

Long-term follow-up of Jewish women with a BRCA1 and BRCA2 mutation who underwent population genetic screening

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Abstract There are two mutations in BRCA1 and one in BRCA2, which are present in up to 2.5% of Jewish women. Population genetic testing for Jewish women has been proposed; however, it is unclear how this would impact the uptake of cancer prevention options and psychosocial functioning in women with a positive result. Two thousand and eighty unselected Jewish women were tested for the Jewish BRCA mutations, and 1.1% were positive. Cancer-related distress was measured before testing, and at 1 and 2 years post-testing. Information on uptake of cancer risk reduction options was collected at 2 years. Breast and ovarian cancer risks were estimated using BRCAPRO. Within 2 years of receiving a positive result, 11.1% of women had prophylactic mastectomy, and 89.5% had a prophylactic oophorectomy. The mean breast cancer risk was estimated to be 37.2% at time of testing, compared to 20.9% at 2 years post-testing. The mean ovarian cancer risk was estimated to be 24.5% at time of testing, compared to 7.5% at 2 years following testing. Distress decreased between 1 and 2 years for women with prophylactic

mastectomy and oophorectomy ($P = 0.02$), and for women with prophylactic oophorectomy only ($P = 0.04$) but not for those with neither surgery. The majority of Jewish women with a BRCA mutation identified through a population screening elected prophylactic oophorectomy, but a few had a prophylactic mastectomy. Uptake of either surgery resulted in decreased distress. Provision of population BRCA testing resulted in reduced risks of breast and ovarian cancers in women with a mutation.

Keywords BRCA1 · BRCA2 · Breast cancer
Genetic testing · Jewish

Introduction

There are two mutations in BRCA1 and one mutation in BRCA2, which together are present in up to 2.5% of Ashkenazi Jewish women [1, 2]. These mutations are responsible for approximately 12% of breast cancers and 35% of ovarian cancers in the Jewish population [3, 4]. Carriers of a BRCA1 mutation (5382insC or 185delAG) face a lifetime risk of breast cancer of approximately 70%, and a risk of ovarian cancer of 30–40% [5]. Carriers of the BRCA2 founder mutation (6174delT) have a lifetime risk of breast cancer of approximately 50%, and a risk of ovarian cancer of approximately 20% [3]. Because these three mutations comprise the majority of deleterious mutations in the Jewish population, genetic testing for the “founder” panel is relatively straightforward and inexpensive, and it has been proposed that testing be offered to the entire Jewish population [6, 7]. More than half of Jewish women identified with a BRCA1 or BRCA2 mutation identified through population genetic testing do not meet genetic testing criteria [6].

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Genetic testing has not been shown to negatively impact on psychosocial functioning in women who are found to have a BRCA1 or BRCA2 mutation in clinic-based studies [8–11]. However, we recently demonstrated that in unselected Jewish women who had genetic testing for BRCA1 and BRCA2 in a population-wide program, that cancer-related distress was significantly elevated at 1-year post genetic testing [7]. It is not clear if this effect is transient or if it persists over the long-term.

Uptake of cancer risk reduction strategies have also been evaluated in women with a BRCA1 or BRCA2 mutation who received genetic testing in clinical cancer genetics programs [12–16]. Within the current study, population genetic testing for the three common Jewish mutations was offered without standard pre-test genetic counseling. Instead, a detailed booklet was provided regarding BRCA1 and BRCA2 and the implications of having a mutation. It was unclear if women who did not receive standard pre-test genetic counseling would elect for cancer risk reduction strategies to the same extent as women who received more intensive pre-test genetic counseling.

We tested 2,080 unselected Jewish women from Ontario [6], and 1.1% of the patients had a positive BRCA1 or BRCA2 result. It has now been a minimum of 2 years since each woman received her positive genetic test result. In the present study, we report on cancer-related distress levels, uptake of cancer risk reduction options and the resulting breast and ovarian cancer risks in Jewish women 2 years after receiving a positive BRCA mutation result through a population genetic screening program.

