Global Scientific JOURNALS

GSJ: Volume 8, Issue 4, April 2020, Online: ISSN 2320-9186
www.globalscientificjournal.com

THE ASSOCIATION OF FIVE MICRORNA POLYMORPHISMS WITH BREAST CANCER RISK IN ASIAN POPULATION: EVIDENCE FROM PUBLISHED LITERATURES

Mustafa Abdo Saif Dehwah[1,*], Emad Najeep Ali Shamsan[2]

[1]*Department of Medical Laboratories, Faculty of Medical and Health Science, Taiz University/AL-TurbaBranch,Taiz 3191, Republic of Yemen.*
[2]*Department of Immunology, Medical College, Qinghai University, PR China; E-mail: 3248088030@qq.com.*
[*]*Correspondence: Mustafa AbdoSaifDehwah, E-mail: mustafadahua@yahoo.com; Tel: 00967773187696*

ABSTRACT

MicroRNAs (miRNAs) are small non-coding RNA molecules, which participate in diverse biological processes and may regulate tumor suppressor genes or oncogenes. Several case–control studies and meta-analyses have investigated the association between breast cancer risk and common single nucleotide polymorphisms (SNPs) in miRNAs. However, the inconsistent results were reported. The aim of the present meta-analysis is to investigate this inconsistency, especially in Asian populations. A systemic literature search inclusive to December 2019 yielded a total of 21 potentially relevant articles withe 38 eligible studies concerning the association of miR-146a rs2910164 G>C, miR-499 rs3746444 A>G, miR-27a rs895819 A>G, miR-423 rs6505162 C>A and miR-608 rs4919510 C>G with breast cancer risk in Asian populations. The final meta-analysis was conducted for elven studies concerning rs2910164, ten studies concerning rs3746444, seven studies concerning rs895819, five studies concerning rs6505162 and five studies concerning rs4919510 gene polymorphisms with breast cancer in Asian populations.

In the present meta-analysis, only the SNPs miR-499 rs3746444 G allele showed a borderline association with an increased breast cancer risk in Asian populations (OR=1.2, 95%CI: 1.00-1.45, P=0.055) and significant association in Chinese populations (OR=1.3, 95%CI 1.138 - 1.393, P=0.000). However, no associations were observed for other miRNAs gene polymorphisms in the overall population or the ethnic subgroups studied.

This meta-analysis indicated that the miR-499 rs3746444 may contribute to the breast cancer susceptibility in Asians and especially in Chinese populations, suggesting its potential use as a genetic risk marker in this population, and may provide useful information for the early diagnosis and prevention of breast cancer. Farther large sample size and well-designed case-control studies are required to verify the risk identified in the present meta-analysis.

KeyWords: miRNAs; single nucleotide polymorphisms; breast cancers; meta-analysis.

I. INTRODUCTION

Breast cancer (BC) is a major public health challenge because the incidence is continuously increasing during the past decades, and the most frequent cancer diagnosed among women worldwide [1]. It is the most common invasive malignant tumors worldwide and the second leading cause of death by cancer in females after lung cancer [2-4], and it's related mortality and morbidity are relatively high particularly in low- and middle-income countries [5, 6].

Breast cancer is a multifactorial disease that results from innate and/or acquired genetic predisposition from somatic mutations in breast tissues and their interaction with hormonal exposure and other risk factors such as environmental carcinogens, lifestyle, dietary, or cultural practices, reproductive patterns, and genetic factors, which play a vital role in the pathogenesis of breast cancer [7-10]. Early identifcation of individuals at risk of the cancer is the key to its prevention. Currently, genetic testing has emerged as a promising strategy for predicting breast cancer risk and the potential of genetic polymorphisms as markers for breast cancer risk assessment was increased rapidly [11]. Recently, polymorphisms in microRNA genes have been widely investigated as the gene products play important roles in regulating the expression of many cancer-related genes [12-14].

MicroRNAs (miRNAs) constitute a group of evolutionarily conserved small, endogenous, single stranded and non-protein coding functional RNA molecules of 19–25 nucleotides in length [15]. Its regulate gene expression at the post-transcriptional level [16] and thereby regulate a wide array of biological processes including cell differentiation, proliferation, development, cell death, and homeostasis [17, 18].There are more than 1,424 miRNA genes in the human genome, regulate the translation or degradation of human messenger RNA by sequence complementarity [19, 20], which primarily bind to the 3' untranslated region (3' UTR) of messenger RNAs, resulting in a downregulation of target proteins through the degradation of this mRNA or through translational inhibition. Over 50% of microRNAs genes are located in cancer-associated genomic regions or fragile sites, functions as tumor suppressors or oncogenes in human carcinogenesis through sequence-specific base-pairing with target mRNAs [21-23]. They have been found to be involved in many physiological and pathological processes involved in tumorigenesis [24]. They are known to regulate about 60% of the genes in the human genome, and might be important for the pathogenesis of breast cancer [7, 25, 26]. It has been reported that mutations present in miRNA sequences could result in the changes in miRNA synthesis and function seen in cancer biology and the single nucleotide polymorphisms (SNPs) are the most common type of variation present in miRNA genes [27 - 29]. SNPs in miRNAs may alter the miRNAs expression, maturation and can alter the effects of microRNAs on their target genes, possibly leading to abnormal biological metabolism and modified cancer susceptibility [30]. Common single-nucleotide polymorphisms (SNPs) in miRNAs may change their properties through altering miRNA expression and/or maturation, and thus they may have an effect on thousands of target messenger RNAs (mRNAs), resulting in diverse functional consequences. Increasing evidence suggests that the genetic polymorphisms in miRNAs have been found to play an important role in the initiation and progression of many different types of cancer including breast cancer [31-33].

Many epidemiological studies have examined the association between the SNPs in miRNAs genes and breast cancer susceptibility [34]. Therefore, several case-control studies in different ethnic populations and meta-analyses have been conducted to evaluate the association between large number of miRNA gene polymorphisms and breast cancer risk. These include the five common miRNAs, miR-146a rs2910164 G>C, miR-499 rs3746444 A>G, miR-27a rs895819 A>G, miR-423 rs6505162 C>A and miR-608 rs4919510 C>G gene polymorphisms [35-91]. However, the results from different studies were inconsistent. For example, studies about miR-499 rs3746444 A>G can be different in four meta-analysis [68, 69, 80]. Therefore, we conducted a meta-analysis to evaluate a more comprehensive and precise result for the association of the five common miRNA SNPs, miR-146a rs2910164 G>C, miR-499 rs3746444 A>G, miR-27a rs895819 A>G, miR-423 rs6505162 C>A and miR-608 rs4919510 C>G with breast cancer risk in Asian populations.

II. MATERIALS AND METHODS

A. Search Strategy

We searched the worldwide literature published in MEDLINE via PubMed, EMBASE, Cochrane CENTRAL, Chinese databases (CNKI, CQVIP, Wanfang databases), and Google Scholar for articles with case–control studies of the association between miRNA polymorphisms and breast cancer risk, published up to 2019, using the following keywords: ‘‘miRNA-146a/miRNA-499/miRNA-27a/miRNA-423/ miRNA-608/’’ and/or ‘‘rs2910164 G>C/rs3746444 A>G/rs895819 A>G/rs6505162 C>A/ rs4919510 C>G/), “single nucleotide polymorphism/SNP/polymorphism/variant/variation /mutation” snd ‘‘breast cancer/breast carcinoma/BC”. The research subjects were limited to human studies published in English or Chinese languages were retrieved. References of the relevant literature and review articles were also evaluated to identify all potentially eligible articles.

B. Inclusion Criteria

The eligible studies must meet the specific inclusion criteria as follows: (1) evaluation of the association between rs2910164 G>C/rs3746444 A>G/rs895819 A>G/rs6505162 C>A/rs4919510 C>G and pathologically confirmed breast cancer; (2) had a case-

control design of human samples; (3) written in English or Chinese language; (3) both cases and controls reporting genotype or alleles frequencies; (4) controls group accord with Hardy-Weinberg equilibrium (HWE) in the control group (P > 0.05).

C. Exclusion Criteria

Studies that met the following criteria were excluded: (1) case reports, ore meta-analysis articles; (2) abstracts or editorials, comments or review articles; (3) duplicate studies; (4) studies on animals or cell-lines; (5) studies without a case-control design.

D. Data Extraction

Repeated publications and studies violating the inclusion criteria or providing insufficient data were excluded. Same data from different studies were only adopted once. The extracted information from all eligible articles included: first author's surname, publication year, sample size of cases and controls, country of origination, ethnicity, sources of controls, genotype method, and genotype frequencies in cases and controls. Hardy–Weinberg equilibrium (HWE) test for the controls were included as quality assessment indicator. If the reported data were incomplete, the corresponding author was contacted to obtain complete data.

E. Statistical analysis

In the current meta-analysis, an allele-contrast model was used to investigate the associations of the miR-146a rs2910164 G>C, miR-499 rs3746444 A>G, miR-27a rs895819 A>G, miR-423 rs6505162 C>A, miR-608 rs4919510 C>G and gene polymorphisms with the risk of breast cancer. The strength of the association of each gene polymorphism and the risk of breast cancer was determined by using odds ratios (ORs) and their corresponding 95% confidence intervals (CIs).

