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Common BRCA1 and BRCA2 Mutations among Latin American Breast Cancer Subjects: A Meta-Analysis

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Abstract

Background: Many BRCA1 and BRCA2 mutations have been characterized in breast cancer subjects; however, the overall prevalence in Latin American remains elusive. The aim of the study was to determine the prevalence of common BRCA1 and BRCA2 mutations in Latin American breast cancer subjects.

Methods: Pubmed, EBSCO, and OVID databases, and study bibliographies were systematically searched for observational studies that examined for mutations in BRCA1 and BRCA2 until March 2015. The pooled prevalence was obtained using the inverse double arcsine square root method. Publication bias was assessed by Begg and Mazumdar's test and the Egger's test. The sensitivity was determined by reevaluation of the pooled estimate after removal of one study.

Results: Out of 294 retrieved studies, 32 studies met the inclusion criteria (n=9938 subjects). Twenty-nine BRCA1 and thirteen BRCA2 pathogenic mutations were described in two or more studies. For BRCA1, the most reported mutations were 185delAG and A1708E. The most prevalent BRCA1 mutations (>0.50%) were del exon 9–12 (1.45%, 95% CI: 0.61–2.63%), 185delAG (0.90%, 95% CI: 0.50–1.42%), R71G (0.64%, 95% CI: 0.43–0.87%), A1708E (0.58%, 95% CI: 0.40–0.79%), 5382insC (0.54%, 95% CI: 0.32–0.82%), and del exon 16–17 (0.54%, 95% CI: 0.32–0.82%). For BRCA2, the most reported mutations were 6174delT and 3036del4; however, the H372N (0.78%, 95% CI: 0.14–1.82%) was the most frequent (>0.50%). Comparing Mexican-based studies to the remaining Latin American reports, we provide evidence that certain mutations are specific only for Mexicans and their descendants (i.e. BRCA1 del exon 9–12 and BRCA2 3492insT, G273R, and W2586X).

Conclusion: Here we identify the most common BRCA1 and BRCA2 mutations among Latin Americans. This information will aid in selecting mutations for genetic testing and in epidemiological studies.

Keywords: BRCA1; BRCA2; Latin America; Meta-analysis; Breast cancer; Polymorphism; Mexico

Introduction

Breast cancer is the most common cancer among Latin American women and the leading cause of cancer-associated deaths [1,2]. It is estimated that 114,900 new cases and 37,000 deaths occur in Latin American populations annually [3]. Unfortunately, Latin American women have a poor 5 year survival rate than most other ethnic groups [4] and the incidence is increasing annually in these countries [5-7]. Genetic cancer risk assessment has become an integral part of disease prevention, especially in countries such as Spain and USA; however, the limited availability of clinical gene testing has prevented the implementation of prevention programs in Central and South American countries.

Five to ten percent of all breast cancers in Latin American women are attributed to germ-line mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 [8,9]. Conversely, in low-income countries with restricted financial resources for genetic testing, this percentage has been suggested to be underestimated. The lifetime risk of developing breast cancer increases up to 80% with certain BRCA1 and BRCA2 mutations [10]. BRCA mutations prevalence varies between country as well as ethnic groups [11]. With more than 300 documented BRCA1 and BRCA2 mutations found in Hispanic countries [12-22] and with limited reports describing the prevalence of BRCA1 and BRCA2 mutations, which can range from 0% to over 50%, we therefore conducted a meta-analysis to determine the prevalence of certain pathogenic mutations in Central and South American countries.

Methods and Materials

Publication search

Pubmed, OVID, and EBSCO databases were searched for all studies that investigated the prevalence of BRCA1 and BRCA2 mutations found among Latin American breast cancer individuals. The following keywords and index terms were used: "Latin, Hispanic, South and Central America" as well as other terms associated with all Latin American countries, "BRCA1 and BRCA2", and "deletion, insertion, mutation, and polymorphism" for any publication published up to March 30, 2015. Only papers published in English, Spanish, and Portuguese were reviewed. Afterwards, the complied publications´ references were hand searched. The titles and abstract were reviewed and reports that were not eligible for this study were eliminated. All

studies had to meet the following criteria: studies focused on examining the prevalence of BRCA1 or BRCA2 mutations in human subjects, with breast cancer, from Latin American countries or their descendants. Non-human studies, in vitro or in vivo studies, reviews, studies that failed to indicate the prevalence of mutations, or focused on other than breast cancer were excluded.

Data extraction

Two of the authors extracted all data independently. If there was a disagreement, another author assessed the publication in question. If a single sample was believed to be use in multiple publications, the publications were assessed to determine which one was the most representative and that data was used for that mutation, or the corresponding author was contacted to resolve the issue. The data collected were geographical location, criteria use to select sample, sample size, the mutation and the number of positive individuals, method used to detect the mutations, and exons and introns examined.

Statistical analysis

The term "Prevalence" corresponds to relative prevalence rate, which was defined as the total number of positive individuals with breast cancer for a specific mutation divided by the total number of breast cancer cases. The prevalence and the 95% confidence interval (95% CI) were calculated for each mutation. Next, the pooled prevalence estimate was calculated using the inverse double arcsine square root method (Stuart-Ord) [23]. It is worthy to note that only studies that examined the exon or the intron of the BRCA1 or BRCA2 gene or specifically indicated they examined for the mutation of interest were included in the meta-analysis, independent if the authors found the mutation or

not. Heterogeneity was determined using the ψ^2-based Q test and its degree was assessed by the I^2 value (inconsistency index). The Fixed Effects Model was used when the sample was considered homogeneous (Mantel-Haenszel method) [24] and the random effects model was used when the sample was considered heterogeneous (DerSimonian and Laird Method) [25]. The stability and sensitivity of the results were assessed by removing one study and re-calculating the pooled prevalence. Publication bias was evaluated by Begg and Mazumdar adjusted rank correlation asymmetry test (Kendall's tau) and the Egger regression asymmetry test [26,27]. The Fisher's exact test was used to determined difference of frequencies between groups. Statistical analyses were performed using StatDirect Statistical Software version 3.0.147 (Cheshire, UK). P-values <0.05 (two-sided) were considered statistically significant.

