



Assessment of Interest for Breast Cancer Prevention Trial Participation among BRCA Mutation Carriers

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Abstract

Purpose: BRCA1 and BRCA2 mutation carriers develop breast cancers with a tumor phenotype unique from spontaneous tumors. We surveyed known BRCA mutation carriers to determine willingness to be contacted about participation in future breast cancer prevention research studies directed to their unique phenotype.

Methods: Data were collected through self-reported surveys at 3 participating institutions from women who: were at least 20 years of age; had a documented germline, deleterious mutation in BRCA1 or BRCA2; and had no prior history of breast cancer. Survey questions related to willingness regarding possible participation in future breast cancer prevention trials, including studies that may involve breast biopsies. Survey results were summarized using descriptive statistics.

Results: Among 56 BRCA1 and BRCA2 mutation carriers who responded, 55.4% of women reported high or very high interest in participating in a randomized control study of chemoprevention agent vs. placebo. Within this population, post-menopausal women demonstrated a higher interest in study participation (64.5%) versus pre-menopausal women (38.9%). When examining willingness to undergo breast biopsy for a chemoprevention study, women expressed near equal willingness (42.9%) and unwillingness (44.6%) for biopsy.

Conclusions: BRCA1 and BRCA2 mutation carriers demonstrated significant interest in breast cancer prevention study participation involving active versus placebo agents, and an equal expression of willingness and unwillingness to undergo breast biopsy. These data should be highly informative for planning future breast cancer chemoprevention trials.

Keywords: Breast cancer prevention trial; BRCA mutation; Patient recruitment; clinical trial

Introduction

Invasive breast cancer is the second most frequently diagnosed cancer in women, accounting for an estimated 29% of new cancer diagnoses in females in 2013. It is the second leading cause of cancer death in women after lung cancer [1]. Germline mutations account for 5-10% of female breast cancer with most mutations found in *BRCA1* or *BRCA2* genes. BRCA1 and BRCA2 mutation carriers have a substantial increase in lifetime cancer risk, at 60-85% compared to 12% in the general population [2-4]. BRCA1 mutation carriers are more likely to develop triple negative breast cancer than BRCA2 mutation carriers or non-carriers, while BRCA2 mutation carriers develop breast cancers similar to that of non-carriers in terms of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2/neu) [5].

Prevention and early detection strategies for BRCA mutation carriers range from closer surveillance with annual mammography and breast MRI, chemoprevention, prophylactic mastectomy (PM), and prophylactic bilateral salpingo-oophorectomy (BSO). There is little data addressing the impact of tamoxifen or aromatase inhibitors

on reducing the incidence of breast cancer in BRCA1 or BRCA2 carriers. In the subset of mutation carriers enrolled onto NSABP P-1 trial, tamoxifen was found to reduce the incidence of ER positive breast cancer by 62% in women with a BRCA2 mutation, but not in women with a BRCA1 mutation. The study was limited by a very small sample population with a BRCA1 or BRCA2 mutation [6]. These chemoprevention approaches have toxicities leading some to discontinue treatment, while others elect to not take the medication at all. Bilateral PM affords a 90% breast cancer risk reduction [7,8], while bilateral BSO demonstrates a 37% risk reduction for breast cancer in BRCA1 carriers, and 64% in BRCA2 [9]. Bilateral BSO also decreases ovarian cancer risk, overall mortality, breast cancer-specific mortality, and ovarian cancer specific mortality [9]. The chemopreventive benefits from several alternative agents are under investigation [10].

Chemoprevention strategies found to be effective in high risk non-mutation carriers may be suboptimal in BRCA1 and BRCA2 carriers due to differences in BRCA1 and BRCA2 associated tumor phenotypes [11], and as such should be investigated separately from that of high risk non-mutation carrier trial. This approach will provide the opportunity to discover potential predictive biomarkers related to the BRCA1 and BRCA2 tumor phenotype that could advance chemoprevention science on multiple fronts, most notably (a) pursuit of an improved prevention strategy for exceptionally high-risk

patients; and (b) characterization of premalignant tissue biomarkers, and potential modulation thereof. To pursue this research course, it is vital to understand the interest of BRCA1 and BRCA2 carriers in participating in chemoprevention studies and the extent to which they would be willing to undergo procedures.

