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Report

Offspring Gender Ratio and the Rate of Recurrent Spontaneous Miscarriages in Jewish Women at High Risk for Breast/Ovarian Cancer

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BRCA1/BRCA2 germline mutations are associated with an increased breast/ovarian cancer risk. Offspring gender ratios may be skewed against male births in _BRCA1_ mutation carriers. In addition, the lack of viable homozygous _BRCA1/BRCA2_-mutation carriers implies that recurrent miscarriages may be associated with homozygous fetuses. Jewish Israeli high-risk women who were tested for being carriers of the predominant _BRCA1/BRCA2_ mutations in Jewish high-risk families were analyzed for the sex of offspring and the rate of spontaneous miscarriages. Overall, 817 women participated: 393 _BRCA1/BRCA2_-mutation carriers (229 with breast/ovarian cancer) and 424 high-risk noncarriers (208 with breast/ovarian cancer). No differences between the male-to-female offspring ratios of all study groups were noted. Among mutation carriers, the offspring male-to-female ratio was 0.97 (444:460), and among mutation carriers with cancer it was 0.92 (262:284). Similarly, no offspring gender skewing was noted among high-risk noncarriers, regardless of health status. The rates of three or more spontaneous miscarriages among participants with at least one live birth were 4.37% (15/343) among mutation carriers and 3% (12/401) among high-risk women ($P =$ not significant). In conclusion, the offspring gender ratio is similar in high-risk Jewish families and in the general population. The issue of the rate of recurrent miscarriages in high-risk Jewish women is unresolved.

Germline mutations in two genes, *BRCA1* (MIM 113705) and *BRCA2* (MIM 600185), are estimated to account for ~80% of all inherited breast and ovarian cancer and <50% of familial site-specific breast cancer (Ford et al. 1994, 1998). In Jewish high-risk individuals of Ashkenazi (East European) decent, three predominant, seemingly founder mutations—185delAG (*BRCA1*), 5382insC (*BRCA1*), and 6174delT (*BRCA2*)—seem to account for a substantial proportion (70%–85%) of germline mutations detected in high-risk families with inherited breast and ovarian cancer, including ~40%–50% of familes with site-specific breast cancer, and in ⩽2.5% of the general Jewish Ashkenazi population (Berman et al. 1996; Neuhausen et al. 1996, 1998; Roa et al. 1996; Abeliovich et al. 1997; Szabo and King 1997). Notably, other mutations in both *BRCA1* and *BRCA2* are infrequent among Jewish Ashkenazi women at a high risk for cancer (Shiri-Sverdlov et al. 2000; Kauff et al. 2002).

The only well-established phenotype of heterozygous *BRCA1/BRCA2* mutation carriers is an increased risk for breast, ovarian, and, to a lesser extent, other cancers (e.g., pancreatic and prostate) (Ford et al. 1994; Struewing et al. 1997; Breast Cancer Linkage Consortium [BCLC] 1999; Thompson et al. 2002; see also BCLC Web site). A recent report suggested that there is a skewing of offspring gender ratios, favoring female offspring in *BRCA1* mutation carriers and not in *BRCA2* mutation carriers, an observation that seemingly supported the role that BRCA1 protein plays in X chromosome inactivation (de la Hoya et al. 2003). Another intriguing fact is that no viable homozygous *BRCA* mutation carriers have been established in any species, including human beings (Gowen et al. 1996; Suzuki et al. 1997; Kuschel et al. 2001). On the basis of the carrier rate in

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the general population of the mutations predominant in Jewish populations (0.9% for the 185delAG *BRCA1* mutation and 1.5% for the 6174delT *BRCA2* mutation), the predicted rate of fetuses born to Jewish Ashkenazim being homozygous for one of these two mutations is expected to be between 1 in 20,000 births for 6174delT and 1 in 40,000 births for 185delAG. Taken together, the fact that no homozygous mutation carrier has been reported (Kuschel et al. 2001) and the lack of viable homozygous mutation carriers in animal models (Gowen et al. 1996; Suzuki et al. 1997) led us to hypothesize that a plausible reason for recurrent spontaneous miscarriages among Jewish Ashkenazi women may be fetal homozygosity for the recurring *BRCA1*/*BRCA2* mutations in this ethnic group.

The aim of this study was to assess the putative effect of being a *BRCA1*/*BRCA2* germline mutation carrier on offspring gender ratio and on the rate of recurrent spontaneous miscarriages.