Results

Characteristic of the studies

Using the search terms, we identified 294 possible studies from the multiple databases and from reviewing study's bibliographies. We excluded 241 studies that focused on cancers other than Breast cancer (n=22), did not focus on Latin Americans (n=6), did not focus on human subjects (n=24), the BRCA genes were not the focus of the study (n=92), did not determine the frequency of BRCA mutations (n=74) or were not a research article (n=23). The remaining 53 studies were extensively evaluated. Thirteen studies were excluded because they lacked sufficient information and eight more studies were excluded due to shared samples. This led to 32 studies, consisting of 9938 subjects, which were included for the meta-analysis (Figure 1). Detailed characteristics of these studies are presented in Table 1. The most represented country
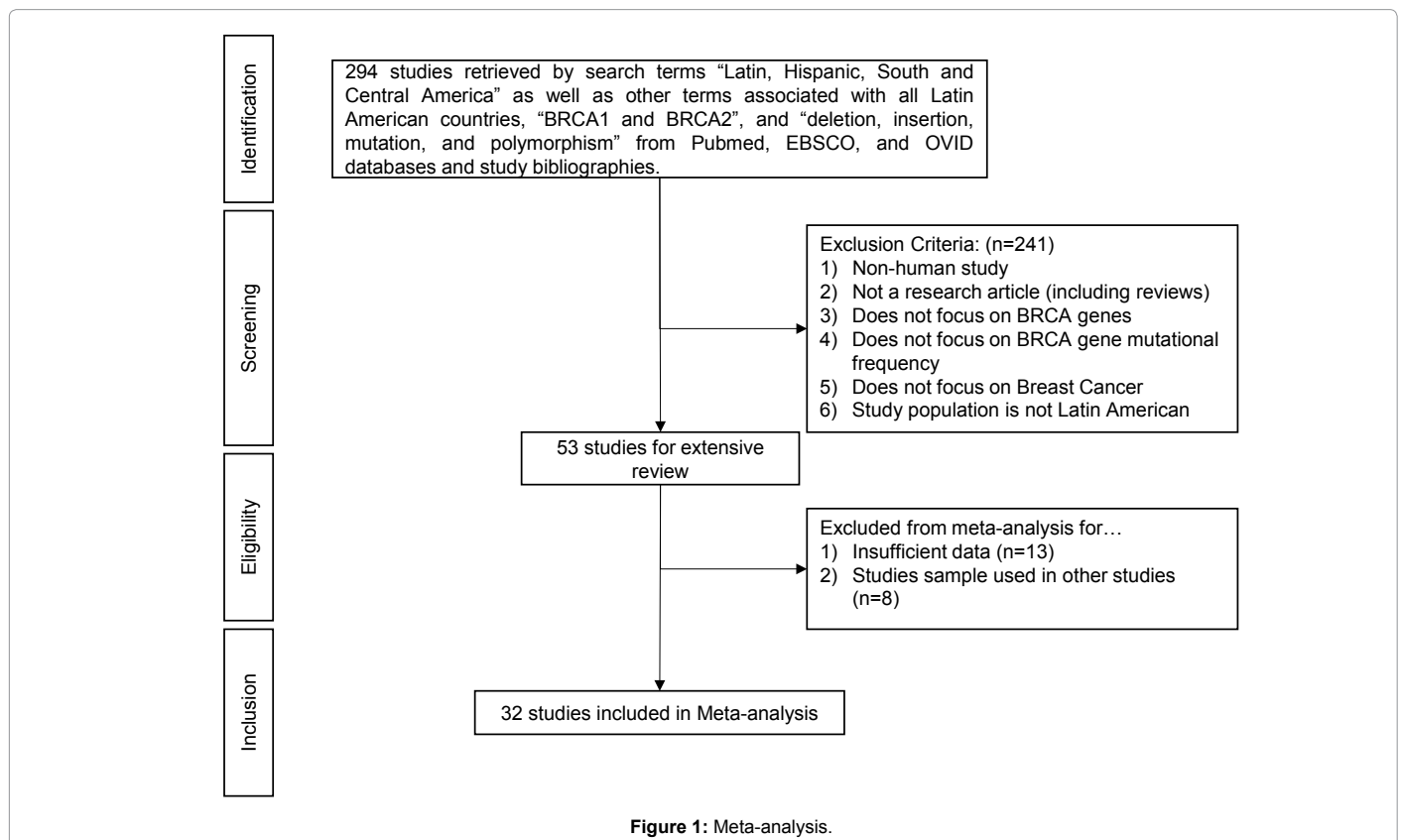

Figure 1: Meta-analysis.

Author, Year Country	BRCA Coverage	Screening Method	# of mutations[a]		N	Study inclusion criteria	Ref.
			BRCA1	BRCA2			
Abugattas, 2014 Peru	HISPANEL-114 mutations	Sequencing	4	1	266	unselected breast cancer patients, diagnosed at any age	[49]
Anton Culver, 2000 USA-Hispanics	BRCA1: 185delAG, 5382insC, R1443X, int5-11T-G, R841W, 4184delTCAA, 2594delC	ASO	0	N/A	42	unselected breast cancer patients, greater than 18 years old	[51]
Carraro, 2011 Brazil	BRCA1 and BRCA2: All exons and adjacent intronic regions	Sequencing	8	10	54	unselected breast cancer patients, aged 35 years or younger at the time of diagnosis	[33]
Delgado, 2011 Uruguay	BRCA1 and BRCA2: All exons and adjacent intronic regions	HDA, PTT, Sequencing	7	14	42	1) at least three cases of female breast cancer with at least one of them diagnosed before the age of 50 2) two cases of female breast cancer at least one diagnosed before 50 years old and at least one of the following additional criteria: paternal transmission, bilateral breast cancer, ovarian cancer, male breast cancer.	[50]
Dufloth, 2005 Brazil	BRCA1: exon 2, 3, 5, 11, 20 BRCA2: exon 10, 11"	SSCP, sequencing	1	2	31	1) early onset (at less than 45 years of age) and/ or bilaterality 2) more than three cases of breast cancer and more than one case of ovarian cancer in the family 3) more than two first-degree relatives involved 4) male breast cancer	[34]
Esteves, 2009 Brazil	BRCA1: exon 11 BRCA2: exon 10, 11	PTT, sequencing	7	3	612	1) women with a history of two or more relatives with breast and/or ovarian cancer along three or more generations 2) two or more cases of breast and/or ovarian cancer in first-degree relatives 3) male relatives with breast cancer diagnosed under 35 years of age 4) cases of bilateral breast cancer	[35]
Ewald, 2011 Brazil	BRCA1: 185delAG, 5382insC BRCA2: 6174delT	PCR	1	0	131	1) the American Society of Clinical Oncology (ASCO) criteria for HBOC 2) a prior probability of harboring a BRCA mutation ≥ 30% by pedigree analysis using the Myriad mutation prevalence tables or the Penn II mutation prediction model 3) Women diagnosed with bilateral breast cancer under the age of 50 years, regardless of family history	[36]
Gallardo, 2006 Chile	BRCA1 and BRCA2: covering coding sequences and intron-exon boundaries (exons 2 to 24)	PCR, SSCP, PTT, HDA, sequencing	15	11	54	1) three cases of breast cancer in first degree relatives 2) two cases of breast cancer in first degree relatives, one diagnosed before age 40 3) one breast cancer and one ovarian cancer in first degree relatives	[39]
Garcia-Jimenez, 2012 Costa Rica	BRCA1: exon 11 BRCA2: exon 10, 11	PTT	1	2	116	1) least three individuals diagnosed with breast cancer at any age or ovarian cancer on one side of the family 2) at least two individuals diagnosed with breast cancer under the age of 50 on one side of the family	[48]
Gomes, 2007 Brazil	BRCA1: exon 11 BRCA2: exon 10, 11	PTT, sequencing	2	2	402	unselected breast cancer patients	[37]
Gonzalez-Hormazabal, 2011 Chile	BRCA1 and BRCA2: All exons and adjacent intronic regions	CSGE, HDA, Sequencing	30	25	326	1) Three or more family members with breast and/ or ovarian cancer 2) Two family members with breast cancer 3) One family member with breast cancer and one with ovarian cancer 4) Single affected individual with breast cancer greater than or equal to age 35 5) Single affected individual with breast cancer greater than or equal to age 50 6) Single affected individual with male breast cancer	[40]
Hall, 2009 USA-Hispanics	BRCA1 and BRCA2: All exons and adjacent intronic regions	Myraid [b]	5	2	1936	Persons undergoing clinical full-sequence for BRCA1/2 mutations at Myraid Genetics Inc. from November 1996 to March 2006	[16]
Hernandez, 2014 Colombia	BRCA1: exon 11 BRCA2: exon 10, 11	PTT, sequencing	2	1	244	unselected breast cancer patients, diagnosed at any age	[43]