We conducted a feasibility study in known BRCA mutation carriers to assess their willingness to be contacted about future chemoprevention trial participation and their willingness to undergo breast biopsy and breast imaging for research purposes as part of the trial. The study provides novel insight into study interest specifically within the BRCA carrier population; data gathered in this study will be used to aid in developing future chemoprevention trials (e.g., predicting accrual rates and targets, defining inclusion and exclusion trial criteria, and timing and number of breast biopsies) that focus on options specific and effective for BRCA mutation carriers.

Research Design and Methods

A survey was conducted among women at least 20 years of age with a documented germline deleterious mutation in BRCA1 or BRCA2 with no prior history of breast cancer to ascertain their willingness to participate in prevention trials of varying durations as well as the number of breast biopsies they were willing to undergo over the course of a prevention trial. Participants had not yet completed any surgical or preventative intervention. Ovarian cancer history was not collected as a part of the survey study.

The survey study was approved by the institutional review boards at the three subject recruiting centers: Mayo Clinic, University of Chicago and Fox Chase Cancer Center.

Individuals with a documented deleterious mutation of BRCA1 or BRCA2 were identified by the primary care provider or genetic counselor during their appointment.

Participants were contacted initially by mail or by telephone to assess their willingness to complete the questionnaire (Appendices A and B). The decision as to whether to use a letter or a phone call as the initial mode of contact was made by the clinicians. If they agreed to participate, the survey was either completed over the telephone or sent by ground mail or email according to the stated preference of the study participant.

Statistics: Descriptive statistics were used to summarize the survey results.

Results

Fifty-six women from 3 institutions participated in this study (Fox Chase: 33 pts; Mayo Clinic: 17 pts; University of Chicago: 6pts). The study remained open from September 1, 2009 to April 12, 2012, with a response rate of 94.3% for 2 of the 3 institutions. The median age of these women was 49 years old (range: 23-73 years) such that 35 (62.5%) were post-menopausal; 18 (32.1%) were pre-menopausal, and 3 (4.4%) did not state their menopausal status. Of those for whom specific mutation information was available (46 participants), 26 (46.4%) had a BRCA1 mutation and 20 (35.7%) had a BRCA2 mutation, with 10 unknown (17.9%).

Interest in participating in a breast cancer prevention study involving randomization between study agent and placebo for 12 months in duration was reported to be: high to very high in 31 (55.4%) women; neutral in 18 women (32.1%); very low to low in 4 (7.1%)

women; and one (1.8%) women did not provide an answer. High to very high interest in participating in such a trial was somewhat greater among the 35 post-menopausal women (23/35; 65.7%) than (7/18; 38.9%) pre-menopausal women (Table 1).

	Menopausal Status			Overall (n=56)
	Pre-Menopausal (n=18)	Post-Menopausal (n=35)	Unknown (n=3)	number (%)
	number (%)	number (%)	number (%)	
Q1: Willingness to enroll on a study with randomization to study agent or placebo for 12 months				
low to very low	3 (16.7)	3 (8.6)	0	6 (10.7)
neutral		8 (22.9)	2 (66.7)	18 (32.1)
high to very high	7 (38.9)	23 (65.7)	1 (33.3)	31 (55.4)
no response	0	1 (2.9)	0	1 (1.8)
Q2: Will to undergo ultrasound guided breast biopsy pre- and post-treatment				
yes	9 (50.0)	14 (40.0)	1 (33.3)	24 (42.9)
no	7 (38.9)	16 (45.7)	2 (66.7)	25 (44.6)
unsure	1 (5.6)	4 (11.4)	0	5 (8.9)
no response	1 (5.6)	1 (2.9)	0	2 (3.6)

Table 1: Interest in Breast Cancer Trial Participation

Nearly equal numbers of the women surveyed expressed a willingness to undergo a breast biopsy (42.9%) compared to an unwillingness to do so (44.6%). Of the remaining 7 patients, 5 indicated they were neutral on the request and 2 refused to answer the question.

