Original Investigation

BRCA1 and *BRCA2* Mutation Testing in Young Women With Breast Cancer

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IMPORTANCE *BRCA* testing is recommended for young women diagnosed as having breast cancer, but little is known about decisions surrounding testing and how results may influence treatment decisions in young patients.

OBJECTIVES To describe the use of *BRCA* testing and to evaluate how concerns about genetic risk and use of genetic information affect subsequent treatment decisions in young women with breast cancer.

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional analysis of data collected following the opening of the study to accrual from October 10, 2006, through December 31, 2014, as part of the Helping Ourselves, Helping Others: Young Women's Breast Cancer Study, an ongoing prospective cohort study. Study participants included 897 women aged 40 years and younger at breast cancer diagnosis from 11 academic and community medical centers.

MAIN OUTCOMES AND MEASURES Frequency and trends in the use of *BRCA* testing and how genetic information is used to make treatment decisions among women who test positive vs negative for a *BRCA* mutation.

RESULTS A total of 780 (87.0%) of 897 women reported *BRCA* testing by 1 year after breast cancer diagnosis (mean age at diagnosis, 35.3 vs 36.9 years for untested women; $P < .001$), with the frequency of testing increasing among women diagnosed from August 1, 2006, through December 31, 2013. Of 39 women who were diagnosed as having breast cancer in 2006, 30 (76.9%) reported testing. In 2007, a slightly lower percentage of women (87 of 124 [70.2%]) reported testing; however, the proportion tested increased each subsequent year, with 141 (96.6%) of 146 and 123 (95.3%) of 129 women diagnosed as having breast cancer in 2012 and 2013, respectively, reporting *BRCA* testing ($P < .001$). Among untested women, 37 (31.6%) of 117 did not report discussion of the possibility that they might have a mutation with a physician and/or genetic counselor, and 43 (36.8%) of 117 were thinking of testing in the future. A total of 248 (29.8%) of 831 women said that knowledge or concern about genetic risk influenced surgical treatment decisions; among these women, 76 (86.4%) of 88 mutation carriers and 82 (51.2%) of 160 noncarriers chose bilateral mastectomy ($P < .001$). Fewer women reported that systemic treatment decisions were influenced by genetic risk concern.

CONCLUSIONS AND RELEVANCE Rates of *BRCA1* and *BRCA2* mutation testing are increasing in young women with breast cancer. Given that knowledge and concern about genetic risk influence surgical decisions and may affect systemic therapy trial eligibility, all young women with breast cancer should be counseled and offered genetic testing, consistent with the National Comprehensive Cancer Network guidelines.

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Editorial

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Breast cancer is the most common cancer diagnosed in women younger than 40 years in the United States.[1] Because *BRCA1* (OMIM 113705) and *BRCA2* (OMIM 600185) mutation carriers are at increased risk for developing early-onset breast cancer, the National Comprehensive Cancer Network (NCCN) guidelines recommend that women diagnosed as having breast cancer at 50 years or younger undergo genetic testing.[2]

Assessment of genetic risk in young women after a breast cancer diagnosis can have implications for subsequent clinical treatment decisions. In 1 study,[3] the 10-year cumulative risk of developing a new cancer in *BRCA* carriers first diagnosed with breast cancer at 30 to 34 years of age was 30.7% and in women 35 to 39 years of age was 23.7%. In addition to consideration of prophylactic mastectomy, breast cancer survivors with a *BRCA* mutation can be presented with information about other risk-reducing strategies, including bilateral salpingo-oophorectomy, which reduces the risk of new primary breast cancer and ovarian cancer, and chemoprevention. Breast cancer survivors are also candidates for increased surveillance options for breast and ovarian cancer, including annual breast magnetic resonance imaging and transvaginal ultrasonography.[2] Genetic findings can also have implications for family members at risk for harboring the same deleterious mutations, who would need to consider many of these same options if they tested positive for the mutation.

Prior studies[4-6] have documented underuse of *BRCA* testing among younger women with breast cancer, although the figures have improved with time. In 1 study[4] that surveyed women diagnosed as having breast cancer at 45 years and younger between 1993 and 2002, less than 20% had undergone *BRCA* testing. In an analysis[5] of 701 women who had been diagnosed as having breast cancer at 40 years and younger published in 2010, 24% reported testing. However, in a 2015 study[6] of more than 300 women with breast cancer at 50 years and younger who were treated at NCCN institutions, 34.1% were referred for genetic counseling and among these women, 95.2% were tested for a mutation.

