European Journal of Human Genetics (2004) 12, 663–667
© 2004 Nature Publishing Group All rights reserved 1018-4813/04 $30.00
www.nature.com/ejhg

SHORT REPORT

# *BRCA1* and sex ratio

Jeffery P Struewing*[,1], Patricia Hartge[2], Sholom Wacholder[3], Margaret A Tucker[4] and Mark H Greene[5]

[1]*Laboratory of Population Genetics, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA;* [2]*Epidemiology and Genetics Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA;* [3]*Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA;* [4]*Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA;* [5]*Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA*

**Two recent papers suggest distorted sex and transmission ratios associated with *BRCA1* mutations. If real, these would provide novel insights into the normal biological function of this gene and have implications for genetic epidemiologic methods used to estimate penetrance. We addressed these observations in two settings: offspring of 283 mutation carriers and 471 mutation negative subjects from *BRCA1/2* mutation-positive families with multiple cases of breast and ovarian cancer (NCI families); and relatives of 115 *BRCA1/2* mutation carriers from the Washington Ashkenazi Study (WAS). The male:female ratio was below one in both *BRCA1* (0.85, 95% CI 0.7–1.1 in NCI families; 0.90, 95% CI 0.6–1.4 in WAS) and *BRCA2* families (0.77, 95% CI 0.5–1.3 and 0.80, 95% CI 0.5–1.2, in the NCI and WAS study groups, respectively). None of the sex ratios deviated significantly from one, and there was no significant difference between *BRCA1* and *BRCA2* families. The reduced sex ratio was due largely to the offspring of males, a distortion that is probably an artifact of ascertainment biases. Among adult daughters without breast or ovarian cancer born to mutation carriers, as expected, fewer than 50% were mutation carriers (39% in *BRCA1* families and 44% in *BRCA2* families). It is difficult, due to ascertainment biases, to draw firm conclusions regarding sex ratios in studies of a sex-limited phenotype. Nonetheless, these observations do not support the idea that *BRCA1* mutation carriers have a lower ratio of male offspring than *BRCA2* mutation carriers.**
*European Journal of Human Genetics* (2004) **12,** 663–667. doi:10.1038/sj.ejhg.5201210
Published online 28 April 2004

**Keywords:** BRCA1; BRCA2; sex ratio; transmission ratio; mutation

## Introduction

Two recent papers have observed surprising findings of distorted sex and transmission ratios associated with *BRCA1* mutation carriers.[1,2] Specifically, a significant deficit of sons was observed among 68 Spanish breast–ovarian cancer families segregating a *BRCA1* mutation, but not among *BRCA2* families nor in *BRCA1/2* mutation-negative families.[1] Further, in a report from Poland, 91 mothers with breast or ovarian cancer and a founder *BRCA1* mutation had 122 daughters. Since 50% would be expected to be mutation carriers at birth, their observation that 61% of daughters who remained free of breast or ovarian cancer into young adulthood were mutation positive suggested a distorted transmission probability, favoring the mutant allele.[2] If real, these observations would provide a novel insight into the normal biological

*Correspondence: Dr JP Struewing, Laboratory of Population Genetics, 41 Library Dr, Room D702, Bethesda, MD 20892-5060, USA.
Tel: +1 301 435 8955; Fax: +1 301 435 8963; E-mail: js140a@nih.gov
Received 30 December 2003; revised 5 March 2004; accepted 18 March 2004

function of *BRCA1* and have implications for genetic epidemiologic methods used to estimate penetrance, such as kin-cohort,[3] because they often rely on the assumption of equal transmission of mutant and wild-type alleles. We addressed these provocative observations in two study settings: a sample of *BRCA1/2* mutation-positive families with multiple cases of breast and ovarian cancer,[4] and a community-based sample of Ashkenazi Jewish subjects tested for founder *BRCA1/2* mutations.[5]

## Materials and methods

We analyzed previously collected data from two study populations. The first consisted of all delineated members of families with multiple cases of breast and ovarian cancer (mean 6.1 cases per family) who were positive for *BRCA1* or *BRCA2* mutations.[4] Among the 28 families segregating *BRCA1* mutations and eight families segregating *BRCA2* mutations, there were 283 mutation carriers (196 tested directly and 87 inferred positive owing to detection of the mutation in offspring) and 471 subjects who tested negative and who were age 20 or older. We determined the sex of the 730 offspring of mutation carriers and of the 754 offspring of mutation-negative subjects. To calculate the transmission ratio, we determined the mutation status and cancer status of all offspring of *BRCA1* and *BRCA2* mutation carriers (tested and inferred, females and males).

