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BRCA1 and BRCA2 mutations and female fertility

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Abstract

Purpose of review—To review recent publications examining *BRCA1* and *BRCA2* mutations and their relationship with female fertility.

Recent findings—Eight relevant studies of female fertility, five of which were published since January 2010 and the remainder in the preceding decade. Several mechanisms suggest that reproduction will be adversely affected among *BRCA1/2* mutation carriers, with one study finding lower oocyte production, another reporting fewer births, and a third showing lower rates of pregnancies. Four articles reported no significant difference in the number of children ever born between carriers and noncarriers whereas a 2012 study showed elevated natural fertility among mutation carriers.

Summary—This review shows that for most articles there are adverse or no fertility effects of being a *BRCA1/2* mutation carrier. When no differences were detected for children-ever-born, those studies relied on current populations in which women had access to contraception. The sole analysis reporting elevated fertility was based on an historic population in which family planning methods were unavailable. Predictions that *BRCA1/2* mutations adversely affect embryogenesis and genome integrity were not supported. The idea that *BRCA1/2* mutations have antagonistic pleiotropic effects (enhancing fertility while reducing survival) was supported in the natural fertility study.

Keywords

BRCA1; BRCA2; fertility; pleiotropy

INTRODUCTION

The *BRCA1* and *BRCA2* mutations have been among the best known, well characterized, and important genetic mutations that predispose women to cancer. Although many mutations have been identified in humans that elevate cancer risk, they often affect a very

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There are no conflicts of interest.

small proportion of the population [1]. *BRCA1* and *BRCA2* mutations are important because women with these mutations have an estimated 40–85% lifetime risk of developing breast cancer and 16–64% risk of ovarian cancer [2–4]. Because the mutations are relatively prevalent in the population [5], *BRCA1* and *BRCA2* mutations may have benefits that enhance fitness.

The purpose of this review is to evaluate the relevant literature addressing the possible association between *BRCA1* and *BRCA2* mutation status and fertility. In this age of the human genome project and genomic medicine, where in new genetic variants associated with human diseases are being identified with increasing frequency, it is important to consider why these variants have not been selected out of the population and, relatedly, whether they are associated with other crucial outcomes. The literature we examine comprises publications addressing the association between *BRCA1* and *BRCA2* mutations and female fertility, the evolutionary and biological mechanisms that may underlie this association, and challenges faced by investigators to demonstrate such an effect. Several aspects of fertility are highlighted including oocyte production, spontaneous miscarriages, children ever born or parity, and ages at first and last birth.

Review process

Empirical articles that examined the association between *BRCA1* and/or *BRCA2* mutations to fertility outcomes were identified using the online PubMed Database. This search was based on the phrase: ‘(’Fertility/genetics’[Mesh] OR ‘Infertility/genetics’ [Mesh]) AND (’Genes, BRCA1’[Mesh] OR ‘Genes, BRCA2’[Mesh] OR ‘Hereditary Breast and Ovarian Cancer Syndrome’[Mesh])’. This search yielded 11 empirical articles. We included seven of these articles, as they directly examined the effects of *BRCA1/2* mutations on female fertility. One additional article was obtained through a search of the citations of these articles; thus, we examined eight articles that directly examine the association between *BRCA1/2* mutations and fertility outcomes. There was no attempt to limit the search by publication date as this literature is small (though growing) and because a few relevant articles were published as long as a decade ago.

Mechanisms

A number of mechanisms linking *BRCA1* and *BRCA2* mutations have been proposed, some suggesting a reduction in fertility and fecundity and others an enhancement. This section briefly describes some of these proposed mechanisms that support the empirical literature.

Mechanisms linking BRCA1 and BRCA2 mutations to reduced fertility

Several investigations have reported that *BRCA1/2* mutations serve to impair embryogenesis [6–9] that would, therefore, limit female fertility. Studies of mice show that homozygous deletions of *BRCA1/2* are lethal to embryonic development [7] whereas mice that were heterozygous showed normal development and were fertile. *BRCA2* mutations in mice may still permit some mutant oocytes to be viable and yield embryos, although there is a significant reduction in germ cells in adult females [10].

