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Prevalence of *BRCA1* and *BRCA2* mutations in unselected breast cancer patients from Peru

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Abstract

The prevalence of *BRCA1* and *BRCA2* mutations among breast cancer patients in Peru has not yet been explored. We enrolled 266 women with breast cancer from a National cancer hospital in Lima, Peru, unselected for age or family history. DNA was screened with a panel of 114 recurrent Hispanic *BRCA* mutations (HISPANEL). Among the 266 cases, thirteen deleterious mutations were identified (eleven in *BRCA1* and two in *BRCA2*), representing 5% of the total. The average age of breast cancer in the mutation-positive cases was 44 years. *BRCA1* 185delAG represented seven of the eleven mutations in *BRCA1*. Other mutations detected in *BRCA1* included: two 2080delA, one 943ins10, and one 3878delTA. The *BRCA2* 3036del4 mutation was seen in two patients. Given the relatively low cost of the HISPANEL test, one should consider offering this test to all Peruvian women with breast or ovarian cancer.

Keywords

Peru; breast cancer; hereditary; *BRCA1*; *BRCA2*

INTRODUCTION

Peru is a South American country of 30 million inhabitants. Breast cancer is the second most common cancer and the third most common cause of death among women in Peru [1]. In

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2008, approximately 4,300 new cases of breast cancer were diagnosed [1]. The age-standardized incidence of breast cancer was estimated to be 34.0 cases of breast cancer per 100,000 per year [1], compared to 83.2 per 100,000 per year in Canada and 123.8 cases per 100,000 per year (whites) in the USA (SEER Registry).

Mutations in *BRCA1* and *BRCA2* are estimated to account for 5% of all breast cancers and 50% of hereditary breast cancers [2]. During the last decade, the scientific community has invested extensive efforts in the search for novel breast cancer susceptibility genes through large-scale genome-wide association studies (GWAS) [3]. However, these studies have not identified any highly penetrant genes and genetic testing for hereditary breast cancer relies predominantly on *BRCA* screening. The lifetime risk of breast cancer in women who carry either mutation is estimated to be as high as 80%, but the risk may vary according to the specific mutation, by the country of residence, and by the family history [4–8].

Genetic testing provides the opportunity to identify highly-predisposed women prior to the development of cancer. Current preventive options include prophylactic mastectomy and oophorectomy, tamoxifen, as well as specialized surveillance programs for mutation carriers who have not yet developed cancer and individualized cancer therapies for women with cancer [2, 9–12]. A recent study shows that among *BRCA* mutation carriers, preventive oophorectomy is associated with a 77% reduction in all-cause mortality and with an 80% reduction in the risk of ovarian, fallopian tube or peritoneal cancer [13]. Genetic testing could be made more accessible to women in developing countries if its cost is reduced or if common *BRCA1/2* founder mutations are discovered. The presence of founder mutations within these ethnic groups has enabled rapid and low cost screening compared to the cost of complete sequencing of both *BRCA* genes [14].

A number of studies have evaluated the *BRCA* mutation status of breast cancer patients in Latin American countries [15, 16–24]. These studies provide strong evidence for an important role of genetics in the etiology of breast cancer in Latin America. Ultimately, evaluation of *BRCA* mutations in unselected cases from other countries in South America will provide more accurate evidence for risk associated with *BRCA* mutations. More importantly, assessing the prevalence of founder mutations in Latin American countries will establish whether low cost panel-based approaches to the implementation of genetic services are feasible in these countries. To determine this, we performed mutation analysis of *BRCA1* and *BRCA2* in unselected patients with breast cancer from Lima, Peru.

MATERIAL AND METHODS

Patient Population

We conducted a study of unselected breast cancer patients, diagnosed at any age, between December 2008 and December 2011, recruited from the major cancer specialized public hospital in Lima, Peru (Instituto Nacional de Enfermedades Neoplásicas, INEN). Patients were approached by the research coordinator to participate in the study during an out-patient visit to the hospital. 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 in person 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 266 of the 300 patients (89%).

