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Use of *BRCA* Mutation Test in the U.S., 2004–2014

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Abstract

Introduction—*BRCA* mutation testing has been used for screening women at high risk of breast and ovarian cancer and for selecting the best treatment for those with breast cancer. To optimize the infrastructure and medical resources allocation for genetic testing, it is important to understand the use of *BRCA* mutation testing in the U.S. health system.

Methods—This retrospective cohort study included 53,254 adult women with insurance claims for *BRCA* mutation testing between 2004 and 2014 from Clinformatics™ Data Mart Database. Data analysis was performed in 2016. This study assessed trends in the use of BRCA mutation testing in women with previously diagnosed breast or ovarian cancer and those without (unaffected women).

Results—Between 2004 and 2014, of those receiving *BRCA* testing, the proportion of *BRCA* tests performed in unaffected women increased significantly (p<0.001), from 24.3% in 2004 to 61.5% in 2014. An increase in the proportion of *BRCA* tests used in unaffected women was found in each characteristic subgroup. In 2014, most subgroups had a proportion surpassing 50%, except for those aged 51–65 years and those without a family history of breast cancer. There was a much lower proportion those aged 20–40 years among tested women with previously diagnosed breast or ovarian cancer than in unaffected women (17.6% vs 41.7%, p<0.001).

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Conclusions—During the past decade, the role of *BRCA* testing has gradually shifted from being used primarily in cancer patients to being used in unaffected women in the U.S.

INTRODUCTION

The discovery of *BRCA1* and *BRCA2* mutations in breast and ovarian cancer–susceptible women in 1994 and 1995[1,2] opened up opportunities for individualized preventive cancer care in high-risk women.[3,4] About 5%–10% of breast cancer cases and 10%–18% of ovarian cancer cases are attributable to germline *BRCA* mutations.[5–8] Tests for mutations in *BRCA* genes can identify high-risk individuals, which can then lead to lifesaving preventive care through prophylactic treatments.[4,9] *BRCA* mutation testing has been recommended by the U.S. Preventive Services Task Force (USPSTF) since 2005 for women whose family history demonstrates an increased risk for *BRCA*-related cancers.[10] However, *BRCA* testing has not been well utilized among U.S. women and the majority of at-risk women do not get referrals for genetic counseling or testing.[11–14] It is estimated that only 30% of living breast cancer patients with a *BRCA* mutation and 10% of asymptomatic *BRCA* mutation carriers have been identified in the U.S.[14] This lack of referrals results in missed opportunities for cancer prevention.

In addition to underuse among patients at risk, *BRCA* testing is often used among women in whom the testing may not be indicated by practice guidelines.[15–18] It is estimated that approximately 60%–80% of patients referred for genetic counseling and testing do not meet the referral requirement based on family history.[11,19] To optimize the infrastructure and medical resources allocated for genetic testing, it is important to understand the current use of *BRCA* mutation testing in the U.S. health system. This study assessed trends in the use of *BRCA* mutation testing in cancer patients and unaffected women among U.S. adult women (aged 20–65 years) from 2004 to 2014.

METHODS

Administrative data from Clinformatics™ Data Mart Database (OptumInsight, Eden Prairie, MN) was used. This data set contains de-identified insurance claim records from >56 million Americans who were insured at least once between 2000 and 2014. The administrative claims records are from a private health insurance provider with plans available in all 50 U.S. states and the District of Columbia. The database includes information on a population that is roughly representative of the working U.S. population.[20] Overall, 73% of the enrollees were non-Hispanic whites, which is higher than that of the general U.S. population. Median household income of the enrollees was $62,500 annually.[21] From this data set, a retrospective cohort was generated including women who received *BRCA* testing between 2004 and 2014. This study did not include women who received *BRCA* tests before 2004, because there were not many (one in 2002 and 176 in 2003 among women of any age). This study included adult women aged 20–65 years, as *BRCA*-related cancers generally have an adult onset[22] and U.S. adults aged >65 years are eligible for Medicare and may not be captured in this data set. There were 16.4 million adult women (aged 20–65 years) covered in this data set between 2004 and 2014. Of 57,011 women aged 20–65 years who received *BRCA* mutation test between 2004 and 2014, a total of 3,757 women who had

<3 months of continuous enrollment in health insurance coverage prior to *BRCA* testing were excluded. Women with <3 months of enrollment prior to *BRCA* testing were excluded because this study wanted to determine whether they had a recent diagnosis of breast or ovarian cancer. A total of 53,254 women were included in the final analyses. This study evaluated whether those women had previously diagnosed breast or ovarian cancer within 3 months prior to the date of *BRCA* testing. This study was exempt from full board review by the IRB at University of Texas Medical Branch.