Methodology

Study population

The study protocol received ethical approval from the research institute. Eligible subjects were women who self-identified as (Ashkenazi or Sephardic) Jewish, who were between the ages of 25 and 70 years, and who resided in Ontario. Women with a family or personal history of cancer were not solicited, but were not excluded. Study subjects were recruited through an article that was published in a national newspaper (on a single occasion) in May 2008. Women were invited to call the study office if they were interested in participating. At the initial phone call, the study was explained, and the woman was asked if she wished to participate. If she was interested, she was given an appointment to come and provide a blood or saliva sample. Before the appointment, each subject was mailed a study package which included a study consent form, an information brochure on BRCA1 and BRCA2, a

family history questionnaire, and a study-specific questionnaire. They were asked to complete and return the relevant documents at the time of their blood/saliva collection appointment.

Women were not offered in-person genetic counseling at the time they provided a DNA sample for this study. However, all women were given a pamphlet on genetic testing for BRCA1 and BRCA2 (available on request). Topics covered in the pamphlet included information on basic genetics and BRCA1 and BRCA2, management options for mutation carriers, genetic testing in the Jewish population, implications of genetic testing, and information about the study and the study team. Before signing the consent form, each woman was asked if she had read the pamphlet and if she had any questions or concerns. A genetic counselor was available to answer any questions about the testing process or implications of testing.

All DNA samples were tested for the three Jewish founder BRCA1 (185delAG and 5382insC) and BRCA2 (6174delT) mutations. The molecular technique that was used to identify carriers of Ashkenazi specific mutations in BRCA1 and BRCA2 was done using a specific assay for Jewish mutations [17]. All mutations found by this method were confirmed by direct sequencing.

The genetic test result was available to all women who wished to receive her result. If the woman was negative for the three BRCA1 and BRCA2 mutations and had no significant family history of breast or ovarian cancer, then she received her negative genetic test result by mail. If the woman was negative for the genetic tests, but had a moderate or strong family history of breast or ovarian cancer, then the result was given by telephone by a genetic counselor, and a follow-up letter was sent. The letter summarized her breast cancer risk and provided recommendations for surveillance. If the woman had a positive genetic test, then the result was disclosed over telephone by the genetic counselor. She was invited to come for a full genetic counseling session within 3 days of receiving her result.

All women were mailed a study-specific follow-up questionnaire and the Impact of Events Scale and 1 and 2 years following genetic testing.

Study questionnaires

Study-specific questionnaire (at time of genetic testing)

This questionnaire was developed for this study; it included questions related to basic demographic information (age, cancer status, education, screening history, and cancer-preventive procedures).

Study-specific follow-up questionnaire (at 1 and 2 years post genetic testing)

This questionnaire was developed for this study; it included questions related to uptake of cancer risk reduction strategies, cancer screening, and cancer diagnoses.

Impact of event scale

The Impact of Event Scale (IES) [18] is a self-report measure designed to measure current subjective distress in relation to a specific stressor. In this study, the stressor was identified as “being at risk of breast cancer.” It measures the frequency of intrusive and avoidant phenomena. The scale consists of 15 items (7 intrusion items and 8 avoidance items). Participants rate the frequency of intrusive and avoidant behaviors using a four-point frequency scale (0 = not at all, 1 = rarely, 3 = sometimes, 5 = often). The IES allows the calculation of a total score (with a possible range of 0–75), and separate intrusion and avoidance subscales scores (with a possible range of 0–35 for intrusion, and 0–40 for avoidance). Cronbach’s alpha based on populations of patients with cancer, women with a family history of breast cancer, survivors of advanced Hodgkin’s Disease, patients with malignant melanoma, individuals tested for Huntington’s Disease, and patients experiencing bereavement are 0.78 for intrusion and 0.82 for avoidance. The IES has been found to have good validity and reliability when measuring cancer-related distress in women at increased risk of developing breast cancer [19].

