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Impact of *BRCA* Mutations on Female Fertility and Offspring Sex Ratio

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Abstract

Positive selection for inherited mutations in breast and ovarian cancer predisposing genes, *BRCA1* and *BRCA2*, may contribute to the high frequency of *BRCA* mutations among the Ashkenazi Jewish population. Impact of *BRCA* mutations on fertility has not been generally explored in epidemiologic studies. There are reports of distorted sex ratios in *BRCA* carrier families but these findings have been attributed to bias. We investigated the effect of *BRCA* mutations on female fertility and offspring sex ratio in a study of 260 Ashkenazi Jewish women with ovarian cancer and 331 controls, unselected for age or family history of the disease. Pregnancy success was similar for 96 mutation carrier (0.84) and 164 noncarrier cases (0.87) and controls (0.83). After adjusting for covariates, there were no significant differences between *BRCA* carrier and noncarrier cases and controls with regards to fertility, despite lower pregnancy rates among all cases compared to controls ($P = 0.0049$). Male/female sex ratios were significantly lower among offspring of carriers (0.71) than offspring of noncarriers (0.95) or those of the controls (0.99). Comparisons among the three groups yielded statistically significant distortion against males among the offspring of known and obligate *BRCA* carriers compared to noncarriers (OR = 0.74, 95% CI:0.55–0.99) and controls (OR = 0.71, 95% CI:0.54–0.94). In conclusion, we did not find evidence for an effect of *BRCA* mutations on female fertility. We found a significant excess of females among the offspring of female carriers of *BRCA1* and *BRCA2* mutations. Potential contribution of observed sex ratio distortions to positive selection for *BRCA* mutations may warrant further investigation.

The high frequency of *BRCA* mutations among certain populations such as Ashkenazi Jews (2.4% overall frequency for *BRCA1* 185delAG and 5382insC and *BRCA2* 6174delT mutations) (Oddoux et al., 1996; Roa et al., 1996), mostly attributed to founder effects (Szabo and King, 1997), may also be suggestive of positive selection for these mutations. Our interest lies in two potential mechanisms influencing positive selection. One is a potential effect for *BRCA* mutations on female fertility. The other is an effect for *BRCA* mutations on altering sex ratios among the offspring of mutation carriers towards females,

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who have been suggested as having a higher effective population size historically (Wilder et al., 2004) and an evolutionary advantage over males for becoming population founders following sex-biased genetic bottlenecks (Hammer et al., 2008; Singh et al. 2007).

The impact of *BRCA* mutations on human fertility has not been generally explored in epidemiologic studies. Recent reports that BRCA1 protein is upregulated in human male and female germ cells and in preimplantation embryos (Giscard d'Estaing et al., 2005), and that it may regulate estrogen receptor (ER) α activity through ubiquitination (Eakin et al., 2007), suggest an effect for *BRCA* mutations on human fertility and/or prenatal survival or pregnancy success.

Studies of the impact of *BRCA* mutations on offspring sex ratios have produced equivocal results. While an earlier study reported distorted sex ratios against male births in *BRCA1* families (de la Hoya et al., 2003), subsequent studies either failed to verify the initial findings of skewed sex ratios or attributed the observed distortions to bias (Domchek et al., 2005; Feunteun et al., 2004; Mealiffe, 2003). Ascertainment bias (ascertainment through female probands and/or based on a family history) and/or selection bias (higher likelihood of females with daughters participating in cancer genetic studies) were suggested to be responsible for findings of excess females in *BRCA1* families (Domchek et al., 2005; Feunteun et al., 2004; Mealiffe, 2003).

We investigated the impact of *BRCA1* and *BRCA2* mutations on female fertility and offspring sex ratio using data collected as part of a hospital-based case-control study of Ashkenazi Jewish women with ovarian cancer, designed to reduce ascertainment and selection biases, with the objective of genetic characterization of the *BRCA* genes (Moslehi et al., 2000).

