Effects of BRCA1 and BRCA2 Mutations on Fertility and Later-Life Survival

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Introduction

Women who are BRCA1 and BRCA2 mutation carriers have an estimated 40% to 85% lifetime risk of developing breast cancer and 16% to 64% risk of ovarian cancer [1, 2]. These are significant excess risks and it raises questions about the potential benefits of BRCA1/2 mutations since they are prevalent in certain subpopulations, Ashkenazi Jewish women, for example. Was there selective pressure that conserved the BRCA1/2 mutations despite their deleterious health effects? Could women with these mutations, whose breast and ovarian cancer arise typically after menopause, be more fertile and better able to keep their offspring alive? There are no known studies that assess shifts in fertility over time among BRCA1/2 mutation carriers in relation to the general population.

The purpose of this study is to address three questions. First, from an evolutionary standpoint, what mechanisms might explain why BRCA1 and BRCA2 mutations persist in human populations given their adverse health consequences effects? Genetic variants have been shown to have multiple functions, with the beneficial effects possibly outweighing the adverse effects [3]. We hypothesize that BRCA1/2 gene mutations have pleiotropic effects by increasing cancer incidence and mortality in middle and later adulthood while also enhancing reproductive fitness. Second, how has fertility behavior changed with the advent of genetic testing where individuals may now make family planning decisions based on a family cancer history or predictive genetic risk information heretofore unavailable? We hypothesize that the family cancer history and the advent of genetic testing along with the availability of effective family planning methods leads to lower levels of fertility over time for female BRCA1/2 mutation carriers in relation to non-carriers. Lastly, what is the mortality consequence of being a BRCA1/2 mutation carrier? We hypothesize that mutation carriers have excess mortality risks in relation to non-carriers given the penetrance of these mutations and their association with relatively common and serious reproductive cancers. This association is expected given that breast and ovarian cancer occur late in life and would be subjected to very weak selection effects over the evolutionary past.

Study Design

BRCA1/2 mutation carriers were selected based on their participation in two longitudinal studies. First, participants from a large, prospective study that analyzed the fertility behaviors and attitudes of BRCA1 mutation carriers were selected. Participants of this study were

members of a large Utah kindred (K2082) with an identified mutation at the BRCA1 locus. To increase our sample size and include mutation carriers of another serious mutation at the BRCA2 locus, participants from the High Risk Breast Cancer Clinic (HRBCC) at the University of Utah's Huntsman Cancer Institute (HCI) were also selected. The HRBCC is a research and clinical resource for individuals with a family history of breast and ovarian cancer. A detailed description of methods, eligibility criteria, and protocol for both studies has been described elsewhere [4, 5]. There were 449 subjects from 66 kindreds (each with a unique founder) selected for this study based on the availability of their genetic test results. Genetic testing for individuals in K2082 or the HRBCC was conducted after these individuals were provided extensive genetic counseling and gave their informed consent. Subjects were then classified as a BRCA1 mutation carrier or a BRCA2 mutation carrier. Both studies were approved by the University of Utah's Institutional Review Board and the Resource for Genetic and Epidemiologic Resource.

Information about the relatives of each of the carriers was obtained from the Utah Population Database (UPDB). UPDB is a linked genealogical resource used for biomedical research. UPDB houses nearly 9 million genealogical, demographic and medical records [6]. Linked genealogical and birth certificate records construct multi-generational pedigrees that range from 2 to 10 generations. Data from Utah's driver licenses, Centers for Medicaid and Medicare Services (CMS), Social Security Death Index, the Utah Cancer Registry, Idaho Cancer Registry and Utah death certificates are linked to the genealogical records to construct a powerful biodemographic research database.

Pedigree information of carriers was used to identify ancestors known to be mutation carriers. Mutation status of ancestors in the UPDB was imputed based on pedigree position and relationship to multiple tested carriers. Families with multiple tested mutation carriers were reviewed to identify the transmission of the gene through the pedigree. Ancestors connected to two or more descendants who were found to be mutation carriers were identified as putative obligate gene carriers (See Figure 1 for a simple example). The largest pedigree identified putative obligate carrier's five generations above the youngest tested carrier. Tested and putative obligate carriers involved in a polygamous relationship were not selected. There were 177 putative obligate carriers identified, yielding a total of 626 tested and obligate carriers combined.

