Participation in Breast Cancer Susceptibility Testing Protocols: Influence of Recruitment Source, Altruism, and Family Involvement on Women's Decisions[1]

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Abstract

Objectives. We offered education, counseling, and family-based *BRCA1/2* testing to women at increased risk of breast cancer and assessed (*a*) their reasons for participating and (*b*) whether source of recruitment, desire to help research (altruism), and the need to communicate with their affected relative about testing distinguish those who did and those who did not complete each phase of our protocol.

Materials and Methods. We sent invitations to 403 women who had completed a questionnaire on *BRCA1/2* testing, 178 of whom were considered high risk because they had more than one relative on the same side of the family with early-onset breast cancer.

Results. Among the 132 high-risk respondents from the mid-Atlantic states (where testing was offered), 36% (n = 47) were interested in counseling. Those who actually attended counseling were more likely to have some college education, a higher perceived risk of breast cancer, and a greater fear of stigma and were less likely to have a daughter than those who did not attend. The reasons for attending that were rated "very important" were to learn about the test (80%), to have the test (43%), and to help research (38%). High-risk women were eligible for testing only if their affected relative was willing to be tested and tested positive. After the session, 83% intended to ask their affected relative to be tested, but only half of the affected relatives actually came for pretest counseling. The proportion of participants who ultimately involved an affected relative was 2.5 times higher among women from a clinical population (25%) than among those from a registry population (10%); in this latter population, an altruistic desire to help research was a greater motivator for participation than interest in being tested.

Conclusions. Source of recruitment influences both motivations to attend education and counseling and actual testing behavior. These results have implications for interpretation of findings from studies in research settings as well as for informed consent and decision-making in the context of family-based testing.

Introduction

It is currently recommended that genetic testing for susceptibility to breast and ovarian cancer (*BRCA1/2* testing) not be performed directly on an at-risk woman without first testing an affected relative to determine whether there is a detectable mutation in the family (1, 2). The question of what sort of barriers are introduced to the testing process for at-risk women by the necessity of first testing an affected relative has received only minimal attention. The early experience with testing for other disorders, such as Huntington's disease, through linkage studies demonstrates that the need to involve relatives is often a reason why testing is declined (3). Women may be unwilling to discuss family history with certain key relatives, or family rifts may make communication impossible (4). One study has shown that women diagnosed with cancer are less favorably disposed to genetic testing than are their at-risk relatives, indicating that some women with breast cancer might be unwilling to undergo testing (2). The reluctance of the affected relative to share his or her test result with the at-risk individual has also been cited as a potential barrier (5).

Not only do we know little about the decision-making process of women who are offered "family-based" testing, but we also do not know the degree to which participation in testing protocols is motivated by a desire to help research. There is a substantial body of literature exploring the reasons that individuals participate in randomized clinical trials (in which the participants are ill and half are offered some sort of therapy; Refs. 6–13) and the impact of selection bias on generalizability of results. There are also studies that explore the reasons that healthy individuals participate in research (14, 15). It is well documented in most of these studies that individuals who participate in research are a self-selected group, frequently motivated by an altruistic desire to help others.

To our knowledge, there have been no studies that explore the degree to which an altruistic desire to help research motivates at-risk individuals to participate in predictive genetic testing protocols. Although one study acknowledged self-selection in predictive testing for Huntington's disease (3), it focused on whether those who are most vulnerable psychologically are selected out, rather than on whether those who want to contribute to science are selected in. Little is known about the effect of selection bias on at-risk women's participation in breast cancer susceptibility testing protocols. We observed in our focus groups (16) that some women are likely to be moti-

Received 10/10/97; revised 12/15/98; accepted 12/21/98.
[1] Report from the Cancer Genetics Studies Consortium. This work was supported by National Institute of Nursing Research Grant R01 NR04062-01. A variation of this paper was presented at the American Society of Human Genetics Annual Meeting, October 28–November 1, 1997, Baltimore, MD.
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vated more by curiosity and altruism than by the usefulness of the information the test can provide.