John, 2007 USA-Hispanics	BRCA1: All exons and adjacent intronic regions	CSGE, 2DGS, Myraid [b]	11	N/A	393	A: patients whose cancers are likely to be hereditary 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 4) at least 1 first-degree relative with breast or ovarian cancer. B: all other patients with cancers less likely to be hereditary	[52]
Judkins, 2012 USA-Hispanics	BRCA1 and BRCA2: All Large genomic rearrangements	multiplex PCR, Myraid [b]				1) invasive or in situ breast cancer diagnosed under age 50 years, or ovarian cancer 2) male breast cancer diagnosed at any age, in conjunction with 2 or more relatives similarly affected 3) breast cancer patient with no deleterious mutation detected by BRCA1/2 sequencing	[53]
Lara, 2012 Venezuela	BRCA1: All exons and adjacent intronic regions	CSGE, sequencing	24	30	58	1) early onset (less than 45 years of age) and/or bilaterality 2) more than three cases of breast cancer and more than one case of ovarian cancer in the family 3) more than two first-degree relatives affected 4) male breast cancer	[17]
Nahleh, 2015 Mexico	BRCA1 and BRCA2: All exons and adjacent intronic regions	Myraid [b]	11	5	88	unselected breast cancer patients, diagnosed at any age	[28]
Ruiz-Flores, 2002 Mexico	BRCA1 and BRCA2: All exons and adjacent intronic regions	HDA, Sequencing	3	7	51	1) breast cancer diagnosed at age 35 or younger, with no first or second-degree relatives affected with breast or ovarian cancer 2) two cases or more of breast cancer with at least one case diagnosed under 60 among first and second-degree relatives 3) one case of breast cancer under 60 and one case of ovarian cancer diagnosed at any age in first and second degree relatives 4) one case of female and one case of male breast cancer diagnosed at any age in first degree relatives	[18]
Sanabria, 2009 Colombia	BRCA1: 185delAG, 5382insC	PCR	0	N/A	30	1) Woman of any age with diagnostics of BC 2) With Family background in first or second degree 3) Woman with diagnostics of BC under 36 year's old, Without Family background	[44]
Sanchez, 2011 Chile	BRCA1 and BRCA2: only Large Genomic rearrangements	MLPA	2	0	74	1) three cases of breast cancer in first degree relatives 2) two cases of breast cancer in first degree relatives, one diagnosed before age 40 3) one breast cancer and one ovarian cancer in first degree relatives	[41]
Silva, 2014 Brazil	BRCA1 and BRCA2: All exons and adjacent intronic regions	Sequencing, MLPA	18	6	120	1) Breast cancer diagnosed ≤45 years of age (no family history) 2) Breast cancer diagnosed ≤ 45 years of age with 1 or more close blood relative with breast/ovarian/fallopian tube/primary peritoneal cancer at any age 3) Breast cancer diagnosed <45 ≤ 50 years of age with 1 or more blood relative with breast/ovarian/fallopian tube/primary peritoneal cancer ≤ 50 years of age 4) Breast cancer diagnosed >50 of age with 1 or more blood relative with breast/ovarian/fallopian tube/primary peritoneal cancer at any age 5) Two primary BC when the first occurrence was prior to age 50 6) Breast cancer with a history of ovarian/ fallopian tube/primary peritoneal cancer at any age 7) For an individual with an ethnicity that is associated with a higher mutation frequency (e.g., Ashkenazi Jewish) 8) Personal history of ovarian/fallopian tube/primary peritoneal cancer 9) Personal history of male breast cancer	[38]
Solano, 2012 Argentina	BRCA1 and BRCA2: All exons and adjacent intronic regions	Sequencing	36	23	134	1) diagnosis within 40 years of age and no BOC family history 2) diagnosis at any age with at least two BOC affected 1st or 2nd degree relatives	[47]

Torres, 2007 Colombia	BRCA1 and BRCA2: All exons and adjacent intronic regions	SSCP, PTT, DHPLC, sequencing	4	9	44	1) one female breast cancer diagnosed at or before 35 years of age. 2) two cases of breast cancer diagnosed at any age. 3) three cases of breast cancer with at least one diagnosed at or before 50 years of age. 4) at least four breast cancers with as a minimum one diagnosed at or before 50 years of age. 5) at least one male breast cancer diagnosed at any age. 6) at least one female breast cancer and one or more ovarian cancers at any age	[45]
Torres, 2009 Colombia	BRCA1: del exon 9-12	PCR	0	N/A	229	unselected breast cancer patients, diagnosed at any age	[46]
Torres-Mejia, 2014 Mexico	"BRCA1: exon 10, 5382insC, del exon9-12, 185delAG R1443X, A1708E, C1787S & G1788D, BRCA2: exon 10, 11 W2586X	ARMS, CNV, MLPA, PTT, RFLP, sequencing	8	11	810	unselected breast cancer patients, diagnosed at any age	[29]
Vaca-Paniagua, 2012 Mexico	BRCA1 and BRCA2: All exons and adjacent intronic regions	Pyrosequencing	13	10	39	1) subjects with breast and/or ovarian cancer and with two or more first- or second-degree relatives with tumors associated with BRCA mutations were studied. 2) male breast cancer. 3) Subjects with early-onset breast cancer 4) subjects with breast and ovarian cancer	[19]
Vidal-Millan, 2009 Mexico	BRCA1 and BRCA2: All exons and adjacent intronic regions	PCR, DHPLC, sequencing	8	6	40	1) BC diagnosis at age 40 or younger, with no first or second-degree relatives 2) at least 2 cases of BC and/or OV at any age in first-degree relatives. 3) one case of male BC diagnosed at any age in first-degree relatives.	[30]
Villarreal-Garza, 2015a Mexico	HISPANEL = 115 mutations	Sequencing	10	1	190	Patients diagnosed with triple-negative breast cancer at age 50 years or younger.	[31]
Villarreal-Garza, 2015b Mexico	HISPANEL = 114 mutations	Pyrosequencing, sequencing, MPLA	8	3	96	unselected breast cancer patients, diagnosed at any age	[32]
Vogel, 2007 USA-Hispanics	BRCA1 and BRCA2: All exons and adjacent intronic regions	Myraid [b]	11	9	95	Subjects had a personal or family history of BC	[20]
Weitzel, 2013 USA-Hispanics	BRCA1 and BRCA2: All exons and adjacent intronic regions	Myraid [b]	11	4	746	Subjects with a personal or family history of BC and/or OV	[21]

[a]Number of different mutations identified
[b]Mutational analysis was done at Myraid Genetic, Inc.
Abbreviations: ARMS: Amplification Refractory Mutation System; ASO: Allele-Specific Oligonucleotide Assays; BC: Breast Cancer; CNV: Copy Number Variation Assay; CSGE: Conformation-Specific Gel Electrophoresis; 2DGS: 2-Dimensional Gene Scanning; DHPLC: Denaturing High-Pressure Liquid Chromatography; HDA: Heteroduplex Analyses; MLPA: Multiplex Ligation-Dependent Probe Amplification; OV: Ovarian Cancer; PTT: Protein Truncation Test; RFLP: Restriction Fragment Length Polymorphism; SSCP: Single Strand Conformational Polymorphism

Table 1: Characteristics of included studies.

Type of Mutation	BRCA1		BRCA2	
	ALL	Pathogenic	ALL	Pathogenic
Latin Americans				
Deletion	51	36	41	34
Insertion	18	11	16	10
Single Nucleotide variant	105	33	103	24
Mixed	1	0	2	1
Total	175	80	162	69
Mexicans				
Deletion	19	18	15	7
Insertion	3	3	4	1
Single Nucleotide variant	35	12	33	4
Mixed	0	0	1	0
Total	57	33	53	12

Table 2: Distribution of BRCA1 and BRCA2 mutation among Latin Americans and Mexicans.

in this study was Mexico (n=7; [18,19,28-32]), followed by Brazil (n=6; [33-38]). Chile [39-42] and Colombia [43-46] both had four studies included in this meta-analysis and Argentina [47], Costa Rica [48], Peru [49], Uruguay [50], and Venezuela [17] each had one study. Six studies focused on Latin American subjects from multiple countries and their descendants [16,20,21,51,52]. The 32 studies used fourteen different methods to screen from BRCAs mutations: sequencing (n=18), protein truncation test (PTT, n=8), PCR (n=6), heteroduplex analyses (HDA, n=4), multiplex ligation-dependent probe amplification (MPLA, n=4), conformation-specific gel electrophoresis (CSGE, n=3), denaturing high-pressure liquid chromatography (DHPLC, n=3), single strand conformational polymorphism (SSCP, n=3), pyrosequencing (n=2), 2-dimensional gene scanning (2DGS, n=1), amplification refractory mutation system (ARMS, n=1), allele-specific oligonucleotide assays (ASO,n=1), copy number variation assay (CNV, n=1), and restriction fragment length polymorphism (RFLP, n=1). Six studies used Myriad Genetics, Inc. to screen for BRCA mutations and large genomic

