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C677T and A1298C methylenetetrahydrofolate reductase polymorphisms and breast cancer susceptibility among Latinos: a meta-analysis

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Abstract

Background Previous meta-analyses have shown an ethnic dependency of the C677T and the A1298C methylenetetrahydrofolate reductase (MTHFR) polymorphisms, with no focus on the Latino population. For Latinos, many studies have examined these polymorphisms and breast cancer susceptibility, yielding no concise result. Therefore, we undertook this meta-analysis to determine the effect these polymorphisms have on breast cancer risk for Latinos.

Methods PubMed, EBSCO, LILACS, Scopus, and Latin American-specific databases were searched for studies exploring the association between the MTHFR polymorphisms and breast cancer susceptibility in Latinos until January 2019. Genotype distributions were extracted and, depending on the level heterogeneity determined by the ψ^2-based Q test and the I^2 test, fixed-effects or random-effects models were used to calculate pooled odds ratios (ORs) with 95% confidence intervals (95% CIs) for the heterozygous, homozygous, dominant, recessive, and allelic genetic models. No publication bias was detected by the Begg–Mazumdar's test and Egger's test.

Results Of the 280 retrieved publications, 9 studies were included: 9 for the C677T polymorphism and 5 for the A1298C polymorphism. For the C677T polymorphism, there was an elevated risk for the homozygous (OR 1.42, 95% CI 1.05–1.92), the dominant (OR 1.16, 95% CI 1.02–1.31), the recessive (OR 1.33, 95% CI 1.01–1.75), and the allelic model (OR 1.17, 95% CI 1.03–1.33, $p < 0.01$). No association between the A1298C polymorphism and the risk to develop breast cancer was determined.

Conclusion The results indicated that, for Latinos, the C677T polymorphism is associated with a significant risk for developing breast cancer, whereas the A1289C polymorphism does not.

Keywords MTHFR · Mutation · Carcinogenesis · Latin America

Perla Meneses-Sanchez and Samantha C. Garcia-Hernandez contributed equally for the first authorship.

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Introduction

Cancer is one of the leading causes of death worldwide. In Latin America, breast cancer is the most frequently diagnosed cancer, with over 150,000 new cases annually

[1]. Numerous reports have demonstrated the association between developing breast cancer and a patient's exposure to ultraviolet and ionizing radiation, chemical and biological carcinogens, as well as diet [2]. One key enzyme associated with the dietary influences on breast cancer development is methylenetetrahydrofolate reductase (MTHFR) [3]. MTHFR, which is encoded by the *mthfr* gene on Chromosome 1, plays an important role for the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a key step in the one-carbon metabolism pathway. 5-methyltetrahydrofolate is utilized by homocysteine to make methionine. Afterwards, methionine transfers a methyl group to SAM, which is eventually used for DNA methylation, promoting the expression of certain oncogenes and suppression of tumor suppressor genes [4, 5]. Thus, MTHFR provides a key link between folate consumption and DNA methylation, which is associated with cancer development. However, the exact mechanism remains unclear. Some have posited that, during cell division, low folate availability results in increased production and incorporation of uracil into the DNA, due to the limited availability of thymidine [5]. In support of this, Gao et al. and Shrubsole et al. both demonstrated that low folate consumption was associated with an increased risk of developing breast cancer [6, 7]. For a comprehensive review about MTHFR and cancer, please refer Crider et al. 2012 [5].

Two single nucleotide polymorphisms have been shown to effect MTHFR enzymatic activity. The first is the C677T polymorphism (Ala222Val, rs1801133), located in exon 4. This polymorphism was shown to decrease enzymatic activity by 75% for the homozygote genotype [8]. The other polymorphism is A1298C (Glu429Ala, rs1801131), located in exon 7. This polymorphism was also shown to decrease enzymatic activity but to a lesser degree [8]. Carriers of these MTHFR polymorphisms were shown to be associated with breast cancer risk. When considering the C677T genotypes, compared to high folate consumption with CC genotype, Gao et al. and Shrubsole et al. both demonstrate that the risk was significantly augmented for the CC, CT and TT genotypes with low folate consumption [6, 7]. Interestingly, these polymorphisms appear to have an ethnic dependency. For example, for the Asian population, the C677T polymorphism was associated with an increased risk for developing breast cancer [9, 10]. However, the results for the A1298C polymorphism are conflicting, with one study determining a benefit for the heterozygous genetic model [11] and others demonstrating no effect at all [12, 13]. Whereas, for Caucasians, the A1298C polymorphism was associated with an increased risk of developing breast cancer [12] and not the C677T polymorphism [9, 10, 13, 14]. Some meta-analyses have tried to elucidate the effect, either determining detrimental effects or no effect at all, with no specific analysis aimed towards Latinos. Nonetheless, there is no definitive assessment among the Latin American population.

Many Latin American countries have examined the risk associated with these MTHFR polymorphisms and breast cancer; however, conflicting results were obtained [15–18]. With so many studies focusing on the C677T and the A1298C polymorphisms and breast cancer susceptibility in Latinos yielding no concise result, we undertook this meta-analysis to determine the effect these MTHFR polymorphisms have on breast cancer risk for Latinos.