Key Points

Question: How does *BRCA* testing affect treatment decisions of women diagnosed as having breast cancer at 40 years and younger?

Findings: This *BRCA* testing frequency increased among women diagnosed between 2006 and 2013; 248 (29.8%) of 831 women said that knowledge or concern about genetic risk influenced treatment decisions.

Meaning: *BRCA* testing has been increasing in young women with breast cancer, with concern about genetic risk, even in women who tested negative, influencing surgical decisions.

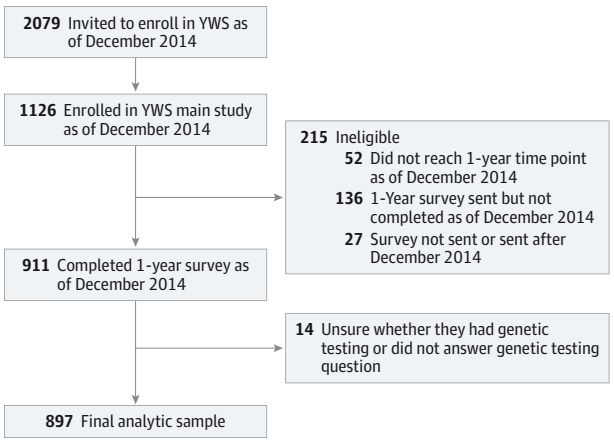
In an effort to characterize experiences surrounding genetic testing among young women with breast cancer, we sought to describe the use of *BRCA* testing in a cohort of women diagnosed as having breast cancer at 40 years and younger and to evaluate how concerns about genetic risk and use of genetic information affect subsequent treatment decisions. In addition, we aimed to understand why some young women do not get tested despite the clinical recommendations for this population.

Methods

Study Design and Population

Helping Ourselves, Helping Others: The Young Women's Breast Cancer Study (YWS) is an ongoing, multicenter, prospective cohort study established to examine biological, medical, and quality-of-life issues in young women diagnosed as having breast cancer at 40 years and younger. Women are identified through review of pathology reports or staff review of clinic lists depending on the study site. Eligible patients are mailed a recruitment package that includes a letter introducing the study, 2 copies of the consent form, and a decline form. Patients who have not returned their consent or decline form are contacted by telephone within 3 weeks to inquire about their interest in study participation and are re-sent recruitment materials as needed. Patients who send in their signed informed consent forms are officially enrolled in the study. After written informed consent and enrollment, women are mailed a baseline survey (median, 4.8 months after diagnosis), additional surveys twice a year for the first 3 years after diagnosis, and annually thereafter. The YWS sites include 9 academic and community hospitals in Massachusetts and academic sites in Denver, Colorado, Rochester, Minnesota, and Toronto, Ontario, Canada, although Toronto participants received a modified version of all the surveys and were not included in this analysis. Women who enrolled in the YWS after the opening of the study to accrual on October 10, 2006, and completed the survey mailed to study participants at 1 year after diagnosis (n = 911), which includes a series of questions about *BRCA* testing through December 31, 2014, were eligible for inclusion in this analysis (**Figure 1**). The YWS is approved by the in-

Figure 1. Flowchart of Study Participants Included in the Analytic Sample



YWS indicates Helping Ourselves, Helping Others: Young Women's Breast Cancer Study.

stitutional review board at the Dana-Farber/Harvard Cancer Center and other participating sites (Newton-Wellesley Hospital, Mayo Clinic, Sunnybrook Health Sciences Center, and University of Colorado Cancer Center).

Outcome Measures

Study population characteristics included age at diagnosis, race/ethnicity (assessed with 2 survey items that ask respondents whether they consider themselves Hispanic or Latina and what race they consider themselves, with the option to choose 1 or more prespecified racial groups, including American Indian or Alaskan Native, Asian, black, Haitian or African American, Native Hawaiian or other Pacific Islander, or white), marital status, educational level, and insurance status. Pathology reports and medical records were reviewed for stage of disease, hormone receptor status, and *ERBB2* (formerly *HER2* or *HER2/neu*) status. A single item on the baseline survey asks women whether any grandparent was of Ashkenazi descent. Family history of breast and ovarian cancer is collected on the survey administered 1 year after diagnosis.

