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EPIDEMIOLOGY

The prevalence of *BRCA1* and *BRCA2* mutations among young Mexican women with triple-negative breast cancer

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Abstract Various guidelines recommend that women with triple-negative breast cancer should be tested for *BRCA1* mutations, but the prevalence of mutations may vary with ethnic group and with geographic region, and the optimal cutoff age for testing has not been established. We estimated the frequencies of *BRCA1* and *BRCA2 (BRCA)* mutations among 190 women with triple-negative breast cancer, unselected for family history, diagnosed at age 50 or less at a single hospital in Mexico City. Patients were screened for 115 recurrent *BRCA* mutations, which have been reported previously in women of Hispanic origin, including a common large rearrangement Mexican founder mutation (*BRCA1* ex9-12del). A *BRCA* mutation was detected in 44 of 190 patients with triple-negative breast cancer (23 %). Forty-three mutations were found in *BRCA1* and one mutation was found in *BRCA2*. Seven different mutations accounted for 39 patients (89 % of the total mutations). The Mexican founder mutation (*BRCA1* ex9-12del) was found 18 times and accounted for 41 % of all mutations detected. There is a high prevalence of *BRCA1* mutations among young triple-negative breast cancer patients in Mexico. Women with triple-negative breast cancer in Mexico should be screened for mutations in *BRCA1*.

Keywords Mexico · Triple-negative breast cancer · *BRCA1* · *BRCA2*

Introduction

Since 2006, breast cancer has been the leading cause of death from cancer in Mexican women, accounting for 15 % of cancer-related deaths and it is the second cause of death among women aged 30–54 [1, 2]. In Mexico, the ratio of mortality to incidence is twice that of the United States (37 vs. 19 %) [3]. It is predicted that in 2015, there will be 23,764 women diagnosed with breast cancer and 6591 will die from it in Mexico [4]. The mean age at diagnosis of breast cancer in Mexico is 50 years [5–8]. Breast cancers in Mexico are also characterized by a high proportion of the triple-negative subtype, which accounts for 23 % of all breast cancers [7]. This contrasts to the proportion in other countries as Canada, where this subtype comprises about 11 % of unselected breast cancer patients [9].

BRCA testing is not broadly available in Mexico and genetic cancer risk assessment services are not commonly provided. Barriers to implementing genetic counseling and testing for Mexican women include the costs of genetic testing and the lack of public insurance coverage for genetic services. There is limited awareness among providers concerning the benefits of genetic risk assessment and few

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clinicians have genetic counseling expertise. In Mexico, genetic testing for *BRCA* mutations is available only in the private sector through laboratories situated outside of the country.

A number of studies have evaluated the prevalence of *BRCA* mutations in breast cancer patients in several Latin American countries, including Argentina, Brazil, Chile, Colombia, Costa Rica, Mexico, Uruguay, and Venezuela [10–21]. The presence of founder mutations within a defined ethnic group enables rapid and low-cost screening, compared to the cost of the complete sequencing of both *BRCA* genes [22], but screening only for founder mutations is contingent on a high proportion of all mutations being recurrent. Founder mutations in *BRCA1* or *BRCA2* have been identified in several Latin American sub-groups, including women from Colombia [13] as well as in Mexican women in the USA [23–25] and in Mexico [18, 19].

The HISPANEL was developed as a genetic screening tool which incorporates 115 recurrent *BRCA* mutations observed in Hispanic women [18, 23–25]. It is estimated that, among Mexican women with breast or ovarian cancer, the sensitivity of the HISPANEL test is 68 %, compared to full-gene screening [18]. This test can be completed in 72 h at a cost of USD $20 per sample. Recently, we reported a *BRCA1* and *BRCA2* mutation in 27 % of 33 Mexican women with triple-negative breast cancers [18]. Because of the high prevalence of mutations seen in this small series, we sought to confirm the mutation frequency in a large series of unselected young Mexican women with triple-negative breast cancer.