METHODS

Cases were 260 Ashkenazi Jewish women with ovarian cancer unselected for age or a family history of the disease and included 51 *BRCA1* 185delAG, 15 *BRCA1* 5382insC, and 30 *BRCA2* 6174delT carriers. Controls were 331 Ashkenazi Jewish women without a personal history of ovarian cancer. Detailed epidemiologic and family history information obtained at the time of ascertainment was available on all participants.

BRCA carriers, noncarriers and controls were compared with respect to the distribution of demographic variables using Chi-square statistics. The three groups were also compared with respect to pregnancy success, pregnancy rate, and fertility. Pregnancy success was defined as the ratio of number of liveborn offspring per woman to number of pregnancies per woman excluding induced abortions. Fertile person-time for each woman was calculated taking into account the reproductive period between 18 and 44 years of age, excluding the time when the subject was on contraception and 2 months after each pregnancy. Pregnancy rate was defined as number of all known pregnancies (regardless of outcome) divided by fertile person-years. Fertility was defined as pregnancy during the reproductive period, modeled as a Poisson outcome while adjusting for covariates (age, oral contraceptive use, body mass index, regularity of menstrual cycle, history and treatment for infertility, and age at menarche). For fertility analysis, we censored the person-time for a subject if she had tubal ligation, hysterectomy, or menopause before 44 years of age. Comparison of Poisson rates for different groups was done by using PROC GENMOD of the Statistical Analysis System (SAS) software (version 9.1; SAS Institute, Cary, NC).

Male/female sex ratios among the liveborn offspring of two generations of women (proband's generation and proband's mother's generation) who were known and obligate mutation carriers, noncarriers, and controls were determined and compared by calculating

odds ratios (OR) and 95% confidence intervals (95%CI). Obligate mutation carriers were restricted to the mothers of the probands and to reduce ascertainment bias, all probands were excluded as offspring from the sex ratio analyses.

RESULTS

Distribution of demographic variables was similar between *BRCA* carrier and noncarrier ovarian cancer cases and controls (Table 1).

No statistically significant differences were observed in the frequency of induced abortions, spontaneous abortions, or stillbirths between carrier and noncarrier cases and controls (Table 2). Pregnancy success was nearly equal for mutation carriers (0.84), non-carriers (0.87) and controls (0.83). Pregnancy success was lower for *BRCA2* carriers (0.78) compared to *BRCA1* carriers (0.88), but the difference did not reach statistical significance (Table 2).

Information on all reproductive and confounding variables for adjusted analyses of fertility was available on 93 *BRCA* carriers, 153 noncarriers, and 307 controls. The average numbers of pregnancies among carriers, noncarriers, and controls are shown in Table 3. In adjusted analyses, cases had a significantly lower pregnancy rate than controls ($P = 0.0049$) (Table 3). There were no significant differences between the carrier and noncarrier cases and controls with regards to fertility after adjusting for covariates (Table 3).

Male/female sex ratios were significantly lower among the offspring of *BRCA* carriers (0.71) than the offspring of noncarriers (0.95) or controls (0.99). Comparisons among the three groups yielded statistically significant distortion against males among the offspring of known and obligate *BRCA* carriers compared to noncarriers (OR = 0.74, 95% CI:0.55–0.99) and controls (OR = 0.71, 95% CI:0.54–0.94) (Table 4).

Similar sex ratio distortions were observed among the offspring of *BRCA* carriers in the two generations. In the proband's generation, male/female sex ratios were lower among the 181 offspring of *BRCA* carrier cases (0.74) compared to 341 offspring of non–carriers (0.92) and 633 offspring of controls (1.00) (Table 5). The reduction in male/female sex ratios were more pronounced among the 114 offspring of *BRCA1* (0.68) versus 67 offspring of *BRCA2* (0.86) carriers, but the difference was not statistically significant. Analysis of sex ratios among the offspring of probands' mothers, following exclusion of the probands as offspring, also yielded lower male/female sex ratios for 75 offspring of *BRCA* carriers (0.63) compared to 321 offspring of noncarriers (0.99) and 572 offspring of controls (0.97) (Table 6).