Breast and ovarian cancer risk estimation

Breast and ovarian cancer risks were estimated using BRCAPRO [<http://astor.som.jhmi.edu/BayesMendel/brcapro.html#>] (Accessed 10/16/2011) by way of the HughesRiskApps interface (<http://www.hughesriskapps.net/> (10/16/2011)) and the BRCAPRO Risk Web Service [<http://bayesmendel.dfci.harvard.edu/risk>] (Accessed 10/16/2011). The baseline risk of breast cancer to age 70 for a 20-year-old woman using this model is 57% for BRCA1 and 49% for BRCA2 carriers, and the ovarian cancer risk is 40% for BRCA1 and 18% for BRCA2 carriers (based on Chen and Parmigiani [20]). Each patient’s information, including age at the time of BRCA mutation identification, was entered into BRCAPRO to estimate the risk of breast and ovarian cancer at the time of identification of BRCA mutation. Then, the interventions chosen by each patient was entered, and the risk of breast and ovarian cancer over time was estimated again. With oophorectomy before age 60, BRCAPRO adjusts the risk of breast cancer down by 54%. With oophorectomy at any age, the risk of ovarian cancer was reduced by 80% (based on Finch et al. [21]). BRCAPRO does not currently

adjust down the risk of breast cancer after prophylactic mastectomy, though modifications in development will soon be incorporated into BRCAPRO. We believe that the decrease in risk of breast cancer after prophylactic mastectomy is about 95% [22], and we have appropriately decreased the risk of breast cancer after mastectomy proportionately.

Statistics

Student *t*-tests were used to compare the mean value of continuous variables and Chi-square test was used to compare the frequency of categorical variables between sub-groups. Paired *t*-tests were used to compare the estimations of cancer risk and cancer-related distress, pre and post genetic testing. Statistical analyses were done by SAS (version 9.1.3), SAS Institute Inc., Cary, NC, USA.

Results

Demographics

Twenty-two women were identified as having a BRCA1 or BRCA2 mutation through population genetic testing, of whom 19 (86.4%) completed the 2-year follow-up questionnaire. The mean age of the 19 participants at time of genetic testing was 46.0 years (range 28–67 years). Eight women (42%) had a BRCA1 mutation, and 11 women (58%) had a BRCA2 mutation. At the time of genetic testing, no women had a personal history of breast or ovarian cancer. One woman was diagnosed with a stage I breast cancer in the year following genetic testing identified through screening mammography.

Uptake of screening and cancer risk reduction options

Before genetic testing, 12 women (63%) had a mammogram, none had a previous breast MRI, and eight women (42%) had undergone ovarian screening. At 1-year post-test, 19 women (100%) had a mammogram, 19 (100%) had an MRI, and 18 (95%) had ovarian screening. Within 2 years of receiving a positive genetic test result, two women (11.1%) had prophylactic mastectomy (of the 18 women without breast cancer), and 17 women (89.5%) had a prophylactic oophorectomy. The mean age of the women who had prophylactic mastectomy was 36.2 years at baseline compared to 47.1 years for those who declined prophylactic mastectomy ($P = 0.15$). The mean age of the women who had prophylactic oophorectomy was 47.5 years at baseline compared to 33.2 years for those without prophylactic oophorectomy ($P = 0.05$). Of the 17 women who were 35 or older at time of testing, 16 women

(94%) had a prophylactic oophorectomy. One woman took tamoxifen, and two women took raloxifene.

Cancer risks

At the time of genetic testing, none of the women had a previous diagnosis of breast or ovarian cancer, and none had undertaken cancer risk reduction options. We estimated the risk of breast and ovarian cancer to age 70 for the cohort of women identified with a BRCA mutation based on the individual mutation and age at time of genetic testing using the BRCAPRO program. We then estimated each woman's risk of breast and ovarian cancer to age 70 at 2 years following genetic testing based on uptake of cancer risk reduction options. The mean breast cancer risk to age 70 at time of genetic testing was 37.2% (range 21.2–52.1%) compared to 20.9% (range 1.1–51.1%) at 2 years following testing ($P < 0.0001$) (paired t -test). The mean ovarian cancer risk to age 70 at time of genetic testing was 24.5% (range 5.9–38.9%) compared to 7.5% (range 1.2–38.8%) at 2 years following testing ($P < 0.0001$) (paired t -test).

