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REPRODUCTIVE DECISION-MAKING IN WOMEN WITH BRCA1/2 MUTATIONS

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Abstract

Expanded genetic testing of BRCA mutations has led to identification of more reproductive-aged women who test positive for the mutation which might impact attitudes and decisions about relationships, childbearing and the use of preimplantation genetic diagnosis (PGD) and prenatal diagnosis (PND). A cross-sectional survey was administered to 1081 self-reported BRCA carriers to investigate how knowledge of BRCA status influences these issues. The mean age at BRCA test disclosure was 44 years and 36% reported a personal history of cancer. Of 163 women who were unpartnered, 21.5% felt more pressure to get married. Of 284 women whose families were not complete, 41% reported that carrier status impacted their decision to have biological children. Women with a history of cancer were more likely to report that knowledge of BRCA+ status impacted their decision to have a child (OR 1.8, 95% CI 1–3.2). Fifty-nine percent thought PGD should be offered to mutation carriers and 55.5% thought PND should be offered. In conclusion, knowledge of BRCA status impacts attitudes regarding relationships and childbearing, and most carriers believe that PGD and PND should be offered to other carriers. This study suggests that BRCA carriers desire and would benefit from reproductive counseling after test disclosure.

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HUMAN STUDIES AND INFORMED CONSENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants for being including in the study.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Keywords

BRCA; BRCA1; BRCA2; fertility preservation; genetic counseling; preimplantation genetic diagnosis; prenatal diagnosis; reproductive decisions

INTRODUCTION

Mutations of *BRCA1* and *BRCA2* (BRCA) genes are associated with an increased risk of breast and ovarian cancer. Female carriers of these mutations have a 65–80% lifetime risk of breast cancer and a 20–45% risk of ovarian cancer (Antoniou et al., 2003; Chen & Parmigiani, 2007; King, Marks, Mandell, & New York Breast Cancer Study, 2003). Treatments for breast and ovarian cancers may render a woman infertile. Risk-reducing salpingo-oophorectomy has been associated with a significant reduction of breast cancer and ovarian cancer (Domchek et al., 2010; A. P. Finch et al., 2014; Kauff et al., 2002; Rebbeck, Kauff, & Domchek, 2009; Rebbeck et al., 2002), and is recommended to BRCA carriers by the age of forty or after completion of childbearing ("ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome," 2009). Additionally, recent literature suggests that BRCA mutations are associated with decreased ovarian reserve and earlier menopause (A. Finch et al., 2013; Lin et al., 2013; Rzepka-Gorska et al., 2006). Given these potential risks to future fertility, women with BRCA mutations may have a more limited reproductive window to complete their family.

A growing awareness and expanded genetic testing for BRCA mutations have led to the identification of many more high-risk women of childbearing age (Botkin et al., 2003; Meijers-Heijboer et al., 2000). These women are faced with decisions surrounding relationships, reproduction and childbearing. Several studies have examined how BRCA carrier status impacts decisions regarding reproduction and parenthood. In two qualitative studies published by the same group, Donnelly et al and Ormondroyd et al reported the reproductive views of 25 women between the ages of 18–45 who were childless at the time of receiving a positive result for BRCA. Personal and family history of cancer appeared to significantly impact decisions regarding reproduction in this group and many of the women felt uncertain about having biological children in the setting of the increased risk of cancer for themselves and for their children (Donnelly et al., 2013; Ormondroyd et al., 2012). One case-control study performed in a 111 Utah-based families descended from a founding couple with an identified BRCA1 mutation of reproductive-aged, fertile men and women (ages 18–45) demonstrated that women who carry the *BRCA1* mutation might be less likely to want children than non-carriers (OR 1.2, 95% CI 0.01–1.3) (Smith, Ellington, Chan, Croyle, & Botkin, 2004).

Due to concern over transmitting a BRCA mutation to a child, many women have demonstrated an interest in technologies such as preimplantation genetic diagnosis (PGD) and prenatal diagnosis (PND) (Quinn et al., 2009; Staton, Kurian, Cobb, Mills, & Ford, 2008). A survey study conducted on 77 individuals with a median age of 42 (of which 62% had children) undergoing *BRCA1/2* testing (prior to knowledge of mutation status) found that 48% would consider PGD, 55% would consider PND and 55% would consider adoption

if tested positive (Fortuny et al., 2009). To date, few studies have been performed on BRCA mutation carriers to evaluate the impact that knowledge of carrier status has on decision-making around relationships, reproductive issues and technologies that would prevent transmission of the mutation to offspring.

The primary objective of this study was to investigate how knowledge of BRCA carrier status impacts women's decisions regarding 1) marriage and relationships, 2) childbearing and fertility treatments and 3) the use of PGD and PND to prevent transmission of the mutation to their offspring in self-reported BRCA mutation carriers whose families were not complete at the time of test disclosure. We hypothesized that age at the time of BRCA mutation test disclosure, personal history of cancer and already having biological children were factors that would influence the decision to have children or pursue infertility treatments.

