

Utilization of BRCA testing in older women with breast and/or ovarian cancer in the state of Texas

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ABSTRACT

Background: Genetic testing for hereditary breast ovarian cancer (HBOC) susceptibility due to BRCA1 and BRCA2 (BRCA1/2) gene mutations became commercially available in the US in late 1996. Medicare began cost coverage in 2000 for some women with existing breast and/or ovarian cancer to assess treatment and family testing options.

Methods: We used the Texas Cancer Registry-Linked Medicare Database for this population-based cross-sectional study. We identified women aged 66 years or older with breast and/or ovarian cancer diagnosed between 2005 and 2007 and used their Medicare claims through 2009 to calculate the rate of testing in Texas and the proportion of women positive for BRCA mutations. We compared our findings to current literature.

Results: We identified 7,744 having at least one of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes identifying risk factors associated with HBOC. Of these 7,744 women, 1,594 (20.4%) were tested, with 1,411 having a documented risk factor and 183 with no documented risk factors. The percentages of women with breast and ovarian cancer and positive mutations were 0.18% and 3%, respectively.

Conclusions: The study of older women with breast and/or ovarian cancer who carry the BRCA1/2 mutation is possible when using a single state's cancer registry-linked claims administrative database. Although the prevalence of this mutation was comparable to published estimates in a similar population, the number was small and may limit detailed study of treatment and patient outcomes.

Impact: Studies such as ours may provide useful information for the nurses, geneticists, and genetic counselors involved in genetic counseling, and follow up of women at high risk for mutations and their families.

Key Words: BRCA, genetic mutation, breast cancer, ovarian cancer, hereditary breast ovarian cancer (HBOC), genetic counseling

INTRODUCTION

After the discovery and association of BRCA1 and BRCA2 (BRCA1/2) with hereditary breast and ovarian cancer (HBOC) occurred in 1990 and 1994, respectively,^{1,2} scientists worked on the development of a molecular test that would allow clinicians to test high-risk women for the presence of these discovered mutations. Genetic testing for HBOC susceptibility (BRCA1/2) became commercially available in the US at the end of 1996.³ The BRCA mutations are being studied currently as biomarkers that might influence future patient counseling, management decisions, and clinical prognosis of these patients.⁴

According to the 2012 Texas Cancer Registry (TCR) statistics, breast cancer remained the most prevalent, and ovarian cancer the eighth-most prevalent, cancer among females in Texas during 2005–2009.⁵ However, information about the presence of BRCA1/2 mutations among women with breast and/or ovarian cancer is not included in the TCR data. The literature does not give us the exact incidence of BRCA1/2 mutations in the general US population or specifically among women older than 65, but a sensitivity analysis done using published incidence estimates reported an estimated prevalence of 1 in 300 to 500 in the general population.⁶ What the literature states

clearly is that about 10% of all cases of ovarian cancer and 3%–5% of all cases of breast cancer are due to germline mutations in BRCA1/2.⁷

Guidelines to routinely test women who might be at risk for BRCA1/2 mutations have been suggested by different institutions including the American Congress of Obstetricians and Gynecologists and the US Preventive Services Task Force (USPSTF).^{7,8} Table 1 outlines the recommendations from the American Congress of Obstetricians and Gynecologists, which have been adopted by the Centers for Medicare and Medicaid Services, to screen high-risk women for the presence of these mutations.⁷

Once the high-risk patient has been identified and the genetic testing has been performed, the molecular evidence of one of these mutations would reveal lifetime risks for developing breast and/or ovarian cancer as follows: BRCA1 or BRCA2 mutation, 65%–74% risk of developing breast cancer; BRCA1 mutation, 39%–46% risk of developing ovarian cancer; BRCA2 mutation, 12%–20% risk of developing ovarian cancer.⁷

For those with the molecular evidence of the mutations but asymptomatic, genetic counseling and prevention strategies are recommended to reduce their risk of developing the HBOC. Some studies have shown that women with BRCA1/2 mutations and with either breast and/or ovarian cancer may respond better to chemotherapy and experience superior outcomes compared with women without mutations.^{9–11} Therefore, the knowledge of the BRCA status in a woman may play an important role as a preventive tool and as a prognostic indicator for those patients already diagnosed with cancer.