Founders were identified for the 66 kindreds with a known mutation. Controls were then selected from UPDB excluding any descendants of these 66 founders. Controls were selected by matching birth year, vital status, death year, and age at first birth. By choosing age at first birth as a matching variable, we restricted the analysis to parous individuals who started their fertility at the same age. Death year (and vital status) was a matching variable because it addresses the potential that fertility differences between putative obligate carriers and controls might be due to differences in reproductive life span that vary because of mortality. This specific matching approach was selected because all putative obligate carriers's had at least one child survive to reproductive age by definition. To account for this possibility, controls were also required to meet the same criteria.

Several exclusion criteria were imposed. Fifty-three controls involved in a polygamous relationship were excluded. Seventy-eight carriers and 34,701 controls born after 1975 were excluded from the analysis as a result of their censored fertility experience.

The final sample included obligate and tested carriers (n = 487) and controls (n = 209,522). The unique infrastructure of UPDB allowed us to have a large number of matched controls that reflect fertility rates of the larger population conditional on the matching characteristics. The distribution of birth years among controls was statistically weighted to mirror the birth year distribution of the pooled obligate and tested carriers born before 1975.

A second file was created to analyze the mortality differences between BRCA1/2 mutation carriers and the general population. The original set of selected controls could not be used because death date was used as a matching variable. A second set of controls was selected from UPDB for the purposes of examining mortality differences between carriers and controls; these controls were matched on gender and birth year. There were only two putative obligate carriers born before 1835, so those subjects and their matched controls were dropped from the analysis. The final sample consisted of putative obligate carriers (n=170) and controls (n=6,837).

Statistical Methods. Children ever born (CEB) is the measure of fertility. To examine the relationship between fertility (CEB) and mutation status we used ordinary least squares regression. The availability of effective birth control methods was considered by performing separate regressions for putative obligate carriers born before 1930 and tested carriers born in or after 1930. The year 1930 was selected because women born later than that would still be

fecund and would have had access to modern family planning methods, most noteworthy exogenous hormones. Separate regressions were also performed for each gender in order to assess the differential effects of BRCA1/2 mutation status on fertility by gender. Mutation status was represented by a dummy variable, carrier vs. control. The other covariates used in this model were birth year and age at first birth.

A second model was estimated to assess effect modification of historical year. This was done by introducing a two-way interaction between mutation status and birth year. This model also included a term for sex × mutation status interaction to test for differential effects of mutation status by gender.

The effect of parental fertility patterns on CEB was also considered to consider the possibility that one's parent's fertility might be associated with both the subject's mutation status and fertility. The number of siblings was first added as a continuous and then categorical variable. Sibling data was not available for all subjects, reducing the sample sizes by 15 and 877 respectively for carriers and controls. The addition of parental fertility patterns did not fundamentally alter the effect of mutation status and consequently were not included in the models.

We investigated whether carriers were more likely to exceed the average number of children for their cohort. The association between fertility and mutation status was estimated by multiple logistic regression. The mean number of children for the sample was 2.7, so subjects with more than 3 children were classified as having "more" children. The dependent variable

is coded 1 if the subjects had three or more children; all other subjects were coded as 0. The other covariates used were birth year and age at first birth.

Finally, we investigated the mortality differences between BRCA1/2 carriers and controls for survival past age 45. This survival restriction was done to allow for fertility to be, for intents and purposes, completed. Survival was estimated for males and females born before 1920 using Cox proportional hazard models. The central comparison, then, is between putative obligate carriers, and controls.

Results

Descriptive statistics are displayed in Table 1. There is approximately a two child difference in CEB between controls and carriers.

Table 1 about here

Figure 2 illustrates CEB among females by mutation status by birth year. There is a clear excess of CEB for the combined group of female tested and putative obligate carriers compared to the controls. There is an unexpected drop in CEB for women born between 1905 and 1909. However, there were only four putative obligate carriers and their matched controls born during that time period. The effect gradually decreases over time leading to a convergence by the 1970 birth cohort.

Figure 1 about here

Table 2 reports the results of birth-year stratified OLS regressions showing the effects of mutation status on CEB. The results show that there is a significant association between mutation status and CEB for the pooled male/female sample (model 1), with obligate carriers having an average of nearly two more children controls among those born before 1930. The interaction model shows the difference between male and female obligate carriers is not significant although female fertility is are more sensitive to carrier status than male fertility although this association is shown more clearly in gender-specific models. For the gender specific models (models 4 and 6), we show that the main effect of carrier status is larger among women and does not change significantly over time. For males, the fertility effects of being a mutation carrier are smaller (p=.058) and decline with time.