Materials and methods

Publication search strategy

PubMed, EBSCO, LILACS, and Scopus databases were searched for published studies that examined the association between the MTHFR polymorphisms and breast cancer susceptibility in Latinos until January 21, 2019. The search strategy included keywords and any of their derivation for MTHFR (methylenetetrahydrofolate reductase, *MTHFR*), polymorphism (polymorphism, SNP, mutation, C677T, rs1801133, A1298C, rs1801131), cancer (cancer, cáncer, carcinoma), and Latin Americans (Latino, Hispanic, etc.) as well for Latin American countries. Furthermore, we manually reviewed the reference lists for more relevant studies. We increased our coverage by also including other Latino databases (DOAJ, Periodica, Bibliat, Latin index, Imbiomed). No language limitation was applied in the literature search.

Inclusion and Exclusion Criteria

Two authors independently examined each publication for inclusion. If the two authors disagreed about a publication, a third author assessed the publication and made a final decision. The inclusion criteria were: (1) evaluated the association between the C677T and/or the A1298C polymorphisms and breast cancer susceptibility; (2) case–control studies; (3) genotype data were available for cases and controls; (4) data based on the Latino population. The exclusion criteria were: (1) no detailed information of genotype data; (2) duplicate of a previously published study; (3) no Latino population or was mixed with another ethnicity; (4) cancer was not confirmed by histological and laboratorial methods. When duplicate data appeared in different publications, this meta-analysis only adopted the most recent study or the study with the most complete information.

Data extraction

To guarantee the accuracy of the extracted information, two authors individually reviewed each publication. The following data were collected: author's name, year of publication, country, polymorphism(s), type of breast cancer, source of the controls (hospital or population based), number of cases and controls, and genotype frequency. Two authors independently assessed the quality of the studies using the Newcastle–Ottawa Quality Assessment Scale [19]. The following aspects of each study were appraised: selection of cases and controls, comparability, and outcome or exposure. For analysis, the quality scores ranged from 0 to 9 (Electronic supplementary material 1 and Electronic supplementary material 2). Studies that scored more than six stars were considered as a high-quality study.

Statistical analysis

The relationship between the C677T and the A1289C polymorphisms and breast cancer susceptibility was analyzed using five genetic models: the dominant model (12 + 22 v. 11), the recessive model (22 v. 12 + 11), the homozygous model (22 v. 11), the heterozygous model (12 v. 11), and the allele model (2 v. 1), where 1 is the wild-type and 2 is the mutation. Hardy–Weinberg Equilibrium (HWE) was tested by the ψ^2-test for the control groups of each study. The level of heterogeneity was determined by the Cochran Q test and the Inconsistency index (I^2). Crude odds ratios (ORs) with 95% confidence intervals (95% CIs) were used to evaluate the strength of association between the C677T and the A1298C polymorphisms and breast cancer susceptibility. Based on the level of heterogeneity, either the Fixed-effect model (Mantel–Haenszel method, $p < 0.10$ and $I^2 < 40\%$) [20] or the Random-effects model (Dersimonian–Laird method) was selected [21]. To examined publication bias, Egger's test, Begg–Mazumdar's test, and examining the funnel plots were performed. Sensitivity analysis was conducted by removing one study at a time and recalculating the pooled ORs to observe the stability of the crude pooled OR. All the statistical analyses were conducted using Review Manager Software (RevMan V5.3, Copenhagen, Denmark) and StatsDirect Statistical Software (StatsDirect V2.8, Cheshire, United Kingdom). Unless noted otherwise, p values < 0.05 (two-tailed) were considered statistically significant. This study was conducted in accordance with the PRISMA guidelines, see Electronic supplementary material 7.