Many aspects of the HBOC have not yet been elucidated. The USPSTF found insufficient evidence regarding the efficacy of preventive interventions while considering the harms of intensive screening and aggressive interventions with regard to asymptomatic women with mutations.⁸ The effect of BRCA1/2 mutations on patients with existing cancer and its influence on outcomes is still not clear.¹⁰

This study was conducted to determine the rate of BRCA testing in the State of Texas among women > 65 years with a diagnosis of breast and/or ovarian cancer, to determine the prevalence of BRCA 1/2 mutation among those tested, and to compare our findings with current literature. Only women >65 years of age were included in this study as the TCR-Medicare data set provides only information about people aged 65 and older.

MATERIALS AND METHODS

The Institutional Review Board at the University of Texas Medical Branch at Galveston approved this study. The privacy review board of the Centers for Medicare and Medicaid Services and the Texas Department of State Health Services has approved studies using these data.

Data Sources

Data from the TCR-Medicare database were used for the analysis. The TCR-Medicare database is a linkage of two large, population-based sources of data performed under the guidance of the National

Table 1. Criteria for genetic risk assessment: recommendations by the American Congress of Obstetricians and Gynecologists

Risk factors	Chance of inherited predisposition to breast & ovarian cancer for the presence of each risk factor	Genetic risk assessment
<ol style="list-style-type: none"> 1. Women with a personal history of both breast and ovarian cancer 2. Women with ovarian cancer and a close relative with ovarian cancer, premenopausal breast cancer, or both 3. Women with ovarian cancer who are of Ashkenazi Jewish ancestry 4. Women with breast cancer at age 50 years or younger and a close relative with ovarian cancer or male breast cancer at any age 5. Women of Ashkenazi Jewish ancestry in whom breast cancer was diagnosed at age 40 years or younger 6. Women with a close relative with a known BRCA1 or BRCA2 mutation 	20%–25%	Recommended as the risk is higher
<ol style="list-style-type: none"> 1. Women with breast cancer at age 40 years or younger 2. Women with ovarian, primary peritoneal, or fallopian tube cancer of high grade, serous histology at any age 3. Women with bilateral breast cancer (particularly if the first case of breast cancer was diagnosed at age 50 years or younger) 4. Women with breast cancer at age 50 years or younger and a close relative with breast cancer at age 50 years or younger 5. Women of Ashkenazi Jewish ancestry with breast cancer at age 50 years or younger 6. Women with breast cancer at any age and 2 or more close relatives with breast cancer at any age (particularly if at least one case of breast cancer was diagnosed at age 50 years or younger) 7. Unaffected women with a close relative who meets one of the previous criteria 	5%–10%	May Be Helpful
<p>Cancer of the peritoneum and fallopian tubes should be considered a part of the spectrum of the hereditary breast and ovarian cancer syndrome.</p> <p>Close relative is defined as a first-degree relative (mother, sister, and daughter) or second-degree relative (grandmother, granddaughter, aunt, and niece)</p> <p>These criteria have been adopted by the Centers for Medicare and Medicaid Services (CMS) for the reimbursement of BRCA testing</p> <p>Table adopted from <i>Hereditary breast and ovarian cancer syndrome</i>. ACOG Practice Bulletin No. 103. American College of Obstetricians and Gynecologists. <i>Obstet Gynecol</i> 2009;113:957–966.</p>		

Cancer Institute,¹² the TCR,¹³ and the Medicare claims data collected by the Centers for Medicare and Medicaid Services.¹⁴ This data set provides detailed information about elderly adults with cancer in Texas.

Approximately 98% of all people aged 65 and older in TCR are matched with Medicare enrollment and claims files. The TCR collects and provides information on participant demographics, cancer prevalence, cancer incidence, stage of disease, first course of therapy, and survival. The Medicare claims data include information on hospital stays, physician services, and hospital outpatient visits. Data use agreements have been signed with both data providers. The data used in this study include cancer patients diagnosed with breast and/or ovarian cancer between 2005 and 2007 and their Medicare claims through 2009. No cases coded for mutations were found prior to 2005. All data are deidentified.

