BRCA mutation carriers

Battle of the *BRCA1/BRCA2* (offspring) sex ratios: truth or consequences

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Recent publications suggesting a skewed ratio of female to male births and a non-dominant transmission of mutant alleles to female offspring of *BRCA* mutation carriers have highlighted important potential implications when counselling affected individuals.^{1,2} As the cancers seen in the hereditary breast and ovarian cancer syndrome (HBOC) are predominantly breast and ovarian cancers, one would expect that families with an increased number of female offspring would be more likely to have family histories suggestive of HBOC—specifically a number of breast or ovarian cancers, or both, in two or more generations. Families with more female offspring may also be more likely to seek genetic counselling. Many women with breast cancer who have female children undergo genetic counselling and testing because of concerns for the risks to their children. For these reasons, these studies are difficult to do, and despite the authors' best efforts are subject to ascertainment bias. It is imperative that results regarding sex ratios in this population be interpreted carefully.

The ideal study would require a more population based approach, with testing carried out on a cohort of individuals and their offspring without attention to their family history. Various issues make this approach impractical, including but not limited to the cost of testing and the nature of genetic testing, in that it is not a "routine" type of laboratory test that can be done without any understanding of the implications of a positive test and a follow up plan in place to deal with individuals who are found to have a mutation.

In the first paper to address this issue, by de la Hoya and colleagues, the sex ratio of offspring was studied in 68 Spanish families who had been previously screened for mutations in *BRCA1* and *BRCA2*.¹ These families were all tested on the basis of a strong family history, with at least three breast or ovarian cancers reported in two generations. The investigators discovered a twofold excess of female births in the *BRCA1* mutation carriers (218 female v

109 male births, or 67%), but this increased ratio of female offspring was not seen in carriers of *BRCA2* mutations or *BRCA* unrelated cases. A sex ratio distortion may not have been seen in the *BRCA2* carriers owing to the later ages of onset of breast cancer often seen in these families as well as the greater likelihood of male breast cancers in affected individuals.

In the second study, by Gronwald *et al*, the prevalence of founder *BRCA1* mutations was measured in 122 unaffected daughters of 91 carrier women.² These 91 carrier mothers were identified from a group of 387 carrier probands. There were 247 with one or more daughters, and to avoid selection bias the families in which daughters were tested before the mothers received their results were eliminated. Seventy five of the daughters (61.5%) were found to be carriers. Sixty three sons were also tested, and only 30 mutations were found (47.6%). In this study, bias was introduced into the study design. The women who participated in the study had to have unaffected daughters, and as such, their population may have been enriched with female offspring (if an affected woman only had sons, she could not participate).

A similar analysis in an English cohort was carried out by Evans *et al*, finding no evidence of non-random transmission.³ In this study, the ratio of positive predictive tests in first degree relatives of proven mutation carriers from 284 *BRCA1* and *BRCA2* families was analysed. As in the Gronwald study, women affected by cancer or whose daughters were affected by cancer were excluded. The frequency of positive tests was 45% overall and 51% in women less than 50 years of age; it was substantially more than 50% in the 30 to 39 year age group, although this was not statistically significant. The investigators felt that the differences between these studies was probably related to differences in ascertainment strategies and that further study of the issue was warranted.

A study of sex ratio among the offspring of individuals with germline

mutations of *BRCA1* or *BRCA2* from three cancer clinics in metropolitan Paris was subsequently carried out by Fuenteun and colleagues.⁴ In all, 592 families were identified, 382 with *BRCA1* mutations and 210 with *BRCA2* mutations. The sex ratio of offspring was reported for both the male and female carriers of mutations in both *BRCA1* and *BRCA2*. When all the male *BRCA1* and *BRCA2* mutation carriers were included, there was an excess of female offspring (0.69 and 0.80, respectively; expected ratio 1.0). When only the male carriers without affected daughters were analysed, the sex ratio was 0.94. For the offspring of all female *BRCA1* and *BRCA2* mutation carriers, a female predominance was also noted (0.77 and 0.78, respectively). When only women without affected daughters were analysed, the sex ratio among offspring remained lower than expected (0.83 for *BRCA1* and 0.81 for *BRCA2*). In this study, Fuenteun and colleagues attempted to correct for ascertainment bias by examining both male and female carriers without affected daughters. In the male carriers, the skewed sex ratios normalised when only those families with unaffected daughters were examined. Surprisingly, this excess of female births was still seen in the female carriers with affected daughters.

