Editorial

Genetics in Clinical Cancer Care: A Promise Unfulfilled among Minority Populations

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With completion of the Human Genome Project, many in the medical community hoped for new opportunities for more effective cancer control through use of genetics in clinical care. Several susceptibility genes for common cancers had been identified and individuals with family histories of cancers such as breast, ovary, and colon were expected to have a more precise estimation of their risk through genetic testing. Many professional organizations advocated use of genetic testing in the context of a comprehensive cancer risk assessment, and practitioners were encouraged to refer patients to centers with adequate educational, counseling, research, and follow-up resources (1). Programs were implemented to offer genetic counseling, and educational programs were initiated for health care professionals on psychosocial and ethical issues surrounding genetic testing. Ten years after *BRCA1* was identified as a major breast cancer susceptibility gene, the promise of genetic testing for familial breast cancer risk is unrealized for the majority of women (2). The spectrum of mutations and characteristics of individuals with mutations among ethnic minorities remain undefined. In addition, lack of full protection against genetic discrimination has limited the clinical utility of *BRCA* testing.

In this issue of *Cancer Epidemiology Biomarkers & Prevention*, Pal et al. (3) report on 10 African American women with early-onset breast cancer who were screened for *BRCA1* and *BRCA2* mutations. Of the 58 women identified in the hospital-based tumor registry who were eligible for the study, 26 (45%) could be contacted but only 10 (17%) women consented to be tested. Thus, only a small fraction of these high-risk women completed the process of genetic testing. Of significance, 4 of the 10 women tested were found to carry deleterious mutations of the *BRCA1* or *BRCA2* genes, including a previously described ancestral mutation, *BRCA1* 943ins10 (4). A review of the pedigrees reveals strong family histories of breast cancer among first-degree and second-degree relatives in 3 of the women, which is consistent with previous reports. This is a rather small study; we and others have reported previously the occurrence of recurrent mutations in African American families and have described a unique mutation spectrum (5-8). In the largest study published to date, Myriad Genetics Laboratory described the results of 10,000 consecutive *BRCA1* and *BRCA2* gene sequence analysis performed in their U.S. laboratory (9). Although only a small proportion of individuals tested (1.6%) reported African ancestry, they found that mutations were as prevalent in high-risk women of African and non-Ashkenazi ancestries as those of European ancestry. The probability of identifying deleterious mutations was related to personal and family history of cancer. Thus, the few reports in African American families have confirmed (*a*) a unique mutation spectrum; (*b*) that mutations are as prevalent in high-risk women of African ancestry as those of European ancestry; and (*c*) that specific features of personal and family history can be used to identify individuals likely to benefit from *BRCA* testing. Nonetheless, the paucity of existing data in ethnic minorities deserves greater attention of the scientific community if we are to meet the needs of the ethnically diverse U.S. populations.

The Open Access Online Breast Cancer Mutation Database serves as a repository for information regarding identified sequence variations in the *BRCA1* and *BRCA2* gene and nearly 2,000 distinct mutations and sequence variations have been deposited in the database (10). As summarized in Table 1, African Americans are more likely to have variants of unknown significance reported, whereas there is very little data for other ethnic groups. In a recent review of 155 high-risk families, including 43 African American families with $\geq$2 primary relatives with breast and/or ovarian cancer ascertained in our cancer risk clinics, the prevalence of deleterious *BRCA1* or *BRCA2* mutations was 45% (11). Although not statistically significant, the prevalence of deleterious *BRCA1* mutations in the African American families was roughly half of that in the non-Hispanic White families (16.3% versus 30.8%), whereas the incidence of *BRCA2* mutations was about the same (11.6% versus 15.4%). The Ashkenazi Jewish families had even higher rates of both mutations than the non-Hispanic White families (41.4% for *BRCA1* and 27.6% for *BRCA2*). Of more significance, African Americans had a higher rate of variants of unknown significance (44% versus 10%; $P < 0.001$). Thus, more than any other racial/ethnic group, African Americans are more likely to get ambiguous results after genetic testing.

The overall genetic diversity in people of African ancestry is well demonstrated. Wagner et al. (12)

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Table 1. Summary of mutations in the Open Access Online Breast Cancer Mutation Database on select minority populations

	Total reports	Deleterious mutations	Polymorphisms	Unclassified variants	Deleterious/unclassified variants
BRCA1 mutation survey					
Total of the following populations	183	87	5	91	0.96
African American	56	14	3	39	0.36
Hispanic	10	3	1	6	0.5
Asian	82	46	1	35	1.3
Native American	35	24	0	11	2.2
Asian subpopulations					
Vietnamese	0	0	0	0	NA
Japanese	0	0	0	0	NA
Chinese	20	3	9	8	0.38
Indian	25	14	7	4	3.5
Korean	1	0	0	1	0
BRCA2 mutation survey					
Total of the following populations	539	102	5	432	0.24
African American	185	15	0	170	0.09
Hispanic	20	5	0	15	0.3
Asian	184	41	1	142	0.29
Native American	150	41	4	105	0.4
Asian subpopulations					
Vietnamese	1	0	0	1	0
Japanese	10	4	0	6	0.68
Chinese	9	2	0	7	0.29
Indian	9	4	0	5	0.8
Korean	0	0	0	0	NA