METHODS

Participants

A cross-sectional survey was administered to known *BRCA1*/2 mutation carriers recruited from the University of Pennsylvania Cancer Risk Evaluation Program through an in-person encounter or mailed invitational letter. Additional participants were recruited through the Facing Our Risk of Cancer Empowered (FORCE) hereditary breast and ovarian cancer advocacy group. FORCE has an existing database of approximately 20,000 individuals interested in hereditary risk factors of breast and ovarian cancer who voluntarily receive information on a regular basis. Information about this study was posted in the FORCE monthly newsletter and on the FORCE website. Women interested in participation were directed to the Basser Center website, which contained full study details and contact information for study coordinators. Women with a self-reported germline BRCA mutation and were greater than 18 years of age at the time of enrollment were eligible for participation. Participants were excluded if they had never been tested for a BRCA mutation, tested negative for the mutation or for a *BRCA1/2* variant of unknown functional importance. Informed consent was obtained from all individual participants included in the study. The University of Pennsylvania Institutional Review Board approved the study.

Instrumentation and Procedures

Participants completed a detailed online questionnaire developed at the University of Pennsylvania. Information obtained included: demographic information (age, race and ethnicity), medical and social history, menstrual and fertility history, relationship history, pregnancy history, desire for pregnancy, and age at BRCA testing. Participants were asked to answer questions about how their BRCA status influenced decisions about childbearing, including timing of conception, decisions not to conceive or to pursue adoption and about their attitude towards diagnostic tools including preimplantation genetic diagnosis and prenatal diagnosis for the BRCA mutation. To develop the survey instrument, we performed a literature search to identify common themes and reproductive dilemmas reported by women with BRCA mutations (Dekeuwer & Bateman, 2013; Fortuny et al., 2009; Menon et al., 2007; Ormondroyd et al., 2012; Staton et al., 2008; Vadaparampil, Quinn, Knapp, Malo,

& Friedman, 2009). We also examined studies for patients with other hereditary cancer syndromes (i.e. Lynch syndrome) (Dewanwala et al., 2011; Douma et al., 2010). When available, questions from previously published studies were utilized. Some questions were developed by the authors to address themes for which validated questions were not available. Three types of questions were utilized: informational questions, multiple-choice questions, and rating scale questions in which participants were asked to rate their agreement with a statement using a 5-point Likert scale. Similar to previous studies, descriptions of PGD and PND were provided. The questionnaire was reviewed and edited by a team of reproductive endocrinologists, oncologists, and genetic counselors and then piloted with a small group of BRCA mutation carriers. A sample of the questions is included in the Supplemental Appendix.

Data Analysis

Differences in demographic characteristics and questionnaire answers were compared between women whose families were not yet complete, women whose families were complete and those who were undecided using Chi-square and Kruskal-Wallis tests as appropriate. For questions related to attitudes towards PGD and PND, responses were categorized as “agree/strongly agree” versus “disagree/strongly disagree” versus “neutral”. We hypothesized that older age (≥ 30 years), personal history of cancer and having biological children were potentially associated with decision-making regarding childbearing, fertility treatments and attitudes toward PGD and PND. We used logistic regression to evaluate the associations with these factors and adjusted for potential confounding factors. All analyses were performed using STATA version 13 (StataCorp, College Station, TX) and two-sided p-values of 0.05 or less were considered statistically significant.

RESULTS

Participant characteristics

Table I demonstrates the demographic characteristics of the entire study population, which consisted of 1081 female BRCA mutation carriers. Approximately 65% (n=700) participants were recruited through online postings and e-newsletter blasts from FORCE. The average age of the participants was 44.1 years at the time of survey and the average age of BRCA test disclosure was 39.5 years. Ninety-one percent were Caucasian and 30% reported Jewish ancestry. Thirty percent of women reported a personal history of breast cancer and less than 1% of women had a history of ovarian cancer. At the time of BRCA test disclosure, 81% of women were partnered, and 60% had completed their families. Women who had completed their families were older than women who had not (44 vs. 30.5 years, $p < 0.001$). A higher percentage of women whose families were complete were partnered (90% vs. 75%, $p < 0.001$) and had biological children (82% vs. 32%, $p<0.001$) at the time of BRCA test disclosure.

Attitude Towards Childbearing and Fertility Treatment

Amongst the 284 women whose families were not complete at the time of BRCA test disclosure, 116 women (40.8%) responded that knowledge of their BRCA status impacted their decision to have biological children. The reasons why a BRCA mutation status

impacted these decisions regarding childbearing are demonstrated in Table II. Four percent of women would pursue adoption in light of their BRCA mutation status. Others would not have children due to risk of transmission to their offspring (17.2%), out of concern that the pregnancy might increase risk of developing cancer (10.3%), or out of concern for what would happen to a child if they were to develop cancer (10.3%). Fifty of the 284 women (17.7%) whose families were not complete reported that knowledge of BRCA+ status would influence them to pursue infertility treatment (including assisted reproductive technology for infertility and fertility preservation) (Table III). Seventeen of the 50 women (34%) reported that knowledge of their BRCA status made them more likely to consider fertility treatments in order to get pregnant more quickly. Twenty women (40%) would consider IVF in order to freeze embryos or oocytes for future use, and 17 (34%) would utilize IVF with PGD in order to avoid transmission of the mutation to offspring. Only 6 women (12%) would consider the use of donor oocytes to avoid transmission of the mutation.

To test our a priori hypotheses and identify factors associated with the decision to have children or pursue fertility treatments given knowledge of a BRCA mutation, unadjusted logistic regression was performed to evaluate the associations with age at the time of BRCA test disclosure, personal history of cancer, already having biological children, partner status and Caucasian race (Table IV). Women with a personal history of cancer were more likely to report that the knowledge of BRCA status impacted their decision to have a child (unadjusted OR 1.8, 95% CI 1–3.2, p = 0.04) and women who were partnered were less likely to report that this knowledge impacted their decision (unadjusted OR 0.5, 95% CI 0.3–0.9, p=0.02). In a multivariable adjusted model including partner status and personal history of cancer, both of these factors remained significantly associated with the decision to have biological children (Personal history of cancer adjusted OR 1.8. 95% CI 1.1–3.3, p = 0.03, Partnered adjusted OR 0.5, 95% CI 0.3–0.9, p = 0.014). Women who already had biological children were less likely to pursue fertility treatments in light of their BRCA+ status (unadjusted OR 0.3, 95% CI 0.1–0.6, p = 0.001).