The second study population included all unrelated Ashkenazi Jewish subjects who participated in a community survey of more than 5000 Washington area Jewish residents who gave permission for future use of their information.[5] All 5082 subjects were tested for the three common founder mutations in *BRCA1* (185delAG and 5382insC) and *BRCA2* (6174delT) and provided detailed family histories, including delineation of the age and cancer status of all first-degree relatives. We determined the sex of the siblings and children of the 58 *BRCA1* mutation carriers (194 relatives), the 57 *BRCA2* mutation carriers (175 relatives), and the 4864 mutation-negative subjects (16 997 relatives).

We calculated sex ratios by comparing the number of male and female offspring of subjects with known mutation status such that values less than one represent fewer sons than daughters. To determine whether the observed sex ratios deviated significantly from the expected value of 1.0, we calculated approximate confidence intervals using Woolf's method.[6] To compare the sex ratios between subjects with differing mutation status within the two study groups, we used the $\chi^2$ statistic to contrast all three groups (*BRCA1* carriers *vs BRCA2* carriers *vs* noncarriers; $\chi^2$ with 2 degrees of freedom) and for each two-way contrast (1 degree of freedom; *BRCA1 vs BRCA2* mutation-positive subjects, *BRCA1 vs* noncarriers, etc.). To assess the transmission ratio of *BRCA1* and *BRCA2*, we calculated the proportion who were mutation carriers among sons, and daughters without breast or ovarian cancer, by attained age (in 10-year intervals) and calculated a $\chi^2$ for trend to test whether the proportion positive decreased with increasing age.

## Results

Within the NCI *BRCA1/2* mutation-positive multiple-case families, the sex ratio among births to *BRCA1* mutation carriers was below one (0.85, 95% CI 0.68–1.06) but it was even lower among *BRCA2* mutation carriers (0.77, 95% CI 0.47–1.27) (Table 1). We found that the reduced sex ratio among children of mutation carriers was due largely to a distortion among the offspring of male mutation carriers (0.70, 95% CI 0.47–1.05 for offspring of male *BRCA1* mutation carriers and 0.42, 95% CI 0.16–1.10 for *BRCA2*); the ratios were only slightly below 1 for offspring of female *BRCA1* and *BRCA2* mutation carriers (0.92 and 0.98, respectively). The results for *BRCA1* differed when we included only offspring of individuals who were directly tested and found to be positive (ie, excluding those inferred positive); the sex ratio was 1.03. In contrast, the sex ratio was reduced even further, to 0.70, when we included only directly tested individuals from *BRCA2* families. Among siblings and children of unrelated subjects in the Washington Ashkenazi Study (WAS), the sex ratio was below one (0.90, 95% CI 0.61–1.34) for *BRCA1* mutation carriers, but was even lower for the *BRCA2* carriers (0.80, 95% CI 0.53–1.22) and near the expected (1.02) among *BRCA1/2*-negative subjects. The sex ratio was reduced only slightly among offspring of mutation-negative subjects from the NCI breast–ovarian cancer families (0.94). None of the sex ratios deviated significantly from the expected value of 1.0 (Table 1).

The sex ratios in *BRCA2* families were lower than for *BRCA1* families, but they were not statistically different between mutation groups within studies: comparing *BRCA1 vs BRCA2,* $\chi^2_{(1\,\mathrm{df})}$ was 0.21 ($P=0.7$) and 0.32 ($P=0.6$) for the multiple-case families and WAS, respectively. None of the comparisons of sex ratios between *BRCA1 vs* noncarriers, *BRCA2 vs* noncarriers, or three-level comparisons (*BRCA1 vs BRCA2 vs* noncarriers, 2 degrees of freedom) had *P*-values below 0.1.