Table 2 about here

The increase in fertility between obligate carriers and controls born after 1930 is half that of the increase between obligate carriers and controls born prior to 1930. In models 4 and 6, we find that for the latter cohort (born 1930-1975), the impact of being a (tested) carrier is now smaller for women than men.

Table 3 reports the results of birth-year-specific logistic regressions that use as the dependent variable whether an individual has three or more children or not. In the pooled- gender sample, obligate carriers born before 1930 are 3.9 times more likely to have more than 3 children than their control counterparts. Tested carriers born after 1930 are only 2.3 times

more likely to have more than 3 children. The female only models show that obligate carriers born before 1930 are nearly 5 times more likely to have more than 3 children, while carriers born after that time are approximately 2 times as likely. This shows a decline in fertility for female mutation carriers during or after the time when modern contraceptives became available. The male-specific model shows that obligate carriers born before and after 1930 are about 3 times more likely to have more than 3 children.

Table 3 about here

Finally, Table 4 shows results of Cox proportional hazard regressions for survival from age 45 among persons born before 1920. These analyses indicate that there are significant and large adverse effects of being an obligate carrier of a BRCA1 and BRCA2 mutation among females. Among males, there is a significant adverse effect of being an obligate carrier of a BRCA2 mutation but this is considerably smaller than that found for females.

Table 4 about here

Discussion

Over five hundred putative and tested obligate BRCA1/2 mutation carriers were compared to 244,276 matched controls to study the fertility differences of mutation carriers over time. To our knowledge there are no other studies that have directly studied fertility differences over time among BRCA1/2 mutation carriers. Our findings are consistent with our hypotheses: (1)

mutation carriers are more fertile than the general population, more so for women, (2) there has been a decline in fertility for female mutation carriers compared to the general population, and (3) female mutation carriers have excess mortality risks in relation to controls.

The association of fertility of mutation carriers has been noted previously but only in passing. A study investigating the effect of parity on breast cancer risk found that women with a BRCA2 mutation had higher fertility rates than the control populations, however the significance of the difference was not tested [7]. Two-thirds of BRCA2 positive cases had 3 or more children compared to 60.3% of the controls. A second study examining the association between parity and cancer risk in mutation carriers found a significantly higher mean number of births for carriers vs. controls [8]. These observations support our findings of increased fertility in mutation carriers.

One explanation for mutation carriers having increased fertility may be BRCA1/2's role in embryogenesis. Recent studies have shown that BRCA1/2 genes are involved in embryogenesis [9-12]. However, the results for these studies do not support our theory of increased reproductive fitness. Murine models have shown that homozygous deletions of BRCA1/2 result in embryonic lethality [10]. Heterozygous mice developed normally and were fertile. It is also widely believed that homozygous BRCA1/2 human embryos will spontaneously abort [1]. However, the parents would have to both carry the same gene mutation and only 25% of the conceptions would end in spontaneous abortion. The rate of marriage between carriers is expected to be low, making a significantly negative effect unlikely.

Other signs of BRCA1/2's involvement in embryogenesis have been studied. BRCA1's involvement in non-random inactivation of the X-Chromosome has also generated interest in sex ratio distortion among mutation carrier's families. It was suggested that BRCA1 families have an excess of female births. The same result was not found for BRCA2 families [12]. These findings would support the hypotheses that mutations in BRCA1 do affect embryogenesis, however multiple studies have shown that sex ratio effect is likely due to ascertainment bias [13].

Another contributor to mutation carrier's increased fertility could be the relationship between parity and cancer risk in mutation carriers. In the general population, an increase in parity is protective against breast cancer [14]. The relationship between parity and cancer risk in BRCA1/2 carriers is debatable. BRCA1 carriers with 4 or more children have been shown to have a 38% decreased life-time risk of breast cancer while BRCA2 carrier's risk increases as parity increases [15]. Another study has also shown that an increase in parity for mutation carriers is protective of ovarian cancer [16]. However, a further investigation found that parous mutation carriers are more likely to develop breast cancer by age 40 than those who are nulliparous [8]. When comparing differences between BRCA1/2 carriers to BRCA1/2 negative individuals with a family history of breast cancer, Jernstom et al. found no significant differences in reproductive risk factors [17]. The effects of breast feeding on BRCA1 mutation carriers are similar to that of the normal population. Carriers who breast fed longer than one year, cumulatively, have a decreased risk of breast cancer. The same association was not found for BRCA2 carriers [18].