Results

Selection of eligible studies

A total of 280 publications were retrieved from searching the multiple databases and from reviewing the publications' bibliographies (Fig. 1). 252 publications were exclude because they were not an original research articles, focused on animals or cell lines, did not focus on breast cancer, or did not examine for MTHFR or its polymorphisms. The remaining 28 publications were extensively evaluated. 16 publications did not focus solely on the Latino population, 1 publication lacked sufficient information, and 2 publications used previously published data. This resulted in 9 publications that were included in this meta-analysis: 9 studies for the C677T polymorphism (case = 2136 and controls = 2436) [15–18, 22–26] and 5 studies for the A1298C polymorphism (cases = 1226 and controls = 1739) [22–26]. Most studies determine the presence of either polymorphism using the restriction fragment length polymorphism method (RFLP; $n = 6$), with the remaining three using other technologies (Table 1). We determined that the Calderon-Garcidueñas study [16] contained a high level of bias (Electronic supplementary material 1 and Electronic supplementary material 2). The genotype distributions of the controls were
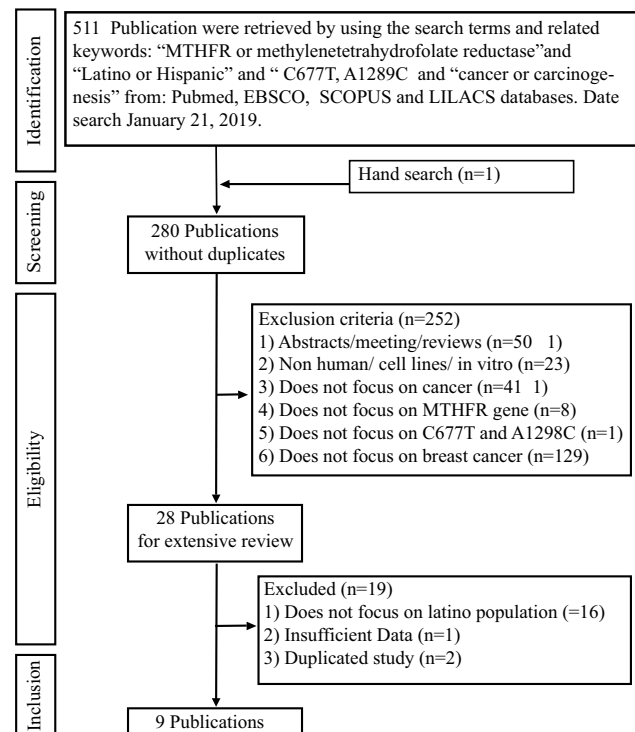

Fig. 1 Flow chart for literature review of studies to be included in the meta-analysis

Table 1 Characteristics of included studies

References	Country	Type of breast cancer[a]	SNP	Group	11[b]	12[b]	22[b]	HWE[c]	Source[d]	Score[e]	Genotyping
Batschauer et al. [15]	Brazil	62 invasive ductal, 6 in situ (*Post-biopsy immunohistological diagnosis*)	C677T	Control	42	34	9	0.592	PB	9	RFLP
				Cases	27	34	7				
Calderón-Garcidueñas et al. [16]	Mexico	Neoplasia in stage IIB y IIIB (*Histological diagnosis*)	C677T	Control	37	60	21	0.695	HB	6*	Microarrangment PHARMA Chip®
				Cases	70	113	51				
Cavalho Barbosa et al. [22]	Brazil	164 invasive ductal, 8 invasive lobulillar, 5 Medullary, 3 Apocrine, 2 Mucinous, 1 papiullary (*Pathological diagnosis*)	C677T	Control	87	70	19	0.388	PB	8	RFLP
				Cases	76	83	17				
			A1298C	Control	72	84	9	0.014*			RFLP
				Cases	68	80	17				
Le Marchand et al. [23]	USA	Invasive breast cáncer (*Registry reports diagnosis*)	C677T	Control	218	319	127	0.593	PB	7	Taqman PCR Core Reagent kit
				Cases	70	117	49				
			A1298C	Control	423	212	29	0.709			
				Cases	146	77	13				
Lopez-Cortes et al. [24]	Ecuador	55 Luminal A, 26 Luminal B, 14 HER positive, 19 Triple negative (*Case history diagnosis*)	C677T	Control	69	113	13	<0.001*	PB	7	RFLP
				Cases	25	75	14				
			A1289C	Control	191	3	1	<0.001*			RFLP
				Cases	110	3	1				
Ma et al. [25]	Brazil	458 invasive cancers (*Clinic-histological diagnosis*)	C677T	Control	222	187	49	0.309	HB	8	TaqMan® SNP Genotyping Assays
				Cases	225	188	45				
			A1298C	Control	279	157	22	0.988			
				Cases	269	168	21				
Ramos-Silva et al. [17]	Mexico	438 invasive ductal, 53 invasive lobililar, 6 mixed (*Clinical-histological diagnosis*)	C677T	Control	167	140	32	0.735	PB	7	RFLP
				Cases	216	178	103				
Rezende et al. [26]	Brazil	174 Invasive ductal, 79 mixed (*Histological diagnosis*)	C677T	Control	111	119	27	0.555	PB	8	RFLP
				Cases	120	103	30				
			A1298C	Control	133	112	12	0.055			RFLP
				Cases	135	104	14				
Zara-Lopes et al. [18]	Brazil	Not indicated (*Imaging studies, histopathological analysis, biopsies*)	C677T	Control	66	65	13	0.596	HB	8	RFLP
				Cases	35	48	17				

RFLP restriction fragment length polymorphism

[a]The type of breast cancer is reported according to the articles. The methods used to determine the type of breast cancers are indicated in italics

[b]11, 12, and 22 indicate the frequency of the wild-type, heterozygote, and homozygote mutant, respectively, where 1 is the C-allele for the C677T polymorphism and A-allele for the A1298C polymorphism, and 2 is the T-allele for the C677T polymorphism and C-allele for the A1298C polymorphism

[c]Hardy–Weinberg equilibrium were calculated by ourselves. A p value <0.05 was considered not in agreement with HWE and indicated with *

[d]The source of the controls: *PB* population base, *HB* Hospital base, and *N/I* Not indicated