All DNA samples were screened for a panel of recurrent mutations, estimated to include 80% of Hispanic *BRCA* mutations, in the laboratory of Dr. Weitzel at City of Hope in Duarte, California [25–26]. The panel consists of 114 *BRCA1* and *BRCA2* mutations distributed across five multiplex PCR reactions and analyzed with Sequenom MassArray technology. All deleterious mutations were confirmed by Sanger sequencing on an ABI capillary sequencer in the laboratories of Dr. Weitzel and Dr. Narod.

RESULTS

A total of 266 breast cancer patients were tested for *BRCA1* and *BRCA2* mutations using HISPANEL. On average, 1.7 years had elapsed between the date of diagnosis and the date of interview and saliva sample collection. The mean age of the patients at diagnosis was 49 years (range 21–76) and the mean age at interview was 50 years (range 23–76). 21% of the patients were diagnosed before the age of 40 and 50.4% were diagnosed before the age of 50.

A mutation was found in 13 of 266 (5%) patients; eleven had a mutation in *BRCA1* (4.2%) and two had a mutation in *BRCA2* (0.8%) (See Table 1). All thirteen mutation positive patients were diagnosed at age 62 or below, and 11/13 were under age 50 years. The prevalence of mutations was 8% among those diagnosed under age 50 years, and 1.6% for participants over the age of 50 years. The average age of diagnosis in the women with a *BRCA* mutation was 44 years, compared to 49 years for the non-carriers.

Six of the 13 women with a mutation had a first-degree relative affected with breast and/or ovarian cancer (46%) (See Table 1). Other cancers in the thirteen families with a *BRCA* mutation included pancreas cancer (3 cases), colon cancer (1 case), prostate cancer (1 case), cervical cancer (1 case), and sarcoma (1 case).

DISCUSSION

We identified a deleterious *BRCA1/2* mutation in 5% (13/266) of the Peruvian women with breast cancer. The frequency of *BRCA* mutations in the current study is comparable to that reported in other South American studies of breast cancer patients unselected for age or family history. The prevalence in these South American studies ranges from 2.3–7.1%, in Brazil (2.3%) [18], Colombia (4.2%) [15], Chile (7.1%) [19], Mexico (4.3%) (unpublished) and Venezuela (3.6%) (unpublished).

Most women with a *BRCA* mutation detected in this study were diagnosed under the age of 50, and about half of them had a family history of breast and/or ovarian cancer (See Table 1). This study did not select cases based on age or family history. Two mutation carriers (15%) diagnosed at ages 57 and 62 would not have been identified if age under 50 years was used as the threshold for testing.

A major strength of the current study was the inclusion of unselected breast cancer cases from INEN in Lima. INEN is the National public cancer center in Peru and women from all provinces of Peru attend this hospital. Thus the women in the study can be considered representative of the Peruvian population. Participants in this study were born in various provinces of Peru; 30% of them were born in Lima, and 55% of them currently reside in Lima, the capital of Peru.

The *BRCA1* 185delAG mutation was the most common mutation found in this study, seen in seven of 13 carriers (54%). This is the most common founder mutation in the Jewish population, but has also been reported among several other non-Jewish ethnic groups, including Mexican, Chilean, and Bahamian groups [20, 27–29]. The proportion of the *BRCA1* 185delAG mutation in the current study (54%) is the highest one reported to date in an unselected breast cancer study in a Latin American country. Of the three mutation carriers who identified themselves as being of indigenous ancestry, two have the *BRCA1* 185delAG mutation. To our knowledge, this is the first study to report the presence of this mutation in indigenous people in South America.

