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# Earlier Age of Onset of *BRCA* Mutation-Related Cancers in Subsequent Generations

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## Abstract

**BACKGROUND—**Women who are diagnosed with a deleterious mutation in either breast cancer (*BRCA*) gene have a high risk of developing breast and ovarian cancers at young ages. In this study, the authors assessed age at diagnosis in 2 generations of families with known mutations to investigate for earlier onset in subsequent generations.

**METHODS—**Of the 132 *BRCA*-positive women with breast cancer who participated in a high-risk protocol at The University of Texas MD Anderson Cancer Center (Gen 2), 106 women could be paired with a family member in the previous generation (Gen 1) who was diagnosed with a *BRCA*-related cancer (either breast cancer or ovarian cancer). Age at diagnosis, location of the mutation, and year of birth were recorded. A previously published parametric anticipation model was applied in these genetically predisposed families.

**RESULTS—**The median age of cancer diagnosis was 42 years (range, 28–55 years) in Gen 2 and 48 years (range, 30–72 years) in Gen 1 ($P < .001$). In the parametric model, the estimated change



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CONFLICT OF INTEREST DISCLOSURES

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in the expected age at onset for the entire cohort was 7.9 years ($P < .0001$). Statistically significant earlier ages at diagnosis also were observed within subgroups of *BRCA1* and *BRCA2* mutations, maternal inheritance, paternal inheritance, breast cancer only, and breast cancer-identified and ovarian cancer-identified families.

**CONCLUSIONS—**Breast and ovarian cancers in *BRCA* mutation carriers appeared to be diagnosed at an earlier age in later generations. The authors concluded that patients who are younger at the onset of *BRCA*-related cancers should continue to be tracked to offer appropriate screening modalities at appropriate ages.

## Keywords

breast cancer; *BRCA1*; *BRCA2*; anticipation; hereditary breast and ovarian cancer syndrome

Hereditary breast and ovarian cancer syndrome (HBOC) related to the breast cancer (*BRCA*) genes initially was identified in families with the use of genetic linkage analysis.[1–3] Since then, over 5000 different mutations in these genes have been identified that are inherited in an autosomal-dominant fashion and are responsible for approximately 5% to 10% of breast cancer diagnoses.[4] Carriers of this mutation have an elevated risk of developing both breast and/or ovarian cancer, and a meta-analysis estimate of the lifetime risk of breast cancer was 47% to 66% in *BRCA1* carriers and 40% to 57% in the *BRCA2* carriers, and the risk of developing ovarian cancer was 35% to 46% and 13% to 23%, respectively, in the same analysis.[5] One of the major risk factors for HBOC is the development of breast cancer at a very young age, Thus, the National Comprehensive Cancer Network (NCCN) guidelines panel has recommend initiating screening at ages 20 to 25 years, or 5 to 10 years earlier than the youngest age at diagnosis in the family.[6] Implementing screening techniques is meant to identify cancers at the earliest time possible; therefore, estimating the onset of disease is vital in timing the initiation of screening and interventions.

Anticipation has been described as a phenomenon observed in inherited diseases such as Fragile X syndrome and Huntington disease, in which the disease occurs at younger ages or with increased severity of disease in subsequent generations.[7,8] The cause of this anticipation has been identified as DNA instability, such as nucleotide repeats that change in length in subsequent generations, altering the phenotype of the disease. However, changes in disease phenotype in subsequent generations also have been identified in other disorders, such as in colon cancer, Alzheimer disease, and diabetes.[9,10] With the increase in *BRCA1* and *BRCA2* testing, there also has been an increase in families being evaluated and screened for HBOC.