BRCA1 is involved in pathways that help to facilitate chromosome and genome integrity [6] leading some to argue that homozygous *BRCA1/2* mutation human embryos should abort spontaneously at higher rates [4, 11]. Pal *et al.* [12] argued that numerous mechanisms alter the processes of cell cycle and division and DNA repair and given that many of these mechanisms are affected by proteins produced by *BRCA* genes, *BRCA1/2* mutations would limit rather than promote reproduction. Oktay *et al.* [13] suggest that *BRCA* mutations may be associated with excess DNA errors in oocytes leading to a smaller oocyte reserve, occult primary ovarian insufficiency, and decreased fertility.

Mechanisms linking BRCA1 and BRCA2 mutations to increased fertility

Two bodies of work centering on the role of telomeres consider how first *BRCA* mutations affect telomere length and second how telomere length then affects fertility [14■■]. Most work has focused on telomeres' effect on disease risk as during normal aging, there is loss in telomeric DNA in dividing somatic cells that can then affect senescence, apoptosis, neoplastic transformation, and survival [15]. Telomere length declines with age in all mitotic tissues except germline tissue.

French *et al.* [16] and Ballal *et al*. [17] examined how the disruption of *BRCA1* may result in telomere lengthening and showed that the overexpression of *BRCA1* limits telomerase activity and reduces telomere length. This suggests that *BRCA1* mutations protect telomeres. This mechanism was not confirmed by McPherson *et al.* [18].

Keefe and colleagues [19–21] suggested that longer telomeres play a role in enhancing reproduction. They indicate that telomerase, the telomere-lengthening enzyme, is inactive in oocytes so they contain their full telomere length at the earliest developmental stages. These authors argued that the lengthy period between fetal life and ovulation in mid-life would expose oocytes to the effects of reactive oxygen that would shorten telomeres. Accordingly, telomeres in oocytes would shorten with increasing age. This mechanism is consistent with declining fertility with age. Studying telomere length and its association with female reproductive aging was addressed by Hanna *et al.* [22] who compared two groups of women: women with idiopathic premature ovarian failure who experienced menopause before age 40 and women with recurrent miscarriages, to two control groups. Women with recurrent miscarriages had significantly shorter age-adjusted telomeres than controls [22]. The telomere length differences between women with recurrent miscarriages and control women in terms of telomere length are consistent with the idea that female reproductive aging is affected by telomere length.

In a study on mice, Keefe and colleagues [19–21] shortened their telomeres, which resulted in a phenotype similar to human age-related oocyte dysfunction. Additionally, they studied eggs donated by reproductive-aged women using in-vitro fertilization and showed that telomere lengths were longer in eggs from women who conceived in relation to those that did not. Aydos *et al*. [23] studied telomere lengths of a small sample of 50-year-old women and showed a positive association between reproductive life-span and telomere length.

Themes

Empirical studies addressing links between *BRCA1* and *BRCA2* mutations and fertility are categorized into several domains. These are summarized in Table 1 [4, 11–13, 14■■, 24, 25, 26■]. Much of this literature is complicated by whether the sample of women studied had access to modern contraception. Cancer susceptibility attributable to *BRCA1/2* mutations may, therefore, affect fertility choices and family planning decisions suggesting a social mechanism as distinct from a biological pathway. Nonetheless, the small literature on this topic has considered several fundamental aspects of fertility starting with oocyte development, miscarriages, parity, and the timing of fertility.

Oocyte production

Oktay *et al.* [13] noted that infertility is associated with breast and ovarian cancer risks and it has been well established that *BRCA* mutations are associated with excess female breast and ovarian cancer susceptibility [14■■]. They tested whether women with and without *BRCA* mutations were correlated with weak responses to a fertility intervention: ovarian stimulation to capture oocytes in order to preserve fertility by embryo or oocyte cryopreservation, all prior to chemotherapy. Low ovarian response was significantly more common among *BRCA1* (but not *BRCA2*) mutation carriers than non-carriers. Oktay *et al.* [13] conclude that at least among women diagnosed with breast cancer, *BRCA1* mutations are more likely to have occult primary ovarian insufficiency. The ability to measure fertility in terms of oocyte yield is a strength of this study, although it is based on a small sample of women with breast cancer (final sample of 14 mutation carriers and 33 noncarriers).