A series of items assessing practices surrounding *BRCA* testing were developed and included in the 1-year survey. Women were asked whether they had their blood sent to be tested for a genetic change (a mutation in the *BRCA1* or *BRCA2* gene) that increases risk of breast cancer. Women who said that they had undergone testing were asked for the results, and response options included the following: no abnormality detected in *BRCA1* or *BRCA2*/no mutation detected; deleterious gene alteration/mutation was detected in *BRCA1*; deleterious gene alteration/mutation was detected in *BRCA*2; deleterious gene alteration/mutation was detected, but I am not sure whether it was in *BRCA1* or *BRCA2*; an indeterminate or unknown variant was detected (an abnormality that is not known to contribute to breast cancer risk); results not yet available; or I am not sure what genetic testing showed. Women were also asked to approximate how long after diagnosis they received their results (<1 month, 1-3 months, 3-6 months, 6-12 months, or >12 months).

Women who said they had not undergone testing or were unsure whether they were tested were asked a series of questions, including whether they discussed the possibility of having a genetic mutation with their physician(s), whether they were counseled about the likelihood of having a genetic predisposition to develop breast cancer and the implications of potentially having one of these gene mutations on future health and treatment, and reasons why they have not been tested.

All women (tested and untested) were asked whether knowledge or concern about genetic risk of breast cancer (including whether testing revealed a deleterious *BRCA* mutation) influenced treatment decisions. Multiple responses were allowed, and response options included the following: no; yes, I chose to have the breast where I have developed cancer removed (mastectomy) rather than have a lumpectomy; yes, I chose to have both breasts removed (bilateral mastectomy); yes, I chose to have my ovaries removed; yes, I chose to have 1 or more of the following treatments that I might not have otherwise taken: tamoxifen citrate; aromatase inhibitor (eg, anastrozole, letrozole, exemestane); ovarian suppression with medication (eg, leuprolide acetate, triptorelin pamoate, or goserelin acetate); chemotherapy; or other (this option was open-ended, and women could write in other ways in which knowledge or concern about genetic risk had influenced their treatment decisions).

Statistical Analysis

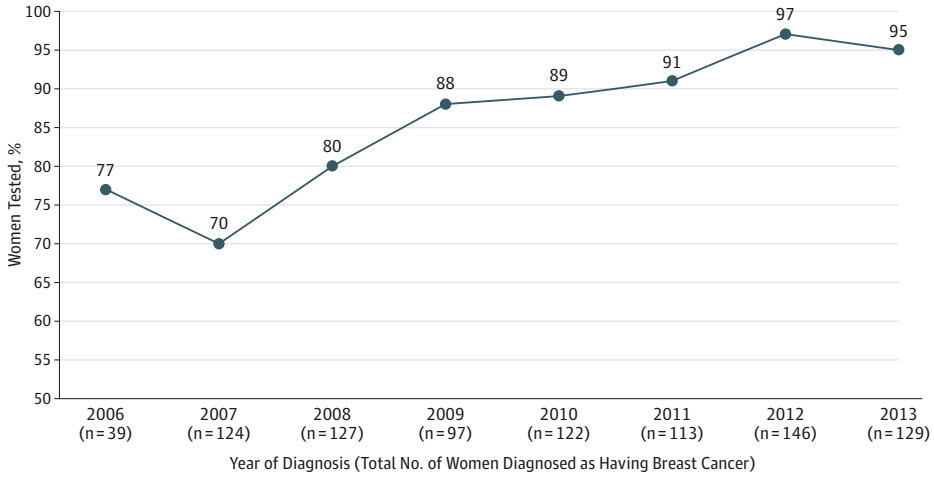
We used descriptive statistics to characterize the study population, *BRCA* testing use, and timing of receipt of testing results and, among untested women, to describe whether genetic risk was discussed with a physician and/or genetic counselor and the reasons for not undergoing testing. To check for changes in *BRCA* testing over time, we used the Cochran-Armitage test for trend. We used unpaired, 2-tailed *t* tests and Fisher exact tests to assess differences in study population characteristics among women who were and were not tested and to evaluate how genetic information was used to make treatment decisions among women who tested positive for a *BRCA* mutation and women who tested negative. The responses of women who answered "other" to how genetic information was used in treatment decisions were examined qualitatively, and the most frequently cited reasons (chose lumpectomy, chose mastectomy, and chose not to have bilateral mastectomy) were collapsed and summarized. Women who responded that they were unsure about testing or did not respond to this question but answered the question asking for their test results were recoded as being tested; those who did not subsequently answer the question about their results (n = 14) were excluded, leaving 897 women in the analytic sample. Sample sizes vary somewhat across analyses owing to nonresponse or discordant responses on specific items. A 2-sided $P \leq .05$ was used as the threshold for statistical significance. Analyses were conducted with SAS statistical software, version 9.4 (SAS Institute Inc).