The effect of an altruistic desire to help research on women's decisions to participate in breast cancer susceptibility testing protocols may depend on the population from which they are recruited. Women from families with a strong history of breast and/or ovarian cancer may have contemplated genetic testing and the clinical management options available for high-risk women a great deal, even before being offered testing (4). Such women, because of higher actual and perceived risk, might also have sought risk assessment through a cancer genetics program. If recruitment into protocols is through clinical services, selection bias is introduced because these women might have more knowledge about testing, have more cancer-related worries, and be more motivated to participate by interest in testing than by altruism. On the other hand, if women are recruited through a registry population (such as through relatives in a cancer registry), they may be less aware of testing, have lower cancer worries, have less appreciation of the possible clinical utility of test results, and be motivated to participate more by their interest in helping research.

As part of a study to develop a model informed consent process for *BRCA1/2* testing, we offered education, counseling, and family-based *BRCA1/2* testing to women who were at increased risk of breast cancer. Here, we describe: (*a*) their motivations for attending education and counseling; (*b*) their interest in and reasons for pursuing testing in their families (*i.e.*, involving their affected relative); and (*c*) the degree to which source of recruitment, an altruistic desire to help research, and the necessity for at-risk women to communicate with their affected relative about testing help to distinguish between those who completed each phase of our study protocol and those who did not.

Materials and Methods

Recruitment. We studied women at increased risk of breast cancer because of family history. They were recruited in two ways. The majority of at-risk women were identified by writing to women who were listed in the Johns Hopkins and Maryland Statewide Tumor Registries as having been diagnosed with breast cancer under the age of 50 and whose diagnoses were made between 1992 and 1994. Eligible probands were sent a letter requesting the names and addresses of their unaffected first-degree relatives between the ages of 21 and 50. Twenty % provided the names of at least one sibling or adult child. We stratified female relatives into sisters and adult daughters, and randomly selected from each category so that we had one female relative per proband. We refer to the women recruited through a registry as our "registry" population. A second source of recruitment was from a group of "outpatients" seen at the Johns Hopkins BOSS[5] because of concerns about their increased risk of breast cancer. Our initial ascertainment focused on unaffected women who had at least one first-degree relative diagnosed with breast cancer under the age of 50 and who had been seen at the clinic prior to the incorporation of *BRCA1/2* education and counseling (and, therefore, had not received it). We call this our "clinical" population. A questionnaire assessing attitudes toward genetic testing for breast cancer susceptibility was sent to a total of 584 at-risk women.

The response rate to the questionnaire was 71%. One year later, we mailed invitations to 403 Caucasian respondents (there are no data on the sensitivity of the test we were offering among nonwhites) to attend an education and counseling session regarding *BRCA1/2* testing. The invitation included an offer of testing if the women's relatives were tested and found to carry a mutation. The invitation for education and counseling included an institutional review board-approved consent form and a detailed family health history form for obtaining information on cancer diagnoses for three generations of relatives. A woman was considered eligible to attend counseling if she completed and returned these forms, if her relative with breast cancer was still living (and, therefore, available for possible genetic testing), and if she herself had not been diagnosed with breast or ovarian cancer. Of the 403 women who were invited to participate in education, counseling, and testing, 132 were considered to be at high risk (defined as having more than one relative on the same side of the family with early-onset breast cancer) and came from the mid-Atlantic states (where testing was offered). Here, we focused our analysis on this subset of women whose family histories might make them appropriate candidates for testing and for whom geographic inconvenience would be less likely to impede their ability to participate.

Content and Process of Counseling. Counseling was conducted by four genetic counselors and two registered nurses who had undergone training in breast cancer genetics and susceptibility testing. The counseling sessions were offered in four different locations and at several different times to minimize inconvenience for the participant. The education and counseling sessions included a review of each woman's family history and pedigree, general information about breast cancer, risk factors for breast and ovarian cancer, *BRCA1/2* mutations, description and limitations of testing, and discussion of the family-based nature of the testing protocol. After the session, women were given a booklet, designed specifically for the study using focus group and survey data reported elsewhere (17–19), which summarized the information discussed during the session. Sessions took ~2 h, including the completion of short pre- and postsession questionnaires. High-risk women were told that, if their affected relative was interested in testing, she would have to come for a separate pretest education and counseling session with a different genetic counselor. The test we were offering was a screening test for the 16 most common *BRCA1* and *BRCA2* mutations. It was offered by OncorMed, Inc., free of charge to participants.