Spontaneous miscarriages

Gal *et al.* [11] reported that no viable homozygous *BRCA1* or *BRCA2* mutation carriers have been detected in humans and mice. This observation led to the hypothesis that a reason for recurrent spontaneous miscarriages among Jewish-Ashkenazi women may be lethal homozygosity for the three common *BRCA1/BRCA2* mutations in this population. Women were tested for predominant *BRCA1/BRCA2* mutations in Jewish high-risk families for differences in the rate of spontaneous miscarriages. In comparing mutation carriers and noncarriers, there were no significant differences in the percentage with at least one spontaneous miscarriage (33 vs. 30%). Among women with a previous pregnancy, no significant differences were detected in terms of those with three or more spontaneous miscarriages (4.37 vs. 3.0%). These differences were largely at the bivariate level with no adjustments for statistical confounding. Friedman *et al*. [4] conducted a case–control study to assess the risk of spontaneous abortions that include nearly 3000 *BRCA1/2* mutation carriers. They reported no differences between carriers and noncarriers in terms of the proportion with spontaneous abortions. In their assessment, Moslehi *et al*. [24] reported no differences between mutation carriers, noncarriers, and controls in terms of the frequency of abortions (separately for induced and spontaneous) or stillbirths.

Children ever born

The most comprehensive fertility assessment of *BRCA1* and *BRCA2* mutations relates to the number of children born. Although some investigators have suggested that mutation carriers

would have reduced fertility, only one study to date has supported this prediction. In their study of predominantly Ashkenazi Jews, Gal *et al.* [11] reported that for the three common *BRCA1/2* mutations in this population, they report a significantly lower number of children for carriers (2.33) than noncarriers (2.51) ($P = 0.045$). This difference appears to be a difference in means without statistical controls for confounders including important confounders such as age and whether affected by cancer.

There are, however, a few investigations concluding *BRCA1/2* mutation status has no impact on female fertility. Pal *et al*. [12], for example, used a case–control study and found that parity was the same between carriers and noncarriers from the same families. Although they predicted that carriers would have fewer children, they reported that both groups averaged 1.9 children. This level of fertility reflects a reproductive era in which effective family planning exists; indeed 80% of the sample had a history of oral contraceptive use. Additionally, half of the carriers had already been diagnosed with breast cancer suggesting that they may have limited their fertility in order to avoid transmitting the risk to their offspring or to prevent their children from witnessing future cancer diagnoses in their mother [27]. Friedman *et al.* [4] also predicted lower fertility but found no differences between carriers and noncarriers in terms of full-term pregnancies. Moslehi *et al.* [24] compared the fertility of mutation carriers and noncarriers with ovarian cancer and controls based on a largely contemporary sample of Ashkenazi Jewish women (born after 1930). They concluded that there was no evidence that *BRCA* mutations affected female fertility but again this may reflect the effects of contraception more than biology.

Some investigators hypothesize that fertility is higher for mutation carriers. In an investigation of breast cancer and the influence of parity, a team led by Tryggvadottir *et al*. [25] reported that female *BRCA2* mutation carriers had a slightly higher mean children ever born (CEB) than noncarriers and controls (3.3, 3.0, and 3.2, respectively), although formal hypothesis testing was not done.

A recent investigation provided evidence showing an increase in children born among mutation carriers. Focusing on obligate carriers of reproductive age based on large multigenerational genealogies when modern contraception was not available (those born prior to 1930), Smith *et al.* [14■■] found *BRCA1/2* mutation status was significantly and positively associated with CEB; carriers during this period had 1.91 more children than noncarriers. This result in combination with the well known excess adult mortality of mutation carriers is consistent with antagonistic pleiotropy. Excess and significant levels of CEB are also detected for post-1930 carriers, although the relative increase is attenuated to 0.61 CEB. The decline in the fertility consequences of carrier status before and after 1930 is significant ($P<0.001$), a likely result of the availability of effective contraception. The significant fertility enhancing effects of *BRCA1/2* mutations were also detected among the founders in these pedigrees: carriers had 1.17 more children than controls.