There have been several reports of anticipation in breast cancer. To date, these reports have been based on very small cohorts; those studies indicated an earlier age at diagnosis and examined the absolute differences between matched pairs. Dagan and Gershoni-Baruch reported a statistically significant difference of approximately 4 years in *BRCA2* mutation carriers and a statistically nonsignificant numerical difference in *BRCA1* carriers.[11] In addition, Peixoto et al and Paltiel et al also observed similar patterns of earlier age of diagnosis for subsequent generations in breast cancer registries.[12,13]

When discussing appropriate screening interventions for women with a known deleterious *BRCA1* or *BRCA2* mutation, potential interventions include clinical breast examination, magnetic resonance imaging, and mammography.[14] Evaluating for patterns of inheritance like anticipation in families with known deleterious *BRCA* mutations may help promote understanding of these genes and provide further insight into the timing of screening initiation and starting other interventions. The objective of the current analysis was to evaluate any trends in age at diagnoses in families with known deleterious *BRCA* mutations at a single institution to add to the growing evidence of genetic anticipation in patients with HBOC. We evaluated families who were referred to the Clinical Cancer Genetic Program at our institution and analyzed age at diagnosis across 2 generations.

## MATERIALS AND METHODS

### Methods

Women who attended the Clinical Cancer Genetics clinic from January 2003 to March 2009 in the Breast Center at The University of Texas MD Anderson Cancer Center were included in this analysis. Patients were accrued prospectively to an Institutional Review Board-approved protocol that allowed for the collection and retrieval of clinical data. Patients consulted a genetic counselor and were followed by faculty from the Clinical Cancer Genetics Program. Family history questionnaires were distributed to patients before their genetic counseling session to help prepare and gather the necessary information for the session. Pedigrees were drawn at the time of the initial visit and were stored in a centralized database. Patients identified all family members, including those who were not affected by cancer. Age at diagnosis and type of cancer diagnosed in family members were provided by the patient (pro-band). For the purposes of this study, all pedigrees were evaluated by the investigator and the clinical genetic counselor for all families that had an identified deleterious *BRCA1* or *BRCA2* mutation. Pedigrees in which a breast cancer and/or ovarian cancer was identified in the previous generation were included in the analysis. Because previous generations often did not have genetic testing and family members were not living, pedigree analysis by a genetic counselor and the investigator were performed to determine the parental side of inheritance. Pedigrees in which there was not an HBOC-related cancer in the previous generation were excluded from the analysis. In total, 132 women were diagnosed with a deleterious *BRCA* mutation during the study period, and 106 families were identified with affected individuals in ≥2 generations. In all, 303 individuals who were affected with an HBOC-related cancer were included in the final analysis.

### Statistical Considerations

Initially, *t* tests for paired data were used to compare the age at diagnosis between generations. A secondary analysis was completed using the method proposed by Larsen et al[15] based on a parametric model for analyzing anticipation that may allow for right-censored observations, inclusion of covariates, and drawing of statistical inference based on the likelihood function, which studies the patient family instead of parent-child pairs. The advantage of this model is that all of the individuals who are known to be at risk in a family can be contained in the study.

We applied the basic model (Model 1), which only included generation and family effects:

$$T_{ij}=\mu_i+m_{ij}\gamma+\varepsilon_{ij}$$

The families are indexed by $i$ 1, 106, and individuals in the families are indexed by $j$ 1, $n_i$. Thus, $m_{ij}$ denotes the generation of the $j^{th}$ individual of the $i^{th}$ family. The older individual in a family is represented as $m_{ij}$ 0, and the younger generation is represented as $m_{ij}$ 1. Also, $T_{ij}$ denotes the age at onset, $\mu_i$ is the estimator mean of the older generation, $\gamma$ is the mean difference of the 2 generations, and $\varepsilon_{ij}$ is the residual of $j^{th}$ individual of the $i^{th}$ family. It is assumed that all of these effects are mutually independent and that the age at onset follows a multivariate normal distribution.

Then, the numeric maximization of the log-likelihood function principle was applied to estimate $\mu_i$ and $\gamma$, and the likelihood ratio test was adopted to test the significance. The log likelihood is as follows:

$$l=\sum_{i}^{n}(\log(\varphi_i(t_{i1},\ldots t_{n_i};\mu,\sigma)))$$

## RESULTS

When evaluating age differences between generations in each family, the *t* test for paired data indicated a median age at diagnosis of 48 years in the older generation (Gen 1) and 42 years in the younger generation (Gen 2); the range of differences between Gen 1 and Gen 2 was approximately 14 to 51 years ($P < .001$). To account for changes in medical care, differences by decade of birth also were taken into account (Table 1).

