ORIGINAL ARTICLE

Racial differences in the incidence of BRCA1 and BRCA2 mutations in a cohort of early onset breast cancer patients: African American compared to white women

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Purpose: To evaluate the frequency and distribution of BRCA1 and BRCA2 mutations in a cohort of young women with breast cancer and to compare the distribution of mutations as a function of race.
Methods: After IRB approved informed consent, 170 white women and 30 African American women with known breast cancer diagnosed at a young age (45 years or less) underwent complete sequencing of the BRCA1 and BRCA2 genes. Each cohort represented approximately 40% of women of the same ethnic background aged 45 years or younger in a breast cancer database.
Results: Of the 200 patients tested, 131 (65%) had wild type mutations, 34 (17%) had deleterious mutations, and 35 (18%) had variants of uncertain significance. There were no significant differences between the white and African American cohorts regarding the percentage of deleterious mutations (17% *v* 17%). However, most African American patients had mutations in BRCA2 (4/5, 80%), while most mutations in the white cohort were in BRCA1 (20/29, 69%). In addition, 46% of the African American women had variants of uncertain significance, compared to only 12% of the white cohort.
Conclusions: Young African American women with breast cancer have a similar frequency of deleterious mutations as white women, but have a significantly higher frequency of variants of uncertain significance. Review of these variants revealed that the majority were unlikely to be associated with disease risk or were likely to be polymorphisms. The implications for genetic testing and counselling in young women with breast cancer are discussed.

Breast cancer is a significant public health issue, with over 200 000 cancers diagnosed each year in American women. Although most breast cancers are diagnosed in postmenopausal women, approximately one third are diagnosed in the premenopausal years.[1] Breast cancer in young women (YBC) has been shown to be clinically more aggressive.[2–8] While YBC has no specific age cut-off, a reasonable upper limit is 45 years of age, so most affected individuals are in the premenopausal years. It is likely that the underlying molecular and genetic basis of breast cancer in younger women is distinct from that of breast cancer diagnosed later in life. This partly explains the unique clinical and biological behaviour of YBC which clearly develops in an entirely different hormonal milieu than postmenopausal breast cancer. While most pre and postmenopausal breast cancers are sporadic (not associated with a strong family history or mutation in BRCA1/2), YBC is much more likely to be genetically linked.[9–12] Hereditary forms of the disease have unique clinical, molecular, and biological features, which may require different screening and management strategies.[12–16]

In addition to the unique hereditary nature of YBC, there are also unique racial differences. Although the incidence of breast cancer in African American women is lower than in white women, a higher percentage of African American women are diagnosed at a younger age compared to white women.[17–19] In a recent study of conservatively treated African American women, we found a younger age of onset of the disease and a higher local-regional relapse rate, which was independent of age.[20] Several other studies have also reported poorer overall survival, disease free survival, and local-regional control rates in African American women.[17 21 22] In an attempt to identify the molecular and biological factors associated with the more aggressive behaviour of breast cancer in African American women, several studies have been conducted which report higher prevalence of somatic p53 alterations in primary breast tumours of African American women, differences in breast density, decreased expression of isoforms of ER receptors, and alterations in other molecular and genetic markers.[17 23]

The contribution of BRCA1 and BRCA2 mutations to the development of YBC in African American women has not been extensively evaluated.[24] Studies to date have demonstrated some unique mutations in African American women, but there is a paucity of data on the frequency and distribution of BRCA1 and BRCA2 mutations in young African American women with breast cancer. Over the past several years, we have been recruiting young women with early stage breast cancer undergoing breast conserving therapy for genetic testing (BRCA1 and BRCA2) as part of ongoing prospective studies. The selection of patients for these studies is unique in that we have been recruiting patients based not on a strong family history or a priori probability of familial breast cancer, but on having a diagnosis of breast cancer at a young age (45 years of age or younger). To date, we have recruited and tested over 200 women with YBC with complete sequencing of the BRCA1 and BRCA2 genes. In the current report, we present the results of 170 Caucasian and 30 African American patients who underwent complete sequencing of the BRCA1 and BRCA2 genes.

Abbreviation: YBC, breast cancer in young women

METHODS

As part of previously described studies we have actively recruited young women seen at our facility for complete sequencing of the BRCA1 and BRCA2 genes. These women were recruited solely on the basis of having early stage, early onset breast cancer, and were not selected based on family history or genetic predisposition to breast cancer. Our breast cancer database included 494 patients with early stage, early onset breast cancer (that is, age <46 years at diagnosis of first breast cancer), who were of African American (n = 71) or white (n = 423) ethnic background. Hispanic and Asian populations, which represented a very small portion of our database, were excluded from this analysis. Of this potential population of 494 patients, we have recruited and completed testing on 30 African American women (42% of the African American population in the database) and 170 white women (40% of the white population in the database).