Pooled ORs were determined for the allelic contrast model (miR-146a: C vs. G, miR-499: G vs. A, miRNA-27a: G vs. A, miRNA-423: A vs. C, miRNA-608: G vs. C). The statistical significance of the pooled OR was determined by using the Z test and a P value of < 0.05 was regarded as significant. The heterogeneity between studies was analyzed by using the chi-square (X^2) test based on the Q statistic, with the significance level P<0.1 [92] and/or I^2 statistic (with values greater than 50% indicating significant heterogeneity) [93]. If no heterogeneity between the individual studies was existed, the pooled ORs were computed by using the fixed–effects method of Mantel–Haenszel (Petos method) [94]. If the significant heterogeneity between the individual studies was existed, the pooled OR was estimated using random-effects model of DerSimonian–Laird (D–L method) [95]. Sensitivity analysis was performed to evaluate the effect of each study on the combined ORs by omitting individual studies one at a time. Publication bias was checked by Begg's funnel plots [96] and Egger's regression test [97]. An asymmetric plot and a P < 0.05 for the Egger's test denoted the existing of significant publication bias.

The publication bias was estimated using the funnel plot [98]. The funnel plot asymmetry was quantified using Egger's regression approach [97], on the natural logarithmic scale of the OR, with the significance level set a P<0.05, which considered to indicate significant asymmetry and the existing of significant publication bias. The population-attributable risk (PAR) was calculated on the basis of estimated ORs and risk allele frequencies in cases group to get a comprehensive view of the impact of the five miRNA SNPs on breast cancer at population level, using the following formula: (OR-1)/OR * risk allele frequency [99]. The statistical analyses were performed by STATA 11.0 software (StataCorp, College Station, TX, USA).

Table 1 The characteristics of the eligible studies included in the present meta–analysis

Study	Country	Genotyping method	Source of controls	Groups	Age	Sample size	Genotype frequency	minor/ major	MAF%	HWE-P
miR-146a rs2910164 G>C							**CC/GC/GG**	**C/G**		
Qi et al. 2015	China	TaqMan	PB	Case		321	43/132/146	218/424	0.34	
				Control		290	20/144/126	184/396	0.32	>0.05
He et al. 2015	China	MassARRAY	PB	Case	2.85±10.78	450	133/242/75	508/392	0.56	
				Control	2.85±10.78	450	153/225/72	531/369	0.59	>0.05
Ma et al. 2013a	China	MassARRAY	HB	Case		191	63/94/35	220/164	0.57	
				Control		192	64/93/34	221/161	0.58	>0.05
Hu et al. 2009	China	PCR–RFLP	PB	Case	51.60±11.08	1009	329/515/165	1173/845	0.58	
				Control	51.77±11.19	1093	362/551/180	1275/911	0.58	>0.05
Alshatwi et al. 2012	Saudi	TaqMan	HB	Case		100	2/50/48	54/146	0.27	
				Control		100	3/46/51	52/148	0.26	>0.05
Bodal et al. 2017	Indian	PCR–RFLP	HB	Case	51.8±12.1	98	0/46/52	46/150	0.24	
				Control	46.3±11.4	99	0/39/60	39/159	0.20	>0.05
Bansal et al. 2014	Indian	PCR–RFLP	PB	Case		121	4/35/82	43/199	0.18	
				Control		164	8/72/84	88/240	0.27	>0.05
Omrani et al. 2014	Iran	ARMS-PCR	PB	Case		236	8/45/183	61/411	0.13	
				Control		203	9/39/155	57/349	0.14	>0.05
Afsharzadeh et al. 2017	Iran	ARMS-PCR	PB	Case		100	6/61/33	73/127	0.37	
				Control		150	9/84/57	102/198	0.34	>0.05
Mashayekhi et al. 2018	Iran	PCR–RFLP	HB	Case	51.8±8.2	353	45/178/130	268/438	0.38	
				Control	51.0±10.2	353	18/145/190	181/525	0.26	>0.05
Nejati-Azar et al. 2018	Iran	PCR–RFLP	HB	Case	49.96±12.02	200	42/84/74	168/232	0.42	
				Control	45.57±11.80	200	42/94/64	178/222	0.45	>0.05
miR-499 rs3746444 A>G							**GG/AG/AA**	**G/A**		
Qi et al. 2015	China	TaqMan	PB	Case	≤50,>50	321	52/117/152	221/421	0.34	
				Control		290	37/112/141	186/394	0.32	>0.05
He et al. 2015	China	MassARRAY	PB	Case	52.85±10.78	450	89/177/184	355/545	0.39	
				Control	53.25±10.96	450	59/188/203	306/594	0.34	>0.05
Hu et al. 2009	China	PCR–RFLP	PB	Case		1009	44/258/707	346/1672	0.17	
				Control		1093	29/248/816	306/1880	0.14	>0.05
Alshatwi et al. 2012	Saudi	PCR–RFLP	PB	Case		100	15/40/45	70/130	0.35	
				Control		100	8/62/30	78/122	0.39	>0.05
Bansal et al. 2014	India	PCR-RFLP	PB	Case		121	11/30/80	52/190	0.21	
				Control		164	15/43/106	73/255	0.22	>0.05
Omrani et al. 2014	Iran	TARMS-PCR	PB	Case	47.1 ± 12.3	236	61/44/131	166/306	0.35	
				Control	45.3 ± 12.8	203	25/48/130	98/308	0.24	>0.05
Afsharzadeh et al. 2017	Iran	ARMS-PCR	PB	Case		100	4/33/63	41/159	0.20	
				Control		150	19/65/66	103/197	0.34	>0.05
Dai et al. 2016	China	MassARRAY	HB	Case	49.09 ±11.02	560	18/135/407	171/969	0.15	
				Control	48.80 ± 8.28	583	11/109/463	131/1035	0.11	>0.05
Doulah et al. 2018	Iran	TARMS-PCR	HB	Case	45 – 64	100	10/35/35	55/105	0.34	
				Control	18 –61	100	4/33/63	41/159	0.20	>0.05
Kabirizadeh et al. 2016	Iran	ASP-PCR	HB	Case		45		47/39	0.55	
				Control		48		37/59	0.39	>0.05
miR-27a rs895819 A>G							**GG/AG/AA**	**G/A**		
Qi et al. 2015	China	TaqMan	PB	Case	≤50,>50	321	61/159/101	281/361	0.44	
				Control		290	56/139/95	251/329	0.43	>0.05
He et al. 2015	China	MassARRAY	PB	Case	52.85±10.78	450	34/165/251	233/667	0.26	
				Control	53.25±10.96	450	37/181/232	255/645	0.28	>0.05
Ma et al. 2013a	China	MassARRAY	HB	Case	21–81	191	16/76/97	108/270	0.28	
				Control		192	14/70/106	98/282	0.26	>0.05
Mashayekhi et al. 2018	Iran	ARMS-PCR	PB	Case	51.8 ± 8.2	353	30/156/167	216/490	0.30	
				Control	51.0 ± 10.2	353	71/155/127	297/409	0.42	>0.05
Zhang et al. 2013	China	Sequencing	PB	Case	41-56	264	16/96/152	128/400	0.24	
				Control	40-56	255	15/103/137	133/377	0.26	>0.05
Zhang et al. 2012	China	PCR–RFLP	PB	Case	54.66±11.18	252	41/144/60	226/264	0.46	
				Control	54.51±11.41	248	59/109/75	227/259	0.47	>0.05
Rah et al. 2015	Korean	Sequencing	HB	Case		136	17/68/51	102/170	0.38	
				Control		224	27/112/85	166/282	0.37	>0.05
miR-423 rs6505162 C>A							**AA/CA/CC**	**A/C**		
He et al. 2015	China	MassARRAY	PB	Case	52.85±10.78	450	16/142/292	174/726	0.19	
				Control	53.25±10.96	450	22/129/299	173/727	0.19	>0.05
Ma et al. 2013a	China	MassARRAY	HB	Case	21-81	191	8/57/127	73/311	0.19	
				Control		192	10/69/110	89/289	0.235	>0.05
Rah et al. 2015	Korea	Sequencing	HB	Case	31.34± 4.97	136	7/44/85	58/214	0.21	
				Control	32.67± 3.87	224	11/66/147	88/360	0.20	>0.05
Zhao et al. 2015	China	Sequencing	PB	Case		180	5/30/79	40/188	0.175	
				Control		189	10/69/110	89/289	0.235	>0.05
Mir et al. 2018	Saudi	ARMS-PCR	PB	Case		100	23/52/25	98/102	0.49	
				Control		124	18/25/81	61/187	0.25	>0.05
miR-608 rs4919510 C>G							**CC/GC/GG**	**G/C**		
Ma et al. 2013a	China	MassARRAY	HB	Case	21–81	191	37/98/57	212/172	0.55	
				Control		192	47/82/61	204/176	0.54	>0.05
Dai et al. 2016	China	MassARRAY	HB	Case	49.09 ± 11.02	560	107/296/127	550/510	0.52	
				Control	48.80 ± 8.28	583	113/287/183	653/513	0.56	>0.05
Rah et al. 2015	Korea	Sequencing	HB	Case		136	30/67/39	145/127	0.53	
				Control		224	44/110/70	250/198	0.56	>0.05
Huang et al. 2012	China	Sequencing	PB	Case	49	1138	192/545/387	1319/929	0.59	
				Control		1434	277/684/456	1596/1238	0.56	>0.05
Hashemi et al. 2016	Iran	PCR-RFLP	PB	Case	48.5±10.8	160	140/20/0	20/300	0.0625	
				Control	49.5±12.4	192	149/43/0	43/341	0.112	>0.05