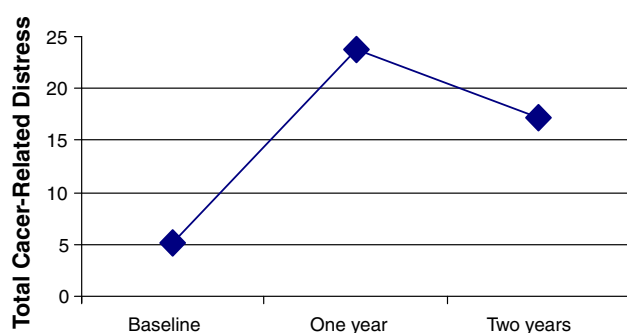


Fig. 1 Course of cancer-related distress levels

Cancer-related distress

Cancer-related distress was measured using the Impact of Event Scale (IES). Only women who had a distress score for the three time points were included ($n = 18$), and of those, one woman was excluded because she was diagnosed with breast cancer in the follow-up period. The analysis was completed on 17 women without cancer. The mean total score pre-testing was 7.1 (range 0–39). The mean scores for the pre-test intrusion and avoidance subscales were 2.5 (range 0–27) and 4.6 (range 0–29), respectively. As previously reported, the mean total distress score at 1 year post-testing was 25.3 (range 2–51) [7] (Fig. 1).

At 2 years post genetic testing, the mean total distress score was 18.9 (range 0–47). Six of the carriers (32%) scored in the subclinical range (0–8), seven women (37%) scored in the mild range (9–25), four women (21%) scored in the moderate range (26–43), and two women (11%) scored in the severe range (44+).

Table 1 presents the cancer-related distress scores over time. There were significant declines in intrusion ($P = 0.0003$), avoidance ($P = 0.004$), and total distress ($P = 0.0002$) between 1 and 2 years after genetic testing. Levels of cancer-related distress were evaluated based on the uptake of risk reduction options. Two women had both prophylactic mastectomy and oophorectomy, 16 women had prophylactic oophorectomy alone, and two women had neither. Total distress decreased significantly from 1 to 2 years of follow-up for those with prophylactic mastectomy and oophorectomy ($P = 0.02$) and for those with prophylactic oophorectomy only ($P = 0.04$), but not for those without either surgery (Table 1; Fig. 2). At two years, total distress levels were significantly different among the three groups ($P = 0.003$) with those with prophylactic mastectomy and oophorectomy having the lowest

Table 1 Cancer-related distress pre and post genetic testing

	Pre-genetic testing score	1 year post-genetic testing score	2 years post-genetic testing score	P value*
	Mean (SD) (range)	Mean (SD) (range)	Mean (SD) (range)	
BRCA mutation carriers ($n = 17$)				
Intrusion score	1.1 (1.9) (0–6)	10.9 (8.6) (0–31)	6.9 (6.2) (0–25)	0.02
Avoidance score	4.1 (8.7) (0–29)	12.9 (8.2) (1–30)	10.4 (9.4) (0–30)	0.19
Total score	5.2 (10.5) (0–35)	23.8 (14.5) (2–48)	17.2 (14.5) (0–47)	0.05
By preventive surgeries**				
Total score				
PO + PM ($n = 2$)	0	31.0 (2.8) (29–33)	3.0 (4.2) (0–6)	0.02
PO only ($n = 13$)	3.4 (9.6) (0–35)	22.5 (13.8) (2–48)	16.8 (13.1) (0–41)	0.06
Neither ($N = 2$)	22.0 (1.4) (21–23)	25.0 (31.1) (3–47)	34.0 (18.4) (21–47)	0.50

* Paired t -test for differences between 1st and 2nd FU

** The differences of total score between 2nd and 1st FU in the three groups is 0.0004 by ANOVA

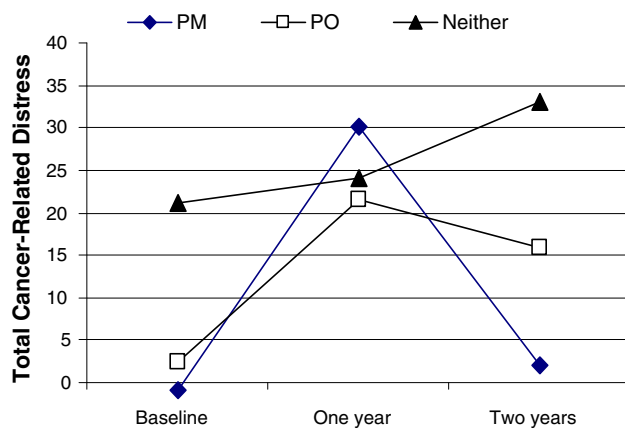


Fig. 2 Course of cancer-related distress levels in carriers by preventive measures

levels and those with no preventive surgery having the highest levels of distress.