Current Procedural Terminology codes and Healthcare Common Procedure Coding System for the *BRCA* mutation test (81211-81217, S3818-S3820, S3822, and S3823) were used to identify women who received *BRCA* testing. Cases of previously diagnosed breast cancer were identified by the ICD-9 code V10.3 for personal history of malignant neoplasm of breast, 174.x for malignant neoplasm of female breast, and 233.0 for carcinoma in situ of breast within 3 months before *BRCA* testing. Cases of previously diagnosed ovarian cancer were identified by ICD-9 code V10.43 for personal history of malignant neoplasm of ovary and 183.0 for malignant neoplasm of ovary within 3 months before *BRCA* testing. Family history of breast cancer was identified by ICD-9 code V16.3 (family history of malignant neoplasm of the breast). Family history of ovarian cancer was identified by ICD-9 code V16.41 (family history of malignant neoplasm of the ovary).

Women's age at *BRCA* testing was categorized into three groups: 20–40 years, 41–50 years, and 51–65 years, for the consideration of different incidences of breast cancer among those age groups and definition of early-onset of breast cancer (age ≤40 years[3], or age ≤50 years [23,24]). Regions of residence were divided according to the U.S. Census Regions (South, Northeast, Midwest, and West).

Statistical Analysis

This study assessed the linear trends in the proportions of unaffected women among those who received *BRCA* testing from 2004 to 2014. The differences in characteristics between women with and without previously diagnosed breast or ovarian cancer were assessed by chi-square test. Age was analyzed both as a continuous variable and a categorical variable. Multivariable logistic regression models were used to assess the trends. When the linear trends were assessed, the predictor in the model was the year of *BRCA* testing, and the dependent variable was unaffected woman or cancer patient. Variables that were controlled for included age and region of residence. AOR for the annual change (1-year increase in the time of *BRCA* testing) was calculated. The interaction terms of age group, region of residence, previously diagnosed breast or ovarian cancer, and family history of breast or ovarian cancer with the year of *BRCA* testing were assessed in the multivariate logistic model. Statistical analyses were conducted using SAS, version 9.4. A two-sided *p*-value <0.05 was considered statistically significant.

RESULTS

Characteristics of the participants are presented in Table 1. The absolute number of *BRCA* tests increased among both women with and without previously diagnosed breast or ovarian cancer (Table 2). Among 53,254 women who received *BRCA* testing, 29.3% were aged 20–

40 years and 36.9% were aged 41–50 years. There was a significant difference in the age distribution between cancer patients and unaffected women (χ^2=3880.9, p<0.001) (Table 1). The proportion of women aged 20–40 years was much higher in unaffected women than in cancer patients (41.7% vs 17.6%) and the mean age was significantly lower in unaffected women (43.0 years, SD=10.3) than in cancer patients (48.6 years; SD=8.6; t-value for testing the difference, 67.9; p<0.001). The largest proportion (48.7%) of the sample resided in the South. A high proportion of women had previously diagnosed breast cancer (47.8%), 4.4% had previously diagnosed ovarian cancer, and 51.3% had been diagnosed with either; 40,900 (76.8%) had a family history of breast cancer, 15,061 (28.3%) had a family history of ovarian cancer, 44,815 (84.2%) had a family history of breast or ovarian cancer, and 11,146 (20.9%) had a family history of breast and ovarian cancer. Of those receiving *BRCA* testing, the proportion of women with a family history of breast or ovarian cancer decreased among both unaffected women and among cancer patients from 2004 to 2014 (Table 2). The decrease was greater in cancer patients (from 73.5% to 63.0%) than in unaffected women (from 98.4% to 95.2%).

