Prevalence of Pathogenic BRCA1 Mutation Carriers in 5 US Racial/Ethnic Groups

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PATHOGENIC MUTATIONS IN THE tumor suppressor gene BRCA1 confer high risks of breast and ovarian cancer. Average cumulative risk by age 70 years has been estimated at 65% for breast cancer and 39% for ovarian cancer. Although mutations in BRCA1 are rare, they are more frequently present in individuals with multiple relatives having breast or ovarian cancer, early-onset breast cancer, or of Ashkenazi Jewish ancestry. Information on the prevalence of BRCA1 mutation carriers in racial/ethnic minority populations is limited.

We examined the prevalence of BRCA1 mutations in a population-based, multiethnic series of female breast cancer patients younger than 65 years at diagnosis who were enrolled at the Northern California site of the Breast Cancer Family Registry during the period 1996-2005. Race/ethnicity and religious ancestry were based on self-report. Weighted estimates of prevalence and 95% confidence intervals (CIs) were based on Horvitz-Thompson estimating equations.

METHODS
Study Sample
Patients younger than 65 years with newly diagnosed breast cancer and meeting defined eligibility criteria, and their family members, were enrolled at the Northern California site of the Breast Cancer Family Registry during the period 1996-2005, as described elsewhere. This analysis is based on women diagnosed with invasive breast cancer between January 1, 1995, and December 31, 2003. Patients were identified through the population-based Greater San Francisco Bay Area Cancer Registry, which ascertains all incident cancers as part of the SEER (Surveillance, Epidemiology, and End Results) program and the California Cancer Registry.

We recruited patients with breast cancer into the family registry using a 2-stage sampling design, with oversampling of patients having characteristics suggesting an inherited basis for their cancers. In stage 1 of sampling, we administered a brief telephone

For editorial comment see p 2910.
 interview to all patients and assessed self-identified race/ethnicity and family history of breast and ovarian cancer. Based on age at diagnosis and family history, patients were classified into either category A (patients whose cancers are likely to be hereditary) or category B (all other patients with cancers less likely to be hereditary). Category A patients were those who met at least 1 of the following criteria: (1) breast cancer diagnosis before age 35 years; (2) bilateral breast cancer, with first diagnosis before age 50 years; (3) prior ovarian or childhood cancer; or (4) at least 1 first-degree relative with breast or ovarian cancer. In stage 2, we invited all patients in category A and a random sample of patients in category B (2.5% of non-Hispanic whites and 33% of all other races/ethnicities) to enroll in the family registry. Participants completed questionnaires on family history of cancer and breast cancer risk factors and provided a biospecimen sample. This 2-stage sampling design provides unbiased estimates of mutation carrier prevalence having greater precision than those obtained from a simple random sample of the same size.

The cancer registry ascertained 8752 patients with invasive breast cancer, including non-Hispanic white patients diagnosed from January 1, 1995, to September 30, 1998, and Hispanic, African American, and Asian American patients diagnosed from January 1, 1995, to April 30, 2003 (Figure). A total of 3181 patients were selected to enroll in the family registry, including 1924 category A patients and 1257 who were randomly sampled from 5288 category B patients. BRCA1 mutation testing was completed for 1103 category A patients (57% of eligible patients) and 624 category B patients (50% of eligible patients). Study participants provided written informed consent, and the institutional review boards of the Northern California Cancer Center, Stanford University, and the Dana-Farber Cancer Institute approved the study.

**BRCA1 Mutation Testing**

The majority of patients were tested for BRCA1 (GenBank AY273801; http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&uid=30039658) alterations during the period 1999-2006 using exon grouping analysis\(^8,9\) (n=846) or 2-dimensional gene scanning\(^10,11\) (n=845) as part of 2 separately funded studies. The remaining patients were tested by full sequencing performed by Myriad Genetics\(^12\) (n=35), and 1 Ashkenazi Jewish patient was tested only for 5382insC and 185delAG. Exon grouping analysis is based on conformation-specific gel electrophoresis. All coding exons and surrounding intronic sequences were amplified with 34 primer pairs and analyzed on ABI-377 instruments (Applied Biosystems, Foster City, California). Polymerase chain reaction fragments with aberrant mobility were sequenced. For 2-dimensional gene scanning, the entirety of BRCA1 coding exons and surrounding intronic sequences were amplified in a 2-step polymerase chain reaction process involving 6 individual multiplex reactions\(^10,11\); these methods permit detection of mutations and polymorphisms in BRCA1 coding regions as well as splice-site mutations.