reported previously high frequencies of *BRCA2* variants in 21 unrelated African controls, and 33 of 45 (73.3%) of the sequence variants were unique to African populations. In a recent study of Nigerian breast cancer patients ages ≤40 years, unselected for family history, we also observed *BRCA1* or *BRCA2* sequence variations in 29 of 39 (74%) of patients, with 69% having sequence variations in *BRCA2* (13). In this breast cancer cohort, unselected for family history, only one protein-truncating mutation in *BRCA2* (3034del4) was observed. However, a significant proportion of the variants detected were rare non-protein-truncating *BRCA2* alleles not observed in 74 normal controls. A protein modeling software predicted that 11 of the different *BRCA1/BRCA2* variants of unknown significance identified are potentially deleterious. It is conceivable that the significant genetic variation in *BRCA1* and *BRCA2* observed in breast cancer cases contributes to breast cancer risk in populations of African ancestry. Nonetheless, these variants cannot be used in the clinical management of high-risk patients until they are further categorized into high-risk or low-risk alleles. Unfortunately, classification using the models such as the one recently developed by Goldgar et al. (14) is not feasible in most cases. Direct epidemiologic observations to show cosegregation with disease require sampling of additional individuals in the pedigree, and demonstrating frequency of the rare alleles in cases and controls require thousands of samples that are not readily available for minority populations. Variants of unknown significance can often be classified as neutral on the basis of single observations if they cooccur (*in trans*) with deleterious mutations, but this is also problematic in minority populations because we do not have a large enough database to make the assumption that homozygotes and compound heterozygotes are embryonically lethal or exceedingly rare in these populations. In a relatively small cohort of 60 Korean patients with early-onset breast cancer, 9 patients had 11 deleterious mutations (6 in *BRCA1* and 5 in *BRCA2*) and 7 variants of unknown significance (15). Interestingly, two patients were compound heterozygotes with deleterious mutations in both *BRCA1* and *BRCA2* genes.

The uncertainty about the exact penetrance for breast and ovarian cancer among *BRCA1/BRCA2* mutation carriers further complicates genetic counseling in ethnic minorities. The highest penetrance estimates were derived from the predominantly multicase families of European ancestry from the Breast Cancer Linkage Consortium, whereas subsequent population-based studies derived much lower estimates, although 95% confidence intervals are large (16-18). In a pooled analysis of 22 studies of >8,000 breast and ovarian cancer cases from 12 different northern European or North American countries, unselected for family history, the cumulative risk of breast cancer by age 70 years was 65% (95% confidence interval, 44-78%) for *BRCA1* and 45% (95% confidence interval, 31-56%) for *BRCA2* (19). Several factors influence penetrance, including modifying genetic and environment factors, and these are likely to be different in different cultural/ethnic backgrounds. For example, in the study by Pal et al., there were no ovarian cancers in the mutation-positive families, whereas most of the Korean patients with identifiable mutations had no family history of cancer (3, 15). In our studies, we have found that reported family history of ovarian cancers was different among African American and non-Hispanic White families, which suggests that even in the background of *BRCA1* and *BRCA2*

mutations ovarian cancer rates are lower in individuals of African ancestry. Larger studies in minority populations are needed to characterize potential modifying factors to arrive at more precise individual risk estimates for minority patients seeking genetic counseling.

The issue of penetrance is particularly important given the touted benefits of genetic testing in identifying *BRCA1* and *BRCA2* mutation carriers. Mutation carriers are counseled about the benefit of prophylactic surgery to reduce their risks. Prophylactic bilateral mastectomy can be expected to have an efficacy of >90% in high-risk women (20, 21). Although prophylactic mastectomy is efficacious, it is only a minority of high-risk women who choose this option for risk reduction and previous studies on health behaviors suggest that African American women are unlikely to consider such prevention approaches (22). The use of intensive surveillance including magnetic resonance imaging of the breast is very promising and may be a more acceptable intervention in the majority of high-risk women (23). Given the levels of risks of ovarian cancer, the >95% efficacy of risk-reducing bilateral salpingo-oophorectomy provides a stronger rationale to identify *BRCA1* and *BRCA2* mutation carriers, as majority of women who test positive are more willing to consider prophylactic oophorectomy (24, 25). Unfortunately, there are very little data on the degree of risk reduction with any of these interventions for minority women.

Although increased efforts devoted to defining the spectrum and penetrance of *BRCA1* and *BRCA2* mutations in African American families are needed, fear of genetic discrimination and stigmatization remains a major barrier to use of genetic services (26). Individuals often make choices in a greater social context and there are economic considerations that limit the adoption of appropriate prevention or surveillance recommendations once these high-risk families are identified. Many professional organizations, including the American Association for Cancer Research, endorse policies of nondiscrimination for mutation carriers, but too many individuals who could potentially benefit from genetic testing remain fearful of insurance discrimination. Data on reimbursement and insurability for prophylactic surgery, particularly prophylaxis, are sparse. A recent study has shown that ~50% of insurance agencies have no policy regarding prophylactic surgery in mutation carriers (27). That notwithstanding, a retrospective review of hospital billing record of 38 *BRCA1* or *BRCA2* mutation carriers undergoing risk-reducing prophylactic surgeries (mastectomy or oophorectomy) found that a total of 97% surgeries were covered, less deductible fees and copayments (28). Unfortunately, there are no data on rates of prophylactic surgery among the >40 million Americans who are uninsured or underinsured and that could add to the burden of being identified as a mutation carrier.

In the post–genome age, genetics will play an increasingly important role in the management of cancer patients and individuals at risk for cancer. Genetic counseling and testing is best provided by a team of health care professionals dedicated to working with mutation carriers, and special efforts should be made to extend resources to minority groups. These professionals must have a firm understanding of the complexities of genetic testing, the available medical and surgical options, and the psychosocial issues that contribute to cancer risk and management. For minority families, one cannot underestimate the need for more studies that will provide much needed information to aid these women and their health care providers make critical decisions about risk-reducing options available to them.

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