Sex Differences in Attitudes Toward Marriage and Childbearing Based on the Assumption of Being BRCA1/2 Mutation Carriers Among Young People

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ABSTRACT

Purpose: This study investigated changes in attitudes toward marriage and childbearing assuming a BRCA1/2 mutation carrier status among healthy, unmarried individuals in Korea.

Methods: A nationally representative sample of healthy, unmarried individuals aged 20–39 years was surveyed. A questionnaire on marriage and childbearing intentions was administered to the participants before and after providing them with information on BRCA1/2 mutation carriers’ breast and ovarian cancer risks and their autosomal dominant inheritance pattern. The participants were asked about their attitudes toward childbearing through preimplantation genetic diagnosis (PGD).

Results: Of the participants who initially wanted to marry, the assumption that they or their partners had BRCA1/2 mutation caused 25.3% to no longer want to get married and 36.2% to change their attitude from wanting to bear children to no longer wanting them. Females were more likely than males to change their attitudes toward marriage and childbearing. The participants who had negative attitudes toward genetic testing were more likely to change their attitudes regarding marriage and childbearing than those who were favorable toward both disclosure and testing. More than 50% of the participants who did not want children were willing to bear children through PGD when it was assumed that they were BRCA mutation carriers.

Conclusion: On the assumption of being carriers, general, young, and healthy females were more likely than males to negatively change their attitudes toward marriage and childbearing. Public education on the implications of living with mutation carriers and reproductive options may be required.

Keywords: Breast Neoplasms; Genes, BRCA1; Genes, BRCA2; Ovarian Neoplasms; Spouses

INTRODUCTION

Germline mutations in the BRCA1/2 gene are associated with an increased risk of several types of cancer, including breast, ovarian, prostate, pancreatic, stomach, and colorectal cancers [1]. These types of cancer, especially hereditary breast and ovarian cancers, are often...
inherited in an autosomal dominant pattern, where one mutated gene is sufficient to cause the disease. Thus, $BRCA1/2$ mutation carriers’ children have a 50% probability of inheriting the mutation and are exposed to an increased risk of several types of cancer. Risk-reducing salpingo-oophorectomy is associated with a reduced risk of developing breast and ovarian cancers and reduced mortality therefrom [2]; thus, it is recommended for $BRCA1/2$ mutation carriers between the ages of 35 and 40 years or after childbearing [3].

Following confirmation of their mutation status, $BRCA$ mutation carriers may have difficulty in finding partners. Those who do have partners report difficulty with disclosing their mutation status and making relationship decisions such as childbearing, due to the increased risk of cancer in themselves and their biological children. In addition, $BRCA1/2$ mutation carriers’ partners are concerned about their children’s mutation status and risk of cancer. Female $BRCA$ mutation carriers and their spouses are less likely to have children than non-carriers [4-6]. Carriers who do want to have children have the option of undergoing preimplantation genetic diagnosis (PGD), i.e., the process of selecting $in\ vitru-fertilized embryos that are $BRCA$ mutation-free before implanting them into the uterus [7]. However, knowledge of PGD remains low, despite its increased acceptability among individuals at high risk of hereditary cancers [7].

Following reports of Angelina Jolie’s prophylactic surgery due to her family history of $BRCA1$ mutation carrier status, public awareness regarding hereditary breast and ovarian cancer syndromes and cancer-causing genetic mutations has increased [8]. However, attitudes toward partner relationships, childbearing, and PGD with $BRCA1/2$ mutation carriers among the general population have rarely been assessed. In addition, different cancer risks in male and female $BRCA1/2$ mutation carriers may cause sex-based differences in attitudes toward the disease. In this study, we investigate how the assumption of a hypothetical $BRCA1/2$ mutation status among healthy, unmarried individuals in South Korea may change their attitudes toward marriage and childbearing.