Mutation	# of studies	n/N	Freq (95% CI), %	Q–test	I²–test	Model	Begg's test	Egger's test	# of studies	n/N	Freq (95% CI), %	Q-test	I²-test	Model	Begg's test	Egger's test
				Heterogeneity			Publication Bias					Heterogeneity			Publication Bias	
BRCA1																
All pathogenic	32	215/9938	5.70 (4.12–7.53)	<0.01	90.80%	RE	0.04	0.01	9	185/2096	8.60 (3.68–15.31)	<0.01	94.70%	RE	0.48	0.08
del exon 9-12	11	88/4811	1.45 (0.61–2.63)	<0.01	83.3%	RE	0.22	0.50	5	44/1676	3.35 (1.18–6.57)	<0.01	87.0%	RE	0.48	0.13
185delAG	29	85/7245	0.90 (0.50–1.42)	<0.01	68.5%	RE	0.04	0.05	9	22/1906	0.94 (0.18–2.29)	<0.01	79.0%	RE	0.76	0.14
R71G	21	30/5007	0.64 (0.43–0.87)	0.53	0.0%	FE	0.09	0.71	7	12/1086	1.24 (0.67–1.98)	0.73	0.0%	FE	0.56	0.36
A1708E	21	32/5786	0.58 (0.40–0.79)	0.27	14.2%	FE	0.37	0.53	8	10/1896	0.67 (0.35–1.08)	0.98	0.0%	FE	0.72	1.00
5382insC	28	25/6554	0.54 (0.25–0.94)	<0.01	61.4%	RE	<0.01	0.01	8	1/1380	0.13 (0.01–0.39)	0.61	0.0%	FE	<0.01	0.33
del exon 16-17	7	18/3369	0.54 (0.32–0.82)	0.19	31.8%	FE	0.56	0.92	3	1/663	0.17 (0.00–0.62)	0.19	40.7%	FE	N/A	N/A
del exon 1-2	7	21/3369	0.46 (0.10–1.09)	0.06	51.0%	RE	0.14	0.97	3	2/729	0.51 (0.01–2.37)	0.04	68.1%	RE	N/A	N/A
2552delC	25	20/6974	0.34 (0.22–0.49)	0.88	0.0%	FE	0.01	0.81	8	7/1896	0.46 (0.21–0.81)	0.82	0.0%	FE	0.40	0.96
R1443X	22	13/5828	0.29 (0.13–0.53)	0.09	30.5%	RE	<0.01	0.10	8	11/1896	0.64 (0.33–1.04)	0.40	3.8%	FE	0.72	0.46
917delTT	23	12/5735	0.20 (0.10–0.33)	0.11	28.1%	FE	0.01	0.06	7	6/1086	0.68 (0.28–1.25)	0.80	0.0%	FE	0.77	0.60
3148delCT	25	12/6947	0.20 (0.11–0.33)	0.79	0.0%	FE	<0.01	0.83	8	1/1896	0.10 (0.01–0.29)	0.61	0.0%	FE	0.01	0.31
943ins10	25	8/6311	0.12 (0.05–0.22)	0.17	21.4%	FE	<0.01	0.07	7	6/1380	0.65 (0.01–1.76)	0.02	59.4%	RE	0.06	0.23
3450del4	25	11/6974	0.15 (0.07–0.25)	0.11	26.3%	FE	<0.01	0.15	8	0/1896	N/A					
Q1200X	25	8/6947	0.15 (0.07–0.25)	0.76	0.0%	FE	<0.01	0.18	8	7/1896	0.45 (0.20–0.80)	0.71	0.0%	FE	0.55	0.71
C61G	21	4/5007	0.12 (0.04–0.23)	0.67	0.0%	FE	<0.01	0.05	7	0/1086	N/A					
3878delTA	25	6/6947	0.11 (0.05–0.20)	0.51	0.0%	FE	<0.01	0.02	8	4/1896	0.39 (0.06–0.99)	0.08	44.9%	RE	0.55	0.08
2925del4	25	7/6311	0.11 (0.04–0.20)	0.21	17.8%	FE	<0.01	0.04	8	7/1380	0.93 (0.17–2.29)	0.01	63.1%	RE	0.18	0.06
C1787S/D1788G	22	6/6398	0.11 (0.04–0.20)	0.52	0.0%	FE	<0.01	0.21	8	6/1896	0.40 (0.07–0.97)	0.09	41.8%	RE	0.18	0.28
S955X	25	5/6947	0.11 (0.03–0.17)	0.83	0.0%	FE	<0.01	0.27	8	4/1896	0.23 (0.07–0.50)	0.41	3.0%	FE	0.06	0.56
1129insA	25	4/6311	0.10 (0.04–0.20)	0.82	0.0%	FE	<0.01	0.13	8	2/1380	0.26 (0.06–0.60)	0.86	0.0%	FE	0.18	0.83
2415delAG	25	3/6311	0.10 (0.03–0.20)	0.96	0.0%	FE	<0.01	0.15	8	3/1380	0.34 (0.10–0.71)	0.80	0.0%	FE	0.11	0.47
K654X	25	2/6311	0.09 (0.03–0.18)	0.98	0.0%	FE	<0.01	0.19	8	1/1380	0.13 (0.01–0.39)	0.61	0.0%	FE	<0.01	0.33
S1040N	23	4/6083	0.08 (0.03–0.17)	0.51	0.0%	FE	<0.01	0.06	7	1/1086	0.16 (0.01–0.48)	0.57	0.0%	FE	<0.01	0.30
3977del4	25	2/6947	0.08 (0.03–0.16)	0.97	0.0%	FE	<0.01	0.17	8	1/1896	0.10 (0.01–0.29)	0.62	0.0%	FE	0.01	0.31
4184del4	26	2/6989	0.08 (0.03–0.16)	0.97	0.0%	FE	<0.01	0.17	8	1/1896	0.09 (0.01–0.28)	0.55	0.0%	FE	<0.01	0.27
Q1135X	25	2/6947	0.08 (0.03–0.16)	0.98	0.0%	FE	<0.01	0.23	8	0/1896	N/A					
R1751X	22	2/5007	0.08 (0.02–0.18)	0.83	0.0%	FE	<0.01	0.13	7	1/1086	0.17 (0.01–0.50)	0.63	0.0%	FE	0.03	0.35
2080delA	25	3/6947	0.08 (0.02–0.16)	0.89	0.0%	FE	<0.01	0.16	8	0/1896	N/A					
IVS7+2T>A	13	2/3756	0.07 (0.01–0.18)	0.45	0.0%	FE	<0.01	0.15	3	0/837	N/A					
BRCA2																
All pathogenic	28	215/9277	4.31 (2.54–6.52)	<0.01	94.7%	RE	0.04	<0.01	8	56/1896	3.08 (1.52–5.15)	<0.01	72.7%	RE	0.40	0.32
H372N	24	56/6554	0.88 (0.24–1.92)	<0.01	90.9%	RE	<0.01	0.11	8	0/1896	N/A					
E49X	18	10/4339	0.38 (0.13–0.75)	0.03	41.9%	RE	<0.01	0.07	7	6/1086	0.68 (0.28–1.25)	0.77	0.0%	FE	0.77	0.63
3492insT	24	24/6554	0.37 (0.24–0.53)	0.29	12.1%	FE	<0.01	1.00	8	12/1896	0.60 (0.15–1.36)	0.05	50.3%	RE	0.18	0.52
6174delT	25	14/6725	0.32 (0.13–0.60)	<0.01	51.3%	RE	<0.01	0.03	8	0/1896	N/A					
Q742X	24	3/5918	0.23 (0.05–0.56)	0.22	26.6%	FE	0.28	0.09	8	3/1380	0.09 (0.03–0.18)	0.83	0.0%	FE	<0.01	0.07
E1308X	24	11/6554	0.20 (0.11–0.32)	0.77	0.0%	FE	<0.01	0.92	8	0/1896	N/A					
G2793R	18	5/4339	0.14 (0.05–0.27)	0.54	0.0%	FE	<0.01	0.27	7	5/1086	0.57 (0.21–1.10)	0.74	0.0%	FE	0.24	0.76
3036del4	24	7/6554	0.11 (0.05–0.21)	0.29	12.6%	FE	<0.01	0.03	8	1/1896	0.15 (0.03–0.37)	0.98	0.0%	FE	0.06	0.67
W2586X	18	2/3702	0.10 (0.02–0.23)	0.76	0.0%	FE	<0.01	0.16	7	2/614	0.56 (0.11–1.33)	0.70	0.0%	FE	0.14	0.23
R3128X	18	2/4339	0.09 (0.02–0.19)	0.75	0.0%	FE	<0.01	0.15	7	0/1086	N/A					
6503delTT	24	3/6554	0.08 (0.03–017)	0.86	0.0%	FE	<0.01	0.16	8	0/1896	N/A					
3034del 4	24	2/6554	0.07 (0.02–0.15)	0.92	0.0%	FE	<0.01	0.12	8	0/1896	N/A					
6714del4	24	2/6554	0.07 (0.02–0.15)	0.91	0.0%	FE	<0.01	0.12	8	1/1896	0.10 (0.01–0.29)	0.62	0.0%	FE	0.01	0.31