After institutionally approved informed consent was obtained, all women underwent complete sequencing of the BRCA1 and BRCA2 genes as described elsewhere.[25] All clinical, radiographic, pathology, and demographic data, including detailed family history information, were entered into a computerised database. BRCA1 and BRCA2 mutations were classified as follows. Patients with known deleterious mutations in BRCA1 or BRCA2 were classified as having genetically linked breast cancer. Patients with changes in BRCA1 or BRCA2 that are not known to be deleterious and whose significance is unknown were classified as having variants of uncertain significance; these changes may contribute to disease risk or may be polymorphisms that are not associated with disease risk. Patients with known polymorphisms or no mutations detected on complete sequencing of BRCA1 and BRCA2 were classified as having sporadic or wild type disease.

Table 1 Patient characteristics

	White	African American	p
n	170	30	
Age	37.8	36.8	
Jewish ancestry	31	0	0.001
Tumour size (cm)	1.70	2.2	0.06
Nodal status			
Negative	98 (58%)	17 (56%)	0.76
Positive	31 (18%)	7 (23%)	
Unknown/no dissection	41 (34%)	6 (20%)	
Histology			
Infiltrating ductal	126 (74%)	20 (69%)	0.05
Intraductal	20 (11%)	5 (16%)	
Lobular	8 (5%)	1 (3%)	
Tubular	2 (1%)	1 (3%)	
Medullary	12 (7%)	1 (3%)	
Adjuvant chemotherapy	22 (42%)	15 (50%)	0.34
Adjuvant hormonal	24 (14%)	4 (13%)	0.92
Detection of primary tumour			
Physical exam (no mammogram)	25 (14%)	3 (10%)	0.09
Mammogram alone (non-palpable)	30 (17%)	9 (32%)	
Physical exam and mammography positive	73 (43%)	14 (50%)	
Physical exam positive with false negative mammogram	42 (25%)	2 (7%)	
ER status			
Negative	60 (35%)	15 (50%)	0.05
Positive	70 (41%)	7 (23%)	
Unknown	40 (24%)	8 (27%)	
PR status			
Negative	64 (38%)	15 (50%)	0.16
Positive	59 (35%)	7 (23%)	
Unknown	47 (27%)	8 (27%)	

RESULTS

Of the 200 patients studied, 170 were Caucasian and 30 were African American. A patient was classified as African American if that is how they described themselves, in accordance with current standards. As noted above, this population represents approximately 40% of patients under the age of 46 in the Department of Therapeutic Radiology breast cancer database. The mean ages of 41.7 for the African American cohort and 40.9 for the Caucasian cohort did not differ significantly from each other and were not significantly different from the mean age of the population in the database under the age of 45.

Table 1 summarises the clinical and pathological variables for both cohorts. Consistent with other studies and our previous reports, the African American patients presented with slightly larger primary tumours. It is of note, however, that the African American patients were more likely to present with a tumour which was detected on routine mammography, while white women were more likely to present with physical findings and a false negative mammogram. This may be related to the relatively increased density of breast tissue in younger white women. There was a slight difference in histological presentation due to a higher percentage of medullary tumours in the white population. There were no other notable differences between the African American and white populations in the current study. The family history patterns were notably similar in the two populations.

The distribution of BRCA1 and BRCA2 mutations is summarised in table 2. As regards known deleterious mutations, there were no significant differences in the two populations. However, white women were slightly more likely to have deleterious BRCA1 mutations, while the African American women were more likely to have deleterious BRCA2 mutations. Of the five deleterious mutations in the African American women, only one was BRCA1, while four were BRCA2. In contrast, of the 28 deleterious mutations in the white women, most (19 or 68%) were BRCA1.

It should be noted that of the 28 deleterious mutations in the white women, 14 were from the 31 women of Jewish ancestry. The incidence of deleterious mutations in African American women (5/30 or 17%) did not significantly differ from the incidence of deleterious mutations among the non-Jewish white women (15/139 or 11%).

A significant difference was noted in the two populations with respect to variants of uncertain significance. Specifically, the African American population had a significantly higher frequency of variants of uncertain significance, particularly in BRCA2. Overall, this resulted in only 11 of the 30 African

Table 2 Results of sequencing of BRCA1 and BRCA2

Mutation	White	African American	p
n	170	30	
Deleterious BRCA1 or BRCA2	29 (17%)	5 (17%)	0.95
Deleterious BRCA1	20 (11%)	1 (3%)	0.16
Deleterious BRCA2	9 (5%)	4 (13%)	0.09
BRCA result wild type	120 (70%)	11 (37%)	0.0001
Variant uncertain significance, BRCA1	8 (5%)	3 (10%)	
Variant uncertain significance, BRCA2	13 (8%)	11 (37%)	
Deleterious BRCA1	20 (11%)	1 (3%)	
Deleterious BRCA2	9 (5%)	4 (13%)	

American patients (36%) testing as wild type, compared to 120 of the 170 white patients (70%). This difference was highly significant at a p level of <0.001.