[e]The bias score was calculated using the Newcastle–Ottawa scale. Values <7 were considered to have a high-level of bias and indicated with *

consistent with HWE, except for the Batschahuer study [15] and the Lopez-Cortes study [24]. The publication years of the involved studies ranged from 2001 to 2017. The characteristics of the included studies are shown in Table 1. For the C677T polymorphism, four different countries are represented in this meta-analysis, with the most representative population being Brazil with 5 studies [15, 18, 22, 23, 25], followed by Mexico with 2 studies [16, 17], 1 study from USA, which focused on the Latino population [23], and 1 study from Ecuador [24]. For the A1289C polymorphism, the most representative country was Brazil with 3 studies [22, 25, 26], followed by USA [23] and Ecuador [24] with 1 study each.

MTHFR C677T polymorphism increased the risk of breast cancer for Latinos

With respect to the C677T polymorphism, the homozygous, recessive, and allelic genetic models presented with significant heterogeneity ($p < 0.10$, $I^2 > 30\%$). Using the Random Effects model for these genetic models, we determined that for the homozygous (OR 1.42, 95% CI 1.05–1.92, $p = 0.02$), the recessive (OR 1.33, 95% CI 1.01–1.85, $p = 0.04$), and the allelic models (OR 1.17, 95% CI 1.03–1.33, $p = 0.01$, Fig. 2), the polymorphism was significantly associated with an increased risk of developing breast cancer. With the remaining models, using the fixed effects model, we determined that the dominant model was associated with an increased risk of developing breast cancer (OR 1.16, 95% CI 1.02–1.31, $p = 0.02$), whereas the heterozygous model did not show any association (OR 1.09, 95% CI 0.96–1.24, $p = 0.20$). However, the results are similar independent of the effects models used.

When the sensitivity of the results was determined by removing one study and recalculating the ORs, the heterozygous and allelic models were resistant (Electronic supplementary material 3). However, for the homozygous model, the results were sensitive to the Lopez-Cortes study (OR 1.34, 95% CI 0.99–1.80), the Ramos-Silva study (OR 1.24, 95% CI 0.96–1.60), and the Zara-Lopes study (OR 1.35, 95% CI 0.99–1.85). For the dominant model, the results were sensitive to the Lopez-Cortes study (OR 1.12, 95% CI 0.99–1.27) and the Ramos-Silva study (OR 1.13, 95% CI 0.99–1.30). Lastly, for the recessive model, the results were sensitive to the Calderon-Garcidueñas study (OR 1.33, 95% CI 0.97–1.82), the Le Marchand study (OR 1.37, 95% CI 0.99–1.90), the Lopez-Cortes study (OR 1.28, 95% CI 0.96–1.72), the Ramos-Silva study (OR 1.15, 95% CI 0.94–1.40), the Rezende study (OR 1.35, 95% CI 0.99–1.85), and the Zara-Lopes study (OR 1.28, 95% CI 0.96–1.70).

Publication bias was assessed by examining the funnel plot for each of the genetic model. The funnel plots demonstrated no significant asymmetry and the shape of the funnel plots suggested no evidence of publication bias (Electronic supplementary material 4). However, a significant publication bias was determined by the Begg–Mazumdar's test and Egger's test only for the heterozygous model (Fig. 2). No correlation was determined by the Begg–Mazumdar's test or bias by Egger's test for the remaining models.

MTHFR A1289C polymorphism not increased the risk of breast cancer for Latinos

With respect to the A1298C polymorphism, none of the genetic models presented with significant heterogeneity ($p < 0.10$, I^2 0%). Using either the fixed-effects or random-effect models, no association between the A1298C polymorphism and the risk to develop breast cancer was observed (Fig. 3). Removing one study had no effect on pooled ORs for any of the genetic models (Electronic supplementary material 5). When publication bias was assessed, no significant asymmetry was determined by examining the funnel plots (Electronic supplementary material 6); furthermore, this was confirmed by the Begg–Mazumdar's test and Egger's test (Fig. 3).

Discussion

Folate deficiency can influence the genetic stability of DNA, which increases the risk of cancer development [4, 27]. Moreover, dysregulation of this pathway is associated with many pathological outcomes, ranging from atherothrombosis to the risk of ischemic stroke to various forms of cancer [14, 28]. Although numerous case–control studies and meta-analyses have investigated the association between the C677T and the A1298C polymorphisms and the risk for developing breast cancer, there is no definite conclusion or a sole focus for the Latin American population. Here, we determined that the C677T polymorphism was associated with an increased risk of developing breast cancer, whereas the A1298C polymorphism had no effect.