Abbreviations: n: Total Number of Subjects; N: Number of Subjects Positive for the Mutation; FE: Fixed–Effects Model; RE: Random–Effects Model; N/A: Not Applicable.
Table 3: Common BRCA1 and BRC2 pathogenic mutations identified in two or more studies.

rearrangements.

Common BRCA1 mutations among Latin Americans

Using the 32 studies, we identified 175 BRCA1 mutations found in Latin American breast cancer patients (Supplemental Table 1). A majority of mutations were single nucleotide variants (n=105, 60.0%, Table 2). However, when only pathogenic mutations were identified (n=80, 45.7%), by using the CLINVAR database or the studies themselves, 36 were deletions (45.0%), 33 were single nucleotide variants (41.25%), and 11 were insertions (13.75%). Fifty pathogenic mutations (62.5%) were reported only once, whereas fifteen mutations (18.8%) were reported four times or more. The most identified mutation for BRCA1 were 185delAG and A1708E, found in eleven and ten studies, respectively.

The pathogenic mutations' pooled prevalence was calculated for mutations presenting two or more studies using the inverse double
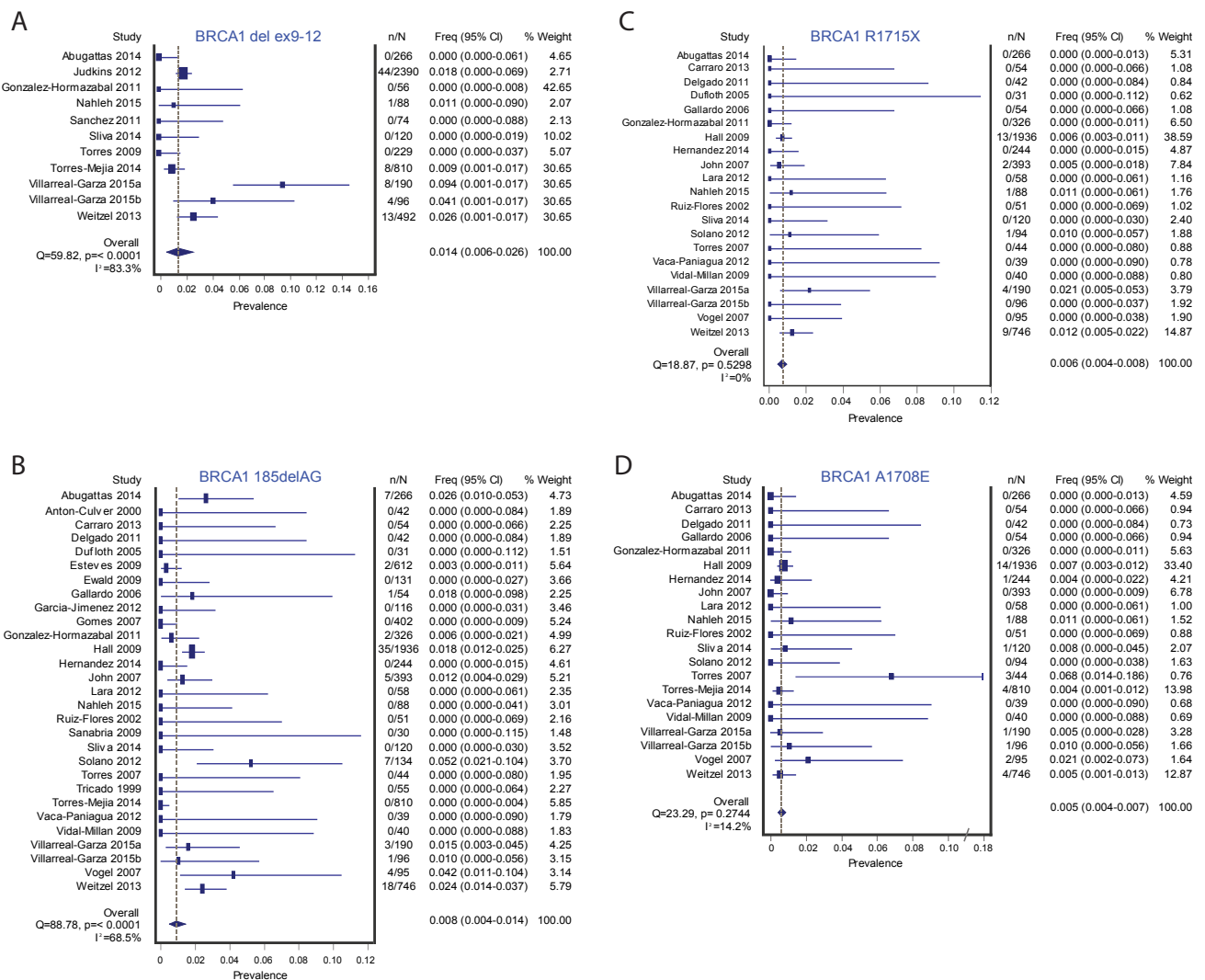
Figure 2: BRCA1 mutations found in Latin American breast cancer subjects.

arcsine square root method. Meta-analysis results are presented in Table 3. The four most prevalent BRCA1 mutations found in Latin American breast cancer subjects were del exon 9–12 (1.45%, 95% CI: 0.61–2.63%, Figure 2A), 185delAG (0.90%, 95% CI: 0.50–1.42%, Figure 2B), R71G (0.64%, 95% CI: 0.43–0.87%, Figure 2C), and A1708E (0.58%, 95% CI: 0.25–0.79%, Figure 2D). The remaining Forest Plots can be found in supplemental material (Supplemental Figure 1).