In an effort to determine the clinical implications of these variants of uncertain significance, we looked at the detailed family history and the risk of secondary malignancies as a function of the type of BRCA mutation. As shown in table 3, the variants of uncertain significance did not appear to be associated with a strong family history or with the second malignancies in this population. In fact, with respect to both strong family history of breast and/or ovarian cancers as well as development of second breast cancers, the variants of uncertain significance appear to be similar to the wild type genotype in this selected population.

Table 4 lists all the variants of uncertain significance together with race and other related information. There does not appear to be a clear association with disease risk for most variants of uncertain significance. Based on available data from the reported literature, the Breast Cancer Information Core, and reports from Myriad Genetics, each of the variants is classified as either a probable polymorphism, unlikely to be significant, or uncertain. The classification of unlikely to be significant is due to the fact that the variant has been observed before in patients with a known deleterious mutation in the same gene or has been found not to segregate with disease in previous families. These data do not prove that these variants are polymorphisms but increase the likelihood that they are not disease causing.

DISCUSSION

Several recent studies have demonstrated the unique clinical and biological behaviour of breast cancers in African American women.[17 21 26] The weight of evidence clearly demonstrates more aggressive biological behaviour as well as an earlier onset of disease in this group. A recent study by Jones *et al* demonstrated a higher incidence of somatic p53 mutations in primary tumour specimens from African American breast cancer patients.[23] Several studies have evaluated other biological differences in breast cancer in African American women, which were summarised in a recent editorial by Newman, who concluded that ''the door to the improved understanding of ethnicity related variation in breast carcinoma risk and outcome has now been wedged open by the powerful tools of molecular oncology''.[27]

The development of YBC is a common problem with substantial clinical, epidemiological, social, and psychological implications. The relatively recent identification of the BRCA1 and BRCA2 genes has contributed substantially to our understanding of the contribution of these genes to familial breast cancer.[28–30] Although BRCA1 and BRCA2 mutations have been extensively studied in some populations, the frequency of mutations in African American populations has not.[24 31–35] Furthermore, most studies evaluating BRCA1/2 mutations tested highly selected populations with strong family histories or with suspected genetic predisposition to breast cancer. It is therefore difficult to assess the contribution of mutations to the general problem of breast cancer diagnosed at a young age from these highly selected populations.

In the current study we did not select patients based on family history or genetic predisposition. These patients were recruited from our database of patients seen in the Department of Therapeutic Radiology for early stage, early onset breast cancer. Although selection biases are always a potential issue, it should be noted that the distribution of African American and white patients in this study did not significantly differ from that in our database. Specifically, we recruited 30 of 71 African American women in the database (42%) compared to 170 of 423 white women (40%). Therefore, our sample is representative of the overall population. Furthermore, there were no significant differences between the African American and white populations with respect to family history, which provides additional evidence that the sample was not biased regarding familial predisposition.

One notable finding from our study is that the frequency of known deleterious mutations in the young African American population did not significantly differ from that of the white population. While larger population studies are clearly indicated, these data do not suggest that a higher frequency

Table 3 Correlation of BRCA type with second malignancies and family history

			p
Second cancers			
WT	28/131 (21%)	}	
BR1_UNC	2/11–18%	}	
BR2_UNC	4/24 (16%)	}	0.001
BR1_DEL	13/21 (62%)	}	
BR2_DEL	6/13 (46%)		
Moderate to strong family history			
WT	23/131 (18%)	}	
BR1_UNC	2/11 (18%)	}	
BR2_UNC	2/24 (8%)	}	0.002
BR1_DEL	12/21 (57%)	}	
BR2_DEL	6/13 (46%)		

