vs. 57%). There were no apparent differences in completion of RRSO by race or ethnicity, time between genetic testing and survey completion, or by educational level, medical insurance, or marital status.

Table 2
The relationship between participant sociodemographic and clinical characteristics stratified by risk reducing salpingo-oophorectomy among participants in the survey of practice patterns after genetic testing

	RRSO	
	Yes (n=95)	**No (n=28)**
Race/Ethnicity		
White	65 (68%)	20 (71%)
Black	12 (13%)	4 (14%)
Hispanic	0 (0%)	1 (4%)
Arab	1 (1%)	0 (0%)
Ashkenazi Jewish	10 (11%)	3 (11%)
Native American	1 (1%)	0 (0%)
Other*	4 (4%)	0 (0%)
Not sure/Refuse to answer	2 (2%)	0 (0%)
Age at BRCA1/2 diagnosis, year	49 (27,81)	37.5 (22,73)
Time between diagnosis and survey, year	6.92 (0.21,20.34)	6.25 (1.16,11.95)
Known BRCA Mutation in the Family		
Yes	38 (40%)	16 (57%)
No	50 (53%)	11 (39%)
Not Sure	7 (7%)	1 (4%)
Personal history of BC		
Yes	56 (59%)	11 (39%)
No	39 (41%)	17 (61%)
Family history of BC or OC in 1st or 2nd degree relatives		
Yes	80 (84%)	19 (68%)
No	8 (8%)	4 (14%)
Unknown	7 (7%)	5 (18%)
Nulliparous		
Yes	5 (5%)	7 (25%)

	RRSO	
No	89 (94%)	21 (75%)
Unknown	1 (1%)	0 (0%)
Insurance		
Medicaid/Medicare only	13 (14%)	6 (21%)
Private Insurance w or w/o Medicare	82 (86%)	22 (79%)
Household income		
≤35,000	12 (13%)	5 (18%)
35,001-100,000	36 (38%)	14 (50%)
>100,000	32 (34%)	8 (29%)
Not sure/Refuse to answer/Unknown	15 (16%)	1 (4%)
Education level		
Some high school	1 (1%)	0 (0%)
High school graduate or GED	8 (8%)	2 (7%)
Some college	17 (18%)	5 (18%)
College degree	43 (45%)	11 (39%)
Graduate degree	26 (27%)	10 (36%)
Married or cohabiting		
Yes	62 (65%)	20 (71%)
No	33 (35%)	7 (25%)
Refuse to answer	0 (0%)	1 (4%)
Abbreviation: BC, Breast Cancer; OC, Ovarian Cancer; RRSO, Risk-Reducing Salpingo-oophorectomy		
Continuous variables are expressed as median (range) and categorical variables as number (percentage).		
* Mixed race (White and Native American), Native American/Irish, Dutch-Indonesian, and Indian		

Table 3 shows the univariable and multivariable analyses of factors predicting the likelihood of completion of RRSO. With each increasing year of age at the time of genetic counseling, there was a 5% increased likelihood for RRSO (OR = 1.05; 95%CI 1.01 – 1.09; p = 0.022). None of the other variables including education, race and ethnicity, type of insurance, personal or family history of cancer were significantly associated with completion of RRSO.

Table 3
Univariable and multivariable logistic regression analyses for risk factors associated with risk reducing salpingo-oophorectomy among participants in the survey of practice patterns after genetic testing