Because of the limitations of evaluating data by using the *t* test for paired data, we also used the parametric model for analyzing anticipation as described above. For the entire cohort, the change in the expected age at onset was 7.9 years, and the mean value of age at onset for Gen 1 was 48.98 years with a likelihood ratio of 36.77 and 1 degree of freedom ($P < .0001$).

Because these pedigrees take into account HBOC-related cancers that include both breast and ovarian cancers, additional analyses were performed after stratification of these characteristics and using the parametric model for analyzing anticipation. Table 2 provides results from the stratification of families with *BRCA1* mutations only, *BRCA2* mutation only, families with only breast cancer diagnosed, and families with both breast and ovarian cancers diagnosed. Differences in age of diagnoses between 2 generations also were observed and were statistically significant when these specific family characteristics were isolated.

## DISCUSSION

In the current analysis, we evaluated families with HBOC-related cancers in at least 2 generations and described trends in differences in age at diagnosis between these generations. We observed an earlier age at diagnosis in younger generations whether we

used the *t* test for paired data or the more inclusive parametric model for analyzing anticipation. In addition, when we examined differences in subsets (*BRCA1* families vs *BRCA2* families, inheritance through the mother's or the father's side, and whether or not the families were affected by breast cancer only or by both breast and ovarian cancer), these age differences remained. The magnitude of the age differences between these subsets varied and, although they may have been affected by the small subset numbers, they add to the growing evidence of genetic anticipation in HBOC.

With the onset of genetic testing for HBOC and other cancer genetic syndromes, providing guidance for the timing of screening and prophylactic interventions will be critical to preventing cancers in future generations. Currently, guidelines, like those published by the NCCN, suggest that screening should be initiated for HBOC-related breast cancer at age 25 years, or 5 to 10 years earlier than the age at earliest diagnosis.[6] At this point, this recommendation appears to be sufficient and appropriate. However, if true genetic anticipation is observed with this syndrome, then monitoring for these shifts in age at diagnosis in future generations will be required to better prepare caregivers and patients with regard to the timing of counseling and interventions.

There are several limitations to this analysis. We have identified families with a known deleterious *BRCA1* or *BRCA2* mutation, but testing was not available for many affected family members from previous generations. The mutations that were identified in this cohort are listed in Table 3. Assumptions had to be made regarding genetic carrier status. Also, because pedigrees were drawn from information provided by the proband, age at diagnosis may have been affected by recall bias. Additional information regarding previous bilateral salpingo-oophorectomy may have influenced age at diagnosis and could not be included it in our data set. This factor should be documented and tracked in prospective series. Genetic counseling sessions at our institution are preceded by a family history questionnaire that is mailed to the proband in advance of their visit. They are encouraged to discuss with family members regarding diagnosis, cancer type, and age at onset. When possible, probands are encouraged to provide pathology reports of family members to evaluate, for instance, the type of ovarian cancer; however, it was very uncommon for patients to be able to provide this documentation. Another potential bias is referral bias. Because our institution is a tertiary cancer center, our patient base is younger on average than the general population with breast cancer.

There may be multiple other factors that influence the age at diagnosis, such as race, exposures, and other environmental factors, that were not available as part of our analysis. Furthermore, improvements in imaging techniques, such as digital mammography and dedicated breast magnetic resonance imaging, may help diagnose HBOC-related breast cancers earlier in more recent generations. These and other factors should be considered in future prospective cohort analyses.

For potential statistical bias, family members may not have had complete information regarding unaffected individuals in their pedigree. This may have affected the statistical analysis as part of the parametric model for analyzing anticipation. This also may bias the result toward younger age at diagnosis in younger generations. In light of this factor, the true

difference between 2 generations may be <7.9 years. Nevertheless, the highly significant result is still a strong proof of the tendency for the younger generation to develop HBOC-related breast cancer at younger ages than their affected older generation.

In the future, as cancer genetic clinics and genetic counseling become more entrenched in the care of patients with cancer and, in this case, patients with breast and ovarian cancers, following these families throughout their care will provide supplementary answers regarding the presence and magnitude of genetic anticipation. Families will be able to have testing, and known mutation carriers can be compared between generations. Also, breast screening timing and techniques can be tracked and factored into these analyses regarding anticipation. Additional features that should be followed include tumor stage at diagnosis, tumor characteristics, and response to systemic therapies. These characteristics should be followed not only to take into account age at diagnosis but also to evaluate for other phenotypic changes that may affect management in the future. Screening guidelines for unaffected *BRCA* deleterious mutation carriers will need to follow these trends to adjust future recommendations if needed.