Materials and methods

Patient population

We conducted a study of young Mexican women with triple-negative breast cancer treated at the National Cancer Institute in Mexico City. Patients diagnosed between January 2006 and January 2012 with triple-negative breast cancer at age 50 years or younger were identified through the hospital database. From a total of 484 patients, 362 were alive, 18 were deceased, and for 104 patients the vital status was unknown. We attempted to contact the living patients. Of these, we were able to contact 204, and the others were not available for follow-up. We excluded nine of them: five were older than 50 years of age at the time of diagnosis and four were not triple-negative breast cancer when the pathology report was re-reviewed. Patients were approached by the research coordinator to participate in the study during an out-patient visit to the hospital or at a scheduled study visit. The research coordinator described the study to the patient and informed her of the implications of genetic testing. After providing written informed consent, the patient was interviewed by the research coordinator for details about her medical and lifestyle history and her family history of cancer. The institutional review boards of the participating centers approved the protocol. A saliva sample was obtained for DNA extraction.

Laboratory methods

DNA was extracted from saliva samples using Oragene DNA extraction kits in the laboratory of Dr. Narod at Women's College Hospital in Toronto. An adequate amount of DNA was obtained for 190 of the 195 patients (97 %). Mutation analysis took place in the laboratory of Dr. Weitzel at City of Hope in Duarte, California, and in the laboratory of Dr. Narod at Women's College Hospital in Toronto. All DNA samples were screened by the HISPANEL assay, a 115 *BRCA* mutation panel developed from data from U.S. Hispanics [23, 25] other published data on *BRCA* mutations among Spanish, Hispanic, or South American populations, [26–33] and entries citing Hispanic ancestry in the Breast Cancer Information Core (http://research.nhgri.nih.gov/projects/bic/Member/index.shtml). The HISPANEL uses five multiplex reactions on the Sequenom® (San Diego, CA 92121) MassARRAY platform (MALDI-TOF MS) to detect insertions/deletions and point mutations, and a PCR assay for the *BRCA1* ex9-12del mutation. All deleterious mutations were confirmed by Sanger sequencing on an ABI capillary sequencer. Re-sequencing of the original stored sample was subsequently performed before reports were issued to the clinician(s) responsible for a given participant's care after counseling, as per the IRB-approved protocol.

Results

The median age of the patients at diagnosis was 43 years (range 23–50) and the mean age at interview was 50 years (range 23–65). All patients were diagnosed before the age of 50. Of the 190 patients, five breast cancers were screen-detected by mammography and the others were found by palpation. The median cancer size was 4 cm and 93 % of patients were stage II or above.

A mutation was found in 44 of 190 patients (23.2 %); 43 had a mutation in *BRCA1* and one had a mutation in *BRCA2* (Table 1). The prevalence of mutations was 30.3 % among women diagnosed at age 40 and under and was 18.3 % for women diagnosed from age 41 to 50 years. The average age of diagnosis in women with a *BRCA1* mutation was 38 years, compared to 41 years for the non-carriers ($p = 0.07$). Twenty of the 44 women (45 %) with a

Table 1 *BRCA1* and *BRCA2* mutations identified in Mexican triple-negative breast cancer patients