BRCA1 mutations were classified according to the Breast Cancer Information Core database\(^13\) and considered pathogenic as described by Couch and Weber.\(^14\) Such mutations include small deletions or insertions causing a frameshift that generates a premature stop codon, nonsense mutations, splice-site mutations predicted to cause aberrant splicing and generation of a premature stop codon, and missense mutations in the ring-finger domain of the gene. Regulatory mutations outside of the coding region and splice junctions, and large genomic rearrangements, are not detected by the methods used here. Screening for these mutations is limited to members of families with a high prior probability of carrying a BRCA1 mutation, and the prevalence of these mutations in unselected populations is unknown.\(^15-18\)

**Statistical Analysis**

We estimated the prevalence of BRCA1 mutation carriers in subgroups of patients with breast cancer; subgroups were defined by self-identified race/ethnicity, age at diagnosis, and family history of breast or ovarian cancer in first-degree relatives. In non-Hispanic whites, we also estimated prevalence specific for Ashkenazi Jewish ancestry.

To account for differential BRCA1 testing frequencies of patients in categories A (likely to be hereditary, based on age at diagnosis and family history of breast or ovarian cancer) and B (less likely to be hereditary), we estimated mutation prevalence using Horvitz-Thompson estimating equations.\(^6,7\) The Horvitz-Thompson prevalence estimate for a given subgroup of cancer patients (Hispanics, for example) is a weighted average of the carrier prevalences among Hispanic patients in the 2 categories. (For example, had 5% of all screened Hispanic patients been classified in category A, the prevalence estimate would be 0.05π\(_A\) + 0.95π\(_B\), where π\(_A\) and π\(_B\) are the prevalences among the tested Hispanic patients in the 2 categories.) This weighted average is an unbiased estimate of the mutation carrier prevalence in all screened Hispanic patients (tested or not), provided that the carrier statuses of tested patients in categories A and B represent those of all patients in these categories. We estimated the variance of this prevalence estimate using a formula described elsewhere.\(^19\)

Had all patients in both categories been tested, the estimates and their variances would reduce to the usual ones for a simple binomial proportion.

A Horvitz-Thompson estimating equation also was used to estimate odds ratios relating carrier prevalence to race/ethnicity, after adjusting for age at breast cancer diagnosis. This estimating equation was based on a logistic regression model for mutation carriage, with independent variables given by categories of race/ethnicity (with non-Ashkenazi, non-Hispanic whites taken
as the referent group) and age at diagnosis (<35 years, 35-49 years, and 50-64 years taken as the referent group). χ² statistics were used to evaluate racial/ethnic differences in mutation type or position in carriers. All statistical analyses were conducted using computer code developed in the Mathematica programming language.

RESULTS

BRCA1 mutation testing was completed for 549 non-Hispanic white female patients with breast cancer, 444 Asian American patients, 393 Hispanic patients, and 341 African American patients. The Asian American patients tested included 200 Chinese, 151 Filipinas, 66 Japanese, 10 Vietnamese, 3 Koreans, and 14 other Asians. The Hispanic patients tested included third-generation US-born Hispanics (n=95), patients with origins in Mexico (n=200), Central America (n=49), South America (n=28), the Caribbean (Puerto Rico, Cuba, Dominican Republic) (n=14), or Spain (n=4); and 3 patients with unspecified origin. Of the 341 African American patients tested, 331 were born in the United States to US-born parents, 1 was born in Europe to US-born parents, 4 were born in Africa, 2 were from Jamaica, and 3 were from the West Indies.

The Figure shows the number of patients with breast cancer who were screened by telephone for possible hereditary breast cancer, selected for enrollment in the family registry and classified into categories A and B, and tested for BRCA1 mutations. The proportion of screened patients in category A varied by race/ethnicity: 27%, 29%, and 21% in Hispanics, African-Americans, and Asian-Americans, respectively, compared with 31% in non-Hispanic whites.

In category A patients, 232 Hispanics (pₛ=58%), 178 African Americans (pₛ=59%), 201 Asian Americans (pₛ=43%), and 492 non-Hispanic whites (pₛ=65%) were tested for BRCA1 mutations. In category B patients, 291 of 10,666 Hispanics (27%), 288 of 738 African Americans (39%), 201 Asian Americans (27%), and 341 non-Hispanic whites (39%) were tested.