DISCUSSION

We did not find significant differences with respect to fertility among *BRCA* carriers and noncarriers after adjusting for confounders. Cases in our study had significantly fewer pregnancies compared to controls, even after adjusting for confounders of fertility, but it is likely that this reflects the known protective effect of parity against ovarian cancer (Permuth-Wey and Sellers, 2009). Despite lower pregnancy rates, pregnancy success was similar for mutation carrier and noncarrier cases and controls.

Theoretically, conferring beneficial effect on fertility and/or pregnancy success could lead to positive selection for a mutation. In vitro evidence suggests a role for BRCA1 in embryogenesis and fertility (Eakin et al., 2007; Giscard d'Estaing et al., 2005); however, molecular mechanisms of this putative effect remain to be elucidated. Although we did not find evidence for an effect of *BRCA* mutations on female fertility or prenatal survival, factors pertaining to the study design may have affected our results. Information on

variables included in the fertility analysis model, such as oral contraceptive use and treatment for infertility, was based on self-reports by the subjects; it was not possible to obtain medical records containing such information on all subjects. The size of the sample may have also influenced our results.

We found an excess of females among the offspring of female *BRCA1* and *BRCA2* mutation carriers in two generations. Our results are in agreement with earlier findings of a large excess of females in *BRCA* positive families (de la Hoya et al., 2003). de la Hoya et al. (2003) reported sex ratio distortions in *BRCA1* families only; we found an excess of females among the offspring of female carriers of both *BRCA1* and *BRCA2* mutations although the ratios were more skewed among the offspring of *BRCA1* carriers. While subsequent studies attributed the observed sex ratio distortions in *BRCA* families to possible confounding by ascertainment and/or selection biases (Domchek et al., 2005; Feunteun et al., 2004; Mealiffe, 2003), it is unlikely that either of these sources of bias would have influenced our results. Details of our study design have been published elsewhere (Moslehi et al., 2000). Ascertainment bias is unlikely since all prevalent cases of ovarian cancer among Ashkenazi Jewish women identified through the departments of gynecologic oncology of the participating hospitals were invited to participate in our study regardless of age or family history. To further reduce ascertainment bias, all probands were removed as offspring in sex ratio analyses. The possibility of selection bias influencing our results is equally remote. Overall participation rate for our study was ~ 82% and reasons for refusal included severe illness, concerns about insurance implications, and inability to speak English (Moslehi et al., 2000). Furthermore, any potential selection bias would have applied to both carrier and noncarrier cases. Survival bias may exist in our study but that would also apply to both carrier and noncarrier cases and is unlikely to explain or influence the sex ratio distortions observed.

A preponderance of females among the offspring of *BRCA* mutation carriers, as seen in our study, could contribute to positive selection for *BRCA* mutations through several mechanisms. Greater fertility and/or pregnancy success, as discussed above, may provide a selective advantage for *BRCA1* and *BRCA2* mutations. If this effect occurs only in females, then higher number of females who are *BRCA* carriers would magnify the selective advantage even further.

Another mechanism through which female preponderance among the offspring of mutation carriers could contribute to positive selection for those mutations is related to the proposed historical excess of breeding females over males (Hammer et al., 2008) and the proposed evolutionary advantage of females for becoming population founders during sex-biased genetic bottleneck events (Hammer et al., 2008; Singh et al., 2007). The Ashkenazi Jewish population is believed to have gone through at least one genetic bottleneck event in its two millennia history (Behar et al., 2004; Risch et al., 1995) and there is a debate in the literature with respect to the contribution of recent versus ancient founder effects to the high frequency of several disease alleles in this population (Goldstein et al., 1999; Risch et al., 1995). Recently, a mitochondrial DNA analysis provided evidence for a strong effect of genetic drift on the Ashkenazi Jewish gene pool marked by an early bottleneck event which is estimated to have occurred about 1,500 years ago (Behar et al., 2004). Although no historical evidence has been presented to indicate that this bottleneck event was sex-biased, evolutionary genetic studies suggest a higher female effective population size (Wilder et al., 2004), greater migration, and dispersion of females in earlier societies (Hamilton, 1967; West et al., 2002; Wilder et al., 2004), and evolutionary advantage of females over males for becoming population founders (Hammer et al., 2008; Singh et al., 2007). Thus an increased number of female population founders with *BRCA* mutations combined with strong genetic drift patterns may have contributed to a higher frequency of *BRCA* mutations in the

Ashkenazi Jewish population. Although this scenario, which is dependent to a large extent on genetic drift, is a possibility, a more plausible explanation for the high frequency of two different mutations, namely, *BRCA1* 185delAG with an estimated frequency of ~1% and *BRCA2* 6174delT with an estimated frequency of ~1.4% in this population (Oddoux et al., 1996; Roa et al., 1996), may be positive selection.