Next, to determine if these mutations were consistent between groups, we examined the prevalence these mutations in a selected subgroup of subjects-Mexicans and Mexican descendants were selected because they had largest number of studies-and compared them to the rest of the Latin American population. Anton Culver 2000, Hall 2009, John 2007 (except for 185delAG analysis) and Vogel 2007 were excluded because Latin American origins could not be determined. The prevalence for the Mexican subjects for del exon 9–12 was 3.35% (95% CI: 1.18-6.57%, Figure 3A), for 185delAG was 0.94% (95% CI: 0.18–2.29%, Figure 3B), for R71G was 1.24% (95% CI: 0.67–1.98%, Figure 3C), and A1708E was 0.67% (95% CI: 0.35–1.08%, Figure 3D). The remaining Forest Plots can be found in supplemental material

(Supplemental Figure 2). Comparison of these mutations indicated that the frequency between Mexicans and other Latin American countries was not similar. The frequency of the R71G mutation was higher in Mexicans than other Latin Americans (Fisher's exact test, p=0.0034), but there was no difference between the two groups for 185delAG (p=0.702) and A1708E (p=0.802). It is important to note that the deletion of BRCA1 exons 9-12 was only found in Mexican subjects.

Common BRCA2 mutation among Latin Americans

Twenty-five studies identified 162 mutations (Supplemental Table 2). The most common type of mutations were single nucleotide variants (n=103, 63.6%). Of the 162 mutations, only 69 (42.6%) of these were pathogenic. Of the pathogenic mutations, the most common type were deletions (n=34, 49.3%) followed by single nucleotide variants (n=24, 34.8%). Thirteen mutations (18.8%) were reported more than once. The most identified mutations were 6174delT and 3036del4, identified in six and five articles, respectively. The frequency of these mutations was determined by meta-analysis (Table 3). The most prevalent BRCA2 mutations found in Latin American Breast cancer subjects was H372N
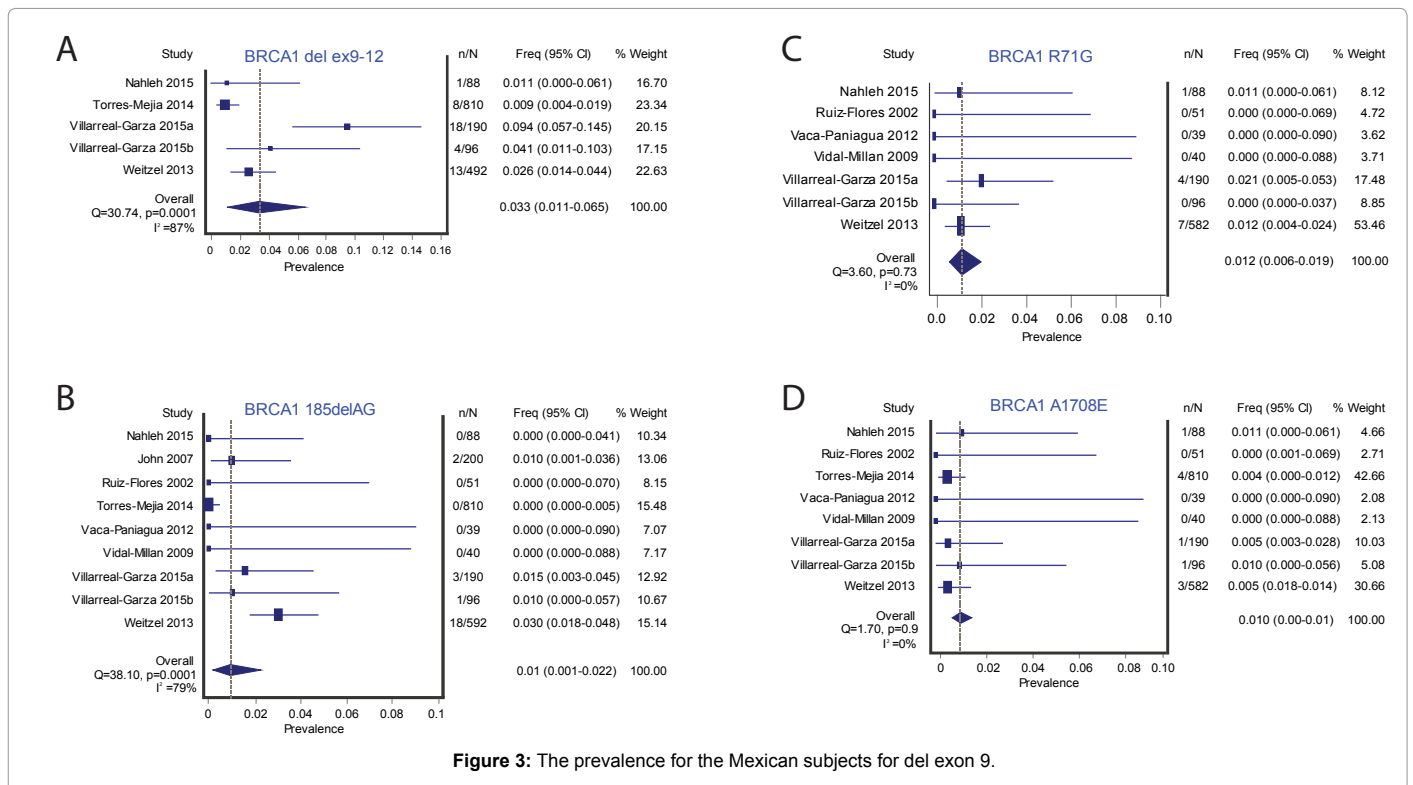
Figure 3: The prevalence for the Mexican subjects for del exon 9.

(0.88%, 95% CI: 0.24–1.92%, Figure 4A). The common Ashkenzai Jewish founder mutation 6174delT's prevalence was determined to be 0.32% (95% CI: 0.24–0.53%, Figure 4B). Only two mutations had a higher prevalence than 6174delT, E49X (0.38%, 95% CI: 0.13–0.75%, Figure 4C) and 3492insT (0.32%, 95% CI: 0.24–0.53%, Figure 4D). The remaining Forest Plots can be found in supplemental material (Supplemental Figure 3).

Next, we determined if the mutational frequencies were consistent between Mexican and other Latin Americans. The prevalence of the pathogenic BRCA2 mutation among Mexicans was calculated (Table 3). The most prevalent BRCA2 mutations found in Mexican subjects were E49X (0.68%, 95% CI: 0.28–1.25%, Figure 5A), 3492insT (0.60%, 95% CI: 0.12–1.36%, Figure 5B), G273R (0.57%, 95% CI: 0.21–1.10%, Figure 5C), and W2586X (0.56%, 95% CI: 0.11–1.33%, Figure 5D). The remaining Forest Plots can be found in supplemental material (Supplemental Figure 4). The 6174delT and H372H mutations were not found among Mexican studies; however, the 3492insT, G273R, and W2586X mutations were only found in Mexican subjects. The E49X mutation prevalence was not different between Mexicans studies and other Latin American studies (p=0.159).

Test for sensitivity and publication bias

We assessed the publication bias for pathogenic mutation prevalence for BRCA1 and BRCA2 (Figure 6). For BRCA1, the Begg-Mazumdar´s test calculated Kendall's tau to be 0.26 (p=0.036), and Egger's test's bias=2.12 (95% CI: 0.69-3.55, p=0.005). For BRCA2, the Begg-Mazumdar calculated Kendall's tau to be 0.28 (p=0.037), and Egger´s test's bias=2.35 (95% CI: 1.42–3.28, p<0.001). Examining the funnel plots, two studies (Lara 2012 and Solano 2012) could bias the results. To assess the sensitivity, one study was removed at a time and the effect on the pooled prevalence was reevaluated. For Latin

American subjects, the pooled prevalence was resistance. These results suggest limited bias, which would minimally affect the results of the meta-analysis. The publication bias for each individual mutation was assessed for each meta-analysis and listed in Table 3.

Discussion

Breast cancer is the most common cancer among females in Latin American countries. While other risk factors, such as high estrogen exposure and age of menarche increases the risk of breast cancer development, mutations in the BRCA1 and BRCA2 genes have a more profound effect in certain population [53]. Genetic testing is an expensive procedure that can aid the development of specific treatment options. Unfortunately, with the large amount of possible mutations to test for, there is a need for a consensus on specific mutations.