Figure. Telephone Screening for Eligibility and BRCA1 Mutation Testing of Patients With Invasive Breast Cancer, by Race/Ethnicity
597 of 1760 Asian Americans (34%), and 81 of 1724 non-Hispanic whites (5%) were randomly selected into the family registry, and BRCA1 mutation testing was completed for 161 Hispanics ($p_B=15\%)$, 163 African Americans ($p_B=22\%)$, 243 Asian Americans ($p_B=14\%)$, and 57 non-Hispanic whites ($p_B=3\%)$.

Weighted estimates of BRCA1 mutation prevalence in patients with breast cancer are shown in Table 1 according to age at diagnosis and family history of breast or ovarian cancer and by race/ethnicity and Ashkenazi Jewish ancestry. In patients without reported Ashkenazi Jewish ancestry, estimated mutation prevalence was highest in Hispanics (3.5%; 95% confidence interval [CI], 2.1%-5.8%), followed by non-Hispanic whites (2.2%; 95% CI, 0.7%-6.9%), African Americans (1.3%; 95% CI, 0.6%-2.6%), and Asian Americans (0.5%; 95% CI, 0.1%-2.0%). Within each racial/ethnic group, prevalence estimates decreased with age at diagnosis and were higher in patients who reported a family history of breast or ovarian cancer than in those who did not. The prevalence was particularly high in African American patients diagnosed before age 35 years (16.7%; 95% CI, 7.1%-34.3%), compared with young Hispanics (8.9%; 95% CI, 3.8%-19.7%), non-white Hispanics without Ashkenazi Jewish ancestry (7.2%; 95% CI, 3.3%-15.2%), and Asian Americans (2.4%; 95% CI, 0.3%-15.4%). The prevalence estimate of 66.7% (95% CI, 15.4%-95.7%) for Ashkenazi Jewish patients was based on only 3 patients tested.

We used logistic regression to evaluate associations between mutation prevalence and race/ethnicity in patients, adjusting for age at diagnosis. Compared with non-Hispanic white patients without Ashkenazi Jewish ancestry, adjusted odds ratios were 1.3 (95% CI, 1.0-1.7) for Hispanics, 0.5 (95% CI, 0.4-0.7) for African Americans, and 0.2 (95% CI, 0.1-0.3) for Asian Americans (data not shown). By comparison, the age-adjusted odds ratio for Ashkenazi Jewish patients was 3.2 (95% CI, 1.0-10.4).

BRCA1 mutation type differed by race/ethnicity (Table 2). In Hispanics, 71% of mutations were frameshift, 14% missense, and 14% nonsense. Of 4 recurrent mutations in Hispanics, 3 were frameshift (185delAG [n=5], 917delTT [n=4], and 5154del5 [n=2]) and 1 was missense (R71G [n=2]). All mutations occurring in Hispanics were unique to Hispanics, except for 185delAG, which also occurred in Ashkenazi Jewish patients, and Q1200X and C61G, which also were found in 1 other non-Hispanic white. Of the 5 Hispanic carriers of the 185delAG mutation, 2 were third-generation US-born, 1 had grandparents born in

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**Table 1. Number of BRCA1 Mutation Carriers and Estimated Prevalence Among Women With Breast Cancer, by Race/Ethnicity, Ashkenazi Jewish Ancestry, Age, and Family History**