Cohort Selection

Using the TCR-Medicare database, the cohort was identified from cancer registry data using the following inclusion criteria: women with International Classification of Diseases for Oncology, Third Edition (ICD-O-3), histology codes consistent with breast and/or

ovarian cancer, any cancer stage based on Surveillance Epidemiology and End Results (SEER) summary stage,^{15,16} women diagnosed between 2005 and 2007, women enrolled in Medicare Part A (which provides hospital insurance to all qualified beneficiaries under the Medicare criteria) and Medicare Part B (which provides medical insurance coverage for physician's services, outpatient services, and home health care. Participation under Part B is voluntary, and beneficiaries pay monthly premiums. Part B is also called Supplementary Medical Insurance), and not in a health maintenance organization for 12 months before and three months after their cancer diagnosis, and women age 66 years and older. Women diagnosed at autopsy or according to death certificate were excluded. A total of 9,372 women met these criteria and were included in this study.

To select the cohort, we followed as closely as possible the guidelines given by the American Congress of Obstetricians and Gynecologists and adopted by the Centers for Medicare and Medicaid Services (Table 1) to identify possible risk factors, BRCA testing, and BRCA mutation carriers. Table 2 shows the codes that we used. From this initial group of 9,372 women, 1,594 were found to have been tested for the presence of the BRCA1/2.

Table 2. Codes used to select the cohort

Use	Codes	Description
Case selection	ICD-O codes C500-C506, C508-C509 C569	All breast sites and histologies All histologies for ovary
Identification of Risk Factors	ICD-9-CM codes V16.3 V16.41 V16.8 V10.3 V10.43	Family history of breast cancer Family history of ovarian cancer Family history of malignant neoplasm, other specified (breast, male) Personal history of malignant neoplasm, breast Personal history of malignant neoplasm, ovary
Identification of Women Tested	ICD-9-CM codes V26.31 HCPCS codes S3818 S3819 S3820 S3822	Testing of female for genetic disease carrier status Complete gene sequence analysis; BRCA1 gene Complete gene sequence analysis; BRCA2 gene Complete BRCA1 and BRCA2 gene sequence analysis for susceptibility to breast and ovarian cancer Single mutation analysis (in individual with a known BRCA1 or BRCA2 mutation in the family) for susceptibility to breast and ovarian cancer
Identification of Women Positive for Mutations	ICD-9-CM codes V84.01 V84.02	Genetic molecular susceptibility to breast cancer (BRCA1 or BRCA2 mutations confirmed by molecular susceptibility testing for breast cancer) Genetic molecular susceptibility to ovarian cancer (BRCA1 or BRCA2 mutations confirmed by molecular susceptibility testing for ovarian cancer)
Abbreviations: ICD-O, International Classification of Diseases for Oncology; ICD-9, International Classification of Disease, ninth revision; HCPCS, Healthcare Common Procedure Coding System		

Statistical Analysis

Demographics included age, race, type of diagnosis, and personal or family history of either breast and/or ovarian cancer, including family history of male breast cancer. We calculated the percentage of women that underwent BRCA testing and the percentage of women coded as positive for the presence of the BRCA mutations. Analyses were conducted using the SAS statistical software, version 9.2 (SAS institute Inc.), and Statistical Package for the Social Sciences, version 17.0.

RESULTS

Table 3 presents the distribution of patient characteristics and the distribution of testing by race and diagnosis. The median age for the

group with breast cancer and for the group with ovarian cancer was 74 and 68 years for the group of women with both breast and ovarian cancer. The majority of women among all diagnostic groups were Non-Hispanic White and consequently had the highest proportion tested. However, within each diagnostic group, statistically significant differences in testing among the racial ethnic groups were observed for those with breast cancer only.