Jewish women who were counseled for breast/ovarian cancer risk by the oncogenetics services at the Sheba Medical Center in Tel-Hashomer or at the Institute of Genetics at Rambam Medical Center from January 1, 1999, until December 31, 2002, were eligible. Exclusion criteria were non-Jewish origin and unwillingness to participate. The study participants were subdivided into mutation carriers and noncarriers, and each group was further subdivided into affected (with breast/ovarian cancer) or unaffected.

The study was approved by the institutional review board of both medical centers, and each participant signed a written informed consent. Data regarding offspring gender and reproductive history, along with detailed personal and family history of cancer and demographic data, were collected routinely at counseling. Ethnic origin was ascertained for at least three prior generations, on the basis of the countries of birth of the parents and grandparents. On the basis of personal and family cancer history, "high risk" status was assigned to (1) women who have at least two first-degree relatives with breast cancer, one of whom was diagnosed at <40 years of age, (2) women who have at least one first-degree relative who had ovarian cancer at any age and at least one first-degree relative with breast cancer, and (3) women who have at least two first-degree relatives with breast cancer at any age, one of whom had bilateral breast cancer.

DNA was extracted from peripheral venous leukocytes by use of the PUREGene DNA extraction kit (Gentra Inc.), in accordance with the manufacturer's recommended protocol. Three predominant Jewish mutations were tested: 185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*. Mutation analysis schemes were based on PCR and restriction enzyme digests that distinguish the wild type from the mutant allele, as described elsewhere (Rohlfs et al. 1997).

Categorical variables were compared with the use of χ^2 tests, and continuous variables were compared using *t*-tests, adjusting for the effect of birth cohort when necessary. All statistical analyses were performed using S-Plus (S-Plus 2000 Professional Release 3, Insightful Corp.).

Overall, 817 women participated in this study, and 393 were carriers of one of the predominant Jewish mutations in *BRCA1* (185delAG, $n = 195$; 5382InsC, $n = 69$) or in *BRCA2* (6174delT, $n = 129$). Of the 393 carriers, 169 were diagnosed with breast cancer, 47 with ovarian cancer, and 13 with both cancer types. Of the 424 noncarriers, 192 were diagnosed with breast cancer, 13 with ovarian cancer, and 4 with both cancer types. Study participants represent 82.6% of the total 989 women who were eligible for this study.

In both mutation carriers and noncarriers, the mean age of unaffected women was significantly younger than the mean age of women diagnosed with cancer ($P = 0$) (table 1). The mean age at counseling in the noncarrier group was significantly older than that of the carriers ($P = .0001$) (table 1). Yet, the mean age at counseling in all groups ranged from 44.4 to 53.6 years, which are considered to be ages at which the reproductive cycle has been completed. The mean age at diagnosis of breast cancer was 43.2 ± 8.9 years for carriers and 48.8 ± 9.8 years for noncarriers ($P = 0$); the mean age at diagnosis of ovarian cancer was 51.4 ± 11.0 years for carriers and 57.5 ± 9.4 years for noncarriers ($P = .04$). The majority of study participants (97.3%), including both carriers and noncarriers, were of Ashkenazi origin, and the rest were of Iraqi origin, of Balkan origin, or born in Israel.

Of the study participants, 91% of the mutation carriers and 95% of the noncarriers gave birth at least once. A statistically significant difference in the mean number of children was noted between carriers (2.33 ± 1.24) and noncarriers (2.51 ± 1.3) ($P = .045$). No significant differences in the distribution of the number of children were noted between affected and unaffected women within each group.

The total number of males born to noncarriers was 542, compared with 522 females (rate ratio 1.038). Among mutation carriers, there were 444 male offspring, compared with 460 female offspring (rate ratio 0.965). Analysis of offspring gender ratio by specific mutation type shows that there were 215 boys and 219 girls (rate ratio 0.98) among 185delAG *BRCA1* mutation carriers, 71 boys and 84 girls (rate ratio 0.84) among 5382InsC *BRCA1* mutation carriers, and 158 boys and 157 girls (rate ratio 1.006) among 6174delT *BRCA2* mutation carriers. Combined analyses of all BRCA1 carriers (185delAG and 5382InsC) showed that there were 286 male and 303 female offspring (rate ratio