Patient	Gene	Exon	Mutation	Age of diagnosis	Family history of breast and ovarian cancer in first- and second-degree relatives
51,039	*BRCA1*	2	185delAG	34	No
53,191	*BRCA1*	2	185delAG	42	No
53,243	*BRCA1*	2	185delAG	46	No
51,088	*BRCA1*	11	2415delAG	38	Yes
53,188	*BRCA1*	11	2925del4	35	No
51,066	*BRCA1*	11	2925del4	37	No
51,084	*BRCA1*	11	2925del4	39	No
51,091	*BRCA1*	11	2925del4	42	Yes
53,239	*BRCA1*	5	330A > G (R71G)	31	No
53,273	*BRCA1*	5	330A > G (R71G)	34	Yes
53,271	*BRCA1*	5	330A > G (R71G)	38	No
51,071	*BRCA1*	5	330A > G (R71G)	42	Yes
53,252	*BRCA1*	5	3717C > T (Q1200X)	41	No
53,247	*BRCA1*	11	3878delTA	44	No
51,068	*BRCA1*	11	3878delTA	49	Yes
51,119	*BRCA1*	13	4446C > T (R1443X)	23	No
53,221	*BRCA1*	13	4446C > T (R1443X)	32	No
53,240	*BRCA1*	13	4446C > T (R1443X)	39	No
53,204	*BRCA1*	13	4446C > T (R1443X)	47	No
53,226	*BRCA1*	18	5242C > A (A1708E)	35	Yes
51,094	*BRCA1*	11	943ins10	37	Yes
51,103	*BRCA1*	11	943ins10	42	Yes
53,237	*BRCA1*	11	943ins10	45	No
51,093	*BRCA1*	11	943ins10	47	Yes
53,255	*BRCA1*	11	943ins10	48	Yes
53,186	*BRCA1*		del exon9-12	31	No
51,127	*BRCA1*		del exon9-12	32	Yes
53,178	*BRCA1*		del exon9-12	32	Yes
51,106	*BRCA1*		del exon9-12	33	No
51,061	*BRCA1*		del exon9-12	34	Yes
53,199	*BRCA1*		del exon9-12	35	Yes
53,205	*BRCA1*		del exon9-12	35	Yes
51,082	*BRCA1*		del exon9-12	38	No
53,249	*BRCA1*		del exon9-12	39	No
53,250	*BRCA1*		del exon9-12	40	Yes
51,080	*BRCA1*		del exon9-12	42	Yes
53,231	*BRCA1*		del exon9-12	42	No
53,206	*BRCA1*		del exon9-12	44	No
51,075	*BRCA1*		del exon9-12	45	No
53,270	*BRCA1*		del exon9-12	46	Yes
51,072	*BRCA1*		del exon9-12	47	Yes
53,253	*BRCA1*		del exon9-12	49	No
51,083	*BRCA1*		del exon9-12	50	Yes
51,085	*BRCA2*	11	2452C > T (Q742X)	46	No

mutation had a first-or second-degree relative affected with breast cancer and two reported a family history of ovarian cancer (4.5 %). Seven mutations were found in two or more families; together these seven recurrent mutations accounted for 39 of 44 mutations detected (89 %) (Table 1).

Discussion

We estimate the prevalence of *BRCA* mutations in young triple-negative breast cancer patients from Mexico to be 23 %. The great majority of the detected mutations (97.7 %) were in *BRCA1* ($n = 43$), only a single *BRCA2* mutation was found.

We restricted testing to women diagnosed under the age of 50, who comprise approximately 50 % of all breast cancers cases in the region [5–8]. At the time, the study was initiated, NCCN guidelines recommended testing for triple-negative breast cancer, be restricted to patients under the age of 51 years. However, given the high prevalence of mutations that we observed in the age group between 41 and 50 years (18.3 %), it is reasonable to consider testing for *BRCA* mutations in older women in Mexico. This is in concordance with changes to the NCCN guidelines, which have revised the recommendation for genetic testing for triple-negative breast cancer to patients under the age of 61 [34].

The 44 mutations reported in this study represent 11 different mutations. Of these, seven were seen more than once. The *BRCA1* ex9-12del large rearrangement was seen in 18 cases and accounted for 42 % of all mutations in the study. This is the most common reported founder mutation in Mexico [18, 24, 25], but has not been seen in other Latin American countries [11].

The *BRCA1* 943ins10 mutation was detected in five cases. This is the most commonly reported African founder mutation and is a Bahamian founder mutation [35–37]. It has been reported 34 times in the BIC database in individuals of African or Latin American descent [23, 38]. The *BRCA1* R71G mutation was seen in four cases. This is a common founder Spanish mutation [39] and has been recorded 36 times in the BIC database. The *BRCA1* 2925del4 mutation was also seen four times.

The *BRCA1* 185delAG mutation was seen in three cases, none of whom identified themselves as being of Jewish ancestry. This mutation is a common founder mutation in the Jewish population and recurrent among non-Jews, including Chilean, Peruvian, and Bahamian women [37, 40, 41]. The *BRCA1* 185delAG mutation is also common among high-risk breast cancer patients of Mexican descent in the United States (10 % of mutations) [23, 25]. The *BRCA1* R1443X mutation, seen four times, has been reported 131 times in the BIC database, mainly in women of Western European origin [38].