The possibility of other nonrandom genetic events, such as nonrandom X chromosome inactivation reported to be associated with *BRCA* mutations in one study (Buller et al., 1999) and disputed in a more recent study (Helbling-Leclere et al., 2007), and nonrandom transmission of mutant alleles to female offspring of *BRCA* carriers (Gronwald et al., 2003) contributing to positive selection for *BRCA* mutations should also be considered. Although these latter processes should contribute to positive selection for *BRCA* mutations in all populations, their effects could be stronger in founder populations, particularly in those where several synergistic selective forces may be involved.

In conclusion, we did not find evidence for an effect of *BRCA* mutations on female fertility; however, we found an excess of females among the offspring of female carriers of both *BRCA1* and *BRCA2* mutations. Our results indicate that a more careful interpretation of reproductive outcomes and sex ratio distortion among the offspring of *BRCA* carriers and their potential contribution to positive selection for *BRCA* mutations is warranted.

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TABLE 1

Distribution of demographic variables among probands

	***BRCA 1/2* carriers [*n* = 96 (%)]**	**Noncarriers [*n* = 164 (%)]**	**Controls [*n* = 331 (%)]**
Average age (years)	57.9	60.1	52.2
Age (years)			
≤30	0	6 (3.7)	3 (0.9)
31–40	7 (7.3)	7 (4.3)	49 (14.8)
41–50	21 (21.9)	36 (21.9)	115 (34.7)
51–60	31 (32.3)	32 (19.5)	97 (29.3)
61–70	23 (24.0)	39 (23.8)	35 (10.6)
>70	14 (14.6)	44 (26.9)	32 (9.7)
Average age of diagnosis of ovarian cancer	54.6	57.1	N/A
BRCA Mutations			
*BRCA1 185*delAG	51 (52.6)		
BRCA1 5382insC	15 (15.5)	N/A	N/A
BRCA2 6174delT	30 (30.9)		
Average BMI (kg m^{-2})	21.8	21.9	22.2
Oral Contraceptive use for regulating periods			
Yes	11 (11.5)	11 (6.7)	52 (15.7)
Oral Contraceptive use for birth control			
Yes	42 (43.7)	56 (34.1)	203 (61.3)
Tubal ligation			
Yes	13 (13.5)	11 (6.7)	75 (22.7)
Periods always/usually regular			
Yes	84 (87.5)	133 (81.1)	262 (79.1)
Medication to become pregnant			
Yes	10 (10.4)	16 (9.8)	34 (10.3)
Education (Last degree obtained)			
College/University/Professional School	76 (79.2)	103 (62.8)	225 (68.0)
High school	13 (13.5)	41 (25.0)	67 (20.2)
Less than high school	4 (4.2)	12 (7.3)	12 (3.6)
Regular consumption of alcohol			
Yes	16 (16.7)	19 (11.6)	42 (12.7)
Smoking history			
Yes (Ever smoker)	45 (46.9)	78 (47.6)	153 (46.2)
Median pack years of smoking	14.6	13.9	8.5
Family history of breast and/or ovarian cancer among first-degree relatives			
Yes	20 (20.8)	15 (9.1)	11 (3.3)