The rate of testing among the entire cohort of women with existing breast and/or ovarian cancer was 17%; the rate of testing among the group of women with existing breast and/or ovarian cancer and documented risk factors for the presence of BRCA1/2 mutations was 20%. The proportion of women in the group with at least one risk

Table 3. Patient characteristics and distribution of testing by race and diagnosis

Characteristic	Cancer Diagnosis			
	Breast only	Ovarian only	Breast & ovarian	All
Median Age (years)*	74	74	68	74
Race				
All	8,926	416	30	9,372
Tested	1,509(16.9%)	72(17.3)	13(43.3%)	1,594(17.0%)
Non-Hispanic White	7,270 (81.4%)	361 (86.7%)	22 (73.3%)	7,653 (81.6%)
Tested	1,261 (17.3%)	66 (18.3%)	12 (40%)	1,339(17.5%)
Black	616 (6.9%)	13 (3.1%)	2 (6.6%)	631 (6.7%)
Tested	94 (15.3%)	2 (15.4%)	1 (3.3%)	97(15.4%)
Hispanic	864 (9.6%)	33 (7.9%)	5 (16.6%)	902 (9.6%)
Tested	122 (14.1%)	4 (12.1%)	None	126(14.0%)
Other	131 (1.4%)	7 (1.6%)	1 (3.3%)	139 (1.4%)
Tested	28 (21.4%)	None	None	28(20.1%)
Unknown	45 (1%)	7 (1.6%)	1 (3.3%)	47 (0.5%)
Tested	4 (8.8%)	None	None	4(8.5%)
Chi-Square**	10.9	2.8	5.8	11.8
P-value	0.03	0.59	0.12	0.02

*Age at diagnosis of first primary after turning 65 years.
 **Pearson 2-sided test with p-value level of significance 0.05.

factor for BRCA1/2 mutations and documented family history of either breast or ovarian cancer was 10%.

The final cohort included a total of 9,372 cases: 8,926 breast, 416 ovarian, and 30 breast and ovarian cancer. Of these 9,372 cases, 7,744 women were identified as having at least one of the ICD-9-CM codes identifying risk factors associated with increased risk for HBOC (codes are listed in Table 2). These groups are described in Table 4 and are not mutually exclusive, as some of these patients had more than 1 risk factor for HBOC. There were 1,594 women tested of whom 1,411 were among the group who had at least one documented risk factor as described in current Medicare reimbursement guidelines (described in Table 1). Of the 1,411 at risk and tested (Table 4), 543 had no codes for family history and two women were positive for mutations. Three hundred and sixty-six women had significant family history and 19 women were positive for the mutations. Twenty-one women total were found coded as positive for the mutation in this cohort (1.6%).

Table 4 also shows the percentage in each risk-factor group who were coded as having been tested and those subsequently found coded as positive for the mutations. Of the groups with at least one risk factor identified, patients with a family history of ovarian cancer (78%) or

male breast cancer (66%) were most likely to be tested. Although the number of women with a personal history of breast cancer was highest, the percentage tested within this risk group was lowest. Due to the small number of patients positive for the mutation among the risk groups, only percentages of positivity can be reported. The greatest proportion found to carry the mutation was observed in those with bilateral breast cancer. Patients with either a personal history of ovarian cancer or a family history of ovarian cancer were the next most likely to carry the mutation. The percentage of women with breast and/or ovarian cancer who had at least one risk factor identified by a code and who were covered by Medicare was 83%.

For the 21 women coded as molecularly positive for the mutation, the greatest prevalence for the mutation was held by those with ovarian cancer only. Again, the small number prevented the reporting of some actual numbers, but Table 5 illustrates the BRCA1/2 mutation prevalence by diagnosis group. The group with the highest prevalence of positivity (3%) was the one with ovarian cancer only, while those with breast cancer only appeared to be at lower risk for the mutation with a prevalence of 0.18%.

Table 6 reports the trends of BRCA testing by year for the 1,411 women with breast and/or ovarian cancer with at least one docu-

Table 4. Testing patterns among those with identified risk factors (N=7,744)

Risk factors*	Number (%)	Percentage tested (%)	Percentage of BRCA positive (%)
Bilateral Breast Cancer	8 (0.1%)	50%	50%
Both Breast & Ovarian	30 (0.4%)	43.3%	None
Personal History of Breast Cancer**	7460 (96.3%)	18.1%	1.18%
Personal History of Ovarian Cancer**	288 (3.7%)	28.8%	12%
Family History of Breast Cancer	719 (9.3%)	36.8%	4.1%
Family history of Ovarian Cancer	91 (1.2%)	78%	11.2%
Family History of Male Breast Cancer	58 (0.7%)	65.5%	None