Attitude Towards Relationships/Marriage

We evaluated the impact that knowledge of a BRCA mutation had on attitudes regarding relationships in 163 women who were unpartnered at the time of BRCA test disclosure (Table V). Twenty-two percent of respondents reported that knowledge of their carrier status made them feel more pressure to get married, while only 2.5% reported that they decided not to get married after learning of their status. Thirty-eight percent related that knowledge of their carrier status influenced what characteristics they were looking for in a life partner. Participants had the option following this question to compose free text regarding the knowledge that BRCA carrier status had on any other decisions about marriage/ relationships. In regards to how knowledge of BRCA carrier status influenced what characteristics they were looking for in a life partner, responses encompassed a need to find someone who was understanding, supportive and emotionally/financially stable. These responses included: “It made me feel like I needed to find an understanding partner – someone who didn’t want to have kids”, “It was important that my partner knew about my BRCA2 gene, and was supportive of me, however I decided to proceed with significant decisions in the future”, “…Dating financially secure men”.

Attitude Towards PGD and PND

After reading a general description of PGD and PND (Supplemental Appendix), participants answered questions regarding their attitude towards these technologies (Table VI). While only eight participants had ever undergone IVF with PGD, the majority of respondents (58.7%) thought that PGD should be offered to women who were BRCA mutation carriers. However, only 34.8% would consider undergoing PGD to reduce the risk of transmitting the mutation to their offspring. None of the participants had used PND to determine the BRCA status of a fetus. Nonetheless, 55.5% thought that PND should be offered to pregnant women who are BRCA carriers, and 29.8% reported that they would consider using PND themselves. Only 4% of women would consider terminating the pregnancy of a fetus that carried the mutation. On comparison of attitudes towards PGD and PND in women whose families were compete vs. not complete v. undecided, responses were similar overall. A personal history of cancer, having biological children, age ≥ 30 years and type of BRCA mutation were not associated with PGD or PND acceptance ($p>0.05$).

DISCUSSION

As the uptake of cancer genetic testing increases and as cancer survivorship improves, more BRCA carriers will seek reproductive counseling from health care practitioners. Given the reproductive risks related to treatments for hereditary cancers and risk-reducing surgery, as well as concerns regarding transmission of the BRCA mutation to their offspring, women with BRCA mutations have unique reproductive concerns. In order to explore decision-making regarding reproduction, we conducted one of the largest observational studies in women with BRCA mutations on decision-making in regard to relationships in unpartnered women, decision-making surrounding reproduction and fertility treatments, and attitudes towards PGD and PND.

Overall, we have shown that the knowledge of BRCA carrier status impacts women's decision-making regarding relationships and childbearing. Unpartnered women reported that knowledge of a BRCA mutation influenced their decisions regarding marriage. Almost forty percent had a greater desire to get married and fifty percent felt more pressure to get married after test disclosure. Women whose families were not complete at the time of BRCA test disclosure reported that their carrier status affected their decision to have biological children. All in all, it appeared that these women desired biological children, with a very small percentage desiring adoption or use of donor oocytes.

The desire for biological children may explain the significant interest in IVF with PGD to reduce the risk of transmitting the mutation to offspring. While few women had undergone either PGD or PND to detect the mutation prior to pregnancy or delivery, the majority believed that these technologies should be offered to women who are carriers, regardless of whether or not their families were complete. This acceptance of PGD and PND was not associated with a personal history of cancer, older age, having biological children or specific BRCA mutation type. Less than 5 percent of women would consider termination of a BRCA mutation positive fetus. In a case-control study comparing fertility desires of 25 *BRCA1* carriers vs. 62 non-carriers, Smith et al. reported that female carriers were significantly less likely to report a desire for future children (Smith et al., 2004). A survey study found that

following disclosure of a BRCA mutation, women (especially those >36 years of age) were less interested in future childbearing (Woodson et al., 2014). In contrast, very few of the women in our study whose families were not complete at the time of survey decided against having children in light of their carrier status. In fact, it appeared that the desire for biological children remained, as few women were interested in adoption or the use of donor oocytes.