Results

Study population characteristics are detailed in eTable 1 in the Supplement. Mean age at diagnosis among women who were tested was younger than that of untested women (35.3 vs 36.9 years, $P < .001$). Among women for whom stage of disease was available, most had stage I (294 [35.0%]) or stage II (339 [40.3%]) disease. Most women had at least a college education (726 [84.5%]) and were insured (851 [99.8%]). Among the women who were tested, a higher proportion of women reported at least 1 second- or third-degree relative with breast or ovarian cancer (404 [52.2%]) compared with women who were not tested (45 [38.5%]); other study population characteristics were similar between tested and untested women.

A total of 780 women (87.0%) reported being tested for a *BRCA* mutation, and only 117 (13.0%) of 897 had not undergone testing for a *BRCA* mutation when surveyed 1 year after diagnosis. **Figure 2** details *BRCA* test use by year of diagnosis. Of the 39 women who were diagnosed as having breast can-

Figure 2. Trends in *BRCA* Testing in 897 Women in the YWS Cohort



YWS indicates Helping Ourselves, Helping Others: Young Women's Breast Cancer Study.

cer in 2006, 30 (76.9%) reported testing. In 2007, a slightly lower percentage of women (87 of 124 [70.2%]) reported testing; however, the proportion tested increased each subsequent year (Cochran-Armitage test for trend, $P < .001$), with 141 (96.6%) of 146 and 123 (95.3%) of 129 women diagnosed as having breast cancer in 2012 and 2013, respectively, reporting *BRCA* testing.

Among the 780 women who had undergone *BRCA* testing, 59 (7.6%) reported a *BRCA1* mutation, 35 (4.5%) reported a *BRCA2* mutation, 35 (4.6%) reported an indeterminate result or variant of unknown clinical significance, and 634 (81.3%) reported a negative test result (**Table 1**). Among the 754 women who responded regarding timing of return of *BRCA* results after diagnosis, 277 (36.7%) said they had received their results less than 1 month after diagnosis, 339 (45.0%) 1 to 3 months after diagnosis, and 78 (10.3%) 3 to 6 months after diagnosis.

Among the 117 women who were not tested, 80 (68.4%) said they had discussed or were counseled about the possibility of having a *BRCA* mutation or genetic predisposition to breast cancer with their physician and/or genetic counselor. Of the 37 women who did not report discussion of these issues with a physician and/or genetic counselor, 7 (18.9%) said they were planning to discuss this in the future, 8 (21.6%) were considering a future discussion, 11 (29.7%) were not sure whether they wanted to discuss this in the future, 1 person responded that she was considering but also was not sure she wanted to discuss this in the future, 5 (13.5%) were not interested in discussing these issues, and 5 (13.5%) did not respond to this question.

The reasons women cited for not undergoing testing are included in eTable2 in the Supplement. A total of 28 (23.9%) women said they did not think they were at risk for having a mutation, with a similar proportion reporting that they were not tested because their physician thought it was unlikely they had a mutation. Other common reasons for not undergoing testing included not being a priority (21 [17.9%]), concerns about potential insurance or work issues related to a positive test result (15 [12.8%]), and inability to afford to undergo testing (13 [11.1%]). A total of 43 untested women (36.8%) said they were thinking about getting tested in the future.

A total of 248 (29.8%) of 831 patients who were tested and reported a positive or negative result responded that knowledge or concern about genetic risk of breast cancer influenced their treatment in some way. Among these women, 76 (86.4%) mutation carriers and 82 (51.2%) noncarriers chose a bilateral mastectomy ($P < .001$) (**Table 2**). Mutation carriers were also more likely ($P < .001$) to have undergone a salpingo-oophorectomy (47 [53.4%]) compared with noncarriers (4 [2.5%]).