Table 1

Demographic and Parity-Related Variables by Study Group

	VALUE FOR								
	Carriers				Noncarriers				
VARIABLE	Total	Unaffected	With Breast/ Ovarian Cancer	*P*	Total	Unaffected	With Breast/ Ovarian Cancer	*P*	*P* FOR CARRIERS VS. NONCARRIERS
N	393	164	229		424	216	208		
Age (years):									
N	390	162	228		422	215	207		
Mean ± SD	48.11 ± 11.15	44.38 ± 10.75	50.75 ± 1.69	0	51.17 ± 11.6	48.79 ± 11.01	53.65 ± 11.7	0	.0001
Range	17–86	17–71	29–86		23–87	25–87	23–86		
Origin:									
N	387	161	226		423	215	208		
Ashkenazi	376 (97%)	155 (96%)	221 (98%)		419 (99%)	213 (99%)	206 (99%)		
Iran/Iraq	3	2	1		2	2	0		
Yemen	0	0	0		1	0	1		
Balkan	2	0	2		1	0	1		
Israeli-born	6	4	2	.28	0	0	0	.26	
No. of live births:									
N	387 (100%)	159 (100%)	228 (100%)		424 (100%)	216 (100%)	208 (100%)		
0	33 (9%)	13 (8%)	20 (9%)		22 (5%)	15 (7%)	7 (3%)		
1	40 (10%)	22 (14%)	18 (8%)		44 (10%)	19 (9%)	25 (12%)		
2	150 (39%)	63 (40%)	87 (38%)		144 (34%)	73 (34%)	71 (34%)		
3	117 (30%)	44 (28%)	73 (32%)		156 (37%)	81 (38%)	75 (36%)		
4	35 (9%)	14 (9%)	21 (9%)		44 (10%)	21 (10%)	23 (11%)		
5+	12 (3%)	3 (2%)	9 (4%)	.39	14 (3%)	7 (3%)	7 (3%)	.56	.18
Mean ± SD	2.33 ± 1.24	2.23 ± 1.2	2.4 ± 1.3	.18	2.5 ± 1.3	2.49 ± 1.3	2.53 ± 1.27	.73	.045
No. of miscarriages[a]:									
N	343 (100%)	144 (100%)	199 (100%)		401 (100%)	200 (100%)	201 (100%)		
0	230 (67%)	100 (69%)	130 (65%)		283 (71%)	136 (68%)	147 (73%)		
1	74 (22%)	30 (21%)	44 (22%)		79 (20%)	41 (21%)	38 (19%)		
2	24 (7%)	12 (8%)	12 (6%)		27 (7%)	17 (9%)	10 (5%)		
3+	15 (4%)	2 (1%)	13 (7%)	.11	12 (3%)	6 (3%)	6 (3%)	.5	.65
Mean ± SD	.52 ± .94	.41 ± .70	.59 ± 1.08	.079	.44 ± .87	.50 ± .95	.39 ± .79	.19	.274
Male-to-female offspring ratio:									
All	444:460 (.98)				542:522 (1.038)				
BRCA1	286:303 (.943)								
185delAG	215:219 (.98)								
5382InsC	71:84 (.84)								
BRCA2	158:157 (1.006)								

[a] Number of spontaneous miscarriages among women who have had at least one live birth.

0.943). The differences in rate ratios between all groups (by specific mutation and by *BRCA1* clustering) are statistically insignificant (table 1).

Of the study participants who had been pregnant at some time in their life ($n = 343$ and $n = 401$ among mutation carriers and noncarriers, respectively), 231 reported having at least one spontaneous miscarriage: 113 (33%) of the carriers and 118 (30%) of the noncarriers ($P = .34$). In terms of unaffected women only, there were 44 carriers (31%) and 64 noncarriers (33%) who reported having at least one spontaneous miscarriage ($P = .87$). Among mutation carriers who had been pregnant, 15 (4.37%) had three or more spontaneous miscarriages (2 unaffected women and 13 women with breast/ovarian cancer, $P = .11$), and, among noncarrier women who had been pregnant, there were 12 women (3%) with three or more spontaneous miscarriages, evenly distributed among affected and unaffected individuals ($P = .5$). The mean number of spontaneous abortions for women who had been pregnant was 0.41 ± 0.7 for unaffected mutation carriers and 0.50 ± 0.95 for noncarriers ($P = .8$).

Among mutation carriers, though the mean rate of spontaneous miscarriages was higher among affected women, compared with asymptomatic mutation carriers, the difference was of borderline significance statistically ($P = .079$). However, these differences could not be shown when stratification for age at counseling was performed.