Table 4 Variants of uncertain significance

Patient ID	Race	BRCA1 or 2	Variant	Classification
1	White	BRCA2	K3326X	PROB_POLY
2	White	BRCA2	C197C and K3326X	PROB_POLY
3	White	BRCA2	Y42C and I505T	UNLIKELY
4	White	BRCA2	V2728I	UNLIKELY
5	White	BRCA1	R1347G	PROB_POLY
6	White	BRCA2	P655R	UNCERTAIN
7	White	BRCA2	A2951T	PROB_POLY
8	White	BRCA1	R1203Q	UNCERTAIN
9	White	BRCA2	K3392T	PROB_POLY
10	White	BRCA2	M1137T and S2247G	UNLIKELY
11	White	BRCA1	R1347G	PROB_POLY
12	White	BRCA1	Q804H	UNCERTAIN
13	AA	BRCA2	A2466V	PROB_POLY
14	White	BRCA2	K3326X	UNLIKELY
15	AA	BRCA2	Q2384K V3079I	UNCERTAIN
16	AA	BRCA2	D1420Y	UNLIKELY
17	White	BRCA2	A1170V	UNCERTAIN
18	AA	BRCA2	A248T	UNCERTAIN
19	White	BRCA1	R1347G	PROB_POLY
20	White	BRCA1	R496H	PROB_POLY
21	White	BRCA1	R1347G	PROB_POLY
22	White	BRCA2	G1529R	UNCERTAIN
23	AA	BRCA2	A2446V	UNLIKELY
24	White	BRCA1	Q1452G	UNCERTAIN
25	AA	BRCA1	T779Ala	UNCERTAIN
26	AA	BRCA2	I1364L and H2116R	UNLIKELY
27	AA	BRCA1	T37R	UNCERTAIN
28	AA	BRCA2	Q713L	UNLIKELY
29	AA	BRCA2	D935N	UNCERTAIN
30	AA	BRCA2	G3212R and Q713L	UNLIKELY
31	AA	BRCA2	Lys1765Asn	UNLIKELY
32	AA	BRCA2	Q2384K and V30791	UNLIKELY
33	AA	BRCA1	T790A	UNCERTAIN
34	White	BRCA2	IVS20-16C>G	UNCERTAIN
35	White	BRCA2	L1356L	PROB_POLY

AA, African American; PROB_POLY, based on available data, these variants are likely to be polymorphisms; UNLIKELY, based on available data, these variants are unlikely to be associated with disease risk (see Discussion); UNCERTAIN, based on available data, the significance of these variants remains uncertain.

of deleterious mutations accounts for the younger age of onset of breast cancer in African American women. However, the relative distributions of mutations did differ, with most African American women having mutations in BRCA2 compared to BRCA1. A recent study by Gao *et al* also reported a higher frequency of BRCA2 mutations compared to BRCA1 mutations in African American breast cancer families.[24] In that study, four of five deleterious mutations and four of six missense variants were BRCA2. However, in another recent study in 10 African American families, Pal *et al* observed deleterious mutations in BRCA1 in two families and BRCA2 in two families.[35] While complete sequencing of both genes remains the standard, these results could have some implications with respect to the priority of which gene to sequence first in African American women.

Another significant finding from the current study is the high frequency of variants of uncertain significance in the African American population. It is difficult to determine what, if any, contribution these variants make to the development of breast cancer in these young women. The table summarising all the variants (table 4), as well as our analysis of family history and other cancers developing in individuals with variants of uncertain significance, however, suggest that many of these variants may not be associated with disease risk. In fact, the phenotype of the variants of uncertain significance was much more consistent with the wild type phenotype than with those of the deleterious mutations in our selected population. Another study by Fackenthal *et al* also observed a higher frequency of BRCA2 variants of uncertain significance in a cohort of young Nigerian breast cancer patients.[36] Of 39 patients, 74% had variants of uncertain significance in BRCA1 or BRCA2.

The possibility that deleterious mutations or variants of uncertain significance in BRCA1 or BRCA2 contribute to the earlier onset of breast cancer in African American women can not be confirmed or excluded from the data presented here. Larger, well designed population based studies will be required to determine the significance of these changes in the BRCA1 and BRCA2 gene in the earlier onset of breast cancer in these populations. The relatively high rate of variants and deleterious mutations in these young African American women, however, clearly warrants further investigation. With increasing numbers of women identified with these variants of uncertain significance, we will be able to better determine their clinical implications and use such data to appropriately counsel patients and their families.

We conclude that African American women with early onset breast cancer have a unique spectrum of mutations in BRCA1/2. The incidence of deleterious mutations in this population of young African American women with breast cancer did not differ significantly from that in young white women. However, more of the deleterious mutations appear to be in the BRCA2 gene. The frequency of variants of uncertain significance in the African American population also appears to be higher. However, correlation of these variants of uncertain significance with clinical indicators, including a strong family history of breast and/or ovarian cancer and the development of second malignancies, indicates that patients with these variants appear to be phenotypically similar to sporadic (wild type) patients in this selected population. Review of the literature and available data on these variants also suggests that these variants are less likely to be related to disease risk. However, further studies are clearly warranted to determine the clinical significance and implications of these variants of uncertain significance among all populations. Such data will further contribute to our understanding of the clinical implications of genetic changes in the BRCA1 and BRCA2 genes and aid in the counselling process.

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