Fewer women reported that systemic treatment decisions were influenced by genetic risk concern, and no significant differences were found between carriers and noncarriers regarding the effect of genetic concerns on choosing chemotherapy, ovarian suppression, or endocrine treatment. Of the 65 women who cited other as the reason for how knowledge or concern about genetic risk influenced their treatment, 40 (61.5%) responded that they chose lumpectomy or mastectomy or chose not to undergo a bilateral mastectomy.

Discussion

With 780 women (87.0%) having been tested for a *BRCA* mutation, the use of testing in our cohort of young women far exceeds the prevalence of testing reported in several other studies[4,5,7] of women with early-onset breast cancer. Since the YWS began enrolling women in 2006, the proportion of women who underwent testing increased, with almost all women diagnosed as having breast cancer in 2012 and 2013 reporting *BRCA* testing when surveyed at 1 year after diagnosis. The high frequency of *BRCA* testing likely reflects the fact that most women enrolled in our cohort were insured, educated, and treated at cancer centers where comprehensive genetic counseling and testing services are widely available.

Secular trends in genetic testing are one explanation of the increase in *BRCA* testing we detected. Of the women who did not undergo testing, 37 said that they had not discussed the possibility that they might have a mutation with their physician and/or genetic counselor. Media attention to hereditary breast cancer risk (eg, the Angelina Jolie effect)[8] might have made women more likely to bring up the issue of genetic risk with their physician and/or genetic counselor, possibly leading to more testing of women who were diagnosed as having breast cancer in 2012 and 2013 relative to earlier years (2006-2011). In an analysis of referral patterns to a group of high-risk hereditary cancer clinics in England, Evans et al[9] reported that referrals for genetic counseling and *BRCA* testing increased substantially between 2012 and 2013. A Canadian study[10] described a similar notable increase in counseling and testing when comparing referral patterns in the 6 months before the Jolie article[8] was published to the 6-month period after publication.

Among the women in our study who were not tested, some might not have initially chosen testing because of more immediate concerns or prioritization of other decisions related to treatment. It is important to consider that the decision to undergo testing and process information about genetic risk in women with a recent breast cancer diagnosis occurs when women are already under stress about the decisions they need to make pertaining to treatment. In a prior study by Weitzel et al,[11] 3 women who were candidates chose not to be tested because of distress related to their recent diagnosis. In a small study[12] of 26 patients with breast cancer from the Netherlands who had undergone rapid genetic counseling and (optional) testing, more than half of women responded that rapid genetic counseling and testing were associated with added distress, separate from the distress they experienced as a result of their diagnosis. In a qualitative study conducted by Zilliacus et al,[13] interviews with women who were diagnosed as having breast cancer at 50 years and younger revealed that, although some women acknowledge that anxiety associated with not knowing what their test results were during a challenging time was a downside, many women also viewed handling "all bad news" at once and negotiating the emotions of these multiple challenges at a single time point as a positive. Furthermore, women also valued the potential for genetic testing to inform surgical choice. Conveying the importance of testing in the context of the decisions they are making regarding their primary treatment, while ensuring that women are supported and concerns about genetic risk and testing are adequately addressed, is essential.

Many women who were tested knew the results of their *BRCA* test within 1 month of diagnosis and therefore likely had this information before making their decision about surgery. Of the women in our study who said concern about genetic risk influenced their treatment decisions, those with a *BRCA* mutation were more likely to choose bilateral mastectomy compared with women who were not tested. Other studies of the effect of *BRCA* testing on treatment decisions have similarly found that women who test positive are more likely to undergo bilateral surgery compared with women who test negative.[11,14-17] Notably, bilateral mastectomy was still relatively common in our study even among noncarriers, suggesting that many women might choose to remove both breasts because of worries about developing another breast cancer and for peace of mind despite knowing they do not carry a known *BRCA* mutation.[18] It might also suggest a need for better communication of the relatively low risk of contralateral breast cancer among women who are noncarriers,[3] that this risk has been decreasing in recent years,[19] and that bilateral mastectomy is not associated with improved survival.[20] Most women in our cohort received chemotherapy; therefore, most women were unlikely to perceive receipt of adjuvant treatment as being affected by their genetic testing results. However, a previous review[21] reports that several clinical trials have used *BRCA* status as a potentially prognostic factor in the neoadjuvant and adjuvant settings. In addition, *BRCA* status can influence systemic therapy trial eligibility. For example, poly(adenosine di-

Table 1. *BRCA* Testing Results

Test Result	No. (%) of Women (n = 780)
BRCA1 positive	59 (7.6)[a]
BRCA2 positive	35 (4.5)
Unsure whether *BRCA1* or *BRCA2* positive	2 (0.3)
Indeterminate or unknown variant detected	35 (4.5)[a]
Tested negative	634 (81.3)
Tested with missing, discordant, not available, unknown, or unclear results	15 (1.9)

[a] One woman reported a *BRCA1* mutation and an indeterminate variant.