Among women who received *BRCA* testing, the proportion of unaffected women increased greatly from 2004 to 2014 (Figure 1A). In 2004, only 24.3% of *BRCA* tests were performed among unaffected women. Since 2006, the proportion of *BRCA* tests conducted in unaffected women increased sharply (for linear trend from 2004 to 2006, the AOR for the annual change was 1.05, 95% CI=0.95, 1.14, p=0.29; for linear trend from 2006 to 2014, the AOR for the annual change was 1.19, 95% CI=1.18, 1.20, p<0.001), with the proportion surpassing 50% in 2012 (50.3%). In 2014, a total of 61.5% of *BRCA* tests were performed in unaffected women. The AOR for the annual change from 2004 to 2014 was 1.19 (95% CI=1.18, 1.20, p<0.001) (Table 3). For each subsequent year of *BRCA* testing, the tested subject had a 19% increase in the odds of being an unaffected woman as opposed to a cancer patient.

Significant interactions between the year of *BRCA* testing and age, region, and family history of breast or ovarian cancer were found (p<0.001 for all tests of the interaction terms). The proportion of *BRCA* tests used in unaffected women increased greatly in each characteristic subgroup, after adjusting for age and region of residence (Figure 1B–D). In 2014, most subgroups had a proportion surpassing 50%, except for those aged 51–65 years and those without a family history of breast cancer. In 2014, among young women (aged 20–40 years), >80% of *BRCA* tests were performed in women without previously diagnosed breast or ovarian cancer. The AOR for the annual change in the proportion of unaffected women among those who received *BRCA* testing stratified by age, region, and family history are presented in Table 3.

DISCUSSION

In this study, a gradual shift was observed in the role of *BRCA* testing from being used primarily in cancer patients to being used in unaffected women from 2004 to 2014. The proportion of tests performed in unaffected women shifted from one in four in 2004 to greater than 60% in 2014. *BRCA* testing in patients with early-onset breast or ovarian cancer can identify those with high-risk mutations, in whom specific treatment options may be

needed.[4,25–28] Another important role of *BRCA* testing is to identify high-risk mutation carriers before they develop breast or ovarian cancer, so they may start cancer screening at an early age, receive intensified screening (MRI/mammogram), and undergo prophylactic treatments (chemotherapy and prophylactic surgery) for the prevention and early detection of breast and ovarian cancer.[4,9,16,29,30] However, the majority of at-risk women do not get referral for genetic counseling and testing.[12–14] Among 220,000 *BRCA* mutation carriers in the U.S., it is estimated that more than 90% have not been identified.[14] The 2008 Genetic Information Nondiscrimination Act may allay the fears of genetic information misuse and boost the utilization of genetic testing. Practice guidelines by the National Comprehensive Cancer Network and USPSTF have continuously loosened the clinical testing criteria for genetic counseling and *BRCA* mutation testing,[10,24,31–33] which may also be partly responsible for the increase in the overall utilization of *BRCA* testing in unaffected women. Since 2011, the Affordable Care Act has mandated coverage for preventive services recommended by USPSTF, including referring eligible women for genetic counseling and *BRCA* testing.[34] Moreover, the 2013 Supreme Court ruling against Myriad Genetics' patent claims of *BRCA* mutation test and subsequent availability of the testing in other clinical labs have greatly reduced the cost of the test.[35–37] Additional efforts are still needed to extend coverage of *BRCA* testing among women at risk of hereditary breast or ovarian cancer. The shifted role of *BRCA* testing was observed across age groups, region of residence, and status of family history of breast or ovarian cancer. Significant interactions between the year of *BRCA* testing and age, region, and family history of breast or ovarian cancer indicated that there were differences in the magnitude of the annual change across those population subgroups. Over the past decade, widespread direct to consumer marketing for genetic tests has raised consumers' interest in *BRCA* testing, and increased women's self-referrals and referrals by their physicians to genetic services even when they are at low-risk for mutations.[38–43] Further studies are needed to assess the factors associated with *BRCA* test use in unaffected women and in cancer patients among population subgroups, in order to maximize the likelihood of identifying mutation carriers so that they may choose proper risk management plans or cancer treatment options accordingly.