Discussion

This study assessed the uptake of cancer risk reduction options and long-term changes in cancer-related distress in Jewish women who participated in a population-based genetic testing program and were found to have a BRCA1 or BRCA2 mutation. We have previously reported on changes in cancer-related distress 1 year after taking part in this population genetic testing protocol [7]. At 1 year after testing, women who were found to have a BRCA1 or BRCA2 mutation experienced heightened cancer-related distress, which was higher than what has been reported by others in the past [8]. In the current article, we report that these distress levels decreased significantly from 1 year post-genetic testing to 2 years post-genetic testing. This decline was particularly strong for women who had undergone prophylactic mastectomy or prophylactic oophorectomy. For women who did not elect either of these risk reduction strategies, cancer-related distress increased, although not significantly.

Before the study, none of the women had undergone prophylactic mastectomy or oophorectomy, or had taken a chemopreventive drug. At 2 years following the receipt of positive genetic test results, 90% of the women had undergone prophylactic oophorectomy, and 11% had undergone prophylactic mastectomy. Sixteen percent of the women had taken a chemopreventive drug. These uptake rates can be compared to reported rates in the context of clinical testing [12, 13]. Specific comparisons with clinical populations from Canada may be most informative, as previous research has suggested some variance in uptake by country which may be the result of varied health care

policies [12, 13]. All of the subjects in the current study were Canadian. In our previous report of uptake of risk reduction options in Canadian women identified with a BRCA mutation through clinical genetic testing, uptake of prophylactic mastectomy was 36%, uptake of prophylactic mastectomy was 61%, and uptake of chemoprevention was 16% [12] (the mean follow-up time was 4.2 years and the mean age of the women was 47.3 years). All of these women were enrolled in clinical assessment programs and received standard pre- and post-test genetic counseling. In contrast, the Jewish women in the current study did not receive standard pre-test counseling. Nevertheless, the uptake rate of prophylactic oophorectomy in the women undergoing population screening was higher than that for women tested in a clinical program (90% vs. 61% respectively). The uptake of prophylactic mastectomy was lower (10% vs. 36%), although this may be due to the shorter follow-up time.

The high rates of uptake could reflect the high levels of cancer-related distress observed in these women following the receipt of a positive genetic test result (which was higher than that observed in studies of women tested in clinical settings). Julian-Reynier et al. [23] reported on 244 French unaffected BRCA1 and BRCA2 mutation carriers 2.3 years after genetic testing. Cancer-related distress at 15 days post receipt of positive genetic test results predicted uptake of prophylactic mastectomy ($P = 0.02$) and prophylactic mastectomy ($P = 0.008$).

There are several limitations to our study. The number of women with BRCA mutations is small and all of the women received post-test genetic counseling at one academic center. This may have influenced the cancer risk reduction strategies that were chosen by the women and may not be generalizable. We also did not incorporate tamoxifen or raloxifene use in our risk estimations. This should have reduced the post-test breast cancer risks in three women, so we may have under-estimated the cancer risk reduction associated with population genetic testing.

It has previously been suggested that genetic testing for the three common founder BRCA1 and BRCA2 mutations be offered to all Jewish women based on the prevalence of the mutations, and because current guidelines for genetic testing for BRCA mutations do not capture all women who have a BRCA mutation [6]. The current study supports the rationale for population-based genetic testing for Jewish women. We have demonstrated that cancer distress levels decreased from 1 to 2 years after genetic testing and that the majority of women elected for one or more cancer risk reduction option. The mean risks of both breast and ovarian cancer decreased significantly as a result of genetic testing in this cohort of BRCA carriers. Offering population genetic testing to all interested Jewish women has the potential to reduce the burden of ovarian cancer in this

group of women. The high frequency of prophylactic oophorectomy and the high protective effect of the surgery make hereditary ovarian cancer to a large extent, a preventable disease. However, it is important that all BRCA carriers be identified before the age of 35 years for the potential to be realized. The current criteria for genetic testing is not identifying all Jewish women with a BRCA mutation. We suggest that genetic testing for founder BRCA1 and BRCA2 mutations be offered to all Jewish women who wish to know their BRCA status.

Conflict of interest The authors declare no conflicts of interest.

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