Data Sources. There were three sources of data. The initial attitudes questionnaire, through which we identified our invitees, included demographic and limited family history information as well as a few previously validated scales. One was a "fear of stigma" scale, which was created from four statements about confidentiality, stigma, and insurance discrimination using a four-point Likert scale [from "strongly disagree" (= 1) to "strongly agree" (= 4)]. Three of these items were used in a previous study (20). A dichotomous "fear of stigma" variable was created by dividing the total score into "low" (4–8) *versus* "high" (9–16). "Cancer worries" is another prevalidated scale that consists of four questions regarding the extent to which respondents have thought about their chances of getting breast cancer and how much this interferes with their lives [on a scale from "not at all" (= 1) to "a lot" (= 5); Ref. 21]. This scale was also dichotomized at the median. Perceived risk of breast cancer compared to others was assessed with one question, which asked: "In your opinion, compared to other women your age, what are your chances of getting breast cancer?" Respondents were dichotomized as either "very high" [responding "much

[5] The abbreviations used are: BOSS, Breast and Ovarian Surveillance Service; CI, confidence interval.

Table 1 Characteristics of sample invited to counseling session, by recruitment source

	% of participants	
	Clinical (n = 24)	Registries (n = 108)
Age, yr		
21–39	54.2	68.5
40–50	45.8	31.5
Education		
High school or less	25.0	31.5
Some college or more	75.0	68.5
Employed full-time	62.5	65.7
Jewish	25.0	11.0
Has a daughter	70.8	41.9[a]
Heard something/a lot about test	60.9	35.5[b]
Perceives breast cancer risk as much higher than that of others her age	69.6	52.3
High cancer worries scale	39.1	47.7
High fear of stigma	56.5	45.3
Believes cancer can happen for no reason	70.8	89.8[b]

[a] $P = 0.01$.
[b] $P < 0.05$.

higher" (= 5)] or "not very high" [responding "much lower" (= 1) to "a little higher" (=4)]. Respondents were also asked how much they agreed [from "strongly disagree" (= 1) to "strongly agree" (= 4)] with the statement: "Someone can get cancer for no apparent reason." Responses to this item were dichotomized at the median.

There were two other questionnaires associated with the education and counseling phase of our study. Before the education and counseling sessions began, we administered a short questionnaire in which women were asked to rate the importance of four reasons in deciding to attend the counseling session. At the completion of the counseling session, a second short questionnaire was administered that assessed the participant's intention to ask the affected family member to be tested and reasons for doing so. This was how we defined one of our behavioral outcomes because our protocol for testing high-risk women required that an affected relative be tested first. Reasons for attending counseling and for intending to involve an affected relative in testing were assessed on four-point Likert scales ["not at all important" (= 1) to "very important" (= 4)]. Those who rated reasons as "very important" were compared with all others.

Results

Description of Invitees by Source of Recruitment. A description of the characteristics of the two groups of participants is provided in Table 1. Of the 132 high-risk women from the mid-Atlantic states, 24 were recruited through the BOSS (clinical), and 108 were recruited through the registries. Although the number of women from the clinical population is small, these women are clearly different from women in the registry population. Respondents from the BOSS were slightly more likely to be Jewish, to have a daughter, to have prior knowledge about *BRCA1/2* testing, and to perceive their risk of breast cancer as much higher than that of other women their age. They were significantly less likely to believe that cancer can occur for no apparent reason.

Interest in Attending Counseling. Among the 132 high-risk questionnaire respondents from the mid-Atlantic states, 36% (n = 47) were interested in counseling, 26% (n = 35) were not, and 38% (n = 50) did not respond to the invitation. There were no differences in women's interest in attending by source of recruitment. Of the 47 women who initially expressed interest in education and counseling, 40 (85%) ultimately completed a session. Table 2 shows the characteristics that distinguish those who attended counseling from those who did not (either because they said they were not interested or because they did not respond to the invitation) by source of recruitment. Large enough numbers among women in the registry population allowed us to assess statistically significant differences between attendees and nonattendees. Those who attended counseling were significantly more likely to have at least some college education, to be employed full-time, to have greater fear of stigma, and to perceive their risk of breast cancer as much higher than that of other women their age and were less likely to have a daughter. On multivariate logistic regression, controlling for age, women from the registry population who had high perceived breast cancer risk were 3.9 times more likely (95% CI = 1.4–10.4) than women with lower perceived risk to attend a session; women with at least some college education were 3.0 times more likely (95% CI = 0.9–10.0) than lower educated women to attend a session; women who had high fear of stigma were 3.0 times more likely (95% CI = 1.1–7.8) than women with lower fear to attend a session; and women without a daughter were 3.2 times more likely (95% CI = 1.0–10.4) than women with a daughter to attend a session. Although there are too few women in the clinical population to assess statistically significant differences between attendees and nonattendees, there were some trends. A greater percentage of those who attended counseling had at least some college education, a lower percentage was Jewish, and fewer had high cancer worries or high fear of stigma.