To address the question of a potential distorted transmission ratio of mutant *BRCA1* alleles, we studied adult daughters without breast or ovarian cancer born to mutation carriers in the NCI multiple-case families; 39% were mutation carriers in *BRCA1* families and 44% were mutation carriers in *BRCA2* families (Table 2). The proportions of all tested sons who were mutation positive were 54 and 55% for *BRCA1* and *BRCA2*, respectively. When only the offspring of individuals directly tested were considered, the carrier proportions among daughters were 46 and 39% for *BRCA1* and *BRCA2*. Although based on small numbers,

**Table 1** Observed sex ratios in NIH *BRCA1/2* families and subjects compared to previous studies

| Gene/study group | Families or individuals (N) | Male offspring (N) | Female offspring (N) | Sex ratio (males:females) | 95% CI |
|---|---|---|---|---|---|
| *BRCA1 mutation positive* | | | | | |
| NCI breast–ovarian cancer families[a] | 28 | | | | |
| All mutation-positive subjects | 227 | 277 | 327 | 0.85 | 0.68, 1.06 |
| Excluding inferred positive subjects | 155 | 144 | 140 | 1.03 | 0.74, 1.43 |
| Age >40 | 199 | 262 | 315 | 0.83 | 0.66, 1.05 |
| Males only | 75 | 80 | 114 | 0.70 | 0.47, 1.05 |
| Females only | 152 | 197 | 213 | 0.92 | 0.70, 1.22 |
| Washington Ashkenazi Study[b] | 58 | 94 | 104 | 0.90 | 0.61, 1.34 |
| Prior studies | | | | | |
| Spanish breast–ovarian cancer families[c] | 17 | 109 | 218 | 0.50 | 0.36, 0.69 |
| Polish breast or ovarian cancer probands[d] | 57 | 53 | 73 | 0.73 | 0.44, 1.19 |
| *BRCA2 mutation positive* | | | | | |
| NCI breast–ovarian cancer families[a] | 8 | | | | |
| All mutation-positive subjects | 56 | 55 | 71 | 0.77 | 0.47, 1.27 |
| Excluding inferred positive subjects | 41 | 30 | 43 | 0.70 | 0.36, 1.34 |
| Age >40 | 45 | 51 | 68 | 0.75 | 0.45, 1.25 |
| Males only | 16 | 11 | 26 | 0.42 | 0.16, 1.10 |
| Females only | 40 | 44 | 45 | 0.98 | 0.54, 1.76 |
| Washington Ashkenazi Study[b] | 57 | 78 | 97 | 0.80 | 0.53, 1.22 |
| Prior studies | | | | | |
| Spanish breast–ovarian cancer families[c] | 15 | 150 | 175 | 0.86 | 0.63, 1.17 |
| *BRCA1/2 mutation negative* | | | | | |
| NCI breast–ovarian cancer families[e] | 36 | | | | |
| Mutation-negative subjects | 471 | 365 | 389 | 0.94 | 0.77, 1.15 |
| Washington Ashkenazi Study[b] | 4864 | 8600 | 8397 | 1.02 | 0.98, 1.07 |
| Prior studies | | | | | |
| Spanish breast–ovarian cancer families[c] | 36 | 344 | 315 | 1.09 | 0.88, 1.36 |

[a]Families from Struewing *et al*[4] and additional families; columns for males and females include all children of individuals whose mutation status was known.
[b]Unrelated Ashkenazi volunteers tested for three founder mutations who gave permission for future use of their information; columns for males and females include siblings and children of tested individuals.[5]
[c]Spanish families with three or more cases of breast or ovarian cancer tested for *BRCA1/2* mutations (total 82 mutation-positive individuals); columns for male and female offspring include all subjects in pedigree.[1]
[d]Includes only subjects unselected for family history among Polish breast or ovarian cancer patients testing positive for one of three founder BRCA1 mutations; columns for male and female offspring include only children of tested subjects.[2]
[e]Includes subjects from *BRCA1/2* mutation-positive families who tested negative for the family mutation; columns for males and females include only children of the 471 subjects who were directly tested and found to be negative.

there was a lower proportion of carriers among older unaffected daughters, with a statistically significant trend ($\chi^2_{(1\,\mathrm{df})} = 6.26$, $P = 0.01$) (Table 2).