In 2006, U.K. Human Fertilization and Embryology Authority approved the use of PGD for hereditary breast and ovarian cancer syndromes. As the use of this technology has become more accepted and prevalent for BRCA mutations, the attitudes of BRCA mutation carriers have changed. Whereas awareness of PGD for this indication has varied over time from 19%–32% (Menon et al., 2007; Rich et al., 2014), the acceptance of PGD appears to have grown. In 2008, a study reported that only 13% of women whose families were not complete would consider the use of PGD for future pregnancies (Staton et al., 2008). A more recent study by Julian-Reynier in 2012 reported that 32.5% of mutation carriers would consider its use for themselves for a theoretical next pregnancy (Julian-Reynier et al., 2012) and a study in 2014 conducted in adults with hereditary cancers found that of 370 respondents, 43% would consider the use of PGD (Rich et al., 2014). What has remained fairly high across time is the percent of BRCA carriers that believe that PGD is acceptable or ethical to offer to carriers. This percentage has ranged from 57–75% from studies published between 2007 and 2014 (Fortuny et al., 2009; Menon et al., 2007; Rich et al., 2014; Vadaparampil et al., 2009). This observation is consistent with what we found in this study, where approximately 35% of our participants would consider undergoing IVF with PGD to reduce the risk of transmission of the mutation to offspring, and 59% believed PGD should be offered to other carriers. As for PND, prior studies have found that approximately 50% of BRCA carriers would undergo testing of their fetus for the mutation (Fortuny et al., 2009; Julian-Reynier et al., 2012), which is higher than the percentage found in this study (31%). A single study reported that 74% of BRCA carriers considered it ethical to offer PND to those who carried the mutation (Fortuny et al., 2009), similar to what was found in this current study (58%). Despite this high level of acceptance and consideration for PND of BRCA in a fetus, only 4% of participants would consider termination of a fetus that carried the mutation. One study that addressed this issue found that 12% of their study population found termination of a BRCA+ fetus acceptable (Julian-Reynier et al., 2012). While there is an interesting discrepancy between acceptability of the use of PND and consideration of pregnancy termination for fetuses with a BRCA mutation, there were unfortunately no follow-up questions regarding attitudes towards pregnancy termination in general or option of free-text responses, so it is difficult to explore contributors to this divergence. However, as terminating carrier fetuses appears to have low acceptance, PGD may be the more suitable option for many of these women and this technology may become more prevalent.

To explore attitudes towards relationships following test disclosure, we performed a restricted analysis of unpartnered BRCA+ women. Younger, reproductive-aged women face special challenges in their approach to relationships and childbearing, as they are less likely to be partnered or to have children at the time of test disclosure. While younger women have been shown to be more interested in genetic testing than older women (Bottorff et al., 2002), it appears that they experience more distress following disclosure of a BRCA mutation

(Lodder et al., 2002; Watson et al., 2004). Qualitative research reports that women may have difficulties establishing new relationships due to anxiety around disclosing their mutation status, but also feel urgency to find a partner in order to have children before they reach an age when it is recommend to undergo prophylactic oophorectomy (Hamilton & Hurley, 2010; Klitzman & Sweeney, 2011). The unpartnered women in our study felt a similar desire and pressure to get married, and almost forty percent of respondents reported that knowledge of their mutation influenced what they were looking for in a life partner, including emotional and financial stability. Given that few women provided free text responses to clarify this response, further exploration on the topic of how BRCA carrier status impacts dating and relationship attitudes is certainly warranted in future studies.

Study Strengths and Limitations

To our knowledge, this the largest quantitative study assessing reproductive desires and attitudes towards PGD and PND among women with BRCA mutations. While prior studies have been performed regarding reproductive attitudes in patients who were undergoing testing, this is the largest study to report findings on a population of carriers of the BRCA mutation who have completed testing. Additionally, this paper is the first to address decision-making in regards to relationships in unpartnered, BRCA+ women. Given that partner status appears to significantly impact a woman's decision to have biological children, exploration of attitudes towards relationships and marriage is of particular importance in this population of women whose families are not complete.

However, we recognize several limitations. These results may not be generalizable to all BRCA carriers as our participants were recruited from an academic referral hospital for women with high-risk mutations and from a national advocacy website. This non-random sampling may influence the interpretation of our results. However, our study population reflects the population of women who are undergoing BRCA testing, so these results would be relevant to that cohort. As BRCA status was self-reported, it is possible that women who tested negative or who carry variants of unknown significance were included in this study cohort. As with any survey study where participants are asked questions regarding past decision-making (in this case, at the time of BRCA test disclosure), there is the possibility of recall bias. For example, women who pursued fertility treatments following a BRCA test disclosure may report that they were more likely to pursue treatments, as compared with women who ultimately did not pursue treatment. While the average time between BRCA test disclosure and completion of the survey was relatively short (5 years), the risk of recall bias is still relevant. To address this limitation, findings from this study must be validated with prospectively collected data. As the link to the study and questionnaire was advertised publicly through the FORCE and Basser center websites, it was not possible to determine the number of non-responders or number of women who declined to participate. Without this denominator, a true response rate could not be estimated. Additionally, as the demographic characteristics of FORCE members were not available, it was difficult to assess if the non-responders were different than those who responded to the survey. Finally, the description of PGD and PND did not include information regarding cost or risks of the procedure, which may influence decision-making surrounding these technologies. And, due to length and time constraints of the questionnaire, it was not possible to elicit free-text

responses on many interesting questions presented in this study. Thus, it is difficult to draw any definitive conclusions regarding the motivation and intention behind our respondents' answer choices. In a future prospective study, these responses will need to be explored in more depth to facilitate genetic counseling and discussion.

