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Interest of individuals from *BRCA* families to participate in research studies focused on male *BRCA* carriers

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Abstract

Background—Although men and women are equally likely to carry a mutation in the *BRCA1* and *BRCA2* (*BRCA*) genes, the clinical significance of mutations in men remains incompletely defined. We sought evaluate interest of individuals from *BRCA* families to participate in a research study focused on men from *BRCA* families.

Methods—Through an anonymous survey posted on the website of the *BRCA* patient advocacy organization, Facing Our Risk of Cancer Empowered (FORCE), data was collected over a 21 month period (August 2010–June 2012) from members of *BRCA* families.

Results—The survey was completed by 405 individuals with known *BRCA* mutations, including 150 males and 232 females. The median age of survey respondents was 49 years (50 years for males and 48 years for females). Overall, 84% of survey respondents indicated prior *BRCA* mutation testing (95.2% females, 67.3% males). For the overall group of survey respondents, 84% (86% females, 84% males) indicated they would tell their male relatives about a research study focused on high risk men from *BRCA* families, and 53% (39% females, 74% males) thought that their male relatives would be interested in participating in such a study.

Conclusion—Despite limited studies focused on men from *BRCA* mutation positive families, our survey suggests that both male and female family members are highly interested in focused on male *BRCA* mutation carriers. The importance of further studying this topic is underscored by emerging literature that suggest cancer surveillance and treatment decisions may improve outcomes in men with *BRCA* mutations.

Keywords

BRCA1; BRCA2; male carriers; research participation

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INTRODUCTION

The *BRCA* genes were discovered more than 15 years ago, yet despite the fact men are just as likely as women to carry a mutation, the clinical significance of *BRCA* mutations in men remains incompletely defined. There are limited data which suggest elevated cancer risks (including prostate cancer and male breast cancer)[1–6] with lifetime cancer risks that may approach that of female carriers.[3–6] Of further importance are recent preliminary data that *BRCA*-associated prostate cancers are particularly aggressive and are associated with reduced survival, with more compelling data in *BRCA2*, [7–12] although also potentially the case in *BRCA1*.[8,9,13,14] Moreover, recent preliminary results from a small study have also suggested potential benefits of PSA screening for male *BRCA* carriers.[14,15] Finally, recent studies suggest benefits for targeted treatments in individuals with *BRCA*-associated cancers, including platinum-based treatments and poly (ADP-ribose) polymerase (i.e., PARP) inhibitors. Taken together, the elevated cancer risks, suggestions of an aggressive prostate cancer phenotype, and emergence of targeted treatments in men who carry a *BRCA* mutation highlight the need to focus research efforts in this high risk understudied population. In fact, in contrast to the hundreds of studies focused on women with *BRCA* mutations, there remains limited study about cancer risks, survival, and targeted treatments in male mutation carriers. Ultimately, participation of men in such studies is needed in order for larger proportions of at risk men to benefit from the latest medical advances. However, due to the limited number of research studies focusing on men in *BRCA* families, it is unclear if men would be able to be recruited into studies evaluating the implications of *BRCA* testing in men. Furthermore, in the evaluation of questions pertaining to rare genetic diseases, an important role can be played by patient advocacy organizations in recruitment and data collection.[16] In fact, the majority of leaders of such organizations feel that they should be engaged in the conduct of clinical research, and that their involvement enhances participant recruitment as well as the amount of research conducted on their condition.

Given the emerging clinical relevance for identification of *BRCA* mutations in men, we collaborated with a *BRCA* patient advocacy organization, Facing Our Risk of Cancer Empowered (FORCE), who posted a survey on their website focused on interest in participation in studies of male *BRCA* carriers. Specifically, the primary objectives of the current study were to: 1) assess whether individuals from *BRCA* families would be willing to share information about a research study focused on at risk male family members; and 2) assess whether these individuals thought their male relatives would be interested in learning more about such a study.

METHODS

As part of an effort through the nonprofit organization, Facing Our Risk of Cancer Empowered (FORCE), a survey was developed to collect information about interest within *BRCA* families in studies of male *BRCA* carriers. The survey included information about: demographics (age, sex, race), clinical data (family history of cancer, *BRCA* testing status, results) and interest in research studies to evaluate both outcomes and new treatments focused on men with *BRCA* mutations (i.e., willingness to share information about such

research studies and perception of whether male family members would be interested in learning more about such studies).

Emails containing information about the survey were sent to the FORCE list-serve members, along with an electronic link to the survey, which was also accessible through the FORCE website (www.facingourrisk.org). Web-based responses to the survey were collected between September 2010 and March 2012.