## Discussion

Our data suggest that the sex and transmission ratios associated with *BRCA1* mutations are not distorted. We have failed to replicate previous observations[1,2] despite similar to or larger sample sizes and believe they represent chance findings. The sex ratio was only modestly reduced in our multiple-case *BRCA1* families (0.85) and in a community-based sample of Ashkenazi Jewish *BRCA1* mutation carriers (0.9). These reductions were less pronounced than in *BRCA2* families from the same studies, and in none of the subgroups analyzed did the sex ratio deviate significantly from the expected value of 1.0. Most importantly, there were no statistically significant differences between *BRCA1*-positive *vs BRCA2*-positive *vs* mutation-negative families as was observed by de la Hoya *et al*.[1]

Assuming equal transmission probabilities for a mutant and wild-type allele and equal prenatal viability, one-half of the offspring of *BRCA1/2* mutation carriers will carry the mutation at birth. When one considers only daughters who remain free of breast and ovarian cancer into

**Table 2** Observed transmission ratios in NIH *BRCA1/2* families compared to a previous study

| | *Unaffected daughter's mutation status* | | | | | |
|---|---|---|---|---|---|---|
| | *NCI families*[a] | | | *Polish probands*[b] | | |
| *Unaffected daughter's age* | *BRCA1 carriers (N)* | *BRCA1 noncarriers (N)* | *Proportion carriers*[c] *(%)* | *BRCA1 carriers (N)* | *BRCA1 noncarriers (N)* | *Proportion carriers (%)* |
| 0–19 | | | | 12 | 14 | 46 |
| 20–29 | 4 | 3 | 57 | 38 | 18 | 68 |
| 30–39 | 8 | 11 | 42 | 16 | 10 | 62 |
| 40–49 | 18 | 21 | 46 | 9 | 5 | 64 |
| 50–59 | 14 | 16 | 47 | | | |
| 60+ | 3 | 24 | 11 | | | |
| Total | 47 | 75 | 39 | 75 | 47 | 61 |

[a]Mutation status of 122 tested daughters without breast or ovarian cancer whose mother or father was identified as *BRCA1* mutation positive from breast–ovarian cancer families (includes parents directly tested and those inferred to be positive).
[b]Mutation status of 122 tested daughters without breast or ovarian cancer whose mother was identified as *BRCA1* positive.[2]
[c]$\chi^2$ (trend test, 1 df) = 6.26, $P = 0.01$.

adulthood, the proportion should be below 50% because women who develop cancer, who will disproportionately be mutation carriers, are removed from the calculation. These considerations make the data from Poland,[2] suggesting an increased transmission rate of mutant *BRCA1* alleles to female offspring, very striking. If true, it would provide an important insight into the normal biology of this gene. In addition, it would have implications for family-based genetic epidemiologic methods used to estimate penetrance because they rely on the assumption of equal transmission probabilities for the mutant and wild-type alleles.[3] We found no evidence to support a distorted transmission ratio. On the contrary, fewer than 50% of unaffected daughters of *BRCA1* mutation carriers were themselves positive, and our observations were consistent with the expected trend of fewer carriers among older, unaffected daughters.