In our study, we determined the prevalence of all BRCA1 and BRCA2 mutations among Latin American breast cancer subjects. This study is similar to Wang et al. and Forat-Yazdi et al., who determine the prevalence in breast cancer families and Iranians, respectively [54,55]; however, neither study examined the prevalence in nor contained Latin American subjects, specifically. Furthermore, Wang et al. and Forat-Yazdi et al. excluded studies from their meta-analysis that determine the absence of a mutation from their sample, which may have led them to overestimated the mutation's prevalence. Here, we did incorporate any report that examined the region for these 80 BRCA1 and 69 BRCA2 pathogenic mutations. For example, Lara 2012 and Solano 2012, the two studies that found BRCA2 H372N, determined the frequency to be 55.2% and 25.5%, respectively, which would give a pooled prevalence of about 38.8%; however, including reports that determine the absence of this mutation, gives the pooled prevalence of 0.88%. Since many studies failed to determine this mutation in larger samples, this result would suggest that including the negative data would yield a more accurate value.
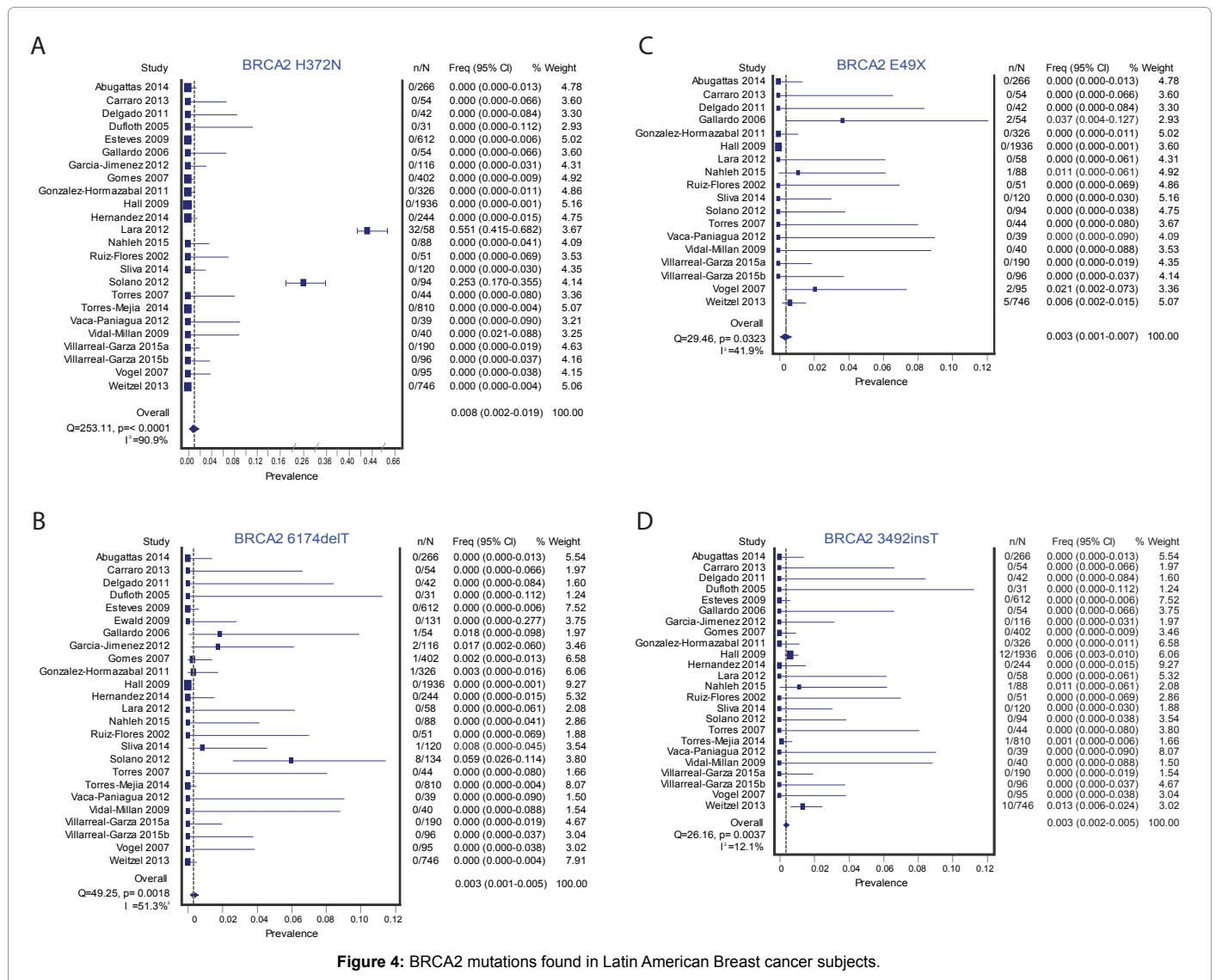
Figure 4: BRCA2 mutations found in Latin American Breast cancer subjects.

The most common BRCA1 mutation for Latin American breast cancer subjects was deletion of exons 9-12. This mutation leads to an inactive form of BRCA1. However, this mutation was only found in Mexican studies and no other country. It is believed to have originated in the state of Puebla [31]; however, Weitzel et al., found this mutation present in subjects that originated from other distant regions of Mexico [21]. This would suggest emigration has led to the dispersion of this mutation. Interestingly, this mutation has not been reported in Southern Mexico or Guatemala, maybe due to a lack of studies. More research is required to determine the regions in Mexico where this mutation is prevalent.

The second most prevalent BRCA1 mutation was 185delAG. Unlike the deletion exon 9-12, the 185delAG mutation has been found in many different regions of Latin America (Argentina, Brazil, Chile, Mexico and Peru). Numerous reports have demonstrated that the BRCA1 185delAG increases the risk of developing breast cancer. This has led to the additional screening of subjects from certain ethnicities for the presence of this mutation, such as the Ashkenazi Jewish descendants. Nonetheless, within the Latin American populations,

there is inconsistent evidence about the prevalence of this mutation in breast cancer subjects, which ranged from 0.0% (19 studies) to 5.22%. Here, we provide evidence that 185delAG frequency was significantly prevalent and was not different between Mexico and all other Latin American countries (0.90% vs. 0.94%, p=0.70); then again, not all countries in Central and South America were properly represented. A similar result was determined for BRCA1 A1708E and BRCA2 E49X. On the other hand, BRCA1 R71G was found in Mexicans as well as Argentinians but was more prevalent in Mexico. Moreover, BRCA2 6174delT and H372N were found in Argentina, Brazil, Chile, Costa Rica, and Venezuela and not Mexico. As well, the BRCA2 3492insT, G273R, and W2586X were found only in Mexico and not any other Latin American country. These examples beg the question that should there be a select set of mutations examined for certain regions of Latin America. Furthermore, it demonstrates that specific regions of Latin American are associated with certain BRCAs mutations.