For the C677T polymorphism, there was a significant presence of heterogeneity among the studies included in this meta-analysis. The diagnosis of breast cancer was confirmed by histology or by biochemical/molecular techniques (Table 1). Thus, it is possible that the level of heterogeneity is due to the different forms and proportions of breast cancer cases. The method used to determine the polymorphism could increase the heterogeneity of the sample; however, most studies used a similar technique—RFLP. Another cause of heterogeneity could be due to the populations themselves. For example, in Mexico the genetic composition of Mexicans—which is composed of Native American, Europeans, and Africans—varies from region to region [29], this is also seen among different regions of Brazil [30]. These

Fig. 2 Forest plots of breast cancer risk associated with the MTHFR C677T polymorphism for the heterozygous (**a**), homozygous (**b**), dominant (**c**), recessive (**d**), and allelic (**e**) genetic models. The squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95% CI), respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity. Plots were generated using Review Manager Software (RevMan V5.3, Copenhagen, Denmark)
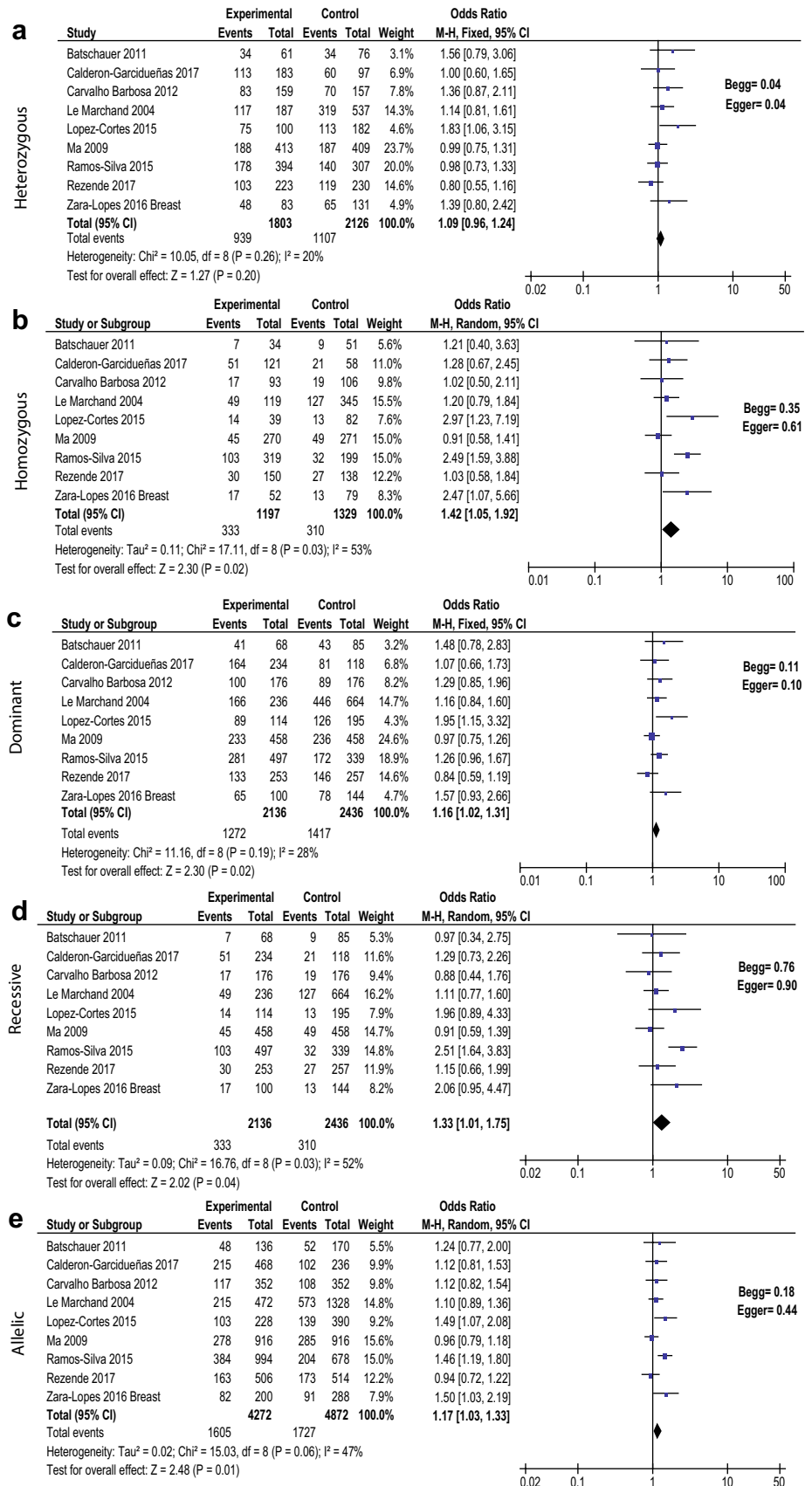
differences do lead to various development rates and pathologies of similar diseases.

Other meta-analyses have determined that for Asians, the C677T polymorphism was shown to augment breast cancer risk [9, 10]. Due to the high level of influence of the European and African immigration, it was not expected that the C677T polymorphism would also increase the risk of developing breast cancer in Latin Americans. Interestingly, the C677T polymorphism was associated with an increased risk of developing breast cancer, except for the heterozygous model. The proposed oncogenic mechanism of the C677T polymorphism is highly correlated with low folate consumption [5]. Many Asian countries and Latin American countries are plagued with low folate consumption [31, 32], thus providing a link between the observed results here and the results for the Asian population. This does posit that folate consumption could attenuate the effects of the C677T polymorphism.