Interest in Pursuing Testing in the Family. The number of eligible participants who responded to the invitation for education and counseling and who ultimately involved an affected family member in testing are presented by recruitment source in Fig. 1. The proportion of participants offered family-based testing who ultimately involved an affected family member was 2.5 times higher among women from a clinical population (25%) than among women from a registry population (10%). Although there is no difference by recruitment source in the proportion of women who expressed interest in attending counseling, there does appear to be a difference among the women who actually underwent counseling. Of those who expressed interest in attending, 100% of women in the clinical population, in fact, attended, whereas 82% of women in the registry population attended. Of the 40 participants counseled, the reasons for attending rated by women as "very important" were to learn about the test (80%), to have the test (43%), and to help research (38%). We subdivided the women who were counseled into those who rated wanting to have the test as more important *versus* those who rated wanting to help research as more important. We used this dominant precounseling motivation in subsequent analyses as a proxy for an underlying or an a priori orientation either toward an altruistic desire to help research or toward interest in being tested. Despite small numbers, Fig. 2 suggests a trend toward an association between women's major motivation for attending counseling and the population from which they were drawn. Women from the clinical population were more likely to attend counseling because they wanted to have the test, whereas women from the registry population were more likely to attend counseling because they wanted to help research.

Immediately after counseling, 33 women (83%) said they

Table 2 Differences in attendance at counseling session, by recruitment source

	% of participants			
	Clinical		Registries	
	Attended (n = 8)	Did not attend (n = 16)	Attended (n = 32)	Did not attend (n = 76)
Age, yr				
21–39	62.5	50.0	65.6	69.7
40–50	37.5	50.0	34.4	30.3
Education				
High school or less	12.5	31.3	15.6	38.2
Some college or more	87.5	68.8	84.4	61.8[a]
Employed full-time	62.5	62.5	81.3	59.2[a]
Jewish	12.5	31.3	12.5	10.7
Has a daughter	62.5	75.0	25.0	49.3[a]
Heard something/a lot about test	50.0	66.7	41.9	32.9
Perceives breast cancer risk as much higher than that of others her age	62.5	73.3	77.4	42.1[b]
High cancer worries scale	12.5	53.3	54.8	44.7
High fear of stigma	37.5	66.7	64.5	37.3[c]
Believes cancer can happen for no reason	75.0	68.8	93.8	88.2

[a] $P < 0.05$.
[b] $P < 0.001$.
[c] $P = 0.01$.