In a comment about these findings, Da Silva [26■] observed that the elevated fertility among carriers would suggest that *BRCA1/2* mutations would be extremely common today, although they are not. He argued that several factors could explain the low population prevalence of the mutation including the grandmother effect [i.e., grandmothers ordinarily

would enhance the fertility of their daughters, but in the case of *BRCA1* mutation carriers, their own excess mortality (being carriers with an elevated risk of adult mortality) would have limited this benefit] and low female reproduction in primitive societies could have created circumstances that selected against *BRCA1/2* mutations (see also Pavard and Metcalf [28]).

Other reproductive outcomes

Differences in fertility, when detected, may arise for different reasons. Several investigations have considered basic elements of fertility and the influence of *BRCA1/2*. The study by Smith *et al.* [14■■] also reported, for the pre-1930 birth cohort, that female mutation carriers had children more quickly (shorter birth intervals) and to more advanced ages. These differences were not detected for more contemporary women. In a contemporary sample with high utilization rates of contraception, Pal *et al.* [12] did not find differences in rates of nulliparity, age at first or age at last birth between *BRCA1/2* carriers and controls. Moslehi *et al.* [24] examined 96 *BRCA1/2* mutation carriers, 160 noncarriers, and 331 controls. They showed that carriers had a significantly lower pregnancy rate than controls (2.56, 2.59, and 2.68, respectively).

CONCLUSION

The evidence linking *BRCA1/2* mutations to female reproductive outcomes is mixed, but for reasons that are explicable. A fundamental challenge facing investigators seeking to demonstrate elevated or attenuated effects on female fertility in observational studies deals with the competing roles of biology and personal choice and their underlying mechanisms. For contemporary populations in which individuals have access to family planning and contraceptive interventions, the effects of *BRCA1/2* mutations may reflect fundamental mechanisms such as the telomere-preserving effects of these mutations that might enhance reproduction, or personal actions that serve to limit fertility. Persons harboring *BRCA* mutations often know or suspect they do because of a strong family history of female breast or ovarian cancer. In previous studies, women who have been tested as well as those from high-risk families but were not tested reported a significantly weaker desire for more children than noncarriers [27]. These fertility limiting behaviors may simply reflect preventive guidelines that are recommended for carriers like seeking bilateral oophorectomies [29]. Prophylactic surgeries have also been sought more often by women with strong family history of breast and ovarian cancer [27]. Detecting associations is further complicated by variability between samples. The studies summarized here have both mutation carriers and noncarriers along with women who have and have not been diagnosed with breast or ovarian cancer.

To address the relative influence of deliberate family planning choices and biology, it is necessary to consider populations in which *BRCA* mutations can be measured and effective contraception is limited or absent. This would entail populations from underdeveloped or primitive populations (perhaps existing hunter-gatherer societies) or from records on historic populations. The former was advocated by da Silva [26■] and the later implemented by Smith *et al.* [14■■]. With low levels of fertility in populations in which *BRCA* status can be

known and with the advent of direct-to-consumer genetic testing, it is likely that women of reproductive age equipped with the knowledge of their mutation status will lead to reductions in fertility for mutation carriers. Additional strategies involving animal models are also attractive as an approach to elucidate the mechanisms that link *BRCA* mutations to fertility.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 262).

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KEY POINTS

- A growing number of biologists and geneticists have predicted that *BRCA1* and *BRCA2* gene mutations, which have been shown to produce elevated risks of breast and ovarian cancer, would also be associated with reductions in female fertility.
- For studies of contemporary women who have access to effective contraception, the evidence shows very small or no effects of *BRCA1/BRCA2* mutations on female fertility.
- A new analysis of women living during natural fertility conditions shows mutation carriers were significantly more fertile as well as being having elevated mortality risks.
- The mechanisms linking *BRCA1* and *BRCA2* mutations to female fertility are not fully understood but factors affecting telomere integrity may play a key role.