In addition, population-based screening for *BRCA1* and *BRCA2* mutations in Ashkenazi Jewish women and the general population has been proposed and evaluated.[35,36,44,45] The estimated prevalence of potentially harmful *BRCA* mutations is 0.2%–0.3% among the general population,[6,46] but tenfold higher (2.1%) in Ashkenazi Jewish women,[47–49] and about 30-fold higher (6.0%) in women with cancer onset before age 40 years.[3,50,51] Owing to the vast differences in the prevalence of potentially harmful *BRCA* mutations within population subgroups and the high-cost of *BRCA* testing, currently USPSTF and the National Comprehensive Cancer Network only recommend screening for individuals with increased risk for potentially harmful *BRCA* mutations based on personal history and family history.[31,52] It is worth mentioning that in three relatively large studies in Canada, Israel, and England, more than one half of Ashkenazi mutation carriers do not qualify for genetic testing based on family history.[53] Most young women with breast cancer do not have a family history of breast or ovarian cancer or Ashkenazi Jewish ancestry, and will not be eligible to undergo *BRCA* mutation testing before a cancer diagnosis.[54–56] In clinical practice, *BRCA* testing is not performed only among women at risk for harmful mutations

based on family history and personal history of cancer. This may be due to inadequate knowledge[57,58] among physicians about indications for the test, understanding the limitations of personal/family history based testing criteria and awareness of new clinical evidences among physicians,[53–56] changing testing guidelines,[10,24,31–33] patient anxiety and patient request, given massive and intensive marketing campaigns targeting the public and the clinicians by Myriad Genetics and others.[59] A survey conducted in 2007 assessed the level of awareness and utilization of *BRCA* testing among U.S. primary care physicians and found that only 19% of physicians correctly identified family history patterns and 45% chose at least one low-risk scenario as an indication for *BRCA* testing.[57] Another vignette-based survey of 3,000 U.S. primary care providers found that about 30% of U.S. physicians would consider referring women not at high risk for genetic counseling and testing.[58] In addition, most of patients referred for genetic counseling and testing do not meet the referral requirements based on family history.[11,19] Nevertheless, with low-cost genetic testing ($200 or $300, roughly the price of a three-dimensional mammogram) available,[37] practical guidelines may further loosen the testing criteria, and more unaffected individuals and cancer patients will choose to receive the test even when they have to pay out of pocket.[60,61]

Limitations

The main strength of this study was the use of administrative data from a large national sample to reliably assess trends and patterns in use of *BRCA* testing in the U.S. health system. This study also had several limitations. First, the analysis was based on medical claims and administrative information from a database of privately insured individuals, and may not be applicable to women covered by public health insurance (e.g., Medicaid) or who were uninsured. The largest proportion (48.7%) of the sample resided in the South, compared with 45.9% of adult women (aged 20–65 years) in the overall database who resided in the South, higher than that in the U.S. general population. Additionally, there is a possibility that family history and personal history of previously diagnosed breast or ovarian cancer were not documented within 3 months prior to *BRCA* testing. Some women may be misclassified as not having previously been diagnosed with breast or ovarian cancer. In general, there are many initiatives to improve documentation in the past 10 years.[62] The 3-month window in the current study captured most of the personal history of breast or ovarian cancer, compared with the personal history from the *BRCA* test request form in the American *BRCA* Outcomes and Utilization of Testing (ABOUT) Study.[60] The ABOUT Study found that 46.7% of 11,159 female Aetna commercial health plan members whose clinicians ordered *BRCA* testing between December 2011 and December 2012 reported a personal history of breast or ovarian cancer,[60] compared with 49.7% in women who received *BRCA* testing in 2012 in the current study. Physicians do not always take or update the family history,[63] and there is a lack of completeness in documented family history.[64] The data set also lacked a detailed and comprehensive family history of breast or ovarian cancer to assess whether those women met testing criteria.[16,52] The ICD-9 codes for family history of breast or ovarian cancer did not capture the number of family members or their relationship to the subject. In addition, this data set did not have sociodemographic information of the enrollees, so disparities in the use of *BRCA* testing across different races/ethnicities and socioeconomic groups could not be assessed.

CONCLUSIONS

The role of *BRCA* testing in the U.S. has gradually shifted over the past decade from being used primarily in cancer patients to being used in unaffected women. Advancement in genetic sequencing technologies and the Supreme Court ruling against the patenting of genes may further reduce testing cost, provide opportunities for practical guidelines to loosen testing criteria, and allow more individuals to benefit from this test.