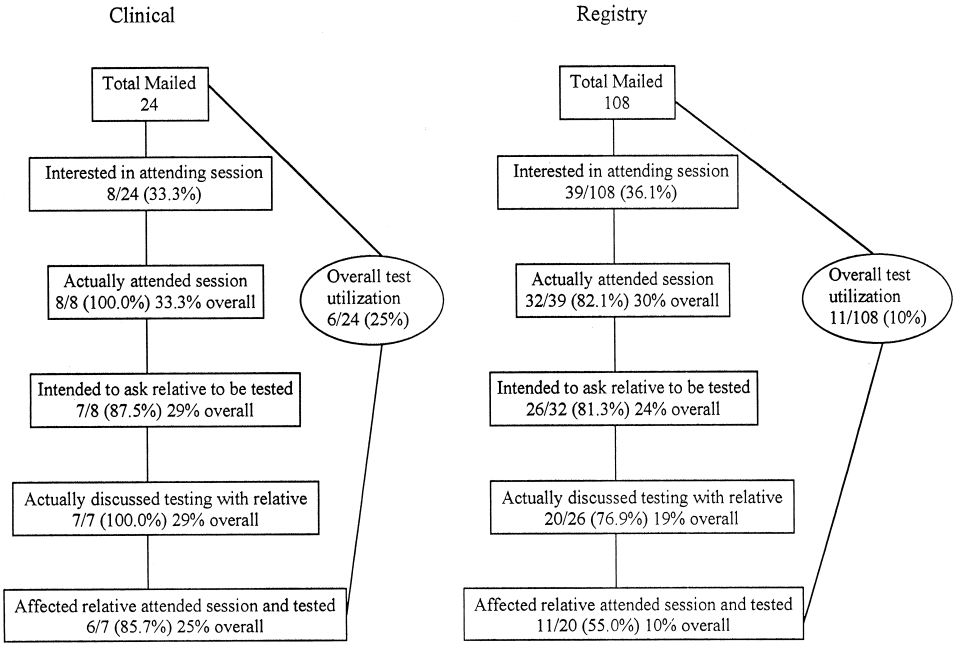

Fig. 1. Response rates and test utilization, by source of recruitment.

intended to ask their affected relative to be tested. When asked about reasons for this intention, 79% of these women said the information would be useful for themselves, 61% thought the information would be useful for their affected relative, 67% thought the information would be useful for other family members such as sisters and daughters, and 59% wanted to help research. As shown in Fig. 1, there was no difference in expressed intention by recruitment source. However, when it came time to actually discuss testing with an affected relative, we observed a greater rate of attrition in the registry population. Whereas only 76.9% of these women discussed testing with a relative, 100% of women from the clinical population had such a discussion. After communicating with an affected relative, there continued to be a greater rate of attrition in the registry population. Overall, of the 33 women who intended to ask their affected relative to be tested, only 17 (51.5%) of the relatives actually came for counseling.

We looked at the association between high-risk women's decision to involve their affected relative in testing and their *a priori* motivation to attend counseling. Despite small numbers, Fig. 3 suggests a clear trend toward an association. Women who attended counseling primarily because they were interested in being tested rather than because of their desire to help research were more likely to involve their affected relative in testing (64%), whereas those who attended counseling primarily because they wanted to assist

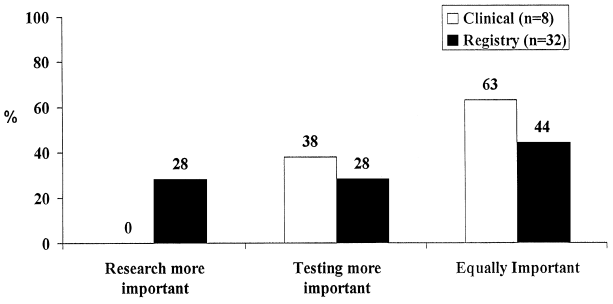

Fig. 2. Relative importance of motifications for those attending education, by recruitment source.

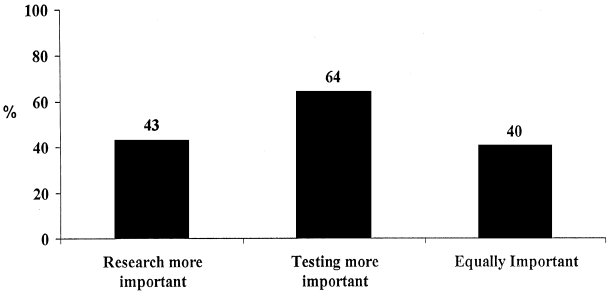

Fig. 3. Percentage of affected relatives actually presenting for counseling, by at-risk relative's motivation for attending counseling (among those intending to ask affected relative; $n = 33$).

research rather than be tested were less likely to involve their affected relative in testing (43%).

Reasons Why Affected Relatives Were Not Scheduled for Counseling. To have a better understanding of the reasons that the affected relatives of 17 high-risk women did not schedule an appointment for counseling, we decided to send a one-page follow-up questionnaire to these high-risk women. The cover letter made clear that we were not intending to pressure them to involve their relative in testing but to explore the status of their decision-making. Eight responded. We then called the remaining nine high-risk women and reached all except one. Fifty-nine % of these 17 high-risk women ($n = 10$) actually had a discussion with their relative about testing or asked their relative to be tested. Seven of the affected relatives declined testing either for logistic reasons (*e.g.*, time and distance) or because they did not want to be tested because of concerns about insurance or because they thought their case was sporadic. In the other three cases, the high-risk women mainly decided not to pursue testing because they believed the test results would not change anything they were already doing. Four of the 17 high-risk women decided not to ask their affected relative to be tested either because they decided the test results would not change anything they were already doing or because the information they received from counseling or the booklet caused them to change their minds on further reflection. The remaining two postponed their decision about discussing testing with their affected relative because the relative was too ill.