TABLE 2

Comparison of pregnancy histories of carrier and noncarrier cases and controls

	BRCA1 **carriers [*n* = 66 (%)]**	***BRCA2*** **carriers [*n* = 30 (%)]**	***BRCA 1/2*** **carriers [*n* = 96 (%)]**	**Noncarriers [*n* = 164 (%)]**	**Controls [*n* = 331 (%)]**
Total number of pregnancies	157	94	251	443	829
Number of liveborn offspring	114 (72.6)	67 (71.3)	181 (72.1)	340 (76.7)	633 (76.4)
Number of induced abortions[a]	28 (17.8)	8 (8.5)	36 (14.3)	54 (12.2)	68 (8.2)
Number of spontaneous abortions and still births	15 (9.5)	19 (20.2)	34 (13.5)	49 (11.1)	128 (15.4)
Pregnancy success[b]	0.88	0.78	0.84	0.87	0.83

[a]Includes therapeutic abortions.

[b]Pregnancy success calculated as the ratio of number of liveborn offspring to number of pregnancies per subject excluding induced abortions.

TABLE 3

Adjusted fertility analysis among carrier and noncarrier cases and controls

	***BRCA 1/2* carriers [*n* = 93 (%)]**	**Noncarriers [*n* = 153 (%)]**	**Controls [*n* = 307 (%)]**
Number of pregnancies			
None	8 (8.6)	17 (11.1)	21 (6.8)
One	8 (8.6)	18 (11.8)	29 (9.4)
Two	35 (37.6)	44 (28.8)	105 (34.2)
Three	25 (26.9)	36 (23.5)	81 (26.4)
Four	8 (8.6)	21 (13.7)	38 (12.4)
More than four	9 (9.8)	17 (11.1)	33 (10.7)
Average number of pregnancies	2.56	2.59	2.68
Median fertile person-years (18–44 years)	25.0	25.0	20.7
Average pregnancy rate	0.13	0.13	0.18
Poisson regression model for fertility[a]			
Parameters	Coefficient	Confidence interval	*P*-values
Cases vs. controls	−0.1723	−0.2922, −0.0524	0.0049
Carriers vs. Noncarriers and controls	−0.0118	−0.1726, 0.1489	0.8853
Carrier vs. Noncarrier Cases			0.5723[b]

[a] Covariates adjusted for: age, oral contraceptive use, body mass index, regularity of periods, history of and treatment for infertility, and age at menarche.

[b] *P*-value calculated by conditional exact test. The exact test was used because of small numbers in each group.

TABLE 4

Comparison of sex ratios among the offspring of known and obligate BRCA carriers, noncarriers, and controls in two generations

	***BRCA 1/2* carriers (*n* = 133)**	**Noncarriers (*n* = 328)**	**Controls (*n* = 662)**	**OR[a] (95% CI)**	**OR[b] (95% CI)**
Offspring sex ratio [M/F]	0.71 [106/150]	0.95 [323/339]	0.99 [599/606]	0.74 (0.55, 0.99)	0.71 (0.54, 0.94)

[a]OR: odds ratio for child being male comparing carriers with noncarriers.

[b]OR: odds ratio for child being male comparing carriers with controls.

TABLE 5

Comparison of sex ratios among the offspring of probands

	***BRCA 1/2* carriers (*n* = 96)**	**Noncarriers (*n* = 164)**	**Controls (*n* = 331)**	**OR[a] (95% CI)**	**OR[b] (95% CI)**
Offspring sex ratio [M/F]	0.74 [77/104]	0.92 [163/178]	1.00 [317/316]	0.81 (0.56, 1.16)	0.74 (0.53, 1.03)

[a]OR: odds ratio comparing carriers with noncarriers.

[b]OR: odds ratio comparing carriers with controls.

TABLE 6

Comparison of sex ratios among the offspring of probands' mothers[a]

	***BRCA 1/2* carriers (*n* = 36)**	**Noncarriers (*n* = 164)**	**Controls (*n* = 331)**	**OR[b] (95% CI)**	**OR[c] (95%CI)**
Offspring sex ratio [M/F]	0.63 [29/46]	0.99 [160/161]	0.97 [282/290]	0.63 (0.38, 1.06)	0.65 (0.40, 1.06)

[a]Probands were excluded as offspring from all analyses.

[b]OR: odds ratio comparing carriers with noncarriers.

[c]OR: odds ratio comparing carriers with controls.