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## Table 1

Paired *t* Tests of Age at Diagnosis by Decade of Birth

| | Median Age (Range), y | | |
|---|---|---|---|
| **Decade of Birth: Gen 2** | **Gen 1** | **Gen 2** | **P[a]** |
| 1930–1939, n = 4 | 55 (39–58) | 52.5 (40–86) | |
| 1940–1949, n = 18 | 50 (32–68) | 46.5 (32–57) | .13 |
| 1950–1959, n = 42 | 50 (33–70) | 43.5 (20–53) | <.001 |
| 1960–1969, n = 28 | 39.5 (23–64) | 38.5 (21–43) | .03 |
| 1970–1980, n = 14 | 44.5 (34–64) | 31 (25–35) | <.001 |

Abbreviations: Gen 1, older generation; Gen 2, younger generation.

[a]Two-sided t test.

**Table 2**

The Expected Age at Onset by Subgroup

| | Mean LR of Age at Onset | | | LR Test | | |
|---|---|---|---|---|---|---|
| **Family Characteristics (n = 106 Families)** | **Gen 2** | **Gen 1** | **Expected Change** | **LR** | **DF** | ***P*** |
| *BRCA1* only, n = 67 | 39.61 | 45.78 | 6.17 | 14.62 | 1 | .0001 |
| *BRCA2* only, n = 39 | 43.77 | 54.33 | 10.56 | 25.98 | 1 | <.0001 |
| Breast cancer only, n = 48 | 39.55 | 47.55 | 8.00 | 16.48 | 1 | <.0001 |
| Both breast cancer and ovarian cancer diagnosed in the family, n = 58 | 42.38 | 50.11 | 7.73 | 14.19 | 1 | .0002 |
| Mutation inherited from mother's side of the family, n = 74 | 41.05 | 49.16 | 8.11 | 27.70 | 1 | <.0001 |
| Mutation inherited from father's side of the family, n = 32 | 40.89 | 49.11 | 8.22 | 27.44 | 1 | <.0001 |

Abbreviations: BRCA, breast cancer gene; DF, degrees of freedom; Gen 1, older generation; Gen 2, younger generation; LR, likelihood ratio.

## Table 3

Deleterious Breast Cancer Gene Mutations Identified in the Study Cohort

| Identified Deleterious Mutations | |
|---|---|
| ***BRCA1*** | ***BRCA2*** |
| 3312insG | 4075delGT |
| 3509delA | 5849del4 |
| 3600del11 | 6174delT |
| 3875del4 | 6662del8 |
| 4154delA | 6759del4 |
| 5194del4 | 7297delCT |
| 5385insC | 802delAT |
| 943ins10 | 8513delC |
| C1251X | 8568del4 |
| C61G | 886delGT |
| Del exon 17 | 9325insA |
| Del exons 1-17 | 9538delAA |
| Del exons 16-17 | 9631delC |
| Del exons 9-12 | 9663delGT |
| Dup exons 3-8 | 983del4 |
| E1134X | 9894delT |
| E1250X | C2689X |
| E143X | D2723H |
| E733X | Del exons 1-2 |
| Exon 13 ins 6kb | |
| IVS13 + 1 G>A | E1812X |
| IVS16+6T>G | E49X |
| IVS20+1G>A | K2013X |
| IVS23+1G>A | Q2042X |
| K679X | Q2957X |
| M1775R | R2520X |
| Q1200X | Y1655X |
| Q544X | Y1894X |
| Q563X | |
| R1443X | |
| R1751X | |
| S713X | |
| S955X | |
| Y1563X | |
| Y978X | |

Abbreviations: A, alanine; BRCA, breast cancer gene; C, cysteine; D, aspartic acid; del, deletion; dup, duplication; E, glutamic acid; G, glycine; H, histidine; ins, insertion; IV, quadrivalent; M, methionine; Q, glutamine; R, arginine; S, serine; T, threonine; X, unspecified amino acid; Y, tyrosine.