*Risk groups are not mutually exclusive; a patient may have had more than 1 documented risk factor
**Personal history of breast or ovarian cancer (ICD-9-CM codes: V10.3, V10.43) identified from claims, may reflect either a current or a past breast or ovarian primary

Table 5. Testing patterns and positive proportions by cancer diagnosis for those with at least one risk factor

Cancer diagnosis	N	Tested N (%)	Population estimates of positivity N (%)
Breast Only	7474	1342 (18%)	14 (0.18%)
Ovarian Only	233	57 (24%)	7 (3%)
Both Breast & Ovarian	30	13 (43%)	0

Table 6. Trends of BRCA testing by year for the 1,411 women with breast and/or ovarian cancer, at least one documented risk factor, and a claim for BRCA testing

Year cancer diagnosis					
	Number with cancer diagnosis and documented risk factor ICD-9 code	Year of test	Number available for first test (excludes those tested in previous year)	Number of tests done	% tested
2005	3,142	2005	3,142	272	8.65
2006	2,380	2006	5,249	402	7.65
2007	2,222	2007	7,068	460	6.50
		2008	6,608	150	2.27
		2009	6,458	127	1.97
Total	7,744			1,411	27.04

mented risk factor and a claim for the BRCA testing. The year of 2005 was the year with the highest percentage of women tested; as we progressed in time, the percentage of women tested decreased. This trend might be secondary to the fact that health care providers have been learning more about the specific indications for testing and have become more educated about the risk factors that increase the possibility of having a BRCA mutation.

DISCUSSION

Genetic testing for HBOC susceptibility (BRCA1/2 mutations) became commercially available in the US at the end of 1996 through the Myriad Genetic Laboratories.³ This test delivers a direct DNA sequencing with analytic sensitivity and specificity both >99%.⁶ The testing provides the opportunity to identify women with the mutation as well as the opportunity to develop new strategies for early detection and prevention. Beyond this, the testing of the patients with the manifestations of the HBOC gives the opportunity of counseling other family members appropriately. Among those with cancer, there is evidence that the presence of a mutation could be a prognostic factor and marker when choosing chemotherapy regimens.¹⁷ However, this testing is expensive - around \$3,000 in the US. Several State Medicaid programs and private medical insurance cover this test for qualifying individuals, but there are many unfunded patients without the opportunity to be tested. Conversely, testing of some whose costs may be covered by publicly funded insurance may be unnecessary if not indicated or the outcome of the test will not be used in decision-making for the patient or family.

We found the TCR-Medicare database to be useful in assessing the frequency distribution of BRCA testing by reported risk factors and the frequency of confirmed mutations in older women in the State of Texas with the HBOC. However, in terms of studying treatment-related outcomes among those with mutations, this data source may be limited.

Our study did not look at claims for genetic counseling as the Secretary's Advisory Committee on Genetics, Health, and Society confirmed the Medicare policies against genetic counselors reimbursement and integration of genetic counselors into the Medicare program.¹⁸ Based on this fact, we did not expect to find many claims using these data. However, future studies using prospectively collected data would be useful in determining the impact of counseling on the decision to be tested.

We were unable to identify any study describing validated algorithms to identify BRCA1/2 mutated patients using administrative data. However, we found three studies that used the same ICD-9-CM codes to identify BRCA1/2 mutated patients in our dataset (Table 7). Our study did not include the validation of the codes V84.01 and V84.02 in the manner that Freeman et al described the validation of the Medicare claims to capture chemotherapy use.¹⁹

Regarding the testing patterns, we found that less than 100% of the patients with a risk factor underwent BRCA testing. This finding is due to the nature of this administrative data source. The ICD-9-CM codes used in this study to identify a risk factor for the mutation were unable to completely distinguish whether or not a patient fully met the criteria for testing. For example, having the code for a single relative with breast cancer is not alone an indication for BRCA testing. Of interest, 50% of the patients with bilateral breast cancer underwent testing as did more than 50% of patients with positive family history for ovarian cancer and positive family history for male breast cancer. Less than 50% of patients with personal history of breast cancer, ovarian cancer, or family history of breast cancer underwent testing (Table 4). Although our definition of personal and/or family

history could be interpreted as being very broad, since these women had Medicare claims, presumably they would have had to have met the risk criteria for reimbursement adopted by Medicare which is described in Table 1.