Practice Implications

In conclusion, the knowledge of BRCA carrier status impacts women's attitudes regarding relationships and childbearing. The majority of BRCA mutation carriers believe that PGD and PND should be offered to other carriers. Counseling of BRCA mutation carriers is typically focused on risk-reducing strategies and cancer prevention, however, for reproductive-aged women, counseling must also include a discussion of reproductive issues, including timing of pregnancy, use of ART for expediting pregnancy, fertility preservation and PGD. We hope that the results of this study will motivate practitioners to incorporate discussions on reproductive issues into their counseling in order to facilitate decision-making on these topics. These issues can be addressed both prior to genetic testing, and following the receipt of genetic test results. Information regarding available reproductive options and preimplantation/prenatal diagnosis should be provided, as well as guidance in decision-making for these women. Psychological support could also be offered at the time of testing given the sensitive nature of these topics. Finally, these results highlight the need for further studies on the impact of genetic counseling on reproductive decision-making in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

ACOG Practice Bulletin No. 103. Hereditary breast and ovarian cancer syndrome. Obstet Gynecol. 2009; 113(4):957–966. DOI: 10.1097/AOG.0b013e3181a106d4 [PubMed: 19305347]

Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, … Easton DF. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003; 72(5): 1117–1130. DOI: 10.1086/375033 [PubMed: 12677558]

Botkin JR, Smith KR, Croyle RT, Baty BJ, Wylie JE, Dutson D, … Lyon E. Genetic testing for a BRCA1 mutation: prophylactic surgery and screening behavior in women 2 years post testing. Am J Med Genet A. 2003; 118A(3):201–209. DOI: 10.1002/ajmg.a.10102 [PubMed: 12673648]

Bottorff JL, Ratner PA, Balneaves LG, Richardson CG, McCullum M, Hack T, … Buxton J. Women's interest in genetic testing for breast cancer risk: the influence of sociodemographics and knowledge. Cancer Epidemiol Biomarkers Prev. 2002; 11(1):89–95. [PubMed: 11815405]

Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007; 25(11): 1329–1333. DOI: 10.1200/JCO.2006.09.1066 [PubMed: 17416853]

Collins IM, Milne RL, McLachlan SA, Friedlander M, Hickey M, Weideman PC, … Phillips KA. Do BRCA1 and BRCA2 mutation carriers have earlier natural menopause than their noncarrier relatives? Results from the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer. J Clin Oncol. 2013; 31(31):3920–3925. DOI: 10.1200/JCO.2013.49.3007 [PubMed: 24081944]

Dekeuwer C, Bateman S. Much more than a gene: hereditary breast and ovarian cancer, reproductive choices and family life. Med Health Care Philos. 2013; 16(2):231–244. DOI: 10.1007/s11019-011-9361-9 [PubMed: 22048863]

Dewanwala A, Chittenden A, Rosenblatt M, Mercado R, Garber JE, Syngal S, Stoffel EM. Attitudes toward childbearing and prenatal testing in individuals undergoing genetic testing for Lynch syndrome. Fam Cancer. 2011; 10(3):549–556. DOI: 10.1007/s10689-011-9448-8 [PubMed: 21567236]

Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, … Rebbeck TR. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010; 304(9):967–975. DOI: 10.1001/jama.2010.1237 [PubMed: 20810374]

Donnelly LS, Watson M, Moynihan C, Bancroft E, Evans DG, Eeles R, … Ormondroyd E. Reproductive decision-making in young female carriers of a BRCA mutation. Hum Reprod. 2013; 28(4):1006–1012. DOI: 10.1093/humrep/des441 [PubMed: 23293217]

Douma KF, Aaronson NK, Vasen HF, Verhoef S, Gundy CM, Bleiker EM. Attitudes toward genetic testing in childhood and reproductive decision-making for familial adenomatous polyposis. Eur J Hum Genet. 2010; 18(2):186–193. DOI: 10.1038/ejhg.2009.151 [PubMed: 19809485]

Finch A, Valentini A, Greenblatt E, Lynch HT, Ghadirian P, Armel S. … Hereditary Breast Cancer Study G. Frequency of premature menopause in women who carry a BRCA1 or BRCA2 mutation. Fertil Steril. 2013; 99(6):1724–1728. DOI: 10.1016/j.fertnstert.2013.01.109 [PubMed: 23414920]

Finch AP, Lubinski J, Moller P, Singer CF, Karlan B, Senter L, … Narod SA. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014; 32(15):1547–1553. DOI: 10.1200/JCO.2013.53.2820 [PubMed: 24567435]

Fortuny D, Balmana J, Grana B, Torres A, Ramon y Cajal T, Darder E, … Brunet J. Opinion about reproductive decision making among individuals undergoing BRCA1/2 genetic testing in a multicentre Spanish cohort. Hum Reprod. 2009; 24(4):1000–1006. DOI: 10.1093/humrep/den471 [PubMed: 19112076]

Hamilton R, Hurley KE. Conditions and consequences of a BRCA mutation in young, single women of childbearing age. Oncol Nurs Forum. 2010; 37(5):627–634. DOI: 10.1188/10.ONF.627-634 [PubMed: 20797954]

Julian-Reynier C, Fabre R, Coupier I, Stoppa-Lyonnet D, Lasset C, Caron O, … Nogues C. BRCA1/2 carriers: their childbearing plans and theoretical intentions about having preimplantation genetic diagnosis and prenatal diagnosis. Genet Med. 2012; 14(5):527–534. DOI: 10.1038/gim.2011.27 [PubMed: 22241105]

Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, … Offit K. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2002; 346(21):1609–1615. DOI: 10.1056/NEJMoa020119 [PubMed: 12023992]

Kim J, Skrzynia C, Mersereau JE. A pilot study of BRCA mutation carriers' knowledge about the clinical impact of prophylactic-oophorectomy and views on fertility consultation: a single-center pilot study. J Genet Couns. 2015; 24(1):149–157. DOI: 10.1007/s10897-014-9747-y [PubMed: 25120035]

King MC, Marks JH, Mandell JB. New York Breast Cancer Study G. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003; 302(5645):643–646. DOI: 10.1126/science.1088759 [PubMed: 14576434]

