Association Between \textit{BRCA1} Mutations and Ratio of Female to Male Births in Offspring of Families With Breast Cancer, Ovarian Cancer, or Both

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Context Defects in X-chromosome inactivation distort sex ratio in mice. The \textit{BRCA1} gene is also involved in X-chromosome inactivation, suggesting the possibility that some sex-ratio distortion may be associated with \textit{BRCA1}-related human cancer syndromes.

Objective To determine whether \textit{BRCA1} mutations are associated with distortion of the sex ratio of births in families with breast cancer, ovarian cancer, or both.

Design and Setting Analysis of germline mutations in participants from Spain who had been screened for \textit{BRCA} between 1998 and 2002.

Participants Sixty-eight families with at least 3 breast cancer cases or ovarian cancer cases, or both types of cancer in 2 generations (germline mutations: \textit{BRCA1}, \(n=17\); \textit{BRCA2}, \(n=15\); and \textit{BRCA} unrelated, \(n=36\)). An average of 4 relatives per family were tested for the corresponding \textit{BRCA} mutation.

Main Outcome Measure Male and female births registered in breast and/or ovarian pedigrees tested for the presence of \textit{BRCA1} and \textit{BRCA2} germline mutations.

Results Of \textit{BRCA1}-related breast and/or ovarian cancer pedigrees, there was a 2-fold excess of female births (218 female vs 109 male births). Of \textit{BRCA2}-related or \textit{BRCA}-unrelated breast and/or ovarian cancer pedigrees, there was not an excess of female births (175 female/150 male and 344 female/315 male, respectively). Of 327 \textit{BRCA1} births, 218 (67\%) were female births compared with 54\% among \textit{BRCA2} pedigrees (175/327; \(P<.001\)) and 52\% among \textit{BRCA}-unrelated pedigrees (344/659; \(P<.001\)). Female births increased in the offspring of \textit{BRCA1} carriers compared with \textit{BRCA2} carriers (67\% vs 52\%; \(P=.004\)).

Conclusion In these families with breast and/or ovarian cancer, mutations in \textit{BRCA1} but not \textit{BRCA2} were associated with a sex ratio skewed against male births.

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To determine the sex ratio of births in the offspring of carriers, we considered either BRCA carriers confirmed by genetic testing (n=56) or nontested obligated carriers (n=26). The χ² test was used in all statistical analyses and was performed using Epi Info statistical software (Version 5.01; Centers for Disease Control and Prevention, Atlanta, Ga).

RESULTS

Overall, BRCA1 pedigrees were strongly skewed against male births: 218 females vs 109 males (Table 1). By contrast, BRCA2 pedigrees (175 female vs 150 male births), and BRCA-unrelated pedigrees (344 female vs 315 male births) were close to the expected 50% sex ratio (Table 2). The excess of female births observed in BRCA1 pedigrees is significant when compared with BRCA2 pedigrees (67% vs 54%; χ² = 11.19; P < .001) or BRCA-unrelated pedigrees (67% vs 52%; χ² = 18.66; P < .001) (FIGURE). The sex ratio was also skewed against male births in the offspring of BRCA1 carriers: 133 female (67%) vs 65 male (33%) (Table 1). On the other hand, the offspring of BRCA2 carriers have shown no evidence of sex-ratio abnormalities: 84 (52%) female births vs 77 (48%) male births (Table 2). These data support an association between BRCA1 defects (but not BRCA2 defects) and sex ratio skewed against male births in the offspring (χ² = 8.35; P = .004).

COMMENT

Taken together, our data confirm a sex-ratio distortion associated with BRCA1 mutations. Our findings were unexpected, but may be partly explained by recent data suggesting both a link between X-chromosome inactivation (XCI) and sex ratio² and a role for BRCA1 in XCI.³,⁴ Although XCI is a poorly understood biological process, XIST and TSIX genes (acting...
on chromosome inactivation) are known to have opposite roles in XCI regulation. In current XCI models, \textit{XIST} RNA accumulation along an X chromosome promotes silencing along that chromosome. The expression of TSIX (its antisense counterpart) blocks \textit{XIST} accumulation and therefore inhibits XCI. An association between \textit{BRCA1} and XCI dysfunction was first described in patients with \textit{BRCA1} germline mutations and/or ovarian cancer.\(^2\) Recently, a direct role for \textit{BRCA1} in XCI has been suggested as \textit{XIST} RNA concentration in the inactive X chromosome is dependent on \textit{BRCA1} status.\(^3\)

Defects in XCI may distort sex ratio as has been shown in homozygous TSIX mutant mice.\(^2\) Lee\(^3\) demonstrated that by abolishing TSIX activity, the sex ratio is skewed against female births. One hypothesis is that \textit{BRCA1} haploinsufficiency affects the ability of \textit{XIST} RNA to accumulate along the X chromosome, mimics \textit{XIST} inhibition, and produces an opposite sex-ratio distortion; ie, a sex ratio skewed against male births.

In conclusion, we report, for the first time to our knowledge, a phenotype associated with \textit{BRCA1} but not \textit{BRCA2} or \textit{BRCA}-unrelated breast and/or ovarian cancer, resulting in a sex ratio skewed against male births in the offspring of mutation carriers.

**Author Contributions:** Study concept and design: de la Hoya, Caldes. Acquisition of data: de la Hoya, Fernández, Tosar, Godino, Sánchez de Abajo, Pérez-Segura, Caldes. Analysis and interpretation of data: de la Hoya, Vidart, Pérez-Segura, Diaz-Rubio, Caldes. Drafting of the manuscript: de la Hoya, Caldes. Critical revision of the manuscript for important intellectual content: Fernández, Tosar, Godino, Sánchez de Abajo, Vidart, Pérez-Segura, Diaz-Rubio, Caldes. Statistical expertise: de la Hoya. Obtained funding: de la Hoya, Diaz-Rubio, Caldes. Administrative, technical, or material support: Fernández, Tosar, Godino, Sánchez de Abajo, Vidart, Pérez-Segura, Diaz-Rubio. Study supervision: Caldes.

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**REFERENCES**


If art teaches anything...it is the privateness of the human condition. Being the most ancient as well as the most literal form of private enterprise, it fosters in a man, knowingly or unwittingly, a sense of his uniqueness, of individuality, of separateness—thus turning him from a social animal into an autonomous “I.”

—Joseph Brodsky (1940-1996)