ELECTRONIC LETTER

Ratio of female to male offspring of women tested for *BRCA1* and *BRCA2* mutations

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J Med Genet 2004;**41**:e103 (http://www.jmedgenet.com/cgi/content/full/41/8/e103). doi: 10.1136/jmg.2004.019687

The functions of the breast cancer susceptibility genes *BRCA1* and *BRCA2* are not fully elucidated, but appear to include the regulation of X chromosome activity. *Xist* is a non-coding RNA that accumulates on the inactive X chromosome and is required for X chromosome inactivation during the silencing step.[1] The RING domain of BRCA1 and *Xist* interact in mammalian cells and it has been suggested that BRCA1 contributes to the initiation of X chromosome inactivation.[2] Women with ovarian cancer possessing germline mutations in *BRCA1* have been found to frequently demonstrate non-random X chromosome inactivation.[3] In the light of these findings, a recent report by de la Hoya *et al* is of interest.[4] In this study of 68 Spanish breast/ovarian pedigrees they reported that 67% of the children of women who carried a *BRCA1* mutation were female. By contrast, only 54% of the offspring of *BRCA2* carriers and 52% of the offspring of non-carriers were female. This highly skewed sex ratio in the offspring of *BRCA1* carriers from Spain prompted us to ask whether this is true in other populations as well.

To address this question, we examined the sex ratios of the offspring of a total of 1040 women (229 BRCA1 carriers, 104 BRCA2 carriers, and 707 non-carriers) from five different studies which were conducted in Montreal, Toronto, and Oslo between 1993 and 2003. In four studies the carriers were identified through hospital-based and population-based ascertainment and were not selected for family history,[5–8] whereas one of the studies (the single study from McGill University, Montreal, Quebec, Table 1) was composed of Ashkenazi Jewish women ascertained via a high risk clinic. Three of the studies were also restricted to Ashkenazi Jews. In these studies the participants were tested for the three Ashkenazi Jewish founder germline mutations in BRCA1 and BRCA2. In the fourth study of ovarian cancer patients in Ontario, *BRCA1* was screened in its entirety using PTT and DGGE and *BRCA2* was screened in part using PTT.[5] The fifth study, restricted to women with ovarian cancer diagnosed in southern Norway, was conducted in Oslo, and the results presented here are restricted to mutation analysis of known Norwegian founder *BRCA1* mutations as previously reported for this series of cases,[8] and the results of an extended mutation search in patients with a positive family history of breast and ovarian cancer. We counted all the female and male births reported by the proband in each pedigree.

We did not find any evidence for sex ratio distortion in the overall sample (Table 1). Among 229 *BRCA1* carriers, there was no statistically significant excess of female births (221 males vs 234 females, $p = 0.54$). The p value was derived from the binomial distribution, using an exact method, comparing the observed proportion with the expected proportion of 0.50. The proportion of female offspring was quite similar for children of *BRCA1* carriers (51.4%), of *BRCA2* carriers (50.2%), and of non-carriers (51.6%). This is in contrast to the striking results of the previous report (65 males vs 133 females offspring among confirmed *BRCA1* carriers, $p \leqslant 0.001$).[4] Three subgroup results were of borderline significance—there were slight excesses of females among children of Ashkenazi Jewish women with ovarian cancer and a *BRCA1* mutation[7] and among Ashkenazi Jewish women with either no founder mutation or a *BRCA2* mutation in the McGill University, Montreal, Quebec study (Table 1). The differences could be related to ascertainment bias, or may be chance findings as a result of the large number of comparisons made. This latter possibility is strengthened by a further analysis of a group of 23 non-Ashkenazi women who were diagnosed with ovarian cancer at McGill University and were seen in high risk clinics, and were found to be *BRCA1* carriers: the number of male and female children from these 23 women was identical (44 in total).

It is noteworthy that *BRCA1* carriers affected by ovarian cancer had significantly fewer children (whether male or female) than all other groups combined (1.89 ± 1.07 and 2.16 ± 1.30, respectively, $p = 0.006$), possibly as a result of the diagnosis of ovarian cancer being at sufficiently young age to adversely affect fertility, but more likely because nulliparity is a risk factor for ovarian cancer. Interestingly, *BRCA2* carriers with ovarian cancer had significantly more children (2.29 ± 1.44) than *BRCA1* carriers with ovarian cancer (1.89 ± 1.07, $p = 0.04$). This difference could be due to parity being less protective against ovarian cancer in *BRCA2* carriers than in *BRCA1* carriers. Another possibility is that fertility might be more likely to be prematurely terminated by a diagnosis of a *BRCA1*-related ovarian cancer than it would be by a diagnosis

Key points

- *BRCA1* may have a role in X-inactivation.
- Some previous evidence presented supporting non-random X-inactivation in *BRCA1* carriers.
- A recent study demonstrated sex ratio bias, favouring female births.
- We studied 1040 women tested for *BRCA1/2* in three centres in Canada and Norway.
- Overall, there was no consistent evidence for a bias in the sex ratio of offspring of *BRCA1* or *BRCA2* carriers.
- Women with *BRCA1* mutations and a previous diagnosis of ovarian cancer had significantly fewer children than did women with ovarian cancer and a *BRCA2* mutation, implying that parity affects ovarian cancer risk differently in the two groups.
- Studies of offspring number, sex ratio, and transmission ratio among *BRCA1/2* carriers are all subject to several possibly hidden biases. It is difficult to exclude them all, particularly when using clinic-based ascertainment strategies.