As expected by the design of the HISPANEL, the remaining four *BRCA* mutations identified in this study have been previously detected in other Hispanic populations. Two individuals harbored the *BRCA1* 2080delA mutation which has been reported in 32 individuals of Spanish, Russian, Italian, Dutch, Japanese, English, and Korean ancestries in the BIC database. Two other individuals harbored the *BRCA2* 3036del4 mutation which has been reported 111 times in families from Europe and North American countries. This mutation is the most frequent *BRCA2* founder mutation in Spain, which could explain the presence of this mutation in Latin American countries [23]. In addition, the *BRCA1* 3878delTA mutation has been reported twice in individuals of Latin American ancestry in the BIC database. The *BRCA1* 943ins10 mutation detected in one case in the study is the most commonly reported African founder mutation [28, 30] and a common Bahamian founder mutation [29]. The mutation has been reported 34 times in the BIC database, mainly in individuals of African descent, but also in individuals of Latin American descent [31–32]. Most recently, this mutation has been reported five times in a study of 200 triple negative breast cancer Mexican patients (2.5%) [26]. Peruvian Hispanic ancestry was reported by 91% of participants and 23% of mutation carriers identified themselves as being of indigenous ancestry.

Our study has several limitations. Family history was only available for the mutation positive patients. We did not perform full sequencing of *BRCA1/2*, nor did we screen for large rearrangements with the exception of the *BRCA1* ex9-12del large rearrangement, which is suggested to be a Mexican founder mutation [27, 33]. This mutation has not been reported to be present in other Latin American countries [34] and was not observed in this

study. Although full *BRCA* sequencing was not conducted, the HISPANEL is estimated to account 77–80% of *BRCA* mutations in Mexican women from the USA and Mexico [25–26]. In the current report we may have underestimated the prevalence of *BRCA* mutations in Peru given that the HISPANEL was developed and validated in Mexican populations from the USA and Mexico [25]. And also there may be other founder mutations (or non-founder mutations) in Peru that are not represented by this panel. However, the HISPANEL can be completed in 72 hours from sample collection, at a cost of \$20 USD per sample (approximately 5% of the cost of complete sequencing by North American commercial laboratories).

We identified a *BRCA* mutation in approximately 5% of women with breast cancer in Peru using HISPANEL. Given the poor survival from breast cancer in Latin American women, the financial and social burden from the morbidity and mortality associated with the disease, there is incentive to identify high-risk women who could benefit from preventive interventions such as preventive salpingo-oophorectomy, which reduces the risks of both breast and ovarian cancer [13, 35].

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BRCA1 and *BRCA2* Mutations Identified in Peruvian Breast Cancer Patients

Table 1

Patient	Gene	Exon	Mutation	HGVs nomenclature	Age of diagnosis	Family History of Breast and Ovarian Cancer in First- and Second-Degree relatives
51560	<i>BRCA1</i>	2	185delAG	BRCA1 c.66_67delAG	34	None
51573	<i>BRCA1</i>	2	185delAG	BRCA1 c.66_67delAG	36	Sister OvCa40, MotherOvCa60
51594	<i>BRCA1</i>	2	185delAG	BRCA1 c.66_67delAG	57	None
51758	<i>BRCA1</i>	2	185delAG	BRCA1 c.66_67delAG	33	MotherBrCa50, Aunt BrCa36, Grandmother BrCa61 & OvCa72
51767	<i>BRCA1</i>	2	185delAG	BRCA1 c.66_67delAG	46	Mother BrCa57
51789	<i>BRCA1</i>	2	185delAG	BRCA1 c.66_67delAG	36	Mother BrCa54, Aunt BrCa54
51796	<i>BRCA1</i>	2	185delAG	BRCA1 c.66_67delAG	47	Sister BrCa49, Mother OvCa72, Niece BrCa36
51663	<i>BRCA1</i>	11	2080delA	BRCA1 c.1961_1962delA	47	None
51788	<i>BRCA1</i>	11	2080delA	BRCA1 c.1961_1962delA	49	None
51505	<i>BRCA1</i>	11	943ins10	BRCA1 c.815_824dup10	31	Sister OvCa39
51538	<i>BRCA1</i>	11	3878delTA	BRCA1 c.3759_3760delTA	62	None
51551	<i>BRCA2</i>	11	3036del4	BRCA2 c.2808_2811delACAA	45	None
51695	<i>BRCA2</i>	11	3036del4	BRCA2 c.2808_2811delACAA	50	None