		Univariable		Multivariable	
	Event/n	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Race/Ethnicity					
White	65/85	Ref.		Ref.	
Black	12/16	0.92 (0.28-3.59)	0.899	0.77 (0.21-3.24)	0.697
Ashkenazi Jewish	10/13	1.03 (0.28-4.90)	0.971	0.94 (0.22-5.19)	0.939
Other[a]	8/9	2.46 (0.41-47.08)	0.409	1.86 (0.28-37.24)	0.582
Age at BRCA1/2 diagnosis	95/123	1.05 (1.01-1.09)	0.009	1.05 (1.01-1.09)	0.022
Education level					
Less than college degree[b]	26/33	Ref.		Ref.	
College/Professional degree[c]	69/90	0.88 (0.32-2.25)	0.804	1.34 (0.43-3.94)	0.596
Insurance					
Medicaid/Medicare only	13/19	Ref.		Ref.	
Private Insurance w or w/o Medicare	82/104	1.72 (0.55-4.91)	0.323	1.39 (0.41-4.36)	0.579
Personal history of BC					
No	39/56	Ref.		Ref.	
Yes	56/67	2.22 (0.95-5.38)	0.070	1.79 (0.69-4.80)	0.236
Family history of BC or OC in 1st or 2nd degree relatives					
No	8/12	Ref.		Ref.	
Yes	80/99	2.11 (0.52-7.45)	0.262	2.90 (0.64-12.42)	0.149
Unknown	7/12	0.70 (0.13-3.70)	0.674	1.26 (0.19-8.27)	0.808

	Univariable	Multivariable
Abbreviations: OR, Odds ratio; CI, Confidence interval; BC, Breast Cancer; OC, Ovarian Cancer		
[a] Hispanic, Arab, Native American, Mixed race (White and Native American), Native American/Irish, Dutch-Indonesian, Indian, Not sure, and Refuse to answer		
[b] Some high school, High school graduate or high school equivalency diploma (GED), and Some college		
[c] College degree and Graduate degree		

Completion Of Rrm

Table 4 shows the univariable and multivariable analyses of factors predicting the likelihood of RRM. Of 127 women in the study sample, 77 (61%) underwent RRM, 53/75 (71%) of whom had a personal history of breast cancer. In multivariable analyses, both personal history of breast or ovarian cancer were positively associated with RRM (OR = 3.92; 95% CI = 1.66 – 9.82; p = 0.002); however, increasing age at *BRCA1/2* diagnosis was negatively associated with RRM (OR 0.96; 95% CI = 0.92 – 0.99 p = 0.013. There was no significant relationship for any of the other variables analyzed and RRM.

Table 4
Univariable and multivariable logistic regression analyses for risk factors associated with risk reducing mastectomy among participants in the survey of practice patterns after genetic testing

		Univariable		Multivariable	
	Event/n	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Race/Ethnicity					
White	58/89	Ref.		Ref.	
Black	8/17	0.48 (0.16-1.36)	0.164	0.41 (0.13-1.28)	0.125
Ashkenazi Jewish	6/13	0.46 (0.14-1.49)	0.193	0.66 (0.17-2.49)	0.536
Other[a]	5/8	0.89 (0.20-4.57)	0.880	0.69 (0.14-4.11)	0.666
Age at BRCA1/2 **diagnosis**	77/127	0.98 (0.95-1.01)	0.194	0.96 (0.92-0.99)	0.013
Education level					
Less than college degree[b]	22/35	Ref.		Ref.	
College/Professional degree[c]	55/92	0.88 (0.39-1.94)	0.751	0.59 (0.22-1.50)	0.277
Insurance					
Medicaid/Medicare only	11/21	Ref.		Ref.	
Private Insurance w or w/o Medicare	66/106	1.50 (0.58-3.87)	0.399	1.90 (0.65-5.66)	0.241
Personal history of BC or OC					
No	24/52	Ref.		Ref.	
Yes	53/75	2.81 (1.35-5.95)	0.006	3.92 (1.66-9.82)	0.002
Family history of BC or OC in 1st or 2nd degree relatives					
No	9/12	Ref.		Ref.	
Yes	62/102	0.52 (0.11-1.85)	0.343	0.43 (0.08-1.70)	0.256
Unknown	6/13	0.29 (0.05-1.48)	0.149	0.17 (0.02-1.06)	0.066