**METHODS**

**Study participants and questions**

The study’s population included 600 males and 600 females who were cancer-free, unmarried individuals, aged 20–39 years. Quota sampling was used to select participants. Seventeen administrative districts were applied as strata, and participants were allocated proportionally according to the population of each stratum as reported in South Korea’s 2019 resident registration record. People in their 20s and 30s were equally selected. A computer-assisted telephone survey was conducted in which the cellular phone numbers were randomly generated. Random digit dialing sampling is typically faster, increases accessibility to respondents, and produces data that are less subjective to interviewer effects than face-to-face interviews [9]. Three calls were made before the next phone number was generated. Informed consent was obtained from the participants prior to their participation in the survey. First, information on sex, birth year, residential area, marital status, and history of cancer was solicited. If a participant did not meet the selection criteria, the survey was stopped. The study was conducted from August 28, 2020 to September 2, 2020, with a response rate of 20.2%.
A questionnaire on marriage and childbearing intention was administered to all the participants. They were then provided information on BRCA1/2 mutation carriers' breast and ovarian cancer risks (lifetime breast and ovarian cancer risks up to 80% and 50%, respectively) and their autosomal dominant inheritance pattern. Those who answered “yes” to intending to marry were asked the following questions: (a) Were they willing to marry a BRCA1/2 mutation carrier. (b) Would their childbearing intention change if, hypothetically, they or their partners had carrier status. (c) Would they want to have children through PGD if they or their partners had carrier status, regardless of their answer to (b).

In addition, all the participants were asked about their attitudes toward BRCA1/2 mutation testing and disclosing positive test results to their families. Information on family history of breast or ovarian cancer and sociodemographic characteristics, including education, income, and job, were also obtained. This study was approved by the Institutional Review Board of the Hanyang University College of Medicine (IRB No. HYI-20-175-1).

**Data repository**
The collected data comprised answers to the questionnaire written in Korean. Therefore, the data were not submitted to a public repository. However, the data are available from the corresponding author on request through E-mail.

**Statistical analysis**
Baseline characteristics were presented as numbers and percentages. Changes in attitudes toward marriage and childbearing (the initial response versus the response after assuming a hypothetical mutation carrier status) were assessed as follows: Regarding intentions to marry, those who changed from “willing” to “unwilling” were considered. Regarding intentions about childbearing, those who changed from “willing” to “unwilling” and those who changed from “unwilling” to “willing” were both considered. Logistic regression was performed to assess associations between baseline characteristics and changes in marriage or childbearing intentions due to a hypothetical carrier status. The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) were presented. The respondents’ intentions to have children through PGD under the assumed hypothetical carrier status were compared to their initial intentions to have children. The χ² tests were used to assess sex-based differences for all relevant variables. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, USA).

**RESULTS**
The baseline characteristics of the participants are presented in Table 1. Comparable distributions between males and females were observed for age, residential area, family history of breast or ovarian cancer, and attitude toward genetic testing. However, educational level tended to be higher among females, while the numbers of students and participants with no income were higher among males.

The proportion of the participants with an intention to marry was 85.8% for males and 76.2% for females (p-value < 0.001, Table 2). The proportion of the participants with initial childbearing intentions was 71.0% for males and 53.0% for females (p-value < 0.001). Of the 972 participants with intentions to marry, 246 (25.3%), including 117 males (22.7%) and 129 females (28.2%), answered that they would not marry a BRCA mutation carrier (p-value
Those who initially intended to marry and who, on the assumption of being BRCA mutation carriers, retained a positive attitude toward childbearing, decreased to 57.5% in males and 39.2% in females (p-value < 0.001). In all the situations, the proportions of the
participants with intentions for marriage and childbearing were statistically higher in males than in females (Table 2).