Klitzman RL, Sweeney MM. "In sickness and in health"? Disclosures of genetic risks in dating. J Genet Couns. 2011; 20(1):98–112. DOI: 10.1007/s10897-010-9331-z [PubMed: 20890722]

Lee S, Ozkavukcu S, Heytens E, Moy F, Oktay K. Value of early referral to fertility preservation in young women with breast cancer. J Clin Oncol. 2010; 28(31):4683–4686. DOI: 10.1200/JCO.2010.30.5748 [PubMed: 20876425]

Lin WT, Beattie M, Chen LM, Oktay K, Crawford SL, Gold EB, … Rosen M. Comparison of age at natural menopause in BRCA1/2 mutation carriers with a non-clinic-based sample of women in northern California. Cancer. 2013; 119(9):1652–1659. DOI: 10.1002/cncr.27952 [PubMed: 23362014]

Lodder LN, Frets PG, Trijsburg RW, Meijers-Heijboer EJ, Klijn JG, Seynaeve C, … Niermeijer MF. One year follow-up of women opting for presymptomatic testing for BRCA1 and BRCA2: emotional impact of the test outcome and decisions on risk management (surveillance or prophylactic surgery). Breast Cancer Res Treat. 2002; 73(2):97–112. [PubMed: 12088120]

Meijers-Heijboer EJ, Verhoog LC, Brekelmans CT, Seynaeve C, Tilanus-Linthorst MM, Wagner A, … Klijn JG. Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation. Lancet. 2000; 355(9220):2015–2020. [PubMed: 10885351]

Menon U, Harper J, Sharma A, Fraser L, Burnell M, ElMasry K, … Jacobs I. Views of BRCA gene mutation carriers on preimplantation genetic diagnosis as a reproductive option for hereditary breast and ovarian cancer. Hum Reprod. 2007; 22(6):1573–1577. DOI: 10.1093/humrep/dem055 [PubMed: 17428877]

Michaelson-Cohen R, Mor P, Srebnik N, Beller U, Levy-Lahad E, Eldar-Geva T. BRCA mutation carriers do not have compromised ovarian reserve. Int J Gynecol Cancer. 2014; 24(2):233–237. DOI: 10.1097/IGC.0000000000000058 [PubMed: 24378620]

Oktay K, Kim JY, Barad D, Babayev SN. Association of BRCA1 mutations with occult primary ovarian insufficiency: a possible explanation for the link between infertility and breast/ovarian cancer risks. J Clin Oncol. 2010; 28(2):240–244. DOI: 10.1200/JCO.2009.24.2057 [PubMed: 19996028]

Ormondroyd E, Donnelly L, Moynihan C, Savona C, Bancroft E, Evans DG, … Watson M. Attitudes to reproductive genetic testing in women who had a positive BRCA test before having children: a qualitative analysis. Eur J Hum Genet. 2012; 20(1):4–10. DOI: 10.1038/ejhg.2011.146 [PubMed: 21811309]

Pal T, Keefe D, Sun P, Narod SA. Hereditary Breast Cancer Clinical Study G. Fertility in women with BRCA mutations: a case-control study. Fertil Steril. 2010; 93(6):1805–1808. DOI: 10.1016/j.fertnstert.2008.12.052 [PubMed: 19200971]

Quinn G, Vadaparampil S, Wilson C, King L, Choi J, Miree C, Friedman S. Attitudes of high-risk women toward preimplantation genetic diagnosis. Fertil Steril. 2009; 91(6):2361–2368. DOI: 10.1016/j.fertnstert.2008.03.019 [PubMed: 18440521]

Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst. 2009; 101(2):80–87. DOI: 10.1093/jnci/djn442 [PubMed: 19141781]

Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE. … Observation of Surgical End Points Study, G. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med. 2002; 346(21):1616–1622. DOI: 10.1056/NEJMoa012158 [PubMed: 12023993]

Rich TA, Liu M, Etzel CJ, Bannon SA, Mork ME, Ready K, … Litton JK. Comparison of attitudes regarding preimplantation genetic diagnosis among patients with hereditary cancer syndromes. Fam Cancer. 2014; 13(2):291–299. DOI: 10.1007/s10689-013-9685-0 [PubMed: 24072553]

Rodriguez-Wallberg KA, Oktay K. Fertility preservation and pregnancy in women with and without BRCA mutation-positive breast cancer. Oncologist. 2012; 17(11):1409–1417. DOI: 10.1634/theoncologist.2012-0236 [PubMed: 23006497]

Rzepka-Gorska I, Tarnowski B, Chudecka-Glaz A, Gorski B, Zielinska D, Toloczko-Grabarek A. Premature menopause in patients with BRCA1 gene mutation. Breast Cancer Res Treat. 2006; 100(1):59–63. DOI: 10.1007/s10549-006-9220-1 [PubMed: 16773440]

Shapira M, Raanani H, Feldman B, Srebnik N, Dereck-Haim S, Manela D, … Meirow D. BRCA mutation carriers show normal ovarian response in in vitro fertilization cycles. Fertil Steril. 2015; 104(5):1162–1167. DOI: 10.1016/j.fertnstert.2015.07.1162 [PubMed: 26335130]

Smith KR, Ellington L, Chan AY, Croyle RT, Botkin JR. Fertility intentions following testing for a BRCA1 gene mutation. Cancer Epidemiol Biomarkers Prev. 2004; 13(5):733–740. [PubMed: 15159303]