Discussion

In this study of women at high risk of breast cancer, we observed a relatively low interest in attending education and counseling about *BRCA1/2* testing, regardless of whether women were recruited from a clinical or a registry population. However, among the women who came for counseling, we observed a difference by source of recruitment in whether they actually pursued testing in the family. Those who were recruited from a clinical population were more likely to involve their affected relatives in testing than were women recruited from a registry population. Among those who did attend education and counseling and did involve their affected relative in testing, the relative importance that women gave to being tested *versus* helping research varied by source of recruitment. Women who were recruited from a clinical population were more motivated by their interest in being tested, whereas women who were recruited from a registry population were more motivated by their interest in helping research.

These findings suggest that most women who actually intend to follow through on family-based testing (by asking their affected relative to attend counseling) are a self-selected group of women who have already decided to pursue testing when they consent to attend counseling. In our study, this was particularly true for women who were already seeking care because they had concerns about their risk of breast cancer. However, in the context of family-based testing, a high-risk woman's desire to undergo testing does not necessarily guarantee that she will pursue testing. First, she must decide whether she is willing to engage her affected relative in a discussion about testing. Then, having done so, she is dependent on her affected relative's wishes. Alternatively, the high-risk woman herself may change her mind before, during, or after a discussion with her affected relative. In our study, half of the women who had intended to involve their affected relative but whose relative did not present for testing either had changed their minds about involving the relative or had decided to postpone the decision. Even when they did decide to ask their relative, more than half the relatives declined. Because family-based testing necessitates communication among family members, it is likely to expose complex family dynamics and patterns of communication. Actual rates of testing might have been higher if we were offering direct testing. Whether the need for family communication serves as a barrier to testing deserves further study.

Our data shed light on several previously unanswered questions. (*a*) How does selection bias operate in women who participate in breast cancer susceptibility testing protocols? (*b*) To what extent does an altruistic desire to assist research motivate women to participate? (*c*) What implications do these selection biases have for the conduct and interpretation of research protocols? (*d*) How do the requirements of family-based testing affect test utilization?

It appears that, in the context of breast cancer susceptibility testing protocols, selection bias reflects a complex interaction between source of recruitment and underlying motivation to participate in research. Women who are recruited from a clinical population and are, therefore, seeking care because they are concerned about their risk of breast cancer, are more likely to attend education and counseling because of their intention to undergo testing and are more likely to involve an affected family member in testing. To the extent that high-risk and affected relatives have similar attitudes, values, and beliefs about testing and research participation, there is unlikely to be significant attrition at successive stages of a family-based testing protocol. If there is consistent follow-through, as there seems to be in a clinical (nonresearch) population, intention may be a good proxy for actual behavior.

In contrast, women who are recruited from a registry

population are more likely to attend education and counseling because of their desire to help research but are not as likely to involve an affected family member in testing. (That the women from a registry population who attended counseling were also less likely to have a daughter lends support to our observation that they are motivated for reasons other than to benefit their family members.) To the extent that these women are less likely to follow through at each successive stage of a family-based testing protocol, attendance at counseling, or intention to involve an affected family member may not be accurate proxies for test uptake.

Strengths and Limitations. Because we were recruiting from among respondents to an initial survey and completion of the survey was a requirement for participation in the education, counseling and testing phase of the study, we were concerned that the women who responded to the first survey would, themselves, be self-selected for their altruistic desire to help research. However, the relatively high rate of response to the survey (22) suggests that the population that was eligible for participation in this testing phase of the study (by virtue of completing a survey) was fairly representative of the eligible population overall. Therefore, our ability to draw conclusions about the target population (women with more than one relative on the same side of the family with early-onset breast cancer) is probably not limited by an incomplete response to the initial questionnaire.

Nevertheless, there are several limitations to our ability to make generalizations based on these findings.