Several studies have been undertaken subsequently in an effort to validate these results, but none has demonstrated a similar skewed sex ratio or non-random transmission. An analysis of 511 *BRCA1* carriers and 278 *BRCA2* carriers from 194 families ascertained from three sources in Australia and the USA found no evidence of sex ratio skewing of offspring.⁵ In the two Australian cohorts, the gender ratio was approximately 50%. In the cohort from the USA, there was a deficiency of male offspring in the *BRCA1* families (41.7% for male carriers and 44.2% for female carriers) which was not seen in the *BRCA2* families. The investigators determined that these data did not support the previous conclusions of a skewed sex ratio in offspring of *BRCA* carriers, and felt that the results seen in the 39 families from the USA reflected an ascertainment bias, as they were originally selected for linkage analysis. Another study addressed this question by examining the sex ratios of the offspring of 1040 women (299 *BRCA1* carriers, 104 *BRCA2* carriers, and 707 non-carriers) from five different centres, finding no evidence of sex ratio distortion.⁶

Another interesting study evaluated the sex ratio of offspring in two groups: the first group comprised 283 *BRCA1* mutation carriers and 471 mutation negative individuals from carrier

families (NCI study); the second, relatives of 115 *BRCA1/2* carriers from the Washington Ashkenazi study.⁷ Although the male to female ratio was less than 1 in both the *BRCA1* and *BRCA2* families, this did not reach statistical significance (the 95% confidence intervals included 1.0). Importantly, there was no difference between *BRCA1* positive and *BRCA2* positive families. To address the question of distorted transmission of *BRCA1* alleles, unaffected adult daughters and sons were studied. Of the adult daughters without breast or ovarian cancers born to mutation carriers, 39% inherited the familial *BRCA1* mutation and 44% the familial *BRCA2* mutation. The proportion of mutation positive individuals decreased with advancing age of the unaffected daughter. Based on an autosomal dominant inheritance pattern, one would expect one half of the offspring of mutation carriers to carry the mutation at birth. Of course, when looking only at unaffected individuals, a transmission rate of less than 50% would be expected. Of the sons of mutation positive individuals, 54% tested positive for the familial *BRCA1* mutation and 55% for the familial *BRCA2* mutation. These data suggest that not only is the sex ratio of offspring not skewed in *BRCA* families, but also the transmission ratios associated with *BRCA1* mutations are not distorted.

Additional studies looking at the offspring of Jewish women with *BRCA1/2* mutations or at high risk for breast and ovarian cancer⁸ and mutation carriers evaluated at the University of Michigan and University of Pennsylvania⁹ also failed to detect skewed sex ratios among the offspring. In addition, Gronwald

and colleagues published an analysis of additional families in Poland.¹⁰ In this analysis, the estimated transmission ratios for daughters and sisters of affected individuals were closer to the expected rate of 50% (52% and 55%, respectively). The investigators concluded, therefore, that these data did not support the earlier claim of non-dominant transmission.

In conclusion, although initial studies indicated a skewed sex ratio among the offspring of *BRCA* mutation carriers, significant ascertainment bias may have affected these results. As most families who present for genetic counselling do so because of their concern for their unaffected daughters, it is difficult to sample the population accurately. Several additional studies evaluating a variety of different populations have failed to verify this sex ratio skewing. Studies assessing the transmission of mutations to offspring are also subject to similar biases. It must be said that, pending further persuasive data, the battle of the *BRCA1/2* offspring sex ratio is over, and it appears to be a tie.

ACKNOWLEDGEMENTS

My thanks to William D. Foulkes MB PhD, Director, Program in Cancer Genetics, McGill University, Montreal, Canada.

J Med Genet 2006;**43**:201–202.
doi: 10.1136/jmg.2004.028977

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Received 5 May 2005

Accepted for publication 10 July 2005

Published Online First 29 July 2005

Conflicts of interest: none declared

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