Based on our purpose of conducting secondary data analysis on the existing survey responses collected through the FORCE organization stripped of any respondent identifiers, the research was given an exempt certification upon review by the University of South Florida's Institutional Review Board (IRB). Eligibility criteria for inclusion in the current analysis were individuals (males or females) who reported presence of a *BRCA* mutation in their family.

Demographic and clinical characteristics of survey respondents were summarized using descriptive statistics, including mean, standard deviations, and proportions. Additional analyses were conducted to explore the association between demographic and clinical variables, and interest in participating in studies focused on male *BRCA* carriers. The association was evaluated by the Fisher exact test, and a two-sided p-value of < 0.05 was considered statistically significant. All analyses were performed using the statistical software package SAS (SAS 9.3: SAS Institute Inc.).

RESULTS

Of the 405 respondents deemed eligible for the analyses, 150 were male, 232 were female, and the remaining 23 had gender missing in the survey (refer to Table 1 for description of study population). Just over half of respondents were 50 years of age or less, and the majority reported race at White. The majority had a history of cancer in the family, with the highest proportion (over 40%) reporting prostate cancer. The sample was almost equally divided between those with a *BRCA1* versus *BRCA2* mutation in the family.

Assessment of demographic and clinical factors with interest of family members to participate in studies of male *BRCA* carriers is summarized in table 2. Briefly, when we subgrouped by gender, results indicated that the majority of both males and females would convey information about this type of study to their at risk male family members.

This high level of willingness was seen across gender, age groups, cancer history and *BRCA* status. Furthermore, higher proportions of males compared to females thought that their male family members would be interested in participating in this type of study ($P<0.001$).

DISCUSSION

The results from our analysis indicate high interest levels for both male and female family members of *BRCA* kindreds in sharing information about studies focused on male *BRCA* carriers. Furthermore, most family members think that at-risk men within their families would be interested in learning more about this type of study, with men indicating this about

men in their families even more often than their female family members (OR=4.5, 95% CI: 2.8 – 7.0; p <0.001).

Overall, there has been a paucity of research efforts focused on men with who pursue *BRCA* genetic counseling compared to the amount of research focused on women's uptake of and outcomes following testing are likely due to their higher cancer risks compared to males. The lack of data on male *BRCA* carriers in turn results in our inability to evaluate surveillance or risk management strategies and develop evidence-based management guidelines to improve outcomes. In fact, Graves et al recently reported that uptake was not different between males and females in their study, in which genetic counseling and testing were provided free of charge.[17] In contrast, Finlay et al reported higher completion rates of genetic testing in female compared to male first-degree relatives (73% vs. 49%) and second-degree relatives (68% vs. 43%) of *BRCA* mutation carriers (p<0.01).[18] Finally, Evans et al concluded that male family members had a substantially higher uptake of genetic testing, suggesting utility of proactive approaches to ensure these high risk men receive appropriate information.[19] Taken together, prior studies suggest that high proportions of men from *BRCA* families are interested in pursuing genetic counseling and testing, especially if it is facilitated (i.e., no charges for services) and a proactive approach is used. These findings also suggest that development of appropriate education and resources focused on *BRCA* mutation in men may enable high risk men to make informed decisions regarding genetic testing. Ultimately, findings from prior studies are consistent with that seen in our study, which showed high levels of interest in research participation in studies focused on male *BRCA* carriers.

Other important factors to consider when studying inherited breast cancer in men are prior research results which suggest that genetic risk information is likely to be a gendered activity, with responsibility for disclosure of results falling primarily on women.[20,21] Furthermore, women with *BRCA* mutations share results more often with their female than their male relatives.[22] In fact, even in families where male mutation carriers are identified, it is primarily their female spouses who discuss implications with children, especially daughters, with men often excluded from these family conversations.[23,24] Especially in view of the recent literature to suggest increasing clinical relevance of *BRCA* mutations in men as well as studies to suggest that men are willing to participate in the genetic counseling and testing process, it is important to provide male carriers with guidance about the importance of communicating genetic information to family members.[25,26] In the end, efforts focused on communication of BRCA results within families including communication by and to male family members is important, in parallel to studies to develop evidence-based management recommendations in these men.