	Univariable	Multivariable
Abbreviations: OR, Odds ratio; CI, Confidence interval; BC, Breast Cancer; OC, Ovarian Cancer		
[a] Hispanic, Arab, Native American, Mixed race (White and Native American), Native American/Irish, Dutch-Indonesian, Indian, Not sure, and Refuse to answer		
[b] Some high school, High school graduate or high school equivalency diploma (GED), and Some college		
[c] College degree and Graduate degree		

Adherence To Nccn Guidelines

Table 5 shows the univariable and multivariable analysis of predictors of compliance with NCCN guidelines. Of 129 women in the study sample, 107 (83%) were considered compliant. There were 64 (60%) who had both RRM and RRSO, 17 (16%) had RRSO and were screening for breast cancer, 3 (3%) had RRM and screening for ovarian cancer, one woman with no cancer history underwent screening for breast and ovarian cancer, and one woman under the age of 30 had received a breast MRI. All 4 women who had a bilateral mastectomy for breast cancer treatment had RRSO. Of 10 women who had TAHBSO for ovarian cancer treatment, half had RRM, and half were screened for breast cancer. One woman was younger than age 25 and not expected to begin screening. One woman had RRSO and had two separate unilateral treatment mastectomies. One woman was unable to have breast MRI due to an incompatible breast implant. Three women lacked ovaries for non-oncologic reasons. Of women who did not have RRM, 63.6% had at least one mammogram and one breast MRI in the past twelve months. Of those who did not have RRSO by age 45, 42% had at least one TVUS and one CA-125 test (37.5% of women under age 45) in the past twelve months. There were five women who indicated future plans to complete RRM, 8 who planned to have RRSO, 6 who planned to have both RRM and RRSO, and one who did not specify surgical plans. None of the other variables were significantly associated with completion of NCCN guidelines.

Table 5
Univariable and multivariable logistic regression analyses for risk factors associated with National Comprehensive Cancer Network guideline adherence among participants in the survey of practice patterns after genetic testing

		Univariable		Multivariable	
	Event/n	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Race/Ethnicity					
White	76/89	Ref.		Ref.	
Black	12/17	0.41 (0.13-1.46)	0.145	0.38 (0.11-1.45)	0.136
Ashkenazi Jewish	10/13	0.57 (0.15-2.79)	0.437	0.55 (0.12-2.96)	0.448
Other[a]	9/10	1.54 (0.26-29.59)	0.694	2.12 (0.32-43.19)	0.511
Age at BRCA1/2 **diagnosis**	107/129	1.02 (0.99-1.06)	0.207	1.03 (0.99-1.07)	0.184
Education level					
Less than college degree[b]	28/36	Ref.		Ref.	
College/Professional degree[c]	79/93	1.61 (0.59-4.19)	0.334	1.94 (0.62-5.90)	0.243
Insurance					
Medicaid/Medicare only	16/21	Ref.		Ref.	
Private Insurance w or w/o Medicare	91/108	1.67 (0.50-4.95)	0.372	1.38 (0.36-4.55)	0.611
Personal history of BC or OC					
No	41/53	Ref.		Ref.	
Yes	66/76	1.93 (0.77-4.97)	0.163	1.68 (0.58-4.91)	0.336
Family history of BC or OC in 1st or 2nd degree relatives					
No	11/12	Ref.		Ref.	
Yes	85/104	0.41 (0.02-2.29)	0.402	0.46 (0.02-2.88)	0.489
Unknown	11/13	0.50 (0.02-5.98)	0.593	0.62 (0.02-8.13)	0.719

	Univariable	Multivariable
Abbreviations: OR, Odds ratio; CI, Confidence interval; BC, Breast Cancer; OC, Ovarian Cancer		
[a] Hispanic, Arab, Native American, Mixed race (White and Native American), Native American/Irish, Dutch-Indonesian, Indian, Not sure, and Refuse to answer		
[b] Some high school, High school graduate or GED, and Some college		
[c] College degree and Graduate degree		