Table 1

Empirical studies addressing links between *BRCA1* and *BRCA2* mutations and fertility

Oocyte production	Spontaneous miscarriages	Children ever born	Timing of reproduction	Author	Population	Sample	Selected results
Themes							
X				Oktay *et al.* [13]	Women with breast cancer that participated in ovarian stimulation to preserve fertility	14 BRCA1/2 carriers	Percentage with low ovarian response rate
						33 BRCA1/2 noncarriers	Carriers: 33.3%; noncarriers: 3.3% (P = 0.014)
							Mean oocyte numbers:
							Carriers: 7.9; noncarriers: 11.3 (P = 0.025)
	X	X		Gal *et al.* [11]	Jewish Israeli women at high risk for breast/ ovarian cancer	393 BRCA1/2 carriers	Percentage experiencing at least three spontaneous abortions:
						424 BRCA1/2 noncarriers	Carriers: 4.37%; noncarriers: 3% (P = not sig.)
							Mean number of children per woman:
							Carriers: 2.33; noncarriers: 2.51 (P = 0.045)
	X	X		Friedman *et al.* [4]	U.S. and Canadian women affected by or at high risk for breast/ ovarian cancer	1878 BRCA1 carriers	Percentage experiencing at least one spontaneous abortion:
						950 BRCA2 carriers	BRCA1: 25.2%; BRCA2: 27.6%; noncarriers: 27.2% (P = not sig.)
						657 BRCA1/2 noncarriers	Mean number of spontaneous abortions per woman:
							BRCA1: 0.37; BRCA2: 0.40; noncarriers: 0.38 (P = not sig.)
							Mean number of full-term pregnancies per woman:
							BRCA1: 2.36; BRCA2: 2.42; noncarriers: 2.43 (P not presented)
	X	X	X	Moslehi *et al.* [24]	Ashkenazi Jewish women affected (cases) or unaffected (controls) by ovarian cancer	96 BRCA1/2 carrier cases	Pregnancy success ratios per women:
						160 BRCA1/2 noncarriers	Carriers: 0.84; noncarriers: 0.87; controls: 0.83 (P = not sig.)
						331 controls	Poisson regression coefficients for pregnancy rate:

Curr Opin Obstet Gynecol. Author manuscript; available in PMC 2014 May 05.

Oocyte production	Spontaneous miscarriages	Children ever born	Timing of reproduction	Author	Population	Sample	Selected results
							Carriers vs. noncarriers and controls: −0.0118 (*P* = not sig.)
							Carrier vs. noncarrier cases: exact value not available, but no statistically significant difference
		X	X	Pal *et al*. [12]	U.S. and Canadian women tested for BRCA1/2 at research centers	2254 BRCA1/2 carriers	Mean parity per woman:
						764 BRCA1/2 noncarriers	Carriers: 1.9; noncarriers: 1.9 (*P* = not sig)
		X		Tryggvadottir *et al*. [25]	Icelandic women with breast cancer	100 BRCA2 carriers	Percentage with 5+ births:
						361 BRCA2 noncarriers	Carriers: 21.3%; noncarriers: 13.4%; controls: 17.8% (*P* not presented)
						1000 population controls	Mean number births per woman:
							Carriers: 3.3; noncarriers: 3.0; controls: 3.2 (*P* not presented)
							Mean breastfeeding duration (in months):
							Carriers: 8.5; noncarriers: 9.2; controls: 9.3 (*P* not presented)
		X	X	Smith *et al.* [14■■]	Precontraceptive period (born before 1930) and postcontraceptive period (1930 – 1974) Utah women	Precontraceptive:	OLS coefficient for number children ever born (carrier vs. noncarrier)
						59 BRCA1/2 carriers	Precontraceptive: 1.91 (*P*<0.0001)
						885 BRCA1/2 noncarriers	Postcontraceptive: 0.61 (P<0.0001)
						Postcontraceptive:	OLS coefficient for mean birth interval (carrier vs. noncarrier)
						122 BRCA1/2 carriers	Precontraceptive: −0.87 (*P* = 0.009)
						1830 BRCA1/2 noncarriers	Postcontraceptive: −0.18 (*P* = not sig)
		X		da Silva [26■]	N/A	None. This is a mathematical simulation in response to Smith *et al*. 2012.	If fertility correlates positively with BRCA1/2 mutations, then prevalence of those mutations should be higher in the population. As BRCA1/2 mutations correlate positively with postreproductive mortality, the ‘grandmother effect’ might select against them, explaining some of the discrepancy

N/A, not available; not sig, not significant; OLS, ordinary least squares.