Central and South America were settled by many different groups from the Iberian Peninsula. We posit that due to emigration from certain regions of Europe has led to the presence of certain mutations in specific regions of Latin America. For example, the BRCA2 3492insT
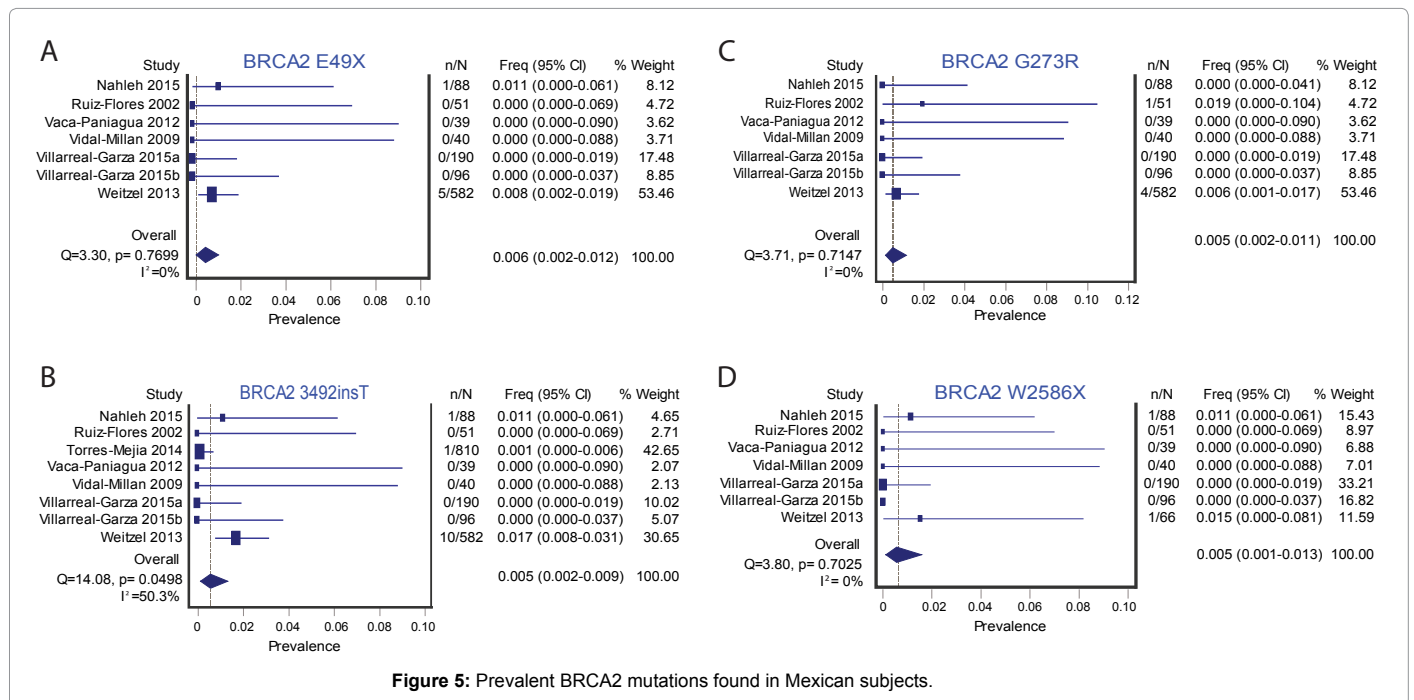
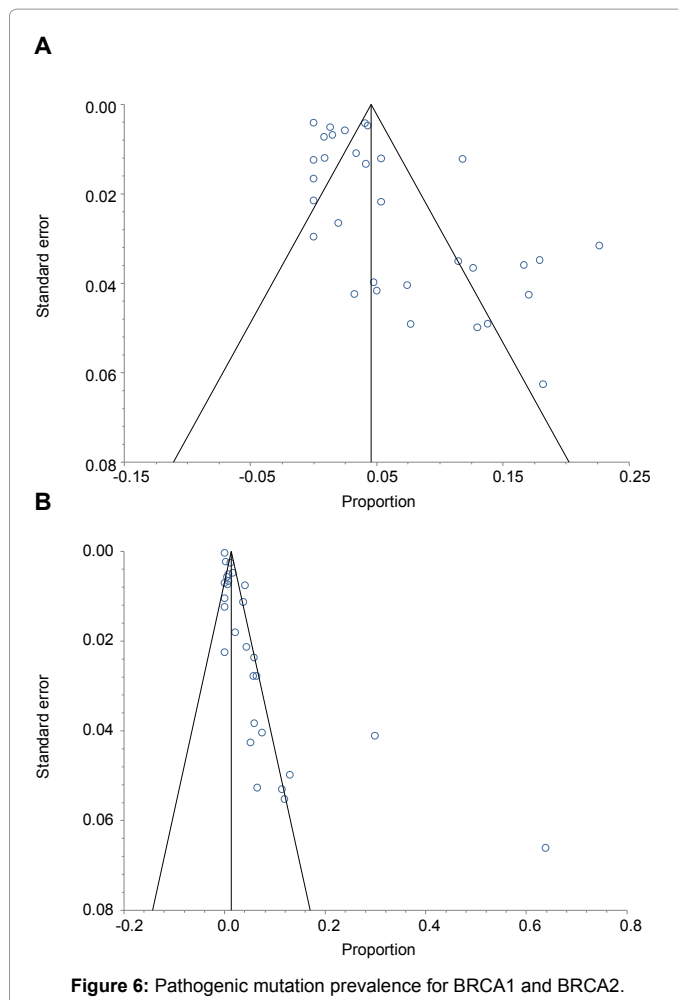**Figure 5:** Prevalent BRCA2 mutations found in Mexican subjects.

Figure 6: Pathogenic mutation prevalence for BRCA1 and BRCA2.

polymorphism has been identified in many regions of Spain: Austurias [56], Valencia [57-60], Aragon [60], Castilla-Leon [61], and Madrid [62], where the mutation frequency ranged between 0.22-2.08%. Interestingly, this mutation has not been reported in Barcelona or Galicia [63], suggesting that this mutation originated from a specific region of Spain. In Mexico, a majority of the population ancestry is from Spain, implying that the BRCA2 3492insT could be found in Mexico. Indeed, this meta-analysis does provide evidence that BRCA2 3492insT was significantly present among Mexicans. A majority of the reports focused on Mexican subjects used in this meta-analysis failed to determine the presence of BRCA2 3492insT. These reports focused on highly-populated regions of Mexico City, the State of Mexico, Nuevo Leon and Veracruz and surrounding regions-most of the states located in the center of Mexico. However, Weitzel et al. did observe the mutation in subjects from Durango, Guerrero, Jalisco, Sinaloa, Sonora, and Zacatecas [21]. With the exception of Guerrero, these states are located in Western Mexico, which would posit the notion that these states present this mutation due to a more pronounced Spanish influence. This is supported by the work of Moreno-Estrada et al., which indicates that subjects from Western Mexico do have a greater Spanish genetic composition than states from Eastern or Southern Mexico [64]. Interestingly, the BRCA2 3492insT mutation has not been observed in other Central or South American countries [15,17,33,39,43,47-50]. As seen with the San Luis Valley studies, due to Spaniard expeditions, the BRCA1 185delAG mutation was introduced and spread among the region, leading to its extraordinary prevalence [65,66]. This would also support the notion that the BRCA2 3492insT mutation is specific for Mexico and Spain. Overall, the region-specific mutational patterns are likely caused by original differences of the native population and induced differences by emigration.

In this meta-analysis there are a few limitations. First, the included studies collected genomic DNA from either blood or a buccal sample, or both. Recent reports have suggest that a blood sample is the superior method, suggesting that studies that used a buccal sample could

underestimate or fail to determine the prevalence of BRCA mutations. Second, studies with smaller sample sizes does increase the prevalence of a single case found but also decrease the chance of discovering a positive case among the sample. Third, due to the emigration pattern that has led to the high diversity of Latin America, many regions of Central and South America are under-represented. For example, as mentioned above, the 3492insT mutation was mainly found on the Western part of Mexico and not in the Northern or the Eastern regions or any other Latin American country. This result demonstrates the need for more region-specific analyses.

In conclusion, this study identifies the most prevalent BRCA1 and BRCA2 mutations found in Latin American breast cancer subjects. Furthermore, we demonstrate that certain mutations are only specific for certain regions, whereas others are constant throughout Latin America. This information will aid in developing a more narrow genetic screening strategy based on the subject's background and lead to cheaper testing. However, with most Latin American countries have not been assessed for BRCA1 and BRCA2 mutations, further studies are required.

Acknowledgment

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