The A1298C polymorphism was not associated with an increased risk of developing breast cancer. Due to different degrees of potency the C677T and the A1298C polymorphisms have on MTHFR enzymatic activity, this does suggests that for breast cancer, the A1298C polymorphism does not inhibit MTHFR activity sufficiently enough to switch to an oncogenic promoting condition, as seen with the C677T polymorphism. Interestingly, others meta-analyses have determined a significant association between the risk of developing breast cancer and the A1298C polymorphism. Intriguingly, this effect is typically seen with the Caucasians [11, 12]. As mention above, Asians have minimal influence on the genetic make-up of Latinos, as do Europeans. Moreover, one study found that the A1298C polymorphism was associated with a decreased risk of developing breast cancer among the Asian population [11]. Taken together, these results suggest that the Latin American population represents a unique group, whose dietary intake must be taken into consideration.

Folate's effect on DNA methylation is dependent on the level of serum folate [27], which comes from its dietary intake. Many women and children from Latin American countries suffer from low folate consumption and other members of the vitamin B family [32–34]. In Cuba, 80% of adults suffer from folate deficiency, whereas in Mexico, Venezuela, and Brazil, the prevalence of fotale deficiency is > 30%. Interestingly, using folate fortification procedures have reduced folate deficiency in selected populations to < 5% [33]. Nevertheless, the availability and compliance of these programs to the majority of the population, or food supplemented with folate, remain inadequate. Therefore, it is possible that for Latinos, which typically consume lower quantities of folate [30, 32, 34] their diets do not provide sufficient amount of folate to inhibit an oncogenic state when MTHFR activity is compromised. This does posit that augmented folate consumption could alter the risk of developing breast cancer.

Hormone changes that precede menopause have been as associated with decreased folic acid absorption, affecting DNA methylation [35]. Therefore, MTHFR polymorphisms are proposed to be a more heightening factor associated with breast cancer development during post-menopause. Indeed, with post-menopausal women, the C677T polymorphism does increase the risk of developing breast cancer [36, 37]; nonetheless, many reports have demonstrated that pre-menopausal status is associated with an increased risk [38, 39]. To add to the confusion, some reports have shown no effect [40]. To address this, Kumar and colleagues performed a meta-analysis for the C677T polymorphism. They determined that there were no associations with breast cancer and the C677T polymorphism for pre-menopausal women (9 studies) and post-menopausal women (9 studies) [10]. Two years later, Naushad and colleagues examined the affect menopausal status has on the association between the C677T polymorphism and breast cancer development [36]. With their meta-analysis, they determined that for post-menopausal women (11 studies), the C677T polymorphism was associated with breast cancer development and not for pre-menopausal women (8 studies). However, for both studies, there was no sub-analysis by ethnicity. For Latin Americans, this effect remains elusive. Here, four studies did examine if menopausal status affects MTHFR polymorphism's effect on breast cancer development. For the Le Marchand study, the analysis was mixed with other ethnicities; thus, no clear conclusion can be made about Latin Americans [23]. For the Batschauer study, they did examine for this effect, determining that the C677T polymorphism had no effect [15]. Interestingly, only two studies, both from Brazil, provided sufficient information for an analysis—the Ma study and the Carvalho Barbosa study. For the Ma study, independent of the menopausal status, neither polymorphism affected the risk [25]. However, the Carvalho Barbosa study indicates that only for post-menopausal women, the CT genotype of C677T is associated with an increase risk [22]. For pre-menopausal women, no associations were found. With a lack of coverage of Latin America and few studies examining this affect, more studies are required.