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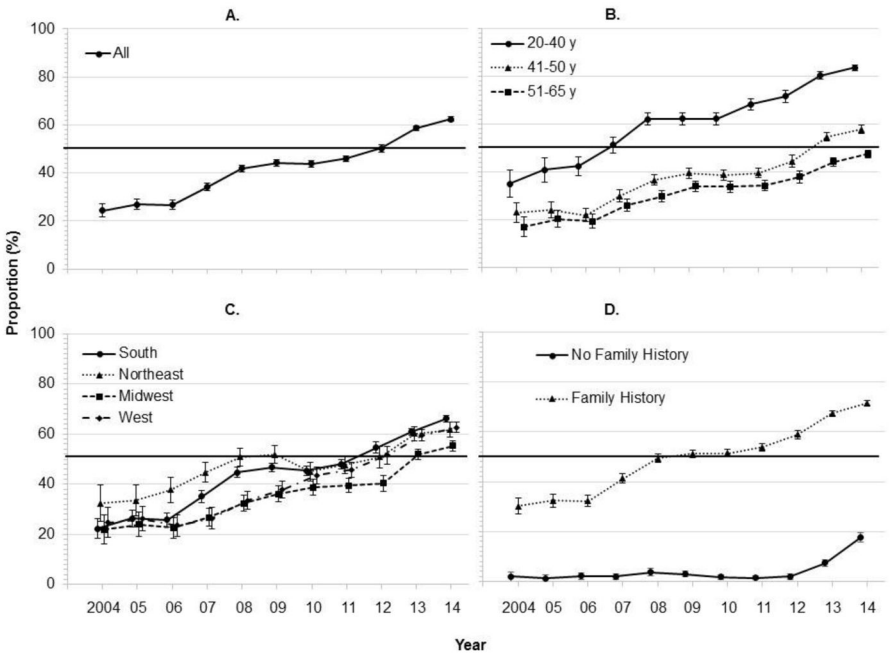

Figure 1. Trends in proportion of unaffected women among women who received *BRCA* tests, from 2004 to 2014

Notes: A. All women. B. By age groups. C. By region of Residence. D. By family history of breast or ovarian cancer. Data are plotted as proportion (%). The whisker represents the 95% CI. *P*-values for the tests of the interaction terms between the year of BRCA testing and age, region, and family history of breast or ovarian cancer were all <0.001.

20–40 y: 20–40 years of age.

Year: the year when *BRCA* testing was performed.

Unaffected women: women who did not have previously diagnosed breast or ovarian cancer.

Table 1

Characteristic of the Participants by Cancer Status (N=53,254)

Characteristics	n (%)	Proportion % (95% CI)		χ^2 [c]	df[d]	*p*-value[e]
		Cancer[a]	No cancer[b]			
Sample size		27,302	25,952			
Age[f]						
20–40 years	15,627 (29.3)	17.6 (17.1–18.1)	41.7 (41.1–42.3)			
41–50 years	19,636 (36.9)	40.8 (40.2–41.4)	32.7 (32.2–33.3)	3,880.9	2	<0.001
51–65 years	17,991 (33.8)	41.6 (41.0–42.2)	25.6 (25.0–26.1)			
Region of residence[g]						
South	25,917 (48.7)	46.7 (46.1–47.3)	50.8 (50.1–51.4)			
Northeast	7,268 (13.7)	13.0 (12.6–13.4)	14.4 (13.9–14.8)			
Midwest	10,547 (19.8)	22.3 (21.8–22.8)	17.2 (16.7–17.7)	236.9	3	<0.001
West	9,495 (17.8)	18.0 (17.5–18.4)	17.7 (17.2–18.1)			
Missing	27 (0.1)					
Family history of breast cancer						
No	12,354 (23.2)	33.9 (33.3–34.4)	12.0 (11.6–12.4)	3,568.4	1	<0.001
Yes	40,900 (76.8)	66.1 (65.6–66.7)	88.0 (87.6–88.4)			
Family history of ovarian cancer						
No	38,193 (71.7)	83.9 (83.4–84.3)	58.9 (58.3–59.5)	4,082.9	1	<0.001
Yes	15,061 (28.3)	16.1 (15.7–16.6)	41.1 (40.5–41.7)			
Family history of breast or ovarian cancer						
No	8,439 (15.9)	29.0 (28.4–29.5)	2.1 (1.9–2.2)	7,221.5	1	<0.001
Yes	44,815 (84.2)	71.0 (70.5–71.6)	97.9 (97.8–98.1)			
Family history of breast and ovarian cancer						
No	42,108 (79.1)	88.8 (88.4–89.1)	68.9 (68.3–69.4)	3,185.2	1	<0.001
Yes	11,146 (20.9)	11.2 (10.9–11.6)	31.1 (30.6–31.7)			