We have presented two possible reasons for the increased reproductive fitness of mutation carriers. BRCA1/2's involvement in embryogenesis could contribute to the increased fertility in both genders. The protective effects of having more children would not explain the increase for male carriers, however their results are not as impressive.

While there are no studies that examine the fertility differences between BRCA1/2 carriers and the general population, there are studies that have looked at fertility intentions after genetic test results have been given. Knowledge of genetic testing status has been shown to affect family planning. Both carriers and those who chose not to be tested or did not know their genetic testing status were less likely to want additional children than non-carriers[19].

Fertility decisions may be influenced by the cancer diagnoses of the mutation carrier or of a close relative. Belief/attitude surveys were administered to cancer survivors of both genders. Approximately one third of the respondents believed that their children would have increased risk of developing cancer [20, 21]. Another study surveyed women diagnosed with breast cancer between 1994 and 1997 to address the communication of breast cancer risk to offspring. Eight percent of the parous women were worried about the cancer risk of their children [22]. Therefore, once the availability of effective contraception is available, BRCA mutation carriers may avail themselves of these family planning methods. This would allow them to reduce fertility and in turn reduce the risk of burdening their children with cancer.

Recent fertility differences may also be attributable to preventive guidelines for mutation carriers. In a study of behavioral differences two years after genetic testing, 46% of carriers had obtained bilateral oophorectomies [23]. A family history of cancer has also been found to influence the decision for prophylactic surgery before genetic testing [19]. This supports our prediction that fertility of carriers will be lower as a result of family history of breast/ovarian cancer.

The results of this study show a significantly higher fertility rate for mutation carriers vs. controls. The higher fertility rate could have be a pleiotropic characteristic of the BRCA1/2 mutation or a protective effect. We have also demonstrated a steeper decline in fertility over time for mutation carriers vs. controls. This could be attributable to a combination of knowledge of family history and preventive guidelines for mutation carriers.

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Table 1- Descriptive Statistics by Mutation Status and Birth Cohort				
Group	**Variable**	**N**	**Mean**	**SD**
Controls Born Before 1930	Birth Year	6,137	1905.66	60.21
	Age at 1st Birth	6,137	24.02	9.73
	Female (=1)	6,137	0.50	1.63
	Children	6,137	4.34	8.63
	Siblings	4,225	8.09	15.50
Controls Born In or After 1930	Birth Year	203,385	1952.64	9.76
	Age at 1st Birth	203,385	23.39	2.80
	Female (=1)	203,385	0.71	0.38
	Children	203,385	3.09	1.47
	Siblings	88,255	4.83	2.31
Putative Obligate Carrier Born Before 1930	Birth Year	143	1899.10	23.47
	Age at 1st Birth	143	24.26	3.78
	Female (=1)	143	0.48	0.50
	Children	139	6.32	3.07
	Siblings	124	9.34	3.94
Putative Obligate Carrier Born In or After 1929	Birth Year	29	1938.24	6.56
	Age at 1st Birth	29	22.14	2.84
	Female (=1)	29	0.69	0.47
	Children	29	4.79	1.90
	Siblings	28	5.57	2.78
Tested BRCA1/2 Mutation Carrier Born Before 1930	Birth Year	21	1921.10	4.43
	Age at 1st Birth	21	23.86	3.65
	Female (=1)	21	0.67	0.48
	Children	21	5.43	2.42
	Siblings	18	7.17	3.13
Tested BRCA1/2 Mutation Carrier Born In or After 1930	Birth Year	294	1954.06	11.27
	Age at 1st Birth	294	24.05	4.37
	Female (=1)	294	0.73	0.44
	Children	294	3.71	1.83
	Siblings	249	5.71	2.39