The *BRCA1* 3878delTA mutation, reported twice, has been identified in two Latin American women in the BIC database. The other mutations were seen once each. The Q1200X mutation is very common among Western Europeans. The A1708E mutation is a Spanish and Colombian founder mutation [27, 42].

Our study has several limitations. *BRCA1* and *BRCA2* mutations were limited to those that have been included in HISPANEL and we did not perform full sequencing. We estimate that HISPANEL will identify at least 68 % of all *BRCA1* and *BRCA2* mutations in Mexican women with breast cancer [18]. Screening with the HISPANEL for Mexican women is justifiable given the low cost. If full sequencing is completed, the prevalence of *BRCA* mutations might be even higher than the observed 23 %.

In some cases where there is an exceptional family history and a negative HISPANEL test, full sequencing might be offered. In the present series, 20 women had a family history of breast or ovarian and no *BRCA1*or *BRCA2* mutation; these women might qualify for full sequencing of *BRCA1* and *BRCA2*. In a recent study of Mexican breast cancer patients living in the United States, a strong association was observed between the triple-negative subtype and a family history of breast or ovarian cancer [43]. The genetic basis for this observation is currently under investigation.

Our patients represent those women who were treated at a single hospital in Mexico City and the prevalence and distribution of mutations among cancer patients elsewhere in Mexico might be different. We studied prevalent cases, on average 6 years had passed from diagnosis to genetic testing. Many women in the registry database had died prior to the initiation of the study. Therefore, if the presence of a *BRCA1* mutation is associated with a relatively poor survival, our estimate might be subject to survivorship bias and the true prevalence might be even higher.

We identified a *BRCA* mutation in 23 % of young women with triple-negative breast cancer in Mexico. Previous studies of other populations report prevalences of between 11 and 20 % [44–46]. In the largest study of unselected triple-negative breast cancer patients ($n = 1824$), 11.2 % had a mutation in *BRCA1* or *BRCA2* [47]. In patients younger than 50 years of age, the prevalence was 16.6 %. For the group between 50 and 59 years, the prevalence of mutations was 9.6 %.

Few studies had assessed the prevalence of *BRCA* mutations among Mexican cancer patients, and all included a limited number of patients [15–17]. One recent study of Mexican breast cancer patients unselected for family history or receptor status revealed a prevalence of *BRCA* mutations that accounted for 4.3 % [19]. In a second Mexican study, *BRCA* mutations were identified in 15 % (14/96) of breast cancer cases overall and 27 % (9/33) of triple-negative breast cancers [18].

Given the very high prevalence of a small number of founder mutations among unselected Mexican women with triple-negative breast cancers, it is rational to consider testing for *BRCA1* mutations to all triple-negative breast cancer patients under age 60. However, to do so, it will

require public coverage for preventive services, including genetic testing, as well as for screening for patients and their family members.

The results of this study highlight the potential benefit for *BRCA* testing of young triple-negative breast cancer patients in Mexico at the time of diagnosis. Ideally, the result of the genetic test will be available to the patient and her doctor prior to the initiation of her treatment. There is increasing evidence that mutation carriers will benefit from a personal approach to treatment which many include tailored chemotherapy, tamoxifen, oophorectomy, and bilateral mastectomy. Byrksi et al. reported that of 107 *BRCA1* carriers treated with neoadjuvant cisplatin, 63 % experienced a pathologic complete response (pCR), and all of the women who experienced a pCR remain alive an average of 4 years after the initiation of treatment [48]. Huzarski et al. reported a survival benefit among *BRCA1* carriers with breast cancer after oophorectomy [49]. Metcalfe et al. reported a decline in 20-year breast cancer mortality associated with a bilateral mastectomy, compared to unilateral surgery [50]. An additional benefit of testing young women with triple-negative breast cancer is that testing can then be offered to unaffected relatives of mutation carriers.

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