Behavioral Factors And Cascade Testing

Most participants answered affirmatively that a diagnosis of HBOC had a significant impact on their lives and 20% felt that there was also a significant financial impact (table S1). Almost all participants (98%) indicated that they disclosed their genetic test results to at least one family member (table S1). The median number of family members informed was 10 (range, 0-100), the median number of relatives who were known to complete testing was 2 (range, 0-20), which resulted in the discovery of a median of 1 relative with a pathogenic variant (range = 0-8) through cascade testing (table S2). The most common reason for failure to disclose genetic results was not being in contact with the family member. Others preferred to keep this information private or expected another family member to pass the information along for them. Some women believed that male relatives, or relatives unaffected by cancer, did not need to be informed about a pathogenic *BRCA1/2* variant in the family (table S2).

Regarding the impact of *BRCA1/2* carrier status on reproductive plans, there were 18 respondents who indicated their *BRCA* diagnosis affected family planning of which 7 women chose not to have any more children, 5 accelerated their plans to have children, and 6 women gave alternate responses, detailed in supplementary table S3.

There was a strong negative association between the RRSO and cancer worry score, not observed for RRM or compliance with NCCN guidelines (Table 6). A higher percentage (74%) of participants who had RRSO had low cancer worry score (<2.75) at the time of survey, compared to those who did not have RRSO (50%) (OR= 2.77; 95% CI 1.06 - 7.30; p = 0.0223).

Table 6: Association between cancer worry score and RRSO, RRM, and NCCN Guideline Adherence among the Karmanos Cancer Institute's Hereditary Breast and Ovarian Cancer Cohort

	RRSO yes (n=95)	RRSO no (n=28)	Fisher's exact p
Cancer worry score			0.022
<2.75	70 (74%)	14 (50%)	
≥2.75	25 (26%)	14 (50%)	

	RRM yes (n=77)	RRM no (n=50)	Fisher's exact p
Cancer worry score			1
<2.75	52 (68%)	33 (66%)	
≥2.75	25 (32%)	17 (34%)	

	NCCN Yes (n=107)	NCCN No (n=22)	Fisher's exact p
Cancer worry score			0.218
<2.75	74 (69%)	12 (55%)	
≥2.75	33 (31%)	10 (45%)	

Note: Cancer worry score was calculated by averaging the 8-item Cancer Worry Scale with 5 response options (1 = Not at all; 2 = Slightly; 3 = Moderately; 4 = Quite a bit; 5= Extremely)

Discussion

Our study results showed relatively high adherence to RRSO, RRM and NCCN guidelines in a cohort of women with HBOC diagnosed at a large comprehensive cancer center. Most women who chose to have RRM had a personal history of breast or ovarian cancer likely because they were incentivized to prevent a 2nd cancer of the same type, which is consistent with findings of similar studies. Personal history of breast or ovarian cancer, however, was not a significant predictor for RRSO or uptake of NCCN guidelines

[8, 10, 13]. Also, since genetic testing generally occurs after a cancer diagnosis, it is easier to incorporate RRM as part of the definitive oncologic surgery. Increasing age was associated with an increased rate of RRSO probably reflecting considerations related to childbearing among younger women.

We found no evidence of racial or ethnic differences in prevention and screening practices among women with HBOC. Although this is a reassuring, and perhaps reflects the ability of genetic counselors to provide unbiased standard recommendations, the study population was underpowered to evaluate racial or ethnic differences and our results should only be considered exploratory. Another analysis of 1,622 women with breast cancer diagnosed at age < 50 included 78 *BRCA1/2* carriers (41% Black) showed a lower rate of RRM and RRS0 among Black (68.8% and 28.1%) compared to White women (95.7% and 76.6%) [7]. Larger studies exploring factors which may predict inequitable screening and prevention among women with HBOC are needed.