Table 2: Effects of BRCA1/2 Mutation Status on Children Ever Born Based on Multiple Linear Regression													
		Model 1. Main Effects		Model 2. Main Effects + Interaction		Model 3. Females Only: Main Effects		Model 4. Females Only: Main Effects + Interaction		Model 5. Men Only: Main Effects		Model 6. Men Only: Main Effects + Interaction	
Putative Positive vs. Control Birth Year < 1930	Variable	Estimate	P	Estimate	P	Estimate	P	Estimate	P	Estimate	P	Estimate	P
	Intercept	3.898	0.000	3.903	0.000	4.016	0.000	4.017	0.000	3.922	0.000	3.942	0.000
	Age (in years) at 1st Birth	-0.270	0.000	-0.270	0.000	-0.281	0.000	-0.280	0.000	-0.297	0.000	-0.299	0.000
	Birth Year (Unit=10)	-0.049	0.000	-0.048	0.000	-0.040	0.000	-0.040	0.000	-0.047	0.000	-0.046	0.000
	Positive (=1)	1.918	0.000	1.196	0.000	1.856	0.000	1.726	0.000	1.937	0.000	0.759	0.058
	Female (=1)	-0.827	0.000	-0.825	0.000								
	Birth Year (Unit=10) x Positive Interaction			-0.315	0.001			-0.110	0.514			-0.045	0.000
	Positive x Female interaction			0.527	0.209								
Tested Positives vs. Controls Birth Year 1930-1975	Intercept	2.842	0.000	2.842	0.000	2.886	0.000	2.886	0.000	2.720	0.000	2.724	0.000
	Age (in years) at 1st Birth	-0.111	0.000	-0.111	0.000	-0.108	0.000	-0.108	0.000	-0.112	0.000	-0.114	0.000
	Birth Year (Unit=10)	-0.040	0.000	-0.040	0.000	-0.038	0.000	-0.038	0.000	-0.040	0.000	-0.044	0.000
	Positive (=1)	0.753	0.000	0.679	0.000	0.699	0.000	0.646	0.000	0.922	0.000	0.763	0.000
	Female (=1)	-0.167	0.000	-0.167	0.000								
	Birth Year (Unit=10) x Positive Interaction			-0.192	0.024			-0.148	0.156			-0.263	0.050
	Positive x Female interaction			-0.192	0.373								

Table 3: Effects of Putative Obligate and Tested BRCA Mutation Carriers on Children Ever Born: Probability of Having 3 or More Children

		Putative Positive Carriers vs. Controls (Birth Year < 1930)					Tested Positive vs. Controls (Birth Year 1930 -1975)				
		Estimate	Pr > ChiSq	Odds Ratio	95% Wald Confidence Limits		Estimate	Pr > ChiSq	Odds Ratio	95% Wald Confidence Limits	
All: Main Effects	Intercept	0.022	0.705				-0.947	0.000			
	Age (in years) at 1st Birth	-0.248	0.000	0.781	0.755	0.807	-0.131	0.000	0.878	0.874	0.881
	Birth Year	-0.032	0.085	0.969	0.964	0.974	-0.045	0.000	0.956	0.955	0.957
	Positive (=1)	1.367	0.000	3.923	2.499	6.159	0.849	0.000	2.338	1.832	2.984
	Female (=1)	-0.890	0.000	0.411	0.342	0.493	-0.190	0.000	0.827	0.807	0.848
All: Main Effects + Interaction	Intercept	0.016	0.786				-0.947	0.000			
	Age (in years) at 1st Birth	-0.248	0.000	0.780	0.755	0.807	-0.131	0.000	0.878	0.874	0.881
	Birth Year	-0.032	0.000	0.968	0.963	0.973	-0.045	0.000	0.956	0.955	0.957
	Positive (=1)	1.124	0.000	3.077	1.676	5.649	0.809	0.000	2.245	1.723	2.924
	Female (=1)	-0.881	0.000	0.415	0.345	0.498	-0.190	0.000	0.827	0.807	0.848
	Birth Year (Unit=10) x Positive Interaction	-0.008	0.539	0.992	0.965	1.019	-0.011	0.355	0.989	0.966	1.012
	Positive x Female Interaction	0.631	0.176	1.880	0.753	4.689	-0.106	0.711	0.899	0.512	1.578
Females Only	Intercept	-0.219	0.026				-0.886	0.000			
	Age (in years) at 1st Birth	-0.210	0.000	0.811	0.765	0.859	-0.126	0.000	0.882	0.878	0.885
	Birth Year	-0.031	0.000	0.969	0.959	0.980	-0.043	0.000	0.958	0.957	0.959
	Positive (=1)	1.550	0.000	4.713	2.477	8.967	0.820	0.000	2.270	1.710	3.014
Males Only	Intercept	0.115	0.135				-1.131	0.000			
	Age (in years) at 1st Birth	-0.301	0.000	0.740	0.710	0.772	-0.161	0.000	0.851	0.845	0.857
	Birth Year	-0.035	0.000	0.966	0.960	0.972	-0.046	0.000	0.955	0.953	0.956
	Positive (=1)	1.192	0.000	3.292	1.751	6.192	1.001	0.000	2.720	1.684	4.393