Our study has a few limitations. First, only five countries are represented in this meta-analysis, which does suggest that parts of the Latin American community are underrepresented. Second, we calculate the crude ORs and they are unadjusted estimations. Third, we did not perform a sub-analysis on the types of breast cancer. As indicated by the elevated level of heterogeneity, the different forms could be possibly affecting the associations. However, even with the crude pooled ORs, we did demonstrate the association between the C677T polymorphism and breast cancer for Latinos.
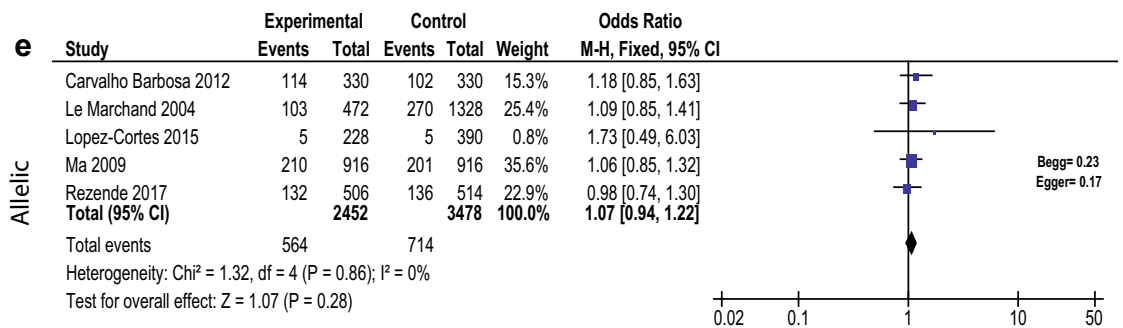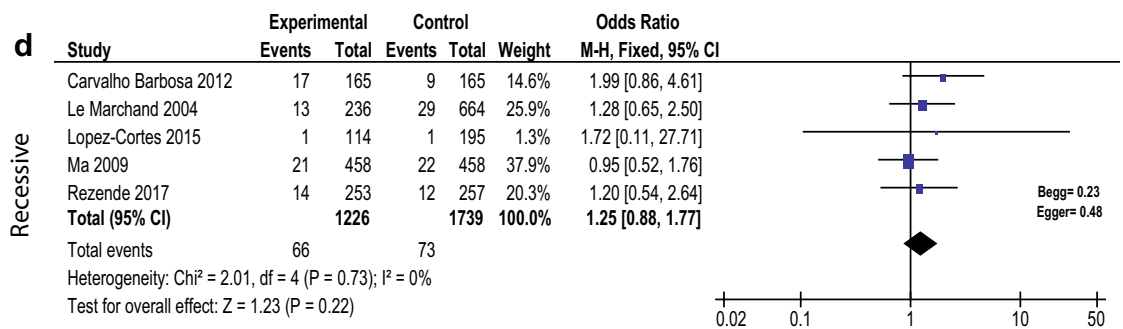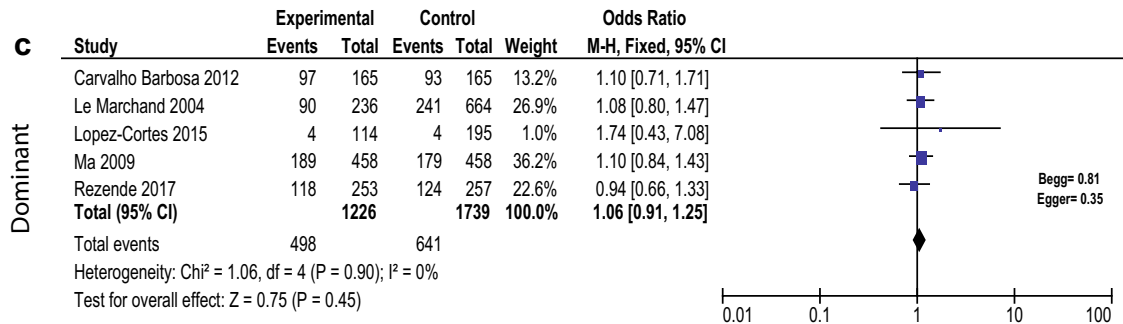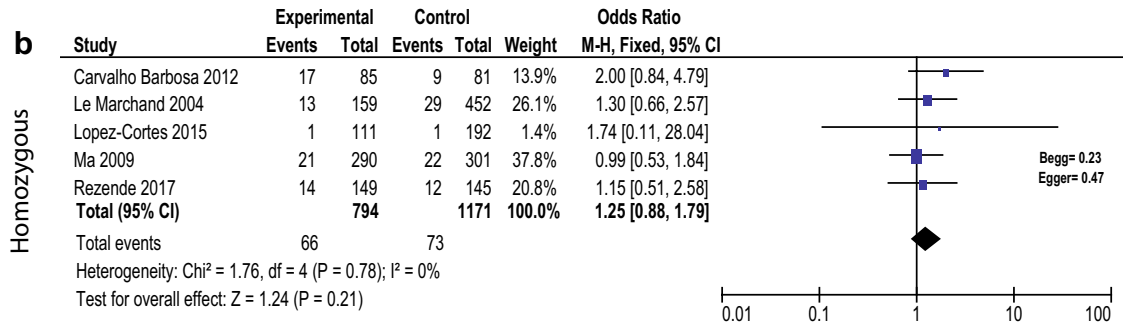
a Heterozygous

Study	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Carvalho Barbosa 2012	80	148	84	156	13.9%	1.01 [0.64, 1.58]
Le Marchand 2004	77	223	212	635	26.6%	1.05 [0.76, 1.45]
Lopez-Cortes 2015	3	113	3	194	0.8%	1.74 [0.34, 8.75]
Ma 2009	168	437	157	436	35.7%	1.11 [0.84, 1.46]
Rezende 2017	104	239	112	245	23.0%	0.91 [0.64, 1.31]
Total (95% CI)		1160		1666	100.0%	1.04 [0.88, 1.23]
Total events	432		568			