<table>
<thead>
<tr>
<th>Category, No. Tested/No. Positive</th>
<th>Prevalence (95% CI), %</th>
<th>Category, No. Tested/No. Positive</th>
<th>Prevalence (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic (n = 393)</td>
<td></td>
<td>African American (n = 341)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>232/18 161/3</td>
<td>178/8 163/0</td>
<td>201/2 243/1</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>56/5 0/1</td>
<td>178/8 163/0</td>
<td>161/3 243/1</td>
</tr>
<tr>
<td>35-49</td>
<td>81/8 75/1</td>
<td>63/3 64/0</td>
<td>148/3 163/0</td>
</tr>
<tr>
<td>50-64</td>
<td>95/5 86/2</td>
<td>85/0 99/0</td>
<td>118/0 0/0</td>
</tr>
<tr>
<td>35-64</td>
<td>176/13 161/3</td>
<td>148/3 163/0</td>
<td>160/1 243/1</td>
</tr>
<tr>
<td>Family historyd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>120/13 0/0</td>
<td>107/3 4/0</td>
<td>119/1 3/0</td>
</tr>
<tr>
<td>No</td>
<td>112/5 161/3</td>
<td>71/5 159/0</td>
<td>81/1 240/1</td>
</tr>
<tr>
<td>Non-Hispanic Whites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ashkenazi Jewish (n = 41)</td>
<td>38/8 3/0</td>
<td>454/13 54/1</td>
<td>2.2 (0.7-6.9)</td>
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<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>3/2 0/0</td>
<td>86.7 (15.4-95.7)</td>
<td>7.2 (3.3-15.2)</td>
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<td>35-49</td>
<td>12/3 1/0</td>
<td>95.1 (1.8-38.1)</td>
<td>5.9 (1.2-25.2)</td>
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<tr>
<td>50-64</td>
<td>23/3 2/0</td>
<td>4.8 (1.2-18.0)</td>
<td>0.3 (0.1-0.9)</td>
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<td>35-64</td>
<td>35/6 3/0</td>
<td>6.4 (2.2-17.2)</td>
<td>1.9 (0.4-7.6)</td>
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<tr>
<td>Family historyd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27/5 0/0</td>
<td>18.5 (7.9-37.5)</td>
<td>2.7 (1.4-5.1)</td>
</tr>
<tr>
<td>No</td>
<td>11/3 3/0</td>
<td>4.3 (1.0-16.9)</td>
<td>2.0 (0.4-10.2)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

a See text for definitions of patient categories A and B.

b The 2 carriers in category A were Vietnamese and Korean; the 1 carrier in category B was Japanese.

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Mexico, I was born in Mexico, and I was born in Ecuador.

In African Americans, 25% of mutations were frameshift, 38% missense, 13% nonsense, and 25% splice. The only recurrent mutation was C61Y in the ring-finger canonical domain (n = 3). Other than R1751X, which was also found in Asian American and non-Ashkenazi non-Hispanic white patients, and IVS5-11T>G, which was also found in African American and non-Ashkenazi non-Hispanic white patients, all other mutations in African American patients were unique. The 3 mutations identified in Asian Americans were nonsense mutations. All mutations identified in Ashkenazi Jewish patients were common frameshift changes, including 185delAG (n = 7) and 5382insC (n = 1). In other non-Hispanic white patients, 36% of mutations were frameshift, 14% missense, 29% nonsense, and 21% splice; none were recurrent.

**COMMENT**

In this population-based series of women with breast cancer diagnosed at age younger than 65 years, estimated prevalence of pathogenic BRCA1 mutations was highest in Ashkenazi Jewish patients (8.3%) followed by Hispanics (3.5%), non-Hispanic whites (2.2%), African Americans (1.3%), and Asian Americans (0.5%). In young patients diagnosed before age 35 years, the prevalence was particularly high in African Americans (16.7%).

Few studies have examined BRCA1 mutations in racial/ethnic minority patients with breast cancer,21,22 and most prevalence estimates have been based on small numbers of carriers. Consistent with the present study, lower prevalence rates in black patients compared with white patients were reported in 2 other population-based series of patients with breast cancer. A study in patients younger than 74 years from North Carolina identified no carriers among 88 blacks, and the prevalence among 120 white patients was estimated at 3.3%.23 In patients aged 35 through 64 years from Seattle, Washington, the prevalence rates were 1.4% and 2.9% for black compared with white patients, respectively,24 and thus slightly higher than the present estimates for patients aged 35 through 64 years (0.5% and 1.9%, respectively).

Lower prevalence among African American compared with white patients also has been observed in
clinical series of patients. In 2 such series, prevalence estimates were 16% and 31% in African American and white patients, respectively, from families with 2 or more affected relatives and 3% and 11%, respectively, in those diagnosed at age 45 years or younger. The latter estimate for African Americans, however, was based on only a single carrier. In contrast, a large series of high-risk patients estimated a similar prevalence in patients of African or European ancestry. Other studies in African American women did not include other racial/ethnic groups for direct comparison.