In this study, no apparent differences in male-to-female offspring ratio were noted in Jewish women who are *BRCA1* or *BRCA2* mutation carriers, and the offspring gender ratio was within that reported for the general Western world populations, −1.06 (Davis et al. 1998). In Israel, the male-to-female ratios were 1.059 (70,173:66,217) in 2000 and 1.045 (71,318:68,217) in 2002 (Central Bureau of Statistics 2001, 2003). In the present study, for high-risk noncarriers, the ratios were also within those of the general population, regardless of disease status. Our data differ from those in a recent report on Spanish *BRCA1*-mutation carriers: in that study, a two-fold excess of female offspring was noted in *BRCA1* mutation carriers (de la Hoya et al. 2003). Notably, among the Spanish mutation carriers, there were three families who are carriers of the 185delAG *BRCA1* mutation. In these three families, the ratio of male to female offspring was 0.533 (24:45). By contrast, in the present study, which encompassed 195 185delAG-mutation carriers, representing 174 independent families, there were 215 boys and 219 girls—a male-to-female ratio of 0.981. The reasons for the inconsistent results in terms of the effect of *BRCA1* mutation on offspring gender ratio in both studies may be attributed to several factors, and the difference in sample size may be the single most important factor. Additionally, the number of families analyzed herein is larger than the number of families analyzed in the Spanish study, and, therefore, our observations are independent of other confounding familial variables. Alternatively, the precise location of gene mutations may affect the resulting protein function, with respect to its putative role in X chromosome inactivation. Another possibility is that there are other genetic factors that control offspring gender ratio in the Spanish population and are in association with *BRCA1* mutations (either genetically or functionally) but are nonexistent in the Jewish Ashkenazi population. The need to assess these factors in a larger study is apparent.

No differences with regard to the rate of recurrent spontaneous miscarriages among all study groups were shown. However, the finding that the rate of recurrent spontaneous miscarriages among all subsets of study participants was higher than that reported for the average risk population (.8%–1%) (Stirrat 1990; Katz and Kuller 1994; Bick et al. 1998) is intriguing, but should be interpreted very cautiously. The often-quoted reference numbers for recurrent ($\geqslant 3$) miscarriages in the general population (.8%–1%) are based on historical, non-Israeli controls (Alberman 1988; Bick et al. 1998). In addition, in the study by Roman et al. (1978), which analyzes the data set that is most often cited, there were no women who were pregnant >4 times, whereas, in the present study, all but one of the women who had $\geqslant 3$ spontaneous miscarriages were pregnant at least 5 times. Thus, comparison of the literature-based historical data on non-Jewish women with the current data is invalid. However, given the biological plausibility that BRCA1/BRCA2 proteins are involved in determining fetal outcome (Gowen et al. 1996; Suzuki et al. 1997), the need for a larger study that will compare spontaneous miscarriage rates among mutation carriers and high-risk women with the rates among an ethnically matched, average-risk population is obvious. This preliminary observation, if confirmed, may signify that, in genetically homogeneous populations with a limited repertoire of mutations in *BRCA1/BRCA2*, the study of recurrent miscarriages should include testing for germline mutations in both genes, especially if there is a suggestive family history.

The limitations of this study should be pointed out. The study population was highly selected for a personal and family history of breast/ovarian cancer. Therefore, the carriers do not represent the total carrier population, and the noncarriers do not represent the general Israeli population. The effect of this inherent limitation on offspring gender ratio is minimal, in all likelihood, since the results were compared within each group and with valid reliable data derived from the Israeli population. Another drawback of the study is the significant age differences among the four subsets of analyzed groups, though the mean ages of all groups were beyond the reproductive period. Although the younger age of mutation carriers, affected and unaffected, may result in a lower number of live births, this fact by itself could not have a significant effect on offspring gender ratio.

We conclude that among Jewish women at high risk for developing breast/ovarian cancer, either because of family history or by virtue of being *BRCA1*/*BRCA2* mutation carriers, there is no skewing of offspring gender ratio. The issue of the rate of recurrent spontaneous miscarriages among Jewish *BRCA1*/*BRCA2* mutation carriers and high-risk women is yet to be resolved by analysis of an appropriate control group.

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Electronic-Database Information

URLs for data presented herein are as follows:

BCLC, http://www.humgen.nl/lab-devilee/BCLC/statbite.htm
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

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