Staton AD, Kurian AW, Cobb K, Mills MA, Ford JM. Cancer risk reduction and reproductive concerns in female BRCA1/2 mutation carriers. Fam Cancer. 2008; 7(2):179–186. DOI: 10.1007/s10689-007-9171-7 [PubMed: 18026853]

Vadaparampil ST, Quinn GP, Knapp C, Malo TL, Friedman S. Factors associated with preimplantation genetic diagnosis acceptance among women concerned about hereditary breast and ovarian cancer. Genet Med. 2009; 11(10):757–765. DOI: 10.1097/GIM.0b013e3181b3f451 [PubMed: 19710615]

Wang ET, Pisarska MD, Bresee C, Chen YD, Lester J, Afshar Y, … Karlan BY. BRCA1 germline mutations may be associated with reduced ovarian reserve. Fertil Steril. 2014; 102(6):1723–1728. DOI: 10.1016/j.fertnstert.2014.08.014 [PubMed: 25256924]

Watson M, Foster C, Eeles R, Eccles D, Ashley S, Davidson R. … Psychosocial Study, C. Psychosocial impact of breast/ovarian (BRCA1/2) cancer-predictive genetic testing in a UK multicentre clinical cohort. Br J Cancer. 2004; 91(10):1787–1794. DOI: 10.1038/sj.bjc.6602207 [PubMed: 15505627]

Woodson AH, Muse KI, Lin H, Jackson M, Mattair DN, Schover L, … Litton JK. Breast cancer, BRCA mutations, and attitudes regarding pregnancy and preimplantation genetic diagnosis. Oncologist. 2014; 19(8):797–804. DOI: 10.1634/theoncologist.2014-0057 [PubMed: 24951607]

Yoshida K, Miki Y. Role of BRCA1 and BRCA2 as regulators of DNA repair, transcription, and cell cycle in response to DNA damage. Cancer Sci. 2004; 95(11):866–871. [PubMed: 15546503]

Table I

Demographic characteristics of the study population

	Total Cohort	Family Complete	Family Not Complete	Undecided[a]	p-value[b]
n	1081	654	284	92	
Mean age (SD) at time of survey, years	44.1 (9.6)	48.2 (7.9)	35.7 (7.3)	39.6 (8.2)	<0.001
Mean age (SD) at BRCA test disclosure, years	39.5 (9.3)	44.0 (7.5)	30.5 (6.2)	35.2 (6.8)	<0.001
BRCA 1	550 (50.9%)	326 (49.8%)	149 (52.5%)	48 (52.2%)	0.41
BRCA2	514 (47.5%)	319 (48.8%)	128 (45.1%)	44 (47.8%)	
BRCA 1 and 2	17 (1.6%)	9 (1.4%)	7 (2.5%)	0 (0%)	
Caucasian race	985 (91.1%)	608 (93.0%)	260 (91.5%)	77 (83.7%)	0.13
Ashkenazi Jewish ancestry	320 (29.6%)	194 (29.7%)	97 (34.2%)	20 (21.7%)	0.07
Partnered at time of BRCA test disclosure	876 (81.0%)	588 (90.0%)	214 (75.4%)	68 (73.9%)	<0.001
Personal history of cancer	387 (35.8%)	273 (41.7%)	65 (22.9%)	34 (37.0%)	<0.001
-Breast Cancer	324 (30.0%)	228 (34.9%)	52 (18.3%)	31 (33.7%)	
-Ovarian Cancer	9 (0.8%)	7 (1.1%)	1 (0.4%)	1 (1.1%)	
Had biological children at the time of BRCA test disclosure	689 (63.7%)	537 (82.1%)	92 (32.4%)	60 (65.2%)	<0.001

Data is shown as n(%) unless otherwise stated.

[a] Numbers may not add to total n due to missing responses

[b] P-values calculated from Kruskal-Wallis (continuous variables) and Pearson chi-square tests (categorical variables)

Table II

Attitudes towards childbearing amongst women whose families were not complete at the time of BRCA test disclosure

Question/Statement	**N = 116 (%)[a], [b]**
I decided to have children earlier.	50 (43.1%)
I decided to pursue adoption.	5 (4.3%)
I decided not to have children because of risk of transmission (of BRCA mutation) to my offspring.	20 (17.2%)
I decided not to have any more children because I was concerned that pregnancy might increase my risk of developing cancer.	12 (10.3%)
I decided not to have children because I was concerned about what would happen to a child if I developed cancer.	12 (10.3%)
Other	17 (14.7%)

[a]Represents the number of individuals who chose this statement as a reason why the knowledge of BRCA status impacted their decisions about childbearing

Table III

Attitudes towards fertility treatment amongst women whose families were not complete at the time of BRCA test disclosure

Question/Statement	**N =50 (%)[a, b]**
This knowledge made me more likely to consider fertility treatment so that I could get pregnant more quickly.	17 (34%)
This knowledge made me more likely to consider in-vitro fertilization so that I could free embryos ore eggs for future use.	20 (40%)
This knowledge made me more likely to consider in-vitro fertilization with preimplantation genetic diagnosis to avoid transmission to my offspring.	17 (34%)
This knowledge made me more likely to consider in-vitro fertilization with donor eggs to avoid transmission of the gene to my offspring.	6 (12%)
Other	7 (14%)

[a]Represents the number of individuals who chose this statement as a reason why the knowledge of BRCA status influenced their thoughts about fertility treatment

[b]Numbers may add over total because individuals could choose multiple statements

Table IV

Associations with impact on decisions to have children and pursuing fertility treatment in women who have not completed childbearing

