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No association of miscarriage and *BRCA* carrier status in Pakistani breast/ovarian cancer patients with a history of parental consanguinity

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To the editor

About 80% of breast and ovarian cancer families and about 50% of site-specific breast cancer families are due to germ line mutations in either *BRCA1* (MIM 113705) or *BRCA2* (MIM 600185) [1–3]. Women carrying a pathogenic mutation in *BRCA1* or *BRCA2* face average lifetime risks of 65% and 45%, respectively, of developing breast cancer, and corresponding ovarian cancer risks of 39% and 11% [4]. In humans, almost all *BRCA* carriers have been found to be heterozygous [5, 6]. The lack of viable homozygous *BRCA* mutation carriers in humans suggests that homozygous fetuses may be more susceptible to spontaneous abortions. Further evidence for this hypothesis comes from in vivo animal studies showing that mice homozygous for mutations in the *BRCA1* or *BRCA2* gene die early in embryogenesis [7, 8].

Two recent studies have explored the impact of *BRCA* mutation status on the occurrence of miscarriages. One study included *BRCA* carriers of Ashkenazi Jewish descent [9], and the other included mutation carriers from United States and Canada [10]. Neither study found a significant difference in the rate of miscarriage between *BRCA* carriers and non-carriers. We conjectured that miscarriages may occur more frequently in *BRCA* carriers from consanguineous parents since their offspring are more often homozygous by descent compared to those of unrelated parents, and living homozygous *BRCA* mutation carriers have not been observed. To explore this question, we studied the rates of miscarriages in Pakistani *BRCA* mutation carriers and non-carriers with a history of parental consanguinity. Pakistan has one of the highest rates of consanguinity in the world (range 60–70%) [11, 12].

Breast and/or ovarian cancer families were recruited at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, between June 2001 and November 2004. Of the 165 female index patients, 30 carried a deleterious *BRCA* mutation, and 135 were without any identifiable mutation. All families, screening methods and mutations have been described previously [13]. Four additional families carrying a deleterious *BRCA* mutation identified recently were also included in this study. Relevant information regarding potential breast cancer risk factors including family history of cancer, hormone use, reproductive history, medical history and life style factors was collected by interview-administered questionnaires. Detailed information on the outcome of each pregnancy (year of each pregnancy, number of miscarriages including spontaneous and therapeutic abortions, number of still and live born), and parental consanguinity was collected. Spontaneous abortion was defined as loss of a pregnancy before the completion of 20 gestational weeks from the

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Table 1 Comparison of parity-related parameters among *BRCA* carriers and non-carriers

Parameter	<i>BRCA</i> carriers ^a N (%)	Non-carriers N (%)	<i>P</i> -value
Total number of patients	29	99	
Age at diagnosis of breast cancer (years) ^b	24	82	
Mean ± SD	35 ± 8	32 ± 8	0.082 ^c
Range	22–50	22–70	
Age at diagnosis of ovarian cancer (years)	5	17	
Mean ± SD	39 ± 6	35 ± 6	0.194 ^c
Range	29–45	26–45	
Year of birth			
Mean ± SD	1965 ± 10	1969 ± 8	
Range	1938–1980	1922–1980	
Total number of pregnancies	116	371	
Mean ± SD	4.0 ± 2.4	3.7 ± 2.2	0.798 ^d
Range	1–8	1–12	
Total number of live births	83	307	
Mean ± SD	2.9 ± 1.9	3.1 ± 1.8	0.389 ^d
Range	0–8	0–8	
Total number of miscarriages	22	60	
Mean ± SD	0.8 ± 1.3	0.6 ± 1.0	0.891 ^d
Range	0–5	0–4	
Study participants with miscarriages			
0	19 (66)	63 (64)	1.000 ^e
>0	10 (34)	36 (36)	
1	3 (10)	20 (20)	
2	5 (17)	11 (11)	
3+	2 (7)	5 (5)	