For women who have not had RRSO in our study (n = 28), less than half were adequately fulfilling screening recommendations for ovarian cancer, which highlights an area that requires particular attention. A cross-sectional study by Garcia, et. al. recorded annual ovarian cancer screening practices over five years among Northern Californian women with pathogenic *BRCA1/2* variants and found that rates of TVUS and CA-125 fell from 45% and 47% respectively in the first year after *BRCA* diagnosis, to 2.3% and 2% in year 5 [10]. This decrease was not accounted for by an increase in RRSO and reflects the difficulty of maintaining recommendations for screening over time. While ovarian cancer screening has not been associated with a reduction in mortality, it is currently the only tool for screening for women who have not had RRSO. Our results highlight the need for ongoing patient and physician education regarding ovarian cancer screening and risk reducing surgery.

Unlike personal breast cancer history, we found no association, between family cancer history and RRM. In addition, family history of a known pathogenic *BRCA1/2* variant had no significant impact on the rate of risk reducing surgery or compliance with screening. Studies on this topic are divided, with some showing no association between family cancer history and screening and/or risk-reducing practices [5, 8, 12], while others showing that family history of ovarian cancer positively influenced the likelihood for risk reducing surgery[9, 13]. The effect of family history likely depends on multiple factors, such as the relationship between the proband and affected family member and the psychological impact of the diagnosis. Our results suggest that providers should not assume that women are more likely to adhere to recommended guidelines when they have a strong family cancer history.

Only 9% of women in our cohort reported having used chemoprevention for high breast cancer risk, and this figure is likely to be an overestimate. Many women answered in the affirmative to our question about chemoprevention, but during phone interviews clarified that they were in fact taking Tamoxifen after a diagnosis of breast cancer. Schwartz, et. al. also reported low rates of chemoprevention, with only 1.7% of participants reporting the use of Tamoxifen or Raloxifene,[12] and only one subject in another study. [10]. The low rate of chemoprevention in our cohort presents an opportunity for improved education and counseling about its potential for breast cancer prevention.

Our findings show that virtually all (127/129) women disclosed their genetic diagnosis to their family members, consistent with the current literature which includes populations of majority White and high socioeconomic status women [15–19]. In a study focused on Black women, the rate of test result disclosure was only 77%, and those with a pathogenic *BRCA1/2* variants were less likely to disclose results to their daughters (OR = 0.25; 95% CI = 0.07 – 0.94; p = 0.41) compared to those who tested negative or who had a variant of unknown significance (VUS) [20]. The most common reason for failure to disclose results in our study was not being in contact with the family member, wanting to keep this information private, or expecting another family member to pass the information along for them. The belief that a *BRCA* diagnosis is not relevant to male family members has also been reported by others[19–24] and underscores the necessity for better patient education.

The impact of HBOC on a participant's life or finances (table S1) has been previously evaluated. Biskupiak, et. al. reported that women with pathogenic *BRCA1/2* variants and a diagnosis of breast cancer have higher overall healthcare costs compared to those with *BRCA* wild type[25] which can be largely related to the cost of prevention and risk reducing surgeries for both breast and ovarian cancer. Although our data did not show a difference in uptake of NCCN recommendations based on sociodemographic factors including insurance and household income, the cost of care may contribute to other unmeasured distress.

Interestingly, our findings suggested a decrease in cancer related worry in women who have undergone RRSO, but not in those who have undergone RRM or who follow NCCN guidelines. This suggests that some women experience anxiety specifically related to ovarian cancer which is likely alleviated after RRSO. Other studies have shown that cancer-related distress is often highest in the period immediately following genetic diagnosis and decreases over time [26–28]. This may suggest that as women have time to follow recommendations, they experience a comparable reduction in anxiety or could reflect the natural reduction in anxiety after exposure to an anxiety stimulus.