Conversely, there were gaps in testing, and this study did not attempt to determine the reasons. However, it can be speculated that reasons might include patient decision to not be tested despite risk factors, lack of information from the health care provider, and/or lack of access to the test. The lack of information regarding these factors limited our capacity to report under or over utilization of the testing.

It is of further interest to note that our database indicates that the younger women with mutations had both breast and ovarian cancer, consistent with the literature that reported that those with HBOC are younger than those with breast or ovarian cancer alone.²⁰

In our cohort of women with claims for positive mutation, the percentage of women with breast cancer with claims indicating the mutation was 0.18%, which falls within the confidence interval published by Whittemore et al in 1997.²¹ Our study found the percentage of ovarian cancer due to the mutations to be 3%. Whittemore et al published a percentage of 3.1% (0.6–13.8) for women 60–69 years of age and 2.8% (0.6–12.4) for women 70–79 years of age.²¹ Therefore, we conclude that our cohort appears to be representative of the general population of women with breast and/or ovarian cancer.

The results from our population based study of women aged 66 years and older show a prevalence rate of positivity for the BRCA mutations to be a bit lower than published previously. When comparing to other studies, a study by Frank et al conducted with 10,000 consecutive gene sequence analyses performed to identify mutations anywhere in the BRCA1 and BRCA2 genes reported on a subgroup of 843 women with significant family history, age 50 and older with breast and ovarian cancer. The positivity rate for mutations among this group of women was 13.3%.²² In our cohort, 366 women had significant family history and 19 were coded as positive for the mutations (5.2%). The difference among these results might be attributable to the younger age among the group of women studied by Frank et al, the fact that our study is a population based and theirs was not, and the possibility that not all mutation carriers had medical claims indicating that they were BRCA carriers.

Additionally, Myriad data reported a 13.8% prevalence of deleterious mutation in BRCA1 or BRCA2 among a group of 232 women with epithelial ovarian carcinoma with an average age of 55 years.²³ It is important to emphasize again that our study is a population-based study of women older than 65 years of age and the women on the above studies were of a subgroup of younger women, all of whom were tested. These differences make comparison of our study results of an overall positivity rate of 1.6% to those in the Myriad data difficult.

This study has limitations, including the fact that available data were limited to that which was coded and to only the first ten codes claimed. This means that if the BRCA related codes were not among the first ten codes, those codes do not appear in the data source. The extracted data were limited to the ICD-9-CM codes documenting mutation status and significant family history. We were unable to identify ethnicities associated with higher mutation frequency such as Ashkenazi Jewish and others. We were unable to assess the exact age at which family members developed the disease or degree of relationship to the affected woman, which are important factors in the study of cancer due to genetic mutations.

Table 7. Codes used by other studies to identify patients with BRCA mutations

Study	ICD-9-CM codes found
Asante, A, 2010- Elective Oophorectomy in the United States Trends and In-Hospital Complications, 1998-2006 ²⁴	V84.01, V84.02
Engel, NJ, 2012- A multidisciplinary clinic for individualizing management of patients at increased risk for breast and gynecologic cancer ²⁵	V84.01, V84.02
McLaughlin, CC, 2005- Surveillance of Prophylactic Mastectomy Trends in Use From 1995 Through 2005 ²⁶	V84.01

Despite these limitations, we believe our findings are important and could be used at the time of genetic counseling for those men and women with a personal and/or a family history of breast/ovarian cancer with or without known BRCA1/2 mutations. As health care providers and investigators, these findings provide guidance regarding the utilization of the BRCA testing in the State of Texas and future research of the HBOC using administrative data. Genetic testing is an evolving technology in the prevention of diseases with ethical, social, and psychological implications in the communities. The public health practice of the community health centers needs to explain to the general population the magnitude of potential benefits and adverse effects related to genetic testing and cancer.

Future endeavors should focus on outcomes of interventions including breast and ovarian cancer screening, risk-reducing mastectomy and salpingo-oophorectomy, chemoprevention with agents such as tamoxifen and raloxifene, and the effect of the mutation on outcomes among the patients with existing cancer. To our knowledge this descriptive population-based study is the first using cancer registry linked Medicare data to study BRCA1/2 mutations in women with breast and/or ovarian cancer.

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