Studying sex ratios in families ascertained because of a sex-limited phenotype, such as familial breast and ovarian cancer, is challenging. One might expect the sex ratio to be below one owing to ascertainment criteria alone (ie, families that by chance contain predominantly male offspring will be less likely to demonstrate the clustering of female cancers required to meet study entry criteria). Moreover, since females are disproportionately affected in these syndromes, female relatives may be more likely to be reported by probands and recorded by investigators when family histories are taken. The absolute magnitude of this sex ratio bias would be difficult to predict *a priori*, even if the family sizes and ascertainment criteria are known, without precise knowledge of penetrance and differential reporting of relatives. Assuming similar penetrance, however, one would not expect the sex ratio to be different between families subsequently found to segregate mutations in *BRCA1 vs BRCA2*. Hence, while the findings of sex ratios below one were not surprising in the Spanish data,[1] that it was significantly lower in *BRCA1*-positive families compared to *BRCA2*-positive and *BRCA1/2*-negative families was noteworthy. We did not observe a significant difference between these mutation subgroups in our study populations.

In calculating sex ratios, we considered all offspring (both mutation known and mutation unknown subjects) only of subjects in whom we had directly tested or inferred their mutation status (ie, the children of subjects whose mutation status was unknown were not included in the calculations). As a result, differences in which subjects decide to get tested in a family may partially explain the reduced sex ratios we observed. Men have less compelling personal health reasons for being tested and instead are more likely to be tested if they have children.[7] If men (and/or women) with daughters are more likely to participate in family genetic studies and are more likely to seek testing than men with sons, this would result in a reduced sex ratio. Similarly, if men are even more likely to be tested if they have daughters with breast or ovarian cancer, this would further reduce the sex ratio associated with mutation carriers because such men will often test positive for the family mutation. Our observation of even lower sex ratios among offspring of male mutation carriers supports this idea.

The observed sex ratio among the offspring of *BRCA1* mutation carriers differed depending on whether subjects were tested directly (1.03) or inferred to be positive (0.71). The lower sex ratio for offspring of inferred mutation carriers may be an artifact. Many of these subjects were deceased women with breast or ovarian cancer. To be inferred positive these women must have had children, and at least one descendant had to have tested positive. This scenario is weighted toward individuals with daughters, because daughters develop the syndromic cancers and more often seek testing. We did not see the same

phenomenon in the *BRCA2* families, but these calculations were based on only 15 subjects who were inferred to be positive for *BRCA2*.

In summary, data from two study settings do not support the hypothesis that the sex and transmission ratios are particularly distorted in *BRCA1* families: we observed no significant differences in the sex ratio comparing *BRCA1*-positive *vs BRCA2*-positive *vs BRCA1/2*-negative subjects, and the proportion of daughters without breast and ovarian cancer born to *BRCA1* mutation carriers decreased with the age of the daughter and was below 50% overall. The reduced sex ratios we observed were more consistent, and of greater magnitude, in our *BRCA2* families, but in no case did the ratios vary significantly from 1.0. We expect that these observations on sex/transmission ratios primarily reflect the biases inherent in family-based studies of a sex-limited phenotype and that the previous observations of significant distortions were due to chance.

## References

1 de la Hoya M, Fernandez JM, Tosar A *et al*: Association between BRCA1 mutations and ratio of female to male births in offspring of families with breast cancer, ovarian cancer, or both. *JAMA* 2003; **290**: 929–931.
2 Gronwald J, Gorski B, Byrski T *et al*: Non-random transmission of mutant alleles to female offspring of BRCA1 carriers in Poland. *J Med Genet* 2003; **40**: 719–720.
3 Wacholder S, Hartge P, Struewing JP *et al*: The kin-cohort study for estimating penetrance. *Am J Epidemiol* 1998; **148**: 623–630.
4 Struewing JP, Brody LC, Erdos MR *et al*: Detection of eight *BRCA1* mutations in 10 breast/ovarian cancer families, including 1 family with male breast cancer. *Am J Hum Genet* 1995; **57**: 1–7.
5 Struewing JP, Hartge P, Wacholder S *et al*: The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. *N Engl J Med* 1997; **336**: 1401–1408.
6 Schlesselman JJ: *Case–Control Studies*. New York, NY: Oxford University Press; 1982.
7 Biesecker BB, Ishibe N, Hadley DW *et al*: Psychosocial factors predicting *BRCA1/BRCA2* testing decisions in members of hereditary breast and ovarian cancer families. *Am J Med Genet* 2000; **93**: 257–263.