The percentage of women willing to undergo a breast biopsy was 40% (17/35) among post-menopausal women and 50% (9/18) among the pre-menopausal women.

Conclusion

Based on our survey study findings of BRCA mutation carriers, the overall interest in participation in a chemoprevention agent versus placebo trial was 55.4%, with a greater interest in post-menopausal women as compared to pre-menopausal women. The low sample size limits quantitative evaluation; however the study exhibits a significant interest of BRCA1 and BRCA2 mutation carriers to participate in a chemoprevention study. Additionally, 42.9% expressed willingness to undergo breast biopsy as part of a future study, supporting the

feasibility of chemoprevention studies that evaluate breast tissue phenotype before and after administration of chemoprevention.

This study had several limitations. The survey utilized did not allow for determination of time from diagnosis of a BRCA mutation carrier status to time of survey. The small sample size precluded evaluating BRCA1 and BRCA2 carriers separately. Additionally, only patients who had appointments with designated providers during the time frame of the study were approached for participation. We cannot confirm that all patients seen were approached for study involvement, resulting in the possibility that physicians approached patients who they felt were more interested in research, or more likely to participate in the study. Finally, the results demonstrate interest in hypothetical, incompletely-defined future research; interest may change for accrual to an actual trial.

To our knowledge, no prior studies have utilized a self-reported survey design to examine chemoprevention study interest within the BRCA1 and BRCA2 mutation carrier population. Women with a family history of breast and ovarian cancer in France, England, and Canada expressed a 58% acceptance for chemoprevention via questionnaire [12]. In examination of the general population, Gillan et al. evaluated recruitment strategies for the UK Breast Screening Program, and found a 46% acceptance to a film-reading protocol [13]. Tija et al evaluated chemoprevention interest in women aged 60-65, and found only 11.2% interest in chemoprevention, notably lower than both the pre-menopausal and post-menopausal interest levels obtained in our study [14]. Additionally, several studies have evaluated tactics for increasing participation in chemoprevention studies for cancers including breast, prostate, and lung [13-19].

Chemoprevention options for BRCA mutation carriers are limited, heightening interest in developing new chemoprevention agents that are effective and well tolerated [20]. Currently, the utilization of chemoprevention in high risk women is low, with perceived personal risk more strongly associated with tamoxifen and raloxifene use [16]. Many studies have highlighted the discrepancies between interest in hypothetical and actual randomized clinical trial participation following breast cancer diagnosis [21-23], a phenomenon also seen in chemoprevention trials for women at high risk of breast cancer [16]. Women were distinctly hesitant to participate due to the perceived risk of side effects from chemoprevention treatment. Physician communication and the opinions of the family physicians also affected interest in clinical trials [15,24]. To adequately address the benefits of preventive interventions for women at high-risk for breast cancer occurrence, there is need for identification and development of biomarkers which can guide therapy and evaluate efficacy [25]. It is paramount that both patients and physicians have access to this valuable information as part of the shared decision making process when considering risk reduction strategies, as it can positively impact uptake of preventive therapy [26].

Conclusion

In conclusion, our feasibility study highlights definite interest from BRCA1 and BRCA2 mutation carriers for participation in chemoprevention research. In looking to future study design, our data support the inclusion of breast biopsy as a viable option for molecularly-targeted analyses of candidate chemopreventive agents specifically for the BRCA mutation carrier population. Additionally our findings will assist with estimation of sample size and design of future chemoprevention trials in this population.

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