Abbreviations: DGGE, denaturing gradient gel electrophoresis; PTT, protein truncation test

Table 1 Sex ratio in *BRCA1* carriers, *BRCA2* carriers, and non-carriers

Group	Probands	Number of offspring		M:F Ratio	p value	Reference
		Male	Female			
BRCA1 mutation carriers						
AJ McGill University clinic*	45	53	50	1.06	0.77	
AJ breast cancer study†	34	33	36	0.92	0.72	6
AJ ovarian cancer study‡	57	37	56	0.66	0.05	7
Ontario ovarian tumour study§	57	56	55	1.02	0.92	5
Norway ovarian cancer study¶	36	42	37	1.14	0.57	8
All	229	221	234	0.94	0.54	
BRCA2 mutation carriers						
AJ McGill University clinic	17	8	19	0.42	0.03	
AJ breast cancer study	15	12	11	1.09	0.83	6
AJ ovarian cancer study	29	30	33	0.91	0.71	7
Ontario ovarian tumour study	43	57	45	1.27	0.23	5
All	104	107	108	0.99	0.95	
BRCA1/2 non-carriers						
AJ McGill University clinic	198	181	219	0.83	0.06	
AJ breast cancer study	364	392	406	0.96	0.62	6
AJ ovarian cancer study	122	129	140	0.92	0.50	7
Ontario ovarian tumour study	23	40	27	1.48	0.11	5
All	707	742	792	0.94	0.20	

*Ashkenazi Jewish women tested for founder germline mutations in *BRCA1* and *BRCA2* at one of the McGill University affiliated hospitals, Montreal, Canada between 1996 and 2003, as part of clinical service. BRCAPRO scores for *BRCA1* carriers ranged from 0.018 to 0.923 with a median of 0.48. The *BRCA2* positive pedigrees were found to have scores that ranged from 0.094 to 0.984 with a median of 0.46. It is highly likely that women with female children are over-represented in this study population.[9 10]

†Ashkenazi Jewish women from six oncology centres in Toronto and Montreal who had been diagnosed with breast cancer before 1 May 1998, as part of a study designed to determine the frequency and penetrance of founder mutations.[6]

‡Ashkenazi Jewish women from 11 medical centres in North America and Israel who had been diagnosed with ovarian cancer and were tested for the founder mutations to examine the familial risks and estimate the proportion of ovarian cancers associated with these mutations.[7]

§Women of various ethnicities were recruited into a Familial Ovarian Tumor Study through the Ontario Cancer Registry.[5]

¶Norwegian series of 615 consecutive ovarian cancers patients who consented to genetic testing were initially screened for the two most frequent local mutations described in Dorum *et al*[8] and two additional mutations (3347delAG and 816delGT). All patients with relatives affected with breast and/or ovarian cancers were later subjected to extensive mutation search in *BRCA1* and *BRCA2* with various methods. Altogether 37 truncating mutations were found (36 in *BRCA1*, one in *BRCA2*), indicating a prevalence of 6.0% of *BRCA1/2* carriers in ovarian cancers in the total series, 18/171 (10.5%) < 50 years of age, 18/300 (6%) at 50–70 years, and 1/144 (0.7%) at 70+ years. Only the data for *BRCA1* are presented here.

of a *BRCA2*-related ovarian cancer. In support of this idea, the average age at diagnosis of ovarian cancer was 59.2 years (±9.64 years) for *BRCA2* carriers and 51.2 years (±9.41 years) for *BRCA1* carriers ($p<0.0001$) in the three available series.[5 7 8] Finally, it may be merely a chance finding.

Overall, these results indicate that subtle ascertainment biases are likely to be present in any study that involves a tested population whose disease status and family history may influence the decision to attend a high risk clinic, or be enrolled in a study. Therefore we consider that the parsimonious explanation for the different results obtained in the studies in Spain, Canada, and Norway is that neither *BRCA1* nor *BRCA2* influence the male/female sex ratio of offspring, and that the observed effects observed are more likely to be due to ascertainment bias. Several different ascertainment biases might be important; for example, women with female offspring may be more likely to seek breast/ovarian cancer susceptibility testing than women with male children only or with no children.[9 10]

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Conflict of interest: none declared

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Revised version received 15 March 2004
Accepted for publication 15 March 2004

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