Table 2. Treatment Decisions Among Women for Whom Genetic Concerns Influenced Their Decisions[a]

Treatment Decision	No. (%) of Women		*P* Value
	BRCA Positive (n = 88)	*BRCA* Negative (n = 160)	
I chose to have the breast where I have developed cancer removed rather than have a lumpectomy	6 (6.8)	17 (10.6)	.37
I chose to have both breasts removed	76 (86.4)	82 (51.2)	<.001
I chose to have my ovaries removed	47 (53.4)	4 (2.5)	<.001
I chose to have one or more of the following treatments that I might not have otherwise taken			
Tamoxifen citrate	13 (14.8)	29 (18.1)	.60
Aromatase inhibitor	1 (1.1)	1 (0.6)	>.99
Ovarian suppression with medication	1 (1.1)	8 (5.0)	.16
Chemotherapy	14 (15.9)	17 (10.6)	.24

[a] Of 897 respondents, we excluded 15 women whose genetic testing results were unknown, 12 women with indeterminate results, 23 women who were not tested, and 16 women with discordant or missing responses to this question. Responses are nonmutually exclusive, with participants asked to select all reasons that apply.

phosphate-ribose) polymerase inhibitors are a new category of targeted therapy that have demonstrated preliminary efficacy almost exclusively in *BRCA*-mutated cancers.[21] Regarding endocrine treatment, similar proportions of women said that concern about genetic risk influenced this treatment decision. Although some data suggest a potential benefit of endocrine treatment in preventing contralateral breast cancer in *BRCA* mutation carriers,[22] prospective or randomized studies of tamoxifen or aromatase inhibitors have not been performed in a chemopreventive setting among *BRCA* carriers with a history of unilateral breast cancer. Furthermore, in our cohort, in which most *BRCA* carriers underwent a bilateral mastectomy, any additional benefit for endocrine therapy as a chemopreventive strategy for contralateral breast cancer would likely be minimal.

It is important to consider our findings in the context of some limitations. Most women included in this analysis would have undergone testing when Myriad Genetics Inc was the only commercial laboratory offering clinical testing and testing for *BRCA1* and *BRCA2* was the only testing available. Given the recent expansion of testing options (eg, genome-wide sequencing, multigene panels), it is clear that testing patterns are changing. Future studies are warranted to evaluate the use and effect of other tests. Regarding the timing of receipt of *BRCA* test results, there was no response option corresponding to prediagnosis testing. However, we would expect the number of women who would have undergone testing before diagnosis to be fairly low, given our clinical experience with this population.

Given that the purpose of this analysis was to evaluate patient perception of the experience surrounding *BRCA* testing, we chose to use self-report of genetic test results. In a prior analysis of a subset of the YWS cohort,[18] we reviewed medical records to confirm self-reports of mutation status and found the 2 ascertainment methods to be highly concordant. Although it is reassuring that most women in our cohort are tested as recommended, a large proportion of these women are treated in academic cancer center settings and almost everyone is insured. Therefore generalizability of our findings, including reasons for not undergoing testing and the degree to which concerns about genetic risk affect treatment decisions, might be limited.

Conclusions

Our findings highlight recent trends, experiences, and perspectives surrounding *BRCA* testing in women diagnosed as having breast cancer at 40 years and younger. Because women in our cohort are asked about *BRCA* testing in future surveys, we will be able to assess whether those women who said they were thinking about getting tested subsequently got tested at a later time. Furthermore, it is possible that mutation carriers who initially did not choose risk-reducing operations might decide to undergo these procedures later in the survivorship period. Longer-term follow-up may provide additional information about the effect of testing on treatment decisions and, ultimately, outcomes over time.

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Author Contributions: Drs Partridge and Rosenberg had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: All authors.
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