Associations with decision to have children	Variable	Unadjusted Odds Ratio (95% CI)	p-value
	Age ≥ 30 years	1.2 (0.7–1.9)	0.50
	Personal history of cancer	1.8 (1.0–3.2)	0.04
	Already have biological children	0.96 (0.6–1.6)	0.88
	Partnered	0.51 (0.3–0.9)	0.02
	Caucasian race	0.25 (0.03–2.3)	0.22
Associations with decision to pursue fertility treatment	Age ≥ 30 years	0.9 (0.5–1.6)	0.75
	Personal history of cancer	1.2 (0.6–2.2)	0.47
	Already have biological children	0.3 (0.1–0.6)	0.001
	Partnered	0.73 (0.4–1.3)	0.30
	Caucasian race	1.3 (0.1–12.0)	0.81

Table V

Attitudes towards relationships amongst women unpartnered at time of BRCA test disclosure

Statement	Response[a]	N = 163 (%)[b]
I had more desire to get married after I learned of my BRCA carrier status.	Yes	33 (20.2%)
	No	64 (39.2%)
	Neutral	43 (26.3%)
I decided not to get married after I learned of my BRCA carrier status.	Yes	4 (2.5%)
	No	99 (60.7%)
	Neutral	17 (10.4%)
I had more reservations about marriage after I learned of my BRCA carrier status.	Yes	24 (14.7%)
	No	85 (52.1%)
	Neutral	24 (14.7%)
I had been planning not to get married and then decided to pursue marriage because of my BRCA carrier status	Yes	4 (2.5%)
	No	100 (61.3%)
	Neutral	19 (11.7%)
Knowledge of my BRCA carrier status influence my decision when to get married.	Yes	28 (17.2%)
	No	65 (39.9%)
	Neutral	18 (11.0%)
Knowledge of my BRCA carrier status made me feel more pressure to get married.	Yes	35 (21.5%)
	No	82 (50.3%)
	Neutral	18 (11.0%)
Knowledge of BRCA carrier status influenced what characteristics I was looking for in a life partner.	Yes	62 (38.0%)
	No	53 (32.5%)
	Neutral	20 (12.3%)

[a]"Yes" responses represent individuals who answered "Strongly agree" or "Agree", "No" responses represent individuals who answered "Strongly disagree" or "Disagree"

[b]Numbers may not add to total n due to missing responses

Table VI

Opinions regarding preimplantation genetic diagnosis (PGD) and prenatal diagnosis to detect the BRCA mutation

Question	Response[a]	Total Cohort	Family Complete	Family Not Complete	Undecided
n		**1081**	654	**284**	**92**
Have you undergone IVF with PGD in the past to reduce the risk of passing a BRCA mutation to your offspring?	Yes	8 (0.7%)	0 (0%)	8 (2.8%)	0 (0%)
	No	1025 (94.8%)	649 (99.2%)	276 (97.2%)	91 (98.9%)
Do you think that PGD should be offered to women who are BRCA mutation carriers?	Yes	635 (58.7%)	397 (60.7%)	177 (62.3%)	56 (60.9%)
	No	119 (11.0%)	80 (12.2%)	27 (9.5%)	11 (12.0%)
	Not sure	264 (24.4%)	397 (60.7%)	71 (25%)	24 (26%)
Would you consider undergoing in-vitro fertilization with PGD to reduce the risk of passing a BRCA mutation to your offspring?	Yes	376 (34.8%)	239 (36.5%)	103 (36.2%)	32 (34.8%)
	No	380 (35.2%)	233 (36.5%)	105 (37.0%)	38 (41.3%)
	Not sure	257 (23.8%)	170 (26%%)	65 (22.9%)	21 (22.8%)
In the past, have you used PND to determine if a fetus carried a BRCA mutation?	Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	No	884 (81.8%)	585 (89.4%)	221 (77.8%)	73 (79.3%)
	Not sure	10 (0.9%)	8 (1.2%)	1 (0.4%)	1 (1.1%)
Do you think that prenatal diagnosis should be offered to pregnant women who are BRCA mutation carriers?	Yes	600 (55.5%)	385 (58.9%)	159 (56.0%)	52 (56.5%)
	No	177 (16.4%)	111 (17.0%)	48 (16.9%)	16 (17.4%)
	Not sure	250 (23.1%)	152 (23.2%)	73 (25.7%)	24 (26.1%)
Would you consider using prenatal diagnosis to determine if a fetus has a BRCA mutation?	Yes	322 (29.8%)	206 (31.5%)	85 (30.0%)	30 (32.6%)
	No	446 (41.3%)	266 (40.7%)	133 (46.8%)	43 (46.7%)
	Not sure	260 (24.1%)	176 (26.9%)	65 (22.9%)	18 (19.6%)
Would you consider pregnancy termination for a fetus with a BRCA mutation determined through prenatal diagnosis?	Yes	43 (4.0%)	33 (5.0%)	9 (3.2%)	1 (1.1%)
	No	748 (69.2%)	454 (69.4%)	220 (77.5%)	70 (76.1%)
	Not sure	223 (20.6%)	149 (22.8%)	54 (19.0%)	18 (19.6%)
	Prefer not to answer	6 (0.6%)	5 (7.6%)	0 (0%)	1 (1.1%)

Abbreviations: IVF = in-vitro fertilization, PGD = preimplantation genetic diagnosis, PND = prenatal diagnosis

Data is shown as n(%) unless otherwise stated.

[a]Numbers may not add to total n due to missing responses