A number of strengths support the current study, including the large proportion of male family members included in the overall sample size compared to prior efforts. Additionally, the inclusion of both male and female respondents enables comparisons between them and enabled us to determine that interest in studies of *BRCA* in men was high across both genders. Assessing women's interest is very important as they are often involved in encouraging male family members to pursue testing and are usually the original family member in whom the *BRCA* mutation is initially detected. As such, they are predominantly

the ones responsible for disseminating the information about mutation carrier status to their other at risk male and female family members, and often encouraging their male family members about the importance of testing. Despite these strengths, there remain limitations of the current study including that the survey was administered anonymously through the *BRCA* patient advocacy organization FORCE, thus clinical data could not be verified. Furthermore, because personal and family history was collected in the same question, we were not able to determine if the respondent had an existing cancer diagnosis. Additionally, self selection bias may have been a factor in those who completed the survey, as they may have an existing interest in studies pertaining to studies in at risk male family members. Similarly, we included groups that tested positive, tested negative and with no testing, which may contribute to heterogeneity in responses. Nevertheless, the majority of respondents (~80%) were tested carriers, thus our findings are mainly attributable to this group. Finally, we were able to assess perceptions of family members regarding interest in studies focused on male carriers, rather than actual uptake to a study. Despite these limitations, data from our study strongly suggests that individuals from *BRCA* families consider studies focused on at risk male family members important and would willingly facilitate recruitment to such studies.

Ultimately, without focused research efforts to evaluate the clinical significance of *BRCA* mutations in men, it is not possible to develop evidence-based management guidelines to improve outcomes. Furthermore, without such data, many insurers within the United States (e.g., Medicare) currently limit coverage for *BRCA* testing in men, even those with prostate cancer. The current study provides evidence for the overwhelming interest of members from *BRCA* families in including men in *BRCA* studies. The results support the feasibility of recruiting at-risk male family members into much needed research on the implications of *BRCA* mutations in men.

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Table 1

Summary of Demographic and Clinical Variables in Respondents

	Overall	Males	Females	Missing
	n (%)	n (%)	n (%)	n (%)
Gender				
male	150 (37)	~	~	~
female	232 (57.3)	~	~	~
missing	23 (5.7)	~	~	~
Age				
≤50	214 (52.8)	78 (53.8%)	135 (60%)	1
>50	157 (38.8)	67(46.2%)	90 (40%)	0
missing	34 (8.4)			
Race				
White	371 (91.6)	145 (96.7)	223 (96.5)	3
Black or African American	3 (0.7)	1 (0.7)	2 (0.9)	
Asian	4 (1.0)	3 (2)	1 (0.4)	
Other	6 (1.5)	1 (0.7)	5 (2.2)	
Missing	21 (5.2)			
Cancer history				
Any Cancer	282 (69.6)	97(70.3)	169(75.8)	16
Prostate Cancer	144 (35.6)	55(43.7)	82(42.7)	7
Breast Cancer	59 (14.6)	21(18.1)	36(21.4)	2
Pancreatic Cancer	45 (11.1)	10(9.9)	34(20.2)	1
Melanoma	55 (13.6)	19(18.3)	33(21.4)	3
***BRCA* status**				
BRCA1 in family	200 (49.4)	74(49.3)	109(47.0)	17
BRCA2 in family	205 (50.6)	76(50.7)	123(53.0)	6
tested/positive	322 (79.5)	97(64.7)	209(90.5)	16
tested/negative	15 (3.7)	4(2.7)	11(4.8)	0
Not tested	64 (15.8)	49(32.7)	11(4.8)	4

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Table 2

Association of Demographic and Clinical Variables with interest in research participation.

	n	Would you tell your male relatives about research study focused on high risk men from *BRCA* families?				P-value	Do you think your male relatives would be interested in a study focused on high risk men?				P-value
		yes	no	unsure	missing*		yes	no	unsure	missing*	
Gender											
male	150	123	3	21	3	0.868	111	10	29	0	7.89E-11
female	232	198	5	28	1		90	29	112	1	
Age											
≤50	214	177	4	31	2	0.5698	112	25	77	0	0.4666
>50	157	135	3	17	2		85	12	59	1	
Cancer history											
Any Cancer	282	226	6	36	14	0.7893	142	26	102	12	0.8135
Prostate Cancer	144	115	2	20	7	0.7761	74	11	53	6	0.5457
Breast Cancer	59	44	0	13	2	0.1286	32	5	20	2	0.8075
Pancreatic Cancer	45	38	2	2	3	0.106	23	4	17	1	0.9441
Melanoma	55	41	1	12	1	0.1733	26	4	23	2	0.4381
***BRCA* status**											
BRCA1 in family	200	158	5	24	13	0.9392	93	18	77	12	0.269
BRCA2 in family	205	168	4	26	7		111	23	66	5	
tested/positive	322	264	8	38	12	0.2859	158	33	120	11	0.0192
tested/negative	15	14	0	0	1		4	4	7	0	
Not tested	64	47	1	12	4		41	4	16	3	

*missing responses to this question removed when calculating p-values