(*a*) Our data are restricted by the demands of our testing protocol. We required that education and counseling be conducted in-person for both the high-risk woman and her affected relative. Geographic distance and inconvenience were significant barriers to women's participation. We know from previous research that when testing is made as convenient as possible, utilization rates increase (20).

(*b*) The generalizability of our findings is limited because our study was conducted through Johns Hopkins Hospital. Many of the women who participated in our study are either Johns Hopkins patients themselves or are relatives of women who received treatment for their breast cancer at Johns Hopkins. To the extent that these women are satisfied with the care offered at Johns Hopkins, they may represent a select group of participants who either trust the health care system or are altruistically motivated to participate in a Johns Hopkins study.

(*c*) There were statistical limitations associated with small numbers in our study. We were only able to recruit a few participants from the clinical population, and we did not retain the majority of participants the closer women came to the possibility of testing. As a result, we were able to demonstrate only trends, not statistically significant patterns of association. Despite these limitations, our findings have implications for offering family-based testing and understanding testing decisions either in research or clinical settings.

Implications. Findings from studies in research settings regarding interest in testing should be interpreted with caution because women may be motivated by an altruistic desire to help research. We need to develop a better means of assessing whether and when participation in genetic susceptibility testing protocols is motivated more by an altruistic interest in contributing to science than a desire to be tested. Because some research participants appear to be inspired more by an intention to assist research than by an interest in being tested, uptake of *BRCA1/2* testing and motivations may be more accurately assessed under less artificial conditions.

If unable to do research under "real-life" circumstances, greater attention should be paid to the population from which participants are recruited and whether the outcomes being measured are appropriate for that population. In a clinical (nonresearch) population, intention may be a good proxy for actual behavior, but we may not be able to assume from a registry population that hypothetical interest in testing, attendance at education and counseling, or intention to be tested are proxies for actual test utilization.

Enrollees from different recruitment populations may also have unique reasons for participating in each phase of a testing protocol. People for whom testing is likely to become a reality appreciate that the stakes are higher as testing draws near than they are at the counseling stage. In our study, "when push came to shove," an altruistic desire to help research was less of a motivator than the perception that testing would benefit the family. This observation was reassuring from the point of view of informed consent. Particularly among participants recruited from a clinical population, we have less reason to be concerned that an altruistic desire to help research will interfere with autonomous decision-making.

Our findings have other implications for informed consent.

(*a*) We observed that, even among those who intended to pursue testing, there is significant drop-off when testing is not immediately available. This pattern is consistent with what we observed when we offered cystic fibrosis carrier screening to the general population (20). Because many people change their minds about testing, a waiting period is advisable after counseling. This is consistent with the recommendations of other studies (3). Because, in our observation, women seem to use this waiting period to read whatever information they have about testing and to have discussions with family members, we believe that a hiatus facilitates informed and autonomous decision-making. However, this waiting period may result in decreased accrual.

(*b*) Family-based testing raises questions about the very essence of autonomous decision-making. Not only does such testing require the involvement of an affected family member, but test results affect entire families. Therefore, testing decisions are usually made by families, not by isolated individuals. High-risk women who, after careful consideration, want to be tested, may not be able to obtain testing if they do not have a comfortable enough relationship with their affected relative to ask her to participate or if their affected relative declines. The informed consent process that occurs during pretest education and counseling must include a discussion not only of the technical requirements of family-based testing but of family dynamics as well. We have an obligation to explore with the high-risk woman all of the ways that her affected relative could directly or indirectly influence her decision. A meaningful informed consent process obliges us to prepare high-risk women for the possibility that they will not be eligible for testing. To offer testing in an ethically responsible way, we must learn as much as possible, through research and sensitive observation, about the complexities of autonomy in a family context.

Acknowledgments

We are indebted to the women who participated in this study. Some of the women were identified with the help of the Maryland Cancer Registry of the Department of Health and Mental Hygiene (Baltimore, MD). The Department of Health and Mental Hygiene specifically disclaims responsibility for any analysis, interpretations, or conclusions. We are also grateful to: our coinvestigators, Drs. Kathy Helzlsouer and Neil A. Holtzman; June Peters and Patti Wilcox for training the counselors; the six individuals who counseled high-risk women; Melanie F. Myers for developing our educational brochure and for counseling affected relatives; and our administrative assistant, Sharon Ennis. We appreciate the support provided by OncorMed, Inc., for genetic testing services.

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