Table 3 shows the factors that were associated with a change to a negative attitude toward marriage under the assumption that the partner was a BRCA1/2 carrier. Females were more likely than males to change their intention to marry (from willing to unwilling: OR, 1.41; 95% CI, 1.03–1.93). Compared with the respondents who had positive attitudes toward BRCA testing and disclosing their test results, those who did not want to undergo testing were more likely to change their intention to marry (OR, 1.65; 95% CI, 1.04–2.61). In addition, blue-collar workers were more likely than white-collar ones to change their attitudes toward marriage if the partners were carriers (OR, 1.60; 95% CI, 1.01–2.55).

Of the participants who initially intended to marry and have children (n = 744), 269 (36.2%) changed their attitude to not wanting children when they assumed a BRCA mutation carrier status. Meanwhile, of those who initially intended to marry but not to have children (n = 228), 36 changed their attitudes and would want to have children if they assumed carrier
status (Table 2). Females were more likely than males to change their decision under the assumption (Table 4: OR, 1.77; 95% CI, 1.31–2.39). The respondents who did not want to disclose their genetic test results changed their reproductive decisions more frequently than those who were willing to disclose their results (OR, 1.67; 95% CI, 1.03–2.72). Another factor was income: a higher income (≥ $30,000/year) was associated with a lower tendency to change decisions regarding childbearing (OR, 0.71; 95% CI, 0.52–0.96) than a lower income.

Of the participants who were willing to have children assuming they were BRCA1/2 carriers, 58.2% of the males and 67.5% of the females were willing to opt for PGD (Table 5). Preference for PGD was not statistically different between the sex. Of the respondents who did not want to have children if they were carriers, 55.6% of the males and 52.5% of the females changed their attitudes and said that they would want to have children through PGD, if possible.

## DISCUSSION

To the best of our knowledge, this is the first study to assess attitudes toward marrying BRCA1/2 mutation carriers among general, healthy, unmarried individuals with an average risk of breast or ovarian cancer using a nationwide sample. In addition, it is the first to investigate...
attitudes toward childbearing and the options available for BRCA1/2 carriers in the general population. In this study, females were more likely than males to change their marriage or childbearing intentions in the event that they or their partners were found to be carrying a BRCA1/2 mutation. Of the respondents who answered “no” to having children given a BRCA carrier status, more than 50% changed their answers to “yes” if they could access PGD. Additionally, those who retained their childbearing intention despite a hypothetical BRCA carrier status chose PGD as an option for having children.

Most previous studies regarding attitudes toward partnerships or reproductive options have involved those with confirmed BRCA1/2 mutation status or high-risk people based on their family and genetic history, mainly females and their partners. Few studies have explored males’ attitudes. Female BRCA1/2 mutation carriers are often concerned about breakups from disclosing their mutation statuses to their partners [4,10]. In the present study, the proportion of the respondents who were willing to marry a hypothetical BRCA1/2 carrier decreased by approximately 8% in males (from 85.8% to 77.3%) and 5% in females (from 76.2% to 71.8%). However, when the respondents were restricted to those who initially wanted to marry, a total proportion of 25.3% (both male and female) replied that they would not marry a BRCA1/2 mutation carrier. A previous study reported that although disclosure of mutation status changed female carriers’ relationships with their male partners, it did not completely end the relationships [5]. Compassion, closeness, and the length of time people have been in a relationship and known each other may be factors in issues related to rejection or acceptance after disclosure of genetic information [4]. In Mauer et al.’s study [5], most of the participants had had a serious relationship with BRCA mutation-positive partners for more than 5 years and were recruited through their carrier partners. Another study involving female unpartnered BRCA1/2 mutation carriers found that only 2.5% of the participants decided not to get married and 21.5% felt pressure to marry [11]. However, a follow-up study on young, female, cancer-free BRCA1/2 mutation carriers established that 10% of the couples had separated within 5 years of disclosure of BRCA1/2 mutation status; this rate was higher than that for non-carriers, and especially higher in carriers without children [12]. In this study, the partner with a BRCA1/2 mutation was hypothetical, which might explain the high proportion of the respondents who rejected carrier partners. Nevertheless, our results could reflect the perceptions of the general population regarding relationships with carrier partners or people with a high risk of hereditary cancer. Additionally, the results showed that rejection of carrier partners was associated with a negative attitude toward genetic testing and disclosure of genetic test