The limitations of our analysis includes the small sample size, cross-sectional design, and the possibility of recall bias. The relatively low diversity in our cohort limits our ability to detect barriers related to race, ethnicity and socioeconomic status. Also some women moved, expired, or could not participate due to disability or language barriers resulting in a biased sample. Nevertheless, our results represents an important contribution on long-term cancer screening and prevention in women with pathogenic *BRCA1/2* variants and draws attention to specific issues affecting our population including low utilization of chemoprevention, lack of understanding of the impact of genetic test results on male relatives, and financial concerns. Lastly, our results showing the lack of racial and ethnic differences in completion of recommendations among women with HBOC suggests an unbiased provision of counseling and follow up recommendations in our patient population who attended genetic counseling. Further research is needed to continue to improve guideline adherence for unaffected carriers and avoid missed opportunities for early detection and cancer prevention in this cohort.

Declarations

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Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest.

Availability of data and material: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions: All authors contributed to the study conception and design. Hadeel Assad, MD contributed to material preparation, conceptualization, data interpretation and manuscript editing. Data collection and the first draft of the manuscript was written by Maria Levitin, MD. Data analysis were performed by Chen Wei, PhD, and Hyejeong Jang. Michael S Simon, MD, MPH contributed to conceptualization, data interpretation and manuscript drafting. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: This project was approved by Wayne State University Institutional Review Board.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: Not applicable.

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Figures

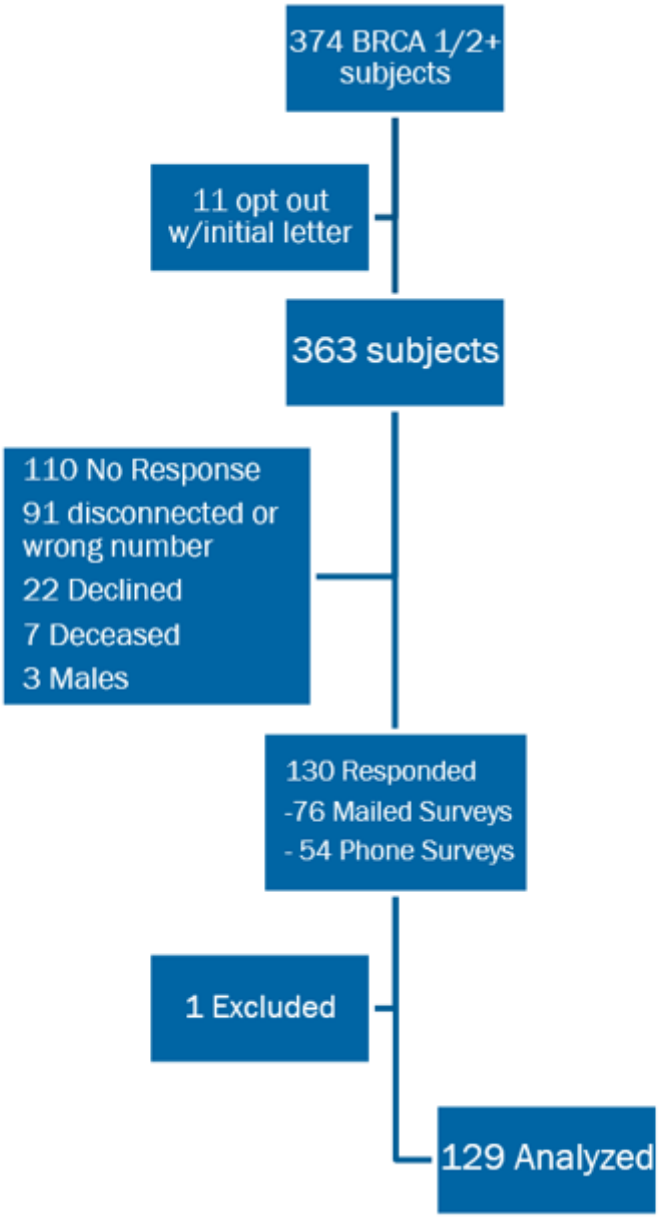

Figure 1

Flow diagram of participants in the survey of practice patterns after genetic testing