Effects of BRCA Gene Mutations on Female Fertility and Offspring Sex Ratio

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Introduction

Ovarian cancer has the highest rate of hereditary incidence worldwide. 10-15% of all ovarian cancer cases are due to inherited genetic mutations and about 90% of those inherited cases are due to mutations in two breast and ovarian cancer susceptibility genes, BRCA1 and BRCA2. Ethnic-specific and founder mutations in the BRCA genes have been reported. Three mutations in these two genes (185delAG and 5382insC in BRCA1 and 6174delT in BRCA2) have a combined frequency of around 2.5% in the Ashkenazi Jewish population. Based on recent in-vitro studies of BRCA protein expressions, we hypothesized that mutations in the BRCA genes may have an effect on fertility. Distorted sex ratios among the offspring of BRCA mutation carriers have been reported by some and disputed by others.

Objectives

Objectives for the present study were to examine the
(i) Effect of BRCA mutations on sex ratio among offspring of known and obligate mutation carriers
(ii) Effect of BRCA mutations on female fertility

Methods and Materials

Analyses for the current study were done on a hospital-based case-control study of ovarian cancer conducted for genetic characterization of the BRCA genes. Cases (n = 286) were Ashkenazi Jewish women of United States of America with ovarian cancer unselected for age or a family history of the disease. Controls (n = 331) were Ashkenazi Jewish women without personal history of ovarian cancer. Detailed epidemiologic and family history information was available for all the study participants. BRCA mutation status of cases was known.

Male to female sex ratios of the offspring of known and obligate BRCA mutation carriers, non-carriers and controls were calculated. Sex ratios among the three groups were compared by calculating odds ratios.

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Extended Abstract

Unadjusted analyses of fertility included comparison of pregnancies between *BRCA* carriers, non-carriers and controls. Adjusted analyses on fertility of the three groups of women were done by incorporating covariates (age, oral contraceptive use, Body Mass Index, regularity of menstrual cycle, history of tubal ligation and hysterectomy) into the model assuming incidence of pregnancies for each woman as a Poisson process. Person time for each woman was calculated by taking the time between 18 and 44 years of age when a woman was at risk for pregnancy. From the person time, we have excluded the time when she was on contraception and two months after each pregnancy when the woman was not considered at risk for pregnancy. We censored subjects if they had tubal ligation, hysterectomy or menopause before 44 years of age.

**Results**

Ovarian cancer case were significantly older than controls (*P*=0.002); mean age at interview was 58, 60, and 52 years for carrier cases, non-carrier cases, and controls, respectively. 67 (25%) cases were carriers of a *BRCA1* mutation and 30 (11%) were *BRCA2* carriers. There were differences with respect to oral contraceptive use, regularity of periods, body mass index, medication to become pregnant, education, alcohol drinking and smoking between cases and controls; these variables were adjusted for in fertility analyses.

Male/female ratios were 0.707, 0.953, and 0.988 among 256 offspring of known and obligate *BRCA* carrier cases (n=133), 662 offspring of non-carrier cases (n=331) and 1205 offspring of controls (n=662), respectively. The sex ratios among the offspring of known and obligate *BRCA* carriers were significantly distorted towards females as compared to non-carriers (OR=0.74, 95%CI: 0.55, 0.99) and controls (OR=0.72, 95%CI: 0.54, 0.94).

The unadjusted analyses of fertility showed no statistically significant differences in average number of pregnancies among the three groups. Adjusted analyses revealed lower pregnancy rates among cases compared to controls, as expected. Application of Poisson regression model on rate of pregnancy also yielded significantly lower fertility for cases compared to controls. *BRCA* mutation carriers were also found to have lower fertility than non-carriers and controls; however, the differences did not reach statistical significance.

**Conclusions and implications**

Our results are in agreement with a previous finding of significantly higher number of females among the offspring of *BRCA* mutation carriers. Several potential mechanisms underlying this observation have been suggested.
Despite the suggestions made through in vitro and animal studies, BRCA mutations may not have a significant impact on fertility as we did not find a statistically significant difference between mutation carrier and non-carrier cases in average number of pregnancies and overall fertility. These results need further confirmation and we provide an effective method for comparison of fertility. Nulliparity is considered to be a risk factor for ovarian cancer among women in the general population; there are also reports of decreased risk of ovarian cancer associated with increase in number of pregnancies. In accordance with those findings, we found lower number of pregnancies and an overall decreased fertility among ovarian cancer cases compared to healthy controls in our study.

Our study design eliminated several sources of bias reported in previous studies as potential confounders of the results. A previous study reporting distortion towards females among the offspring of BRCA carriers was criticized for using cases selected based on the presence of a significant family history of breast and ovarian cancer. Increased likelihood for women with daughters seeking genetic testing and counseling was quoted as a potential bias for their observations. The cases in our study were unselected for a family history of the disease; all cases were recruited from hospitals and criteria for recruitment did not include an increased likelihood of being a BRCA carrier. Furthermore, in order to eliminate any type of ascertainment bias in our tests, we performed the analyses 2 ways: once by including the proband (An individual or member of a family being studied in a genetic investigation) in the analyses and once by removing the probands and performing the analyses on the offspring of the known and obligate BRCA carriers among the mothers of the probands. We found a significantly higher number of females among the offspring of BRCA carriers in both analyses.

Results of this study contribute to increased understanding of biological mechanisms associated with BRCA mutations, which may lead to better counseling services and management options for mutation carriers.

Limitation of our study include secondary usage of data and relatively small number of BRCA carriers (n<100) in our sample.