Table 5. The choice of PGD for childbearing among participants with initial intention to marry (n = 972)

| Choice of PGD                                      | Total | Males | Females | p-value* |
|---------------------------------------------------|-------|-------|---------|----------|
| Among participants who want children even if BRCA+ (n = 511) |       |       |         |          |
| PGD                                               | 416 (61.8) | 181 (58.2) | 135 (67.5) | 0.107     |
| Natural pregnancy                                 | 192 (37.6) | 128 (41.2) | 64 (32.0)  |           |
| Undetermined                                      | 3 (0.6)    | 2 (0.6)    | 1 (0.5)   |           |
| Among participants who do not want children if BRCA+ (n = 461) |       |       |         | 0.532     |
| PGD                                               | 248 (53.8) | 113 (55.4) | 135 (52.5) |           |
| Still do not want children                        | 213 (46.2) | 91 (44.6)  | 122 (47.5) |           |
| Among participants who initially wanted children but do not want children if BRCA+ (n = 269) |       |       |         | 0.624     |
| PGD                                               | 189 (70.3) | 89 (68.5)  | 100 (71.9) |           |
| Still do not want children                        | 80 (29.7)  | 41 (31.5)  | 39 (28.1)  |           |
| Among participants who initially did not want children and do not want children if BRCA+ (n = 192) |       |       |         | 0.739     |
| PGD                                               | 59 (30.7)  | 24 (32.4)  | 35 (29.7)  |           |
| Still do not want children                        | 133 (69.3) | 50 (67.6)  | 83 (70.3)  |           |

BRCA+: participant or their partner hypothetically had BRCA mutation.

*χ² test for differences between males and females.
results, which was comparable with the attitudes observed in previous studies. This suggests the importance of communicating health concerns related to BRCA1/2 mutations and their consequences not only to carriers but also to healthy populations [5,11,13-15].

BRCA1/2 mutation carrier status affects people’s decisions regarding childbearing and reproduction due to a 50% probability of passing their mutation on to children [11,16]. Chan et al. [11] showed that, of female BRCA1/2 mutation carriers with incomplete families, 41% reported changes in their childbearing intention, such as not wanting children or any additional children, due to the risk of transmission or increased risk of cancer. In this study, one inference is that one-third of the healthy population would forego childbearing on the assumption of being carriers. A follow-up study found a birth rate of 25% among 126 female BRCA1/2 mutation carriers within 5 years of genetic testing [12]. Childbearing decisions reflect personal and family experiences of cancer, including family responses to the disclosure of BRCA1/2 mutation status and cancer diagnosis [16]. In addition, risk-reducing management affects the timing of having children; tamoxifen treatment delays childbearing, as patients who undergo it are advised against conception, while risk-reducing surgeries increase the pressure to have children as soon as possible [16]. A personal history of cancer and having a partner were factors in the decision on having children among BRCA mutation carriers [11]. Among cancer-free BRCA1/2 mutation carriers, a younger age, having a partner, and a family history of breast or ovarian cancer were associated with a higher motherhood rate; however, the age association was absent in nulliparous females. In addition, education and occupation were not associated with motherhood [12]. The target study population for the present study comprised cancer-free males and females; thus, a direct comparison with previous studies that targeted BRCA1/2 mutation carriers might be limited. Nonetheless, the associations of high income and non-disclosure of mutation-positive genetic test results with a change in attitude toward childbearing are comparable with those in previous studies [6,11-14,16,17]. Disclosure of BRCA1/2 mutation status was associated with higher levels of family support during decision-making [18]. However, older age and a family history of breast or ovarian cancer showed no association with the effects of a hypothetical carrier status on marriage and childbearing intention.