Table 4. Effects of BRCA1/2 Mutations on Survival among Putative Obligate Carriers and Controls for Individuals born before 1920 and who survived to age 45.

Females					
Variable	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**
Birth Year	-0.01077	0.00114	89.8257	<.0001	0.989
BRCA1	0.77900	0.18470	17.7890	<.0001	2.179
BRCA2	1.15505	0.27982	17.0389	<.0001	3.174
Age 1st Birth	-0.02413	0.00618	15.2377	<.0001	0.976
CEB	0.0005088	0.00823	0.0038	0.9507	1.001

Males					
Variable	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**
Birth Year	-0.00656	0.00111	34.7084	<.0001	0.993
BRCA1	0.13355	0.16816	0.6308	0.4271	1.143
BRCA2	0.45552	0.22517	4.0925	0.0431	1.577
Age 1st Birth	-0.00401	0.00459	0.7613	0.3829	0.996
CEB	-0.01493	0.00654	5.2060	0.0225	0.985

Figure 1. Example of Identifying Putative Obligate Carriers

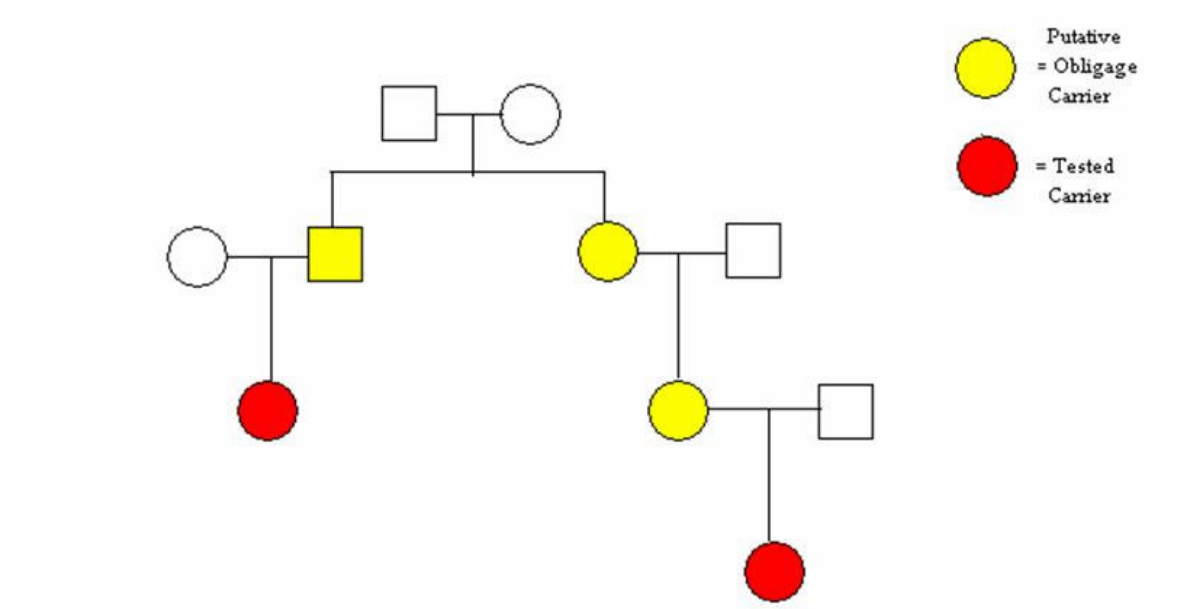

Figure 2. Children Ever Born among BRCA1/2 Mutation Carriers and Matched Controls.
Putative Obligate and Tested carriers Combined
Females Only