SD, standard deviation

^a The carrier group includes *BRCA1* and *BRCA2* carriers^b Including three patients who developed ovarian cancer as a second cancer; exclusion of these patients yielded mean ages at breast cancer diagnoses of 34 years in carriers and 31 years in non-carriers (t-test, *P* = 0.262).^c t-test: pooled (equal variance)^d Wilcoxon's signed rank test^e No miscarriage versus one or more miscarriages, Fisher's exact test

previous menstrual period or fetal weight of < 500 g according to the recommendation of the World Health Organization [14]. Parental consanguinity was classified into four types: no consanguinity, first cousins, second cousins and more distant relatives. A total of 128 breast/ovarian cancer patients comprising 29 *BRCA* carriers and 99 non-carriers who had at least one pregnancy were included in the study. Mean and standard deviation (SD) was calculated for total number of pregnancies, live births, and miscarriages. The Wilcoxon's signed rank test was performed to test if *BRCA* carriers and non-carriers were independent of the number of pregnancies and its outcome (number of live births and number of miscarriages, respectively). The Student's *t*-test was used to test for independency of age at diagnosis and carrier status. All other variables were dichotomized, and tested using Fisher's exact test. Two-sided *P*-values of 0.05 or less were considered as statistically significant. All statistical analyses were performed using SAS, version 9.1.

A comparison of parity-related parameters between *BRCA* carriers and non-carriers is shown in Table 1. The mean age at diagnosis of breast and ovarian cancer among carriers and non-carriers did not show any significant

difference (*t*-test, *P* = 0.082 and *P* = 0.194, respectively). In addition, no difference was found between the two groups in the mean number of pregnancies, live births, miscarriages, and in the proportion of study participants with and without miscarriages.

No association was noted between miscarriage and parental consanguinity, disregarding *BRCA* carrier status (miscarriage among related couples versus miscarriage among unrelated couples: Fisher's exact test, *P* = 0.463; miscarriage among married first and second cousins versus miscarriage among unrelated couples: Fisher's exact test, *P* = 0.435) (data not shown), which is in agreement with previous studies conducted in countries with high rates of consanguinity [15–18].

When *BRCA* status was considered, there was no statistically significant difference between the occurrence of miscarriage among related and unrelated study participants (Table 2). Even when the analysis was restricted to marriages between close relatives (first or second cousins), no significant association with miscarriages could be shown.

In the two previous studies the rate of three or more spontaneous miscarriages among Israeli Jewish *BRCA* carriers with at least one live birth was 4.4% (15/343) and

Table 2 Comparison of miscarriages between *BRCA* carriers and non-carriers, and parental consanguinity

	Study participants with miscarriages		Study participants without miscarriages		Total N	P-value ^b
	<i>BRCA</i> carriers ^a N (%)	Non-carriers N (%)	<i>BRCA</i> carriers ^a N (%)	Non-carriers N (%)		
All study participants	10 (7.8)	36 (28.1)	19 (14.8)	63 (49.2)	128	1.000
Unrelated study participants	3 (5.2)	20 (34.5)	6 (10.3)	29 (50.0)	58	1.000
Related study participants	7 (10.0)	16 (22.9)	13 (18.6)	34 (48.6)	70	1.000
First and second cousins	5 (9.4)	12 (22.6)	11 (20.8)	25 (47.2)	53	1.000
First cousins	3 (7.0)	10 (23.3)	11 (25.6)	19 (44.2)	43	0.491
Second cousins	2 (20.0)	2 (20.0)	0 (0.0)	6 (60.0)	10	0.133
Distant relatives	2 (11.8)	4 (23.5)	2 (11.8)	9 (52.9)	17	0.584

^a The carrier group includes *BRCA1* and *BRCA2* carriers

^b Fisher's exact test

3.0% (12/401) in non-carriers [9]; the rates were 2.5% (71/2,846) and 2.3% (15/657), respectively, in women from United States and Canada [10]. We found similar rates in Pakistani women: 6.9% (2/29) for *BRCA* carriers and 5.1% (5/99) for non-carriers.

The limitations of this study are that it is not population-based as the study subjects were recruited based on a personal or family history of breast and/or ovarian cancer in a hospital, and the small study size.

In conclusion, our findings suggest no difference in the occurrence of miscarriage between *BRCA* carriers and non-carriers when parental consanguinity was taken into consideration. Additional studies are warranted.

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