There were notable differences between the sex in their attitudes and changes thereof on the assumption of a carrier status in themselves or their partners. Generally, females were more likely than males to avoid marrying BRCA1/2 mutation carriers and more likely to change their attitudes toward childbearing if they were mutation carriers, suggesting a more cautious stance. Male and female BRCA1/2 mutation carriers have different perceptions of their risks, which may influence their decision-making [13]. Individual risk perception was higher in female than in male BRCA1/2 mutation carriers, while carriers often considered that increased cancer risk was mostly associated with “females’ cancer.” When they discussed their BRCA1/2 mutation statuses with their partners, males without children focused on the risks to children rather than to themselves, whereas female BRCA mutation carriers were most concerned about both their own cancer risk and passing the mutation to their offspring, followed by increased cancer risk in the next generation. However, male carriers were less concerned about their risk and more focused on the risk of cancer in their children, especially in their daughters. This observation influenced the reason for disclosure: female carriers disclosed their mutation status to manage individual cancer risk and estimate options for family planning, whereas males only disclosed concerns about offspring [13]. These differences may explain the higher rejection of partners with a BRCA1/2 mutation and changes in attitudes toward childbearing observed in females than in males.
PGD is an option for BRCA1/2 mutation carriers who want to have offspring without mutations [17]. Despite the controversies surrounding PGD, several countries have approved it for adult-onset hereditary cancer mutations, such as BRCA1/2 gene mutations [19]. However, knowledge of PGD among carriers has been low, despite moderate acceptability and a high need for information on it [7]. Couples or partners of carriers also presented moderate PGD acceptability, although they had limited information available. The preference for PGD varies according to study subjects, setting, and mutation status [14,20,21]. In the present study, approximately 60%–70% of the respondents who wanted children despite having a hypothetical carrier status chose PGD, and more than 50% of those who did not want children if they were carriers changed their decision if PGD would be available. Based on the results of this and previous studies [14,20,21], information on PGD must be provided to high-risk people, such as BRCA1/2 mutation carriers, to inform their decisions on reproduction.

This study had several limitations. First, the attitudes toward having the BRCA1/2 mutation carrier status or toward having a partner with the status were assessed based on hypothetical scenarios; thus, the results may not be generalizable to confirmed BRCA1/2 mutation carriers or high-risk groups with hereditary cancers. However, the responses may reflect the perceptions of BRCA1/2 carriers in the general population. Second, this study focused on single associated factors, and did not consider models for the decision-making process, which should be considered in combination with single factors for decision making regarding family planning [4,6,20]. Third, the participants’ attitudes toward marriage assuming they themselves had BRCA1/2 mutations were not solicited. Fourth, the participants were not provided information on the costs or risks of PGD. In addition, due to time constraints, the information on the cancer risk and other health consequences of BRCA1/2 mutation was provided in a summarized form. Thus, the preference for genetic testing or PGD may be overestimated in this study’s sample. Finally, the low response rate (20.2%) of the study could cause selection bias. However, in Korea, the response rates in previous population-based surveys ranged from less than 10% to approximately 25% [22-24].

In conclusion, general, young, and healthy females assuming a hypothetical mutation carrier status changed their attitudes toward marriage and childbearing more negatively than males. Attitudes and future plans may also be affected by BRCA1/2 testing. Thus, genetic counseling should be offered before and after the test to provide detailed information on the benefits and harms of BRCA1/2 testing, followed by options for reducing risks. Childbearing intention may also change with awareness of PGD as an option, even for those who initially had no intention of bearing children. However, there are technical limitations and regulation issues involved with PGDs. For couples with mutations for hereditary cancers, the regulations may be relaxed to provide options for family planning. Public education regarding the implications of living with mutation carriers and hereditary cancers may be required. In addition, groups at high risk of hereditary cancers should be informed of their options for reproduction.

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