Of particular interest in the present study is the 2-fold higher prevalence in young African American patients compared with young non-Hispanic white patients (16.7% and 7.2%, respectively). Confirmation of this finding is needed. Since certain features of breast cancer in African Americans (ie, young age at diagnosis, high tumor grade, and negative estrogen receptor status) are also common features of BRCA1-associated breast cancers, it has been suggested that BRCA1 mutations may contribute to the higher breast cancer incidence in young African Americans compared with other racial/ethnic groups.

Previous reports of BRCA1 mutations in patients with breast cancer and of Spanish origin are based largely on clinical series of patients from high-risk families in Spain, Chile, Mexico, and Colombia. Most of these studies identified fewer than 7 carriers. Only 3 studies to date have reported on BRCA1 mutations in Hispanic patients living in the United States, and they were also limited to high-risk patients. A population-based study from Spain reported prevalence of 0.7% based on a single carrier in 136 patients with breast cancer diagnosed at age younger than 46 years, which is considerably lower than the prevalence of 3.5% found in the present study of 393 Hispanic patients. The higher prevalence in Hispanics compared with non-Hispanic whites is in large part due to the presence of 185delAG in 5 of 21 carriers (24%). This mutation was also the most common BRCA1 mutation in Hispanics from Los Angeles, observed in 4 of 25 carriers (16%). Similarly, 185delAG was the most common mutation in the Spanish Breast Cancer Consortium, found in 10 of 60 carriers (16%). Other studies in Spain and Chile, and in Hispanics from Colorado, also have identified 185delAG mutations. We found this mutation in 2 patients with origin in Mexico and 1 patient born in Ecuador. The presence of this mutation in populations of Spanish origin may reflect unrecognized Jewish ancestry.

Data on BRCA1 mutations in Asian patients with breast cancer are sparse. Prior studies have included a broad range of Asian ethnicities, including Chinese, Japanese, and Fijians, which are the 3 Asian populations with the highest representation in the present study. We found a prevalence of 0.5%, based on only 3 carriers (1 Japanese, 1 Korean, 1 Vietnamese) identified in 444 patients tested. Similarly, in patients younger than 35 years, the prevalence was lowest in Asian Americans (2.4%) as compared with other racial/ethnic groups. A considerably higher prevalence of 7% to 8% has been reported for Chinese women from Singapore with early-onset breast cancer. Earlier data on BRCA1 mutations in each category of race/ethnicity and found that they were similar in age at diagnosis. Due to possible insensitivity of the laboratory tests used in the study, we may not have detected all BRCA1 mutations. A 2-dimensional gel test and exon grouping analysis were used to test the majority of patients. The former method has performed well in a validation study in which direct DNA sequencing was used as the standard. Similarly, exon grouping analysis has been validated and
compared favorably to full-sequence analysis (sensitivity of 97.4% in detecting BRCA1 and BRCA2 sequence changes) (A.M., unpublished data, 2007). Nevertheless, both mutation tests are likely to miss large deletions, genomic rearrangements, and certain other types of gene inactivation. Thus the prevalence estimates may be somewhat low. In addition, this report focused on BRCA1 mutations only, because mutation testing for BRCA2 will not be completed until 2008. The prevalence of BRCA2 mutations as well as of unclassified variants in BRCA1 and BRCA2 may vary by race/ethnicity and will be evaluated separately in this population-based series of patients with breast cancer.

The present study included multiple racial/ethnic groups, therefore allowing direct comparison of carrier prevalence estimates. Since certain mutations may be unique to specific populations, the full spectrum of mutations needs to be determined. Such information may facilitate mutation screening in a clinical setting and is needed to guide resource allocation for genetic testing, genetic counseling, and planning of preventive interventions in all population subgroups.

Author Contributions: Dr John had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: John, Miron, Li, West, Whittemore. Acquisition of data: John, Miron, Phipps, Li, West. Analysis and interpretation of data: John, Miron, Gong, Felberg, Li, Whittemore. Drafting of the manuscript: John, Miron. Critical revision of the manuscript for important intellectual content: John, Miron, Gong, Phipps, Felberg, Li, West, Whittemore. Statistical analysis: Gong, Felberg, Li, Whittemore. Obtained funding: John, Li, West. Administrative, technical, or material support: Miron, Phipps, Felberg, Li, West. Study supervision: Miron, Li, West, Whittemore.

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REFERENCES