Begg= 0.81
Egger= 0.58
Heterogeneity: Chi² = 1.12, df = 4 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)

b Homozygous

Study	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Carvalho Barbosa 2012	17	85	9	81	13.9%	2.00 [0.84, 4.79]
Le Marchand 2004	13	159	29	452	26.1%	1.30 [0.66, 2.57]
Lopez-Cortes 2015	1	111	1	192	1.4%	1.74 [0.11, 28.04]
Ma 2009	21	290	22	301	37.8%	0.99 [0.53, 1.84]
Rezende 2017	14	149	12	145	20.8%	1.15 [0.51, 2.58]
Total (95% CI)		794		1171	100.0%	1.25 [0.88, 1.79]
Total events	66		73			

Begg= 0.23
Egger= 0.47
Heterogeneity: Chi² = 1.76, df = 4 (P = 0.78); I² = 0%
Test for overall effect: Z = 1.24 (P = 0.21)

c Dominant

Study	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Carvalho Barbosa 2012	97	165	93	165	13.2%	1.10 [0.71, 1.71]
Le Marchand 2004	90	236	241	664	26.9%	1.08 [0.80, 1.47]
Lopez-Cortes 2015	4	114	4	195	1.0%	1.74 [0.43, 7.08]
Ma 2009	189	458	179	458	36.2%	1.10 [0.84, 1.43]
Rezende 2017	118	253	124	257	22.6%	0.94 [0.66, 1.33]
Total (95% CI)		1226		1739	100.0%	1.06 [0.91, 1.25]
Total events	498		641			

Begg= 0.81
Egger= 0.35
Heterogeneity: Chi² = 1.06, df = 4 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.75 (P = 0.45)

d Recessive

Study	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Carvalho Barbosa 2012	17	165	9	165	14.6%	1.99 [0.86, 4.61]
Le Marchand 2004	13	236	29	664	25.9%	1.28 [0.65, 2.50]
Lopez-Cortes 2015	1	114	1	195	1.3%	1.72 [0.11, 27.71]
Ma 2009	21	458	22	458	37.9%	0.95 [0.52, 1.76]
Rezende 2017	14	253	12	257	20.3%	1.20 [0.54, 2.64]
Total (95% CI)		1226		1739	100.0%	1.25 [0.88, 1.77]
Total events	66		73			

Begg= 0.23
Egger= 0.48
Heterogeneity: Chi² = 2.01, df = 4 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.23 (P = 0.22)

e Allelic

Study	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Carvalho Barbosa 2012	114	330	102	330	15.3%	1.18 [0.85, 1.63]
Le Marchand 2004	103	472	270	1328	25.4%	1.09 [0.85, 1.41]
Lopez-Cortes 2015	5	228	5	390	0.8%	1.73 [0.49, 6.03]
Ma 2009	210	916	201	916	35.6%	1.06 [0.85, 1.32]
Rezende 2017	132	506	136	514	22.9%	0.98 [0.74, 1.30]
Total (95% CI)		2452		3478	100.0%	1.07 [0.94, 1.22]
Total events	564		714			

Begg= 0.23
Egger= 0.17
Heterogeneity: Chi² = 1.32, df = 4 (P = 0.86); I² = 0%
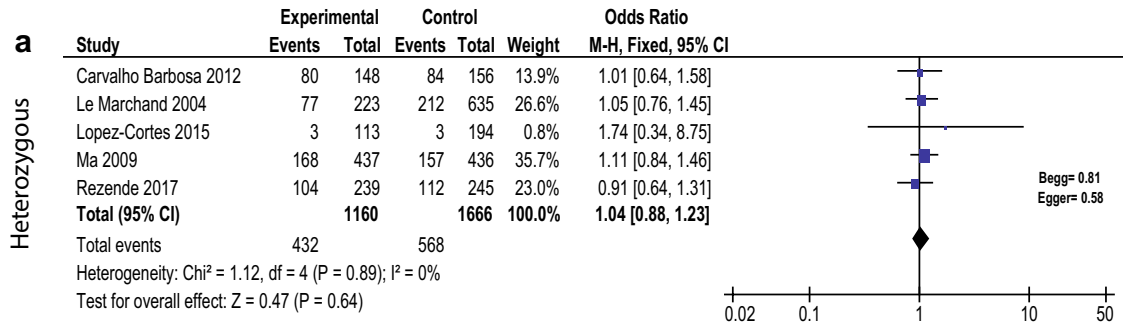Test for overall effect: Z = 1.07 (P = 0.28)

◀**Fig. 3** Forest plots of breast cancer risk associated with the MTHFR A1298C polymorphism for the heterozygous (**a**), homozygous (**b**), dominant (**c**), recessive (**d**), and allelic (**e**) genetic models. The squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95% CI), respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity. Plots were generated using Review Manager Software (RevMan V5.3, Copenhagen, Denmark)

Conclusion

Overall, the results indicated that, for Latinos, the C677T polymorphism is associated with a significant risk for developing breast cancer. On the other hand, the A1289C polymorphism does not show an association. In Latin American women with a history of breast cancer, examining for the C677T polymorphism could identify at risk subjects, who should consider folate monitoring and supplementation management.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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