[a] Cancer: previously diagnosed of breast or ovarian cancer.

[b] No cancer: not previously diagnosed of breast or ovarian cancer.

[c] χ^2: χ^2 statistic for testing the difference in characteristics between women with and without previously diagnosed breast or ovarian cancer.

[d] df of the aforementioned χ^2 test.

[e] *p*-value: the *p*-value of the aforementioned χ^2 test.

[f] Age: mean age in unaffected women was 43.0 years, SD 10.3, and mean age in cancer patients was 48.6 years, SD 8.6.

[g] Region of residence: South included Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, Texas, Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, and West Virginia; Northeast included Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, and Pennsylvania; Midwest included Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota; West included Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, Alaska, California, Hawaii, Oregon, and Washington.

Table 2

Family History of Breast or Ovarian Cancer Among Adult Women by Year of the *BRCA* Test and Cancer Status (N=53,254)

Item	**Proportion (%)**										
Year	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
Test in women with previously diagnosed breast or ovarian cancer											
Sample size (n)	755	1,074	1,549	2,175	2,711	3,000	2,824	3,167	2,010	4,182	3,855
Family history of cancer											
Breast	68.9	71.7	70.8	68.9	67.7	69.5	68.1	67.8	65.2	62.5	58.7
Ovarian	17.0	19.8	18.5	16.0	16.2	17.1	17.0	16.7	16.2	14.8	13.5
Breast or ovarian	73.5	76.5	75.8	73.3	72.5	74.8	73.3	72.8	70.4	67.5	63.0
Breast and ovarian	12.3	15.0	13.5	11.6	11.4	11.8	11.8	11.7	10.9	9.8	9.2
Test in unaffected women[a]											
Sample size (n)	243	396	566	1,130	1,949	2,378	2,201	2,694	2,038	5,958	6,399
Family history of cancer											
Breast	90.5	92.7	91.9	91.9	90.1	92.1	92.9	91.4	87.4	86.6	82.8
Ovarian	38.3	36.6	38.3	39.6	37.8	37.9	42.7	43.7	42.0	42.0	41.3
Breast or ovarian	98.4	99.2	98.6	98.9	98.5	99.0	99.4	99.5	99.4	98.2	95.2
Breast and ovarian	30.5	30.1	31.6	32.5	29.3	31.0	36.3	35.5	30.0	30.5	28.9

[a]Test in unaffected women: *BRCA* mutation testing in women without previously diagnosed breast or ovarian cancer.

Table 3

AORs for the Annual Change in the Proportion of Unaffected Women Among Those who Received *BRCA* Testing, Overall and Stratified by Participant Characteristics (N=53,254)

Characteristics	AOR (95% CI)[a]	*p*-value
Overall	1.19 (1.18–1.20)[b]	<0.001
Age		
20–40 years	1.25 (1.23–1.26)[c]	<0.001
41–50 years	1.18 (1.17–1.19)[c]	<0.001
51–65 years	1.15 (1.14–1.17)[c]	<0.001
Region of residence		
South	1.20 (1.19–1.21)[d]	<0.001
Northeast	1.11 (1.09–1.13)[d]	<0.001
Midwest	1.19 (1.17–1.21)[d]	<0.001
West	1.23 (1.21–1.25)[d]	<0.001
Family history of breast cancer or ovarian cancer		
No	1.44 (1.37–1.51)[b]	<0.001
Yes	1.21 (1.20–1.22)[b]	<0.001

[a] AOR for the annual (1-year increase in the time of *BRCA* testing) change in the proportion of unaffected women among those who received *BRCA* testing.

[b] Adjusted for age and region of residence.

[c] Adjusted for region of residence.

[d] Adjusted for age.