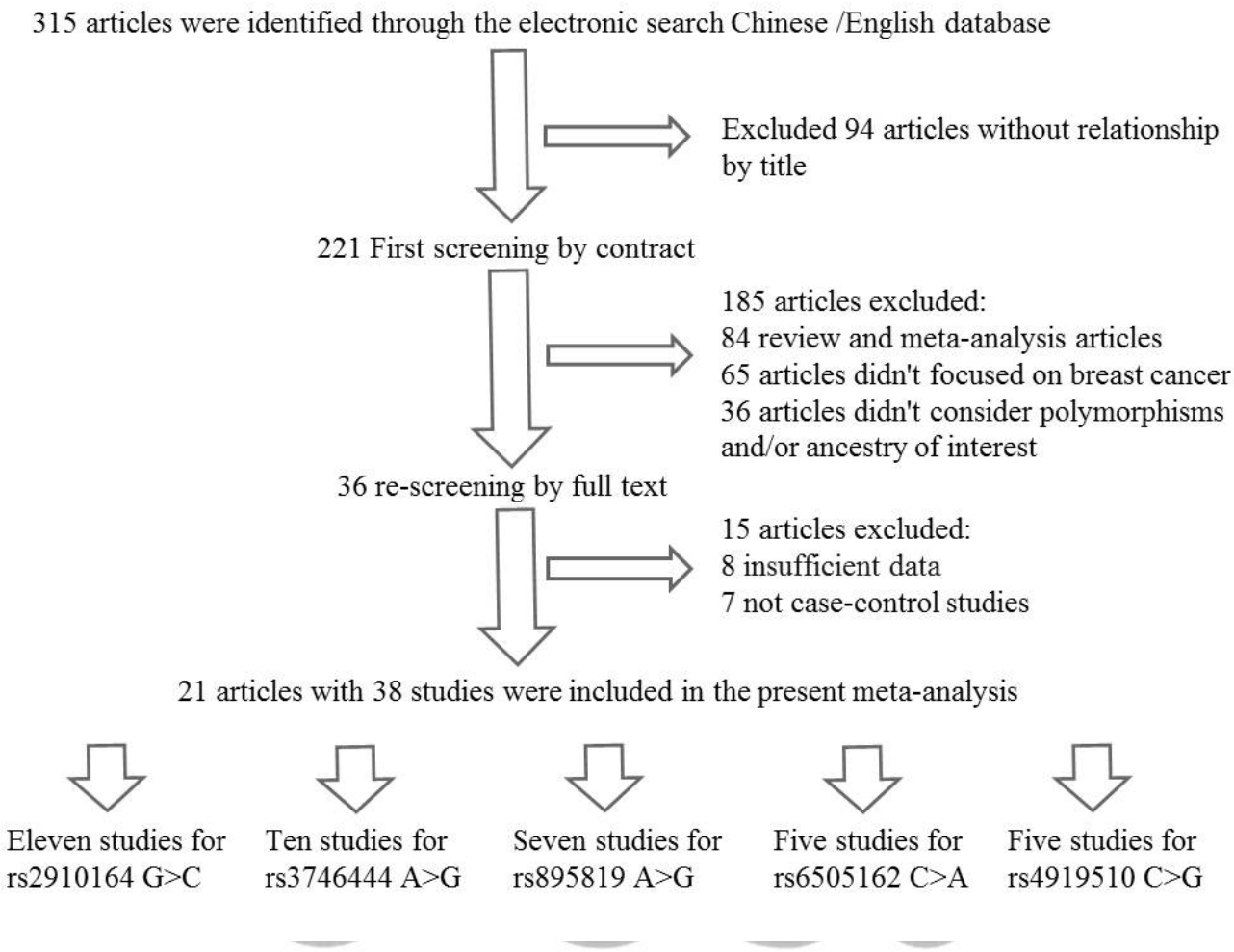

Figure 1 Flow chart of search strategy for eligible studies

III. RESULTS

A. Characteristics of included studies

A total of twenty-One potentially relevant articles withe thirty-eight eligible studies were included in the present meta-analysis (Fig. 1) describing a flow chart of search strategy for eligible studies. Eleven studies (3,179 cases and 3,294 controls) concerning the association between miR-146a rs2910164 G>C and breast cancer [35-45], ten studies (4,042 cases and 3,181 controls) concerning the association between miR-499 rs3746444 A>G and breast cancer [35, 36, 38, 39, 41, 42, 44, 46-48], seven studies (1,967 cases and 2,012 controls) concerning the association between miR-27a rs895819 A>G and breast cancer [35-37, 43, 49-51], five studies (1,057 cases and 1,179 controls) concerning the association between miR-423 rs6505162 C>A and breast cancer [36, 37, 51-53] and five studies (2,185 cases and 2,625 controls) concerning the association between miR-608 rs4919510 C>G and breast cancer [37, 46, 51, 54, 55]. Table 1 lists the main characteristics of the 38 eligible studies included in the present meta-analysis. No study was excluded for deviating from the Hardy-Weinberg equilibrium (HWE).

Egger regression analysis indicated no publication bias for the miR-146a rs2910164 G>C, miR-499 rs3746444 A>G, miR-27a rs895819 A>G, miR-423 rs6505162 C>A and miR-608 rs4919510 C>G gene polymorphisms which indicated reliability of the pooled results (t=-0.08, P=0.936, 95%CI –3.315~3.08, t=-0.14, P=0.893, 95%CI–4.41~4.97, t=1.43, P=0. 213, 95%CI –4.3~15.03, t=0.35, P=0.747, 95%CI –18.18~22.7, t= -1.63, P=0. 201, 95%CI –6.78~2.19, respectively) (data not shown).

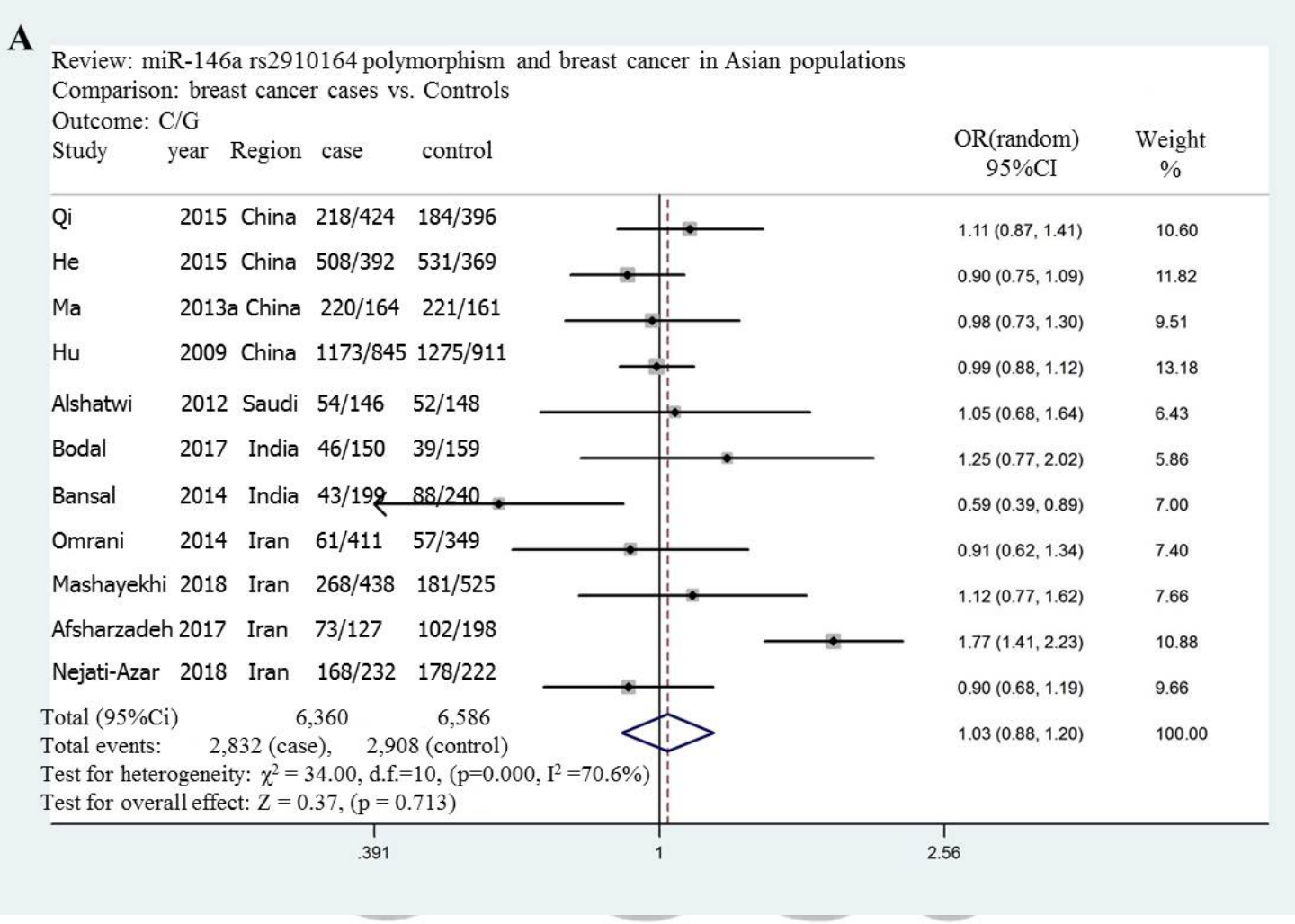

Figure 2A Forest plot for the association between miR-146a rs2910164 polymorphism (G>C) and breast cancer risk in Asian populations under allele contrast model comparison. For each study, the estimate of OR and its 95% CI is plotted with a closed square and horizontal line. The size of the black squares is proportional to the weight that the study has in calculating the summary effect estimate (diamond). The center of the diamond represent the summary estimates of ORs across all listed studies (pooled OR) and the ends of the diamond correspond to the 95% CI. When a confidence interval exceeds the chosen X-axis limit, it will display an arrow head.

B. Mir-146a rs2910164 G>C and breast cancer

Figure 2A represents the forest plot of risk allele OR of an individual studies and meta–analysis for association between miR-146a rs2910164 G>C gene polymorphism and breast cancer in a total of 3,179 patients and 3,294 control subjects from the eleven studies. Five studies, Chinese [35], Saudi [39], Indian [40] and Iranian [43, 44] showed a trend of elevated OR for the risk allele C of the miR-146a rs2910164. One study from China [38] showed no association. Five studies, Chinese [36, 37], Indian [41] and Iranian [42, 45] showed a trend in the opposite direction. The overall frequency of the risk allele C was to 44.53% in cases and 44.15% in controls. Significant between-study heterogeneity was observed (P=0.000, I^2=70.6%). A random effect model was performed and generated a combined allelic OR of 1.03 (95%CI 0.9 - 1.2, P=0.713) for the C allele of miR-146a rs2910164 in Asian populations. The population attributable risk (PAR) of the breast cancer related to this variant was 1.25%.

In the stratified meta-analysis on the basis of ethnicity, four Chinese studies including 1,971 patients and 2,025 control subjects were enrolled. One study [35] showed a trend of elevated OR for the risk allele C. One study [38] showed no association. Two studies [36, 37] showed a trend in the opposite direction. The overall frequency of the risk allele C was to 53.73% in cases and 54.62% in controls. No significant heterogeneity was detected between studies (P = 0. 0.614, I^2 = 0.0%). A fixed effect model was performed and generated a combined allelic OR of 0.98 (95%CI 0.9 - 1.08, P=0.720) for the risk allele C of miR-146a rs2910164 in Chinese populations (data not shown). Seven non-Chinese studies including 1,208 patients and 1,269 control subjects were enrolled. Four studies, Saudi [39], Indian [40] snd Iranian [43, 44], showed a trend of elevated OR for the risk allele C. Three studies, Indian [41] and Iranian [42, 45], showed a trend in the opposite direction. The overall frequency of the risk allele C was to 29.14% in cases and 27.5% in controls. Sig-

nificant between-study heterogeneity was observed (P =0.000, I^2 = 79.1%). A random effect model was performed and generated a combined allelic OR of 1.04 (95%CI 0.78 - 1.4, P=0.766) for the C allele of miR-146a rs2910164 in non-Chinese populations (data not shown).

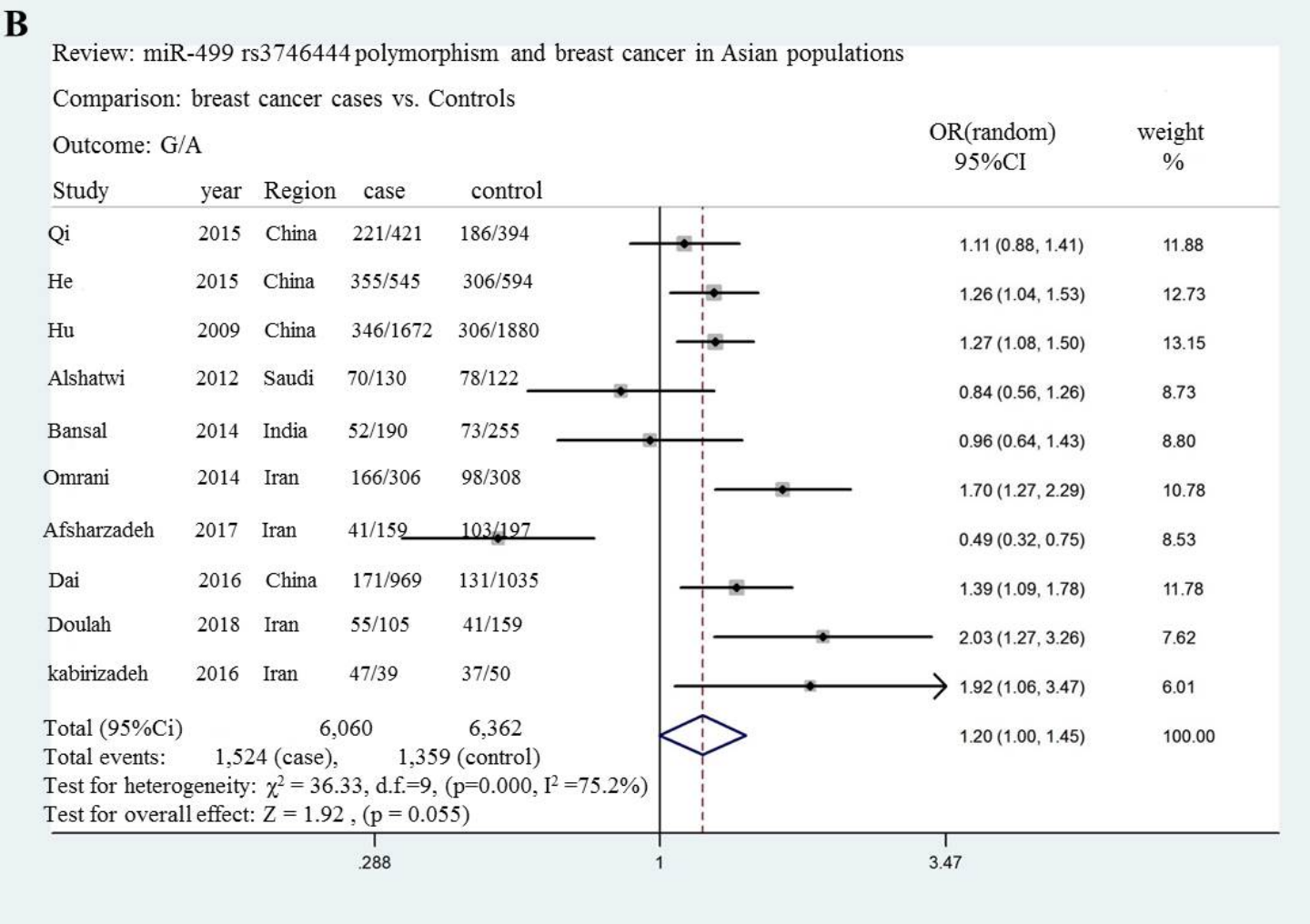

Figure 2B Forest plot for the association between miR-499 rs3746444 polymorphism (A>G) and breast cancer risk in Asian populations under allele contrast model comparison.

C. Mir-499 rs3746444 A>G and breast cancer

Figure 2B represents the forest plot of risk allele OR of an individual studies and meta–analysis for association between miR-499 rs3746444 A>G gene polymorphism and breast cancer in a total of 3,042 patients and 3,181 control subjects from the ten studies. Seven studies, Chinese [35, 36, 38, 46] and Iranian [42, 47, 48] showed a trend of elevated OR for the risk allele G of the miR-499 rs3746444. Three studies, Saudi [39] Indian [41] and Iranian [44] showed a trend in the opposite direction. The overall frequency of the risk allele G was to 25.15% in cases and 21.4% in controls. Significant between-study heterogeneity was observed (P= 0.000, I^2=75.2%). A random effect model was performed and generated a combined allelic OR of 1.2 (95%CI 1.00 - 1.45, P=0.055) for the G allele of miR-499 rs3746444 in the Asian populations. The population attributable risk (PAR) of the breast cancer related to this variant was 4.2%.

In the stratified meta-analysis on the basis of ethnicity, four Chinese studies including 2,340 patients and 2,416 control subjects enrolled. Three studies [35, 38, 46] showed a trend of elevated OR for the risk allele G. One study [36] showed a trend in the opposite direction. The overall frequency of the risk allele G was to 23.25% in cases and 42.5% in controls. No heterogeneity between-study was observed (P = 0.631, I^2 = 0.0 %). A random effect model was performed and generated a combined allelic OR of 1.3 (95%CI 1.14 - 1.39, P=0.000) for the G allele of miR-499 rs3746444 in Chinese populations (data not shown). Six non-Chinese studies including 702 patients and 765 control subjects were enrolled. Three studies from Iranian [42, 47, 48] showed a trend of elevated OR for the risk allele G. Three studies, Saudi [39], Indian [41] and Iranian [44] showed a trend in the opposite direction. The overall frequency of the risk allele G was to 31.7% in cases and 28.1% in controls. Significant between-study heterogeneity was observed (P =0.000,

I^2 = 85.3%). A random effect model was performed and generated a combined allelic OR of 1.2 (95%CI 0.7 - 1.8, P=0.502) for the G allele of miR-499 rs3746444 in non-Chinese populations (data not shown).

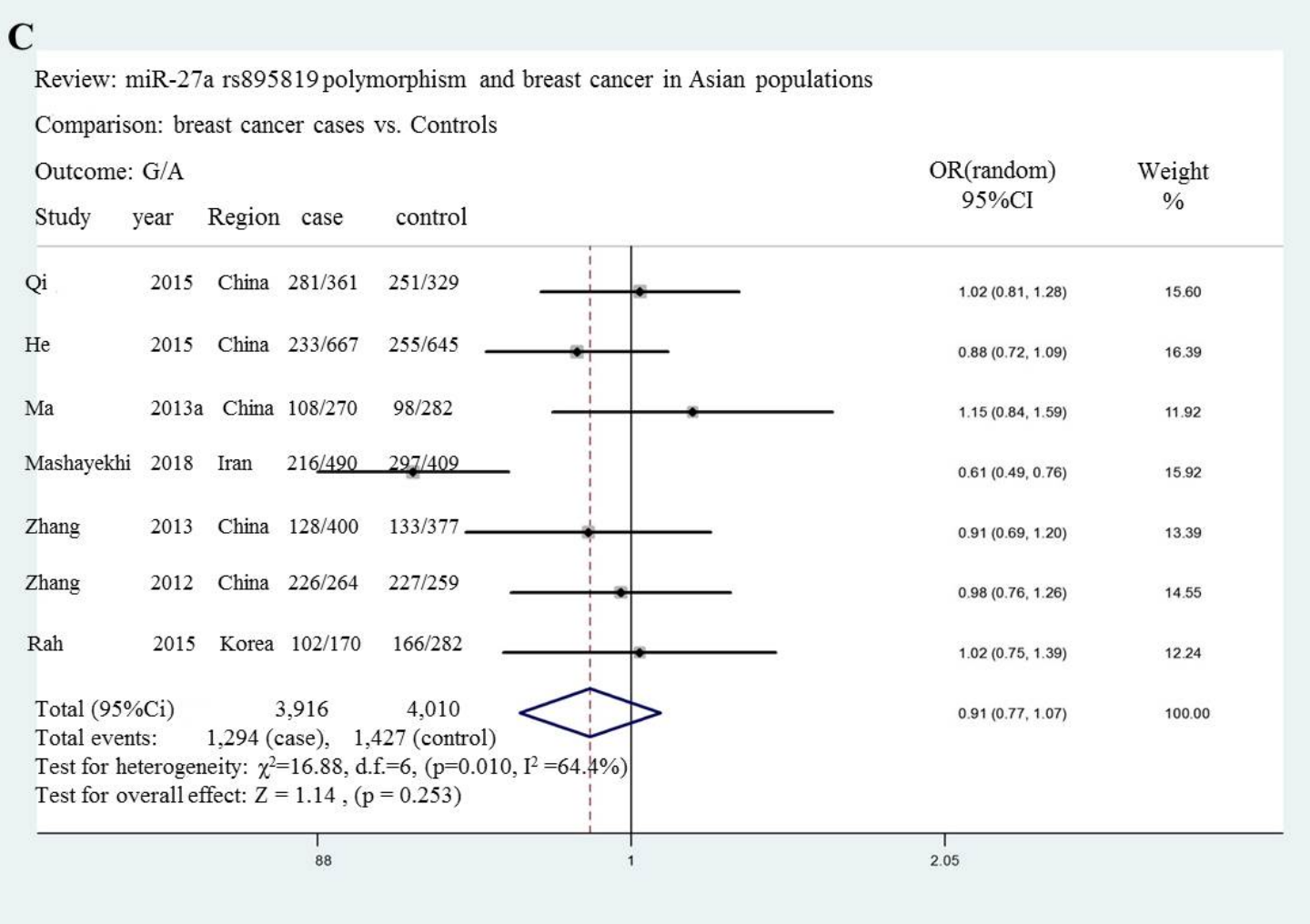

Figure 2C Forest plot for the association between miR-27a rs895819 polymorphism (A>G) and breast cancer risk in Asian populations under allele contrast model comparison.

D. Mir-27a rs895819 A>G and breast cancer

Figure 2C represents the forest plot of risk allele OR of an individual studies and meta–analysis for association between miR-27a rs895819 A>G gene polymorphism and breast cancer in a total of 1,967 patients and 2,012 control subjects from the seven studies. Three studies, Chinese [35, 37] and Korean [51] showed a trend of elevated OR for the risk allele G of miR-27a rs895819. Four studies, Iranian [43] and Chinese [36, 49, 50] showed a trend in the opposite direction. The overall frequency of the risk allele G was to 33.04% in cases and 35.6% in controls. Significant between-study heterogeneity was observed (P= 0.010, I^2=64.4%). A random effect model was performed and generated a combined allelic OR of 0.91 (95%CI 0.77 - 1.07, P=0. 0.253) for the G allele of miR-27a rs895819 in the Asian populations.

In the stratified meta-analysis on the basis of ethnicity, five Chinese studies including 1478 patients and 1435 control subjects enrolled. Two studies [35, 37] showed a trend of elevated OR for the risk allele G. Three studies [36, 49, 50] showed a trend in the opposite direction. The overall frequency of the risk allele G was to 33.22% in cases and 33.75% in controls. No significant heterogeneity was detected between studies (P = 0. 0.684, I^2 = 0.0%). A fixed effect model was performed and generated a combined allelic OR of 0. 97 (95%CI 0.86 - 1.1, P=0.555) for the risk allele G of miR-27a rs895819 in Chinese populations (data not shown). Two non-Chinese studies including 489 patients and 577 control subjects were enrolled. One study from Korea [51] showed a trend of elevated OR for the risk allele G. One study from Iran [43] showed a trend in the opposite direction. The overall frequency of the risk allele G was to 32.5% in cases and 40.12% in controls. Significant between-study heterogeneity was observed (P =0.008, I^2 = 85.9%). A random effect model was performed and generated a combined allelic OR of 0.78 (95%CI 0.47 - 1.3, P=0.330) for the G allele of miR-27a rs895819 in non-Chinese populations (data not shown).

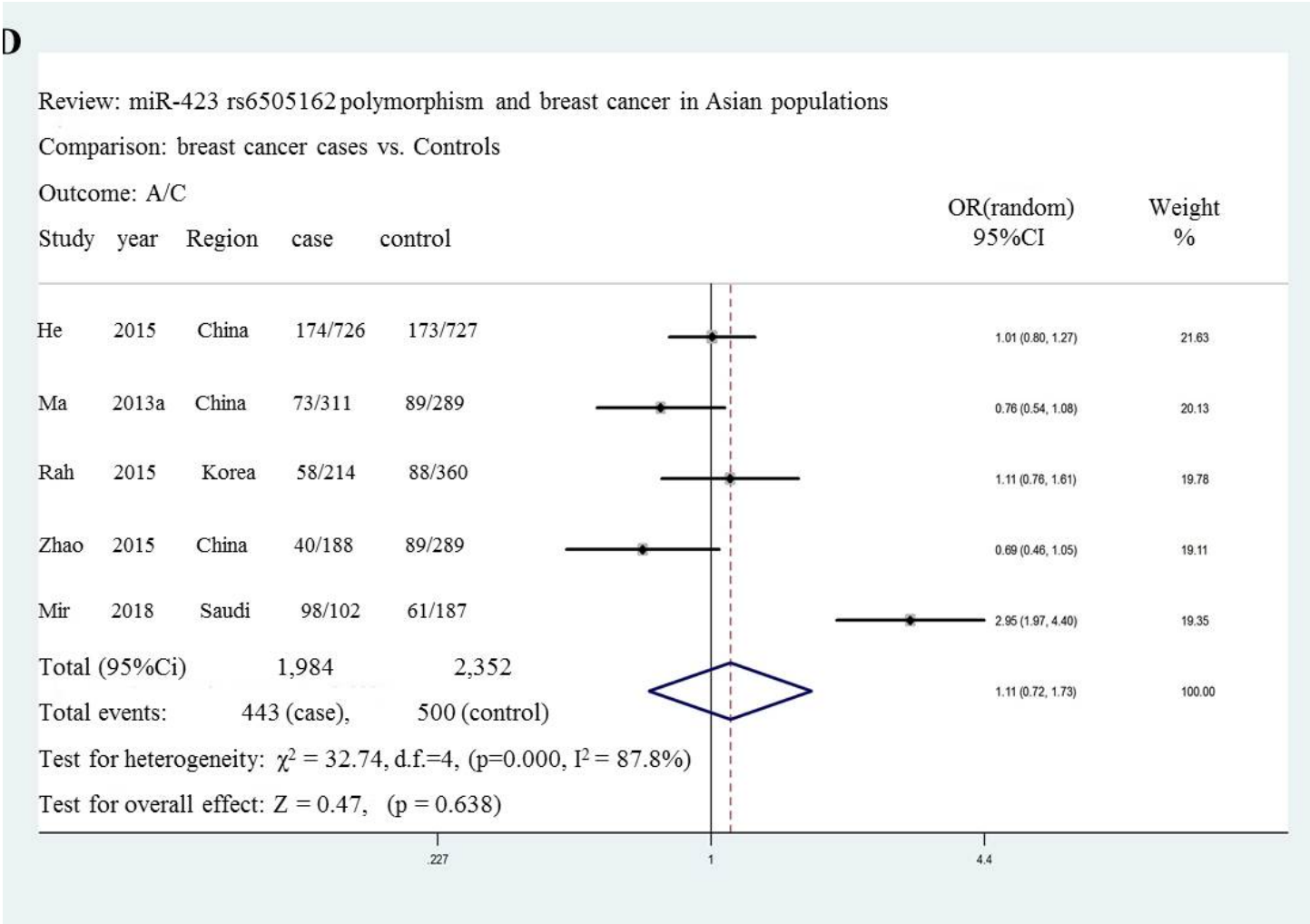

Figure 2D Forest plot for the association between miR-423 rs6505162 polymorphism (C>A) and breast cancer risk in Asian populations under allele contrast model comparison.

E. Mir-423 rs6505162 C>A and breast cancer

Figure 2D represents the forest plot of risk allele OR of an individual studies and meta–analysis for association between miR-423 rs6505162 C>A gene polymorphism and breast cancer in a total of 1,057 patients and 1,179 control subjects from the five studies. Three studies, Chinese [36], Korean [51] and Saudi [53] showed a trend of elevated OR for the risk allele A of miR-423 rs6505162. Two studies, from China [37, 52] showed a trend in the opposite direction. The overall frequency of the risk allele A was to 22.33% in cases and 21.26% in controls. Significant between-study heterogeneity was observed (P = 0. 0.000, I^2 = 87.8%). A random effect model was performed and generated a combined allelic OR of 1.11 (95%CI 0.72 - 1.73, P=0.638) for the A allele of miR-423 rs6505162 in Asian populations. The population attributable risk (PAR) of the breast cancer related to this variant was 2.2%.

In the stratified meta-analysis on the basis of ethnicity, three Chinese studies including 821 patients and 831 control subjects enrolled. One study [36] showed a trend of elevated OR for the risk allele A. Two studies [37, 52] showed a trend in the opposite direction. The overall frequency of the risk allele A was to 19.0% in cases and 21.2% in controls. No significant heterogeneity was detected between studies (P = 0. 0.199, I^2 = 38.0%). A fixed effect model was performed and generated a combined allelic OR of 0.875 (95%CI 0.73 - 1.04, P=0.137) for the risk allele A of miR-423 rs6505162 in Chinese populations (data not shown). Two non-Chinese studies including 236 patients and 348 control subjects were enrolled. The two studies, Korean [51] and Saudi [53] showed a trend of elevated OR for the risk allele A. The overall frequency of the risk allele A was to 33.05% in cases and 21.41% in controls. Significant between-study heterogeneity was observed (P =0.000, I^2 = 91.8%). A random effect model was performed and generated a combined allelic OR of 1.8 (95%CI 0.69 - 4.69, P=0.228) for the risk allele A of miR-423 rs6505162 in non-Chinese populations (data not shown).

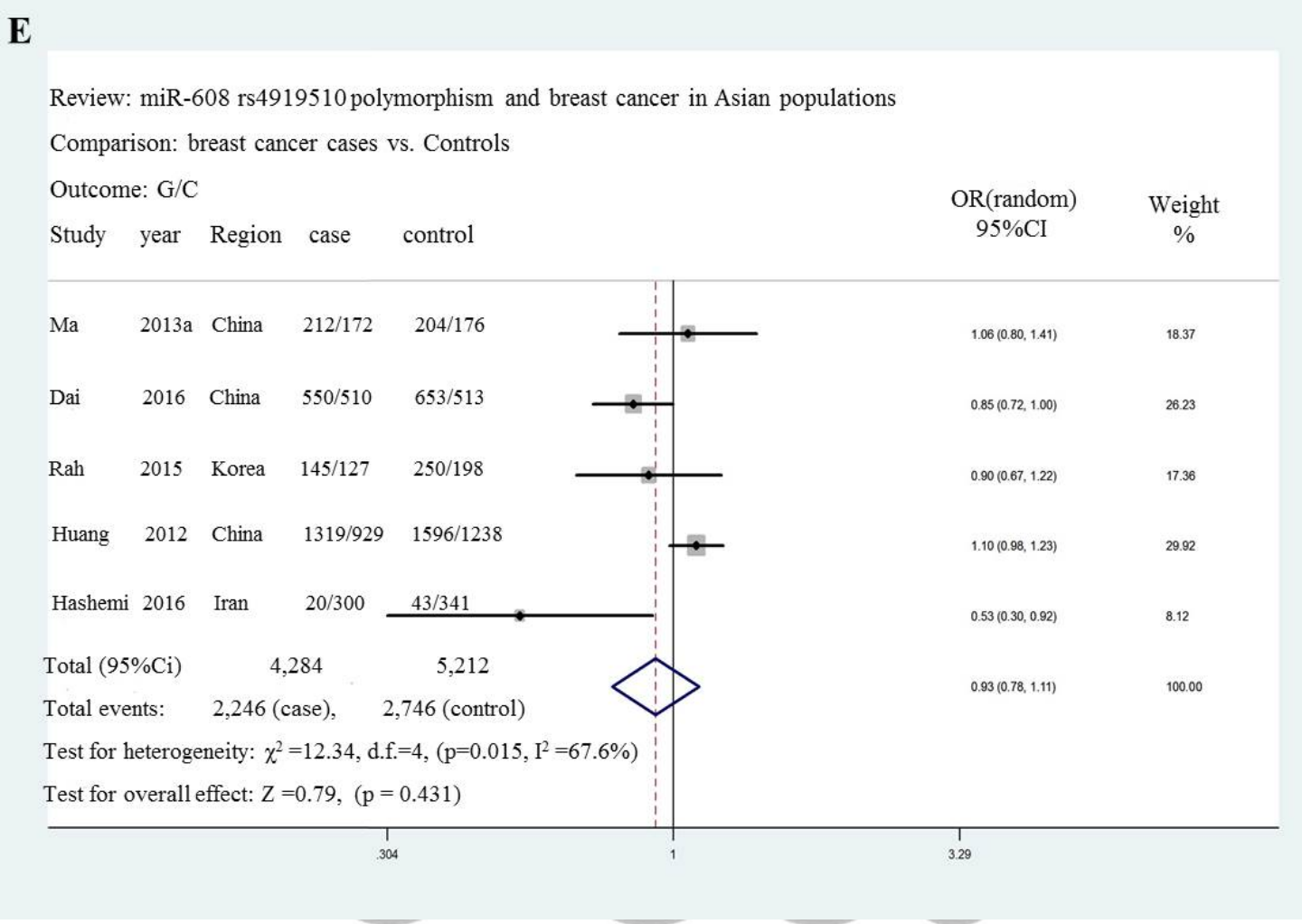

Figure 2E Forest plot for the association between miR-608 rs4919510 polymorphism (C>G) and breast cancer risk in Asian populations under allele contrast model comparison.

F. Mir-608 rs4919510 C>G and breast cancer

Figure 2E represents the forest plot of risk allele OR of an individual studies and meta–analysis for association between miR-608 rs4919510 C>G gene polymorphism and breast cancer in a total of 2,185 patients and 2,625 control subjects from the five studies. Two studies from China [37, 54] showed a trend of elevated OR for the risk allele G of miR-608 rs4919510. Three studies, Chinese [46], Korea [51] and Iranian [55] showed a trend in the opposite direction. The overall frequency of the risk allele G was to 52.45% in cases and 52.7% in controls. Significant between-study heterogeneity was observed (P = 0.015, I^2 = 67.6%). A random effect model was performed and generated a combined allelic OR of 0.93 (95%CI 0.78 - 1.11, P=0.431) for the G allele of miR-608 rs4919510 in Asian populations.

In the stratified meta-analysis on the basis of ethnicity, three Chinese studies including 1,889 patients and 2,209 control subjects enrolled. Two studies [37, 54] showed a trend of elevated OR for the risk allele G. One study [46] showed a trend in the opposite direction. The overall frequency of the risk allele G was to 56.4% in cases and 56.0% in controls. Significant between-study heterogeneity was observed (P = 0.036, I^2 = 69.8%). A random effect model was performed and generated a combined allelic OR of 1.00 (95%CI 0.83 - 1.2, P=0.966) for the G allele of miR-608 rs4919510 in Chinese populations (data not shown). Two non-Chinese studies including 296 patients and 416 control subjects were enrolled. The two studies, Korean [51] and Iranian [55] showed a trend of decreased OR for the risk allele G. The overall frequency of the risk allele G was to 27.9% in cases and 35.22% in controls. Significant between-study heterogeneity was observed (P =0.095, I^2 = 64.2%). A random effect model was performed and generated a combined allelic OR of 0.73 (95%CI 0.43 - 1.2, P=0.229) for the risk allele G of miR-608 rs4919510 in non-Chinese populations (data not shown).

IV. DISCUSSION

Breast cancer is the one of most common malignant diseases in the world. Many treatment measures have been conducted in recent decades. However, the morbidity and mortality are still high, and the prognosis is still poor. Recently, with the elucidation of pathogenesis mechanism for the interactions between microRNAs and cancer development, an increasing amount of attention has been paid to the association between the SNPs of microRNAs and breast cancer risks. Over the past decade, a growing number of case-control studies have examined the association of several miRNAs SNPs with the risk of breast cancer in same or different ethnicities have been published; [35-63]. However, the results were inconsistent and ofen contradictory.

Besides, several meta-analyses have been published [64-90], but, there was no clear consensus has been reached. Given the controversial results in previous meta-analyses, and no previous meta-analysis was independently conducted in Asian populations. Therefore, we conducted a more comprehensive approach and subgroup analysis of all Asian eligible case–control studies to investigate this inconsistency, and evaluate more reliably the association between these five common miRNA SNPs (miR-146a rs2910164 G>C, miR-499 rs3746444 A>G, miR-27a rs895819 A>G, miR-423 rs6505162 C>A and miR-608 rs4919510 C>G) and breast cancer risk, especially in Asian populations.

In the overall estimates, the results of the present meta-analysis demonstrate that only G allele of miR-499 rs3746444 was showed a borderline association with an increased risk of the breast cancer in Asian populations, a combined allelic OR of 1.2 (95%CI 1. 00 - 1.45, P=0.055) for the G allele of miR-499 rs3746444 polymorphismin Asian populations, and significant association with an increased risk of the breast cancer in Chinese populations, a combined allelic OR of 1.3 (95%CI 1.138 - 1.393, P=0.000) for the G allele of miR-499 rs3746444 polymorphism in Chinese populations.This finding is consistent with the results of previously published meta-analyses, in which the G allele of miR-499 rs3746444 was significantly associated with an increased risk of breast cancer in the overall population and especially in Asians but not Caucasians [64, 67, 68, 70, 73 -76], in all subject but not in Asians ore Caucasian population [65, 69, 77, 78, 79], and in Chinese but not in Asians [80]. Moreover, the other meta-analysis confirmed that the miR-499 rs3746444 was significantly associated with the risk for multiple types of cancer in different system; respiratory, digestive, urinary and gynecological systems [81]. In addition, the result of Torruella-Loran et al., (2016) study reported that the variant allele of the rs3746444 polymorphism gave rise to a higher level of miR-499 and caused a significant decrease in the expression of tumor suppressor genes, thereby leading to an increase in breast cancer susceptibility [82]. Recently, in silico analysis showed that the A-to-G substitution resulted in a higher affinity of miR-499 for tumor suppressor genes, which could explain the increased breast cancer susceptibility associated with the variant allele [76]. However, the result of present meta-analysis was inconsistent with the other meta-analysis [66]. The difference may be due to the limited number of studies used in this analysis and the relatively small number of patients suitable for inclusion (nine in the present study vs. three in [66], which may have generated a fluctuated risk estimate [83]. Furthermore, no significant association was detected for the other SNP, miR-146a rs2910164, miR-27a rs895819, miR-423 rs6505162 and miR-608 rs4919510 gene polymorphisms with breast cancer risk in the overall population or the ethnic subgroups studied. For miR-146a rs2910164, the present meta-analysis did not detect any association between this SNP and breast cancer risk in Asian populations. Similarly, in the ethnic subgroup analysis, the significant association were not observed in Chinese nor non-Chinese populations. Consistent with previously reported results [66 - 68, 70, 72, 74, 79, 80, 84 - 87], which reported no association of this SNP with the breast cancer risk in Caucasians or Asians. However, inconsistent with the others [64, 88], which reported a significant association of this SNP with an increased risk of breast cancer in Caucasian but not in Asians population. For miR-27a rs895819 A>G, the present meta-analysis did not detect any significant association between this SNP and breast cancer risk in Asian populations, consistent with previously reported results [74], which reported no association of this SNP with the risk of breast cancer. However, some previously meta-analyses were reported a significant association of miR-27a rs895819 A>G with decreased breast cancer risk, especially in Caucasians but not Asians [70, 72, 89] or in all subject but not in Asian ore Caucasian populations [64, 90, 91]. For miR-423 rs6505162, the present meta-analysis did not detect any significant association between this SNP and breast cancer risk in Asian populations, consistent with previously reported results [70, 71, 91], which reported no association of this SNP with the breast cancer risk in Caucasians or Asians. For miR-608 rs4919510 C>G the present meta-analysis did not detect any significant association between this SNP and breast cancer risk in Asian populations, consistent with previously reported results [70, 72].

There are several specific limitations complicate the interpretation this meta-analysis. Firstly, the sample size was still relatively small for the stratified analyses. Secondly, lack of original data of the included studies, which would allow for the adjustment by other covariants including age, gender, obesity, family history, environmental factors, lifestyle, smoking, drinking, and other personal habits. Thirdly, although we limit our meta-analysis to Asian populations, meta-analysis still revealed significant between-study heterogeneity, that was especially high for the miR-423 rs6505162 C>A polymorphism, which could interfere with our results. Between-study heterogeneity probably due to: 1) Different baseline characteristics with regard to the distributions of age and gender, histological type, tumor stage; 2) The sources of the control groups are slightly different: some from the population base, some from the hospital base. The different sources of control may affect the representativeness of the sample; 3) Difference in the Genotyping methods among the included studies which could bring about the existence of heterogeneity; 4) Hardy-Weinberg equilibrium is the principal law in population genetic studies. Generally, meeting Hardy-Weinberg equilibrium suggests that samples have representation. The genotypic distributions of these SNPs were in Hardy-Weinberg equilibrium in both breast cancer patients and control groups in all selected studies for the present meta-analysis. Sometimes Hardy-Weinberg equilibrium was met, but the genotype frequency was

not always consistent to that of the local population, although we used several statistical methods to minimize the effect of the heterogeneity, including the random effects model, subgroup analysis, and meta-regression. Nevertheless, our results should be interpreted with caution.

In spite of these limitations, we believe that the results of the present meta-analysis are reliable for the several reasons. First, the genotype distributions in the controls of this SNP were all mostly consistent with HWE. Second, no apparent publication bias was observed by either Begg's funnel plot or Egger's test. Third, all included studies used high quality genotyping methods according to the methodological quality assessment. Fourthly, the present study includes more new case-control studies thsn that of previously reported meta-analysis, which will expand the sample size and thus get a more precise evaluation of association between these SNPs and breast cancer risk. Moreover, the present meta-analysis provided the most comprehensive evaluation of the associations between the five common miRNAs SNPs, miR-146a rs2910164 G>C, miR-499 rs3746444 A>G, miR-27a rs895819 A>G, miR-423 rs6505162 C>A, miR-608 rs4919510 C>G gene polymorphisms and the breast cancer risk in Asian populations.

Interestingly, the etiology of breast cancer varies according to age of onset, menopausal status of women, exposure to hormone replacement therapies (HRTs), and patient ethnicity [100]. These multiple factors have been associated with differences in risk and outcome. MiRNA expression varies between tumor types, and can exert a range of functional effects depending on the cellular context [101]. MiRNA expression and targeting should be significantly altered by the presence of single nucleotide polymorphisms (SNPs). SNPs that affecting proteins responsible for post-transcriptional processing of miRNAs can signicantly affect miRNA function. miRNAs go through two rounds of enzymatic processing after initial transcription-processes, which implicate miRNA-specicexonucleases, transport proteins, and signaling cascades [102]. The resulting changes to levels of mature miRNA can have signicant effects on breast cancer. The overall effect of a miR-SNP on miRNA function depends on its location; miR-SNPs can result in over-expression, degradation, or transcriptional or translational inhibition of miRNAs or targeted mRNA [103].

V. CONCLUSION

To the best of our knowledge, this is the first, largest and most recent meta-analysis to investigate the association between five common miRNA SNPs and the breast cancer risk in Asian populations. Though with limitations, this meta-analysis suggested that G allele of miR-499 rs3746444 polymorphism was associated with the risk of breast cancer in Asians and especially in Chinese populations. However, no significant association was found for miR-146a rs2910164, miR-27a rs895819, miR-423 rs6505162 and miR-608 rs4919510 polymorphisms with the risk of breast cancer. These results should be treated with some caution due to the limitations above. Therefore, more adequately powered studies with available complete information are still warranted to achieve a more comprehensive evaluation and reliable result for the associations of the five miRNAs SNPs with the risk of breast cancer in Asian populations.

Author contributions

Mustafa AbdoSaifDehwa designed the study, analysed the data, prepared the manuscript and revised critical data; and EmadNajeep Ali searched the literature

REFERENCES

[1] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries", CA Cancer J Clin, vol. 68, no. 6, 2018, pp. 394-424. Doi: 10.3322/caac.21492.

[2] S. Vasishta, S. Ramesh, S. Babu, and A.S. Ramakrishnegowda, "Awareness about breast cancer and outcome of teaching on breast self-examination in female degree college students", Indian J Med Res, vol. 9, no. 2, 2018, pp.56–59. Doi.org/10.1016/j.injms.2018.03.002.

[3] R. Taheripanah, F. Balash, R. Anbiaee, M. Mahmoodi, and A.A. Sene, (2018). "Breast cancer and ovulation induction treatments". Clin. Breast cancer, 18(5): 395-399. Doi: 10.1016/j.clbc.2018.03.003.

[4] M.C. van Maaren, M. Lagendijk, M.M. Tilanus-Linthorst, L. de Munck, R.M. Pijnappel, M.K. Schmidt,... and S. Siesling, "Breast cancer-related deaths according to grade in ductal carcinoma in situ: A Dutch population-based study on patients diagnosed between 1999 and 2012", Eur J Cancer, vol. 101, 2018, pp. 134–142. Doi: 10.1016/jj.ejca.2018.07.003.

[5] T. Aryandono, and S. Harijad, "Survival from operable breast cancer: prognostic factors in Yogyakarta, Indonesia", Asian Pac J Cancer Prev, vol.7, no. 3, 2006, pp. 455-459.

[6] D.R. Youlden, S.M. Cramb, N.A.M. Dunn, J.M. Muller, C.M. Pyke, and P.D. Baade, "The descriptive epidemiology of female breast cancer: An international comparison of screening, incidence, survival and mortality", Cancer Epidemiol, bol. 36, no. 3, 2012, pp. 237–48. Doi: 10.1016/j.canep.2012.02.007.

[7] S.L. Robbins, V. Kumar, and R.S. Cotran, "Robbins and Cotran Pathologic Basis of Disease". Philadelphia, PA: Saunders/Elsevier, 2010.

[8] T. Strachan, and A. Read, "Human molecular genetics", Fourth Edition, New York: Garland Science, 2011.

[9] R.A. Weinberg, "The biology of cancer", First Edition, Garland Science, 2007.

[10] K. McPherson, C.M. Steel, and J.M. Dixon, "ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics", BMJ, vol. 321, no. 7261, 2000, pp.

624–628. Doi: 10.1136/bmj.321.7261.624.

[11] C. Wendt, and S. Margolin, "Identifying breast cancer susceptibility genes - a review of the genetic background in familial breast cancer", ActaOncol, vol. 58, no. 2, 2019, pp. 135–146. Doi: 10.1080/0284186X.2018.1529428.

[12] S. Anfossi, X. Fu, R. Nagvekar, and G.A. Calin, "MicroRNAs, Regulatory Messengers Inside and Outside Cancer Cells", AdvExp Med Biol, vol.1056, 2018, pp. 87–108. Doi: 10.1007/978-3-319-74470-4_6.

[13] S.L. Teoh, and S. Das, "The Role of MicroRNAs in Diagnosis, Prognosis, Metastasis and Resistant Cases in Breast Cancer", Curr Pharm Des, vol. 23, no. 12, 2017,1845-1859. Doi: 10.2174/1381612822666161027120043.

[14] S. Das, I. N. Mohamed, S. L. Teoh, T. Thevaraj, K.N.K.A. Nasir, Z. Zawawi,... and D.K. Zhou, "Micro-RNA and the Features of Metabolic Syndrome: A Narrative Review", Mini Rev Med Chem, vol. 20, no.7, 2020, pp. 626–635. Doi: 10.2174/1389557520666200122124445.

[15] M. Bhaskaran, and M. Mohan, "MicroRNAs: History, biogenesis, and their evolving role in animal development and disease", Vet Pathol, vol. 51, no.4, 2014, 759–774. Doi: 10.1177/0300985813502820.

[16] N. Dahiya, T. Sarachana, L. Vu, K.G. Becker, W.H. Wood 3rd, Y., Zhang, and C.D. Atreya, "Platelet micro- RNAs: an overview", Transfus Med Rev, vol. 29, no. 4, 2015, pp. 215–219. Doi: 10.1016/j.tmrv.2015.08.002.

[17] Z. Ghosh, B. Mallick, and J. Chakrabarti, "Cellular versus viral microRNAs in host-virus interaction", Nucleic Acids Res, vol. 37, no. 4, 2009, pp.1035–48. Doi: 10.1093/nar/gkn1004.

[18] K.N. Ivey, and D. Srivastava, "MicroRNAs as regulators of differentiation and cell fate decisions", Cell Stem Cell, vol. 7, no. 1, 2010, pp. 36–41. Doi: 10.1016/j.stem.2010.06.012.

[19] M. Esteller, "Non-coding RNAs in human disease", Nat Rev Genet, vol. 12, no. 12, 2011, pp. 861–74. Doi: 10.1038/nrg3074.

[20] X. Li, W. Chen, and W. Zeng, "MicroRNA-137 promotes apoptosis in ovarian cancer cells via the regulation of XIAP", Br J Cancer, vol. 116, no. 1, 2017, pp.66–76. Doi: 10.1038/bjc.2016.379.

[21] G.A, Calin, C. Sevignani, C.D. Dumitru, T. Hyslop, E. Noch, S. Yendamuri,... and C.M. Croce, "Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers", ProcNatlAcadSci U S A, vol. 101, no. 9, 2004, pp. 2999–3004. Doi: 10.1073/pnas.0307323101.

[22] A. Esquela-Kerscher, and F.J. Slack, "OncomiRs—microRNAs with a role in cancer", Nat Rev Cancer, vol. 6, no. 4, 2006, pp. 259–269. Doi: 10.1038/nrc1840.

[23] R.A. Shivdasani, "MicroRNAs: regulators of gene expression and cell differentiation", Blood, vol. 108, no. 12, 2016, pp. 3646–53. Doi: 10.1182/blood-2006-01-030015.

[24] A. Gaur, D.A. Jewell, Y. Liang, D. Ridzon, J.H. Moore, C. Chen,... and M.A. Israel, "Characterization of microRNA expression levels and their biological correlates in human cancer cell lines", Cancer Res, vol. 67, no. 6, 2007, pp. 2456–2468. Doi: 10.1158/0008-5472.CAN-06-2698.

[25] T. A. Farazi, J. I. Spitzer, P. Morozov, and T. Tuschl, "MiRNAs in human cancer", J Pathol, vol. 223, no. 2, 2011a, pp. 102–15. Doi: 10.1002/path.2806.

[26] Z. Yu, R. Baserga, L. Chen, C. Wang, M.P. Lisanti, and R.G. Pestell, "MicroRNA, Cell Cycle, and Human Breast Cancer" Am J Pathol, vol. 176, no. 3, 2010, pp. 1058–1064. Doi: 10.2353/ajpath.2010.090664.

[27] T.A. Farazi, H.M. Horlings, J.J. Ten Hoeve, A. Mihailovic, H. Halfwerk, P. Morozov,... and T. Thomas, "MicroRNA sequence and expression analysis in breast tumors by deep sequencing", Cancer Res, vol. 71, no. 13, 2011b, pp.4443–4453. Doi: 10.1158/0008-5472.CAN-11-0608.

[28] H.C. Lee, C.W. Yang, C.Y. Chen, and L.C. Au, "Single point mutation of microRNA may cause butterfly effect on alteration of global gene expression", BiochemBiophys Res Commun, vol. 404, no. 4, 2011, pp.1065–1069. Doi: 10.1016/j.bbrc.2010.12.114.

[29] B.M. Ryan, A.I. Robles, and C.C. Harris, "Genetic variation in microRNA networks: the implications for cancer research". Nat Rev Cancer, vol. 10, no. 6, 2010, 389–402. Doi: 10.1038/nrc2867.

[30] M.S. Nicoloso, H. Sun, R. Spizzo, H. Kim, P. Wickramasinghe, M. Shimizu,... and G.A. Calin, "Single-nucleotide polymorphisms inside microRNA target sites influence tumor susceptibility", Cancer Res, vol. 70, no. 7, 2010, pp. 2789-2798. Doi: 10.1158/0008-5472.CAN-09-3541.

[31] L.E. Mullany, R.K. Wolff, J.S. Herrick, M.F. Buas, and M.L. Slattery, "SNP regulation of microRNA expression and subsequent colon cancer risk", PLoS One, vol. 10, no. 12, 2015, e0143894. Doi: 10.1371/journal.pone.0143894.

[32] V. Pipan, M. Zorc, and T. Kunej, "MicroRNA polymorphisms in cancer: a literature analysis", Cancers (Basel) vol. 7, no. 3, 2015, pp. 1806–1814. Doi: 10.3390/cancers7030863.

[33] S. Chang, S. He, G. Qiu, L. Lu, J. Wang, J. Liu,... and X. Che, "MicroRNA-125b promotes invasion and metastasis of gastric cancer by targeting STARD13 and NEU1", TumourBiol, vol. 37, no. 9, 2016, pp. 12141–12151. Doi: 10.1007/s13277-016-5094-y.

[34] E. O'Day, and A. Lal, "MicroRNAs and their target gene networks in breast cancer", Breast Cancer Res, vol. 12, no. 2, 2010,201. Doi: 10.1186/bcr2484.

[35] P. Qi, L. Wang, B. Zhou, W.J. Yao, S. Xu, Y. Zhou, and Z.B. Xie, "Associations of miRNA polymorphisms and expression levels with breast cancer risk in the Chinese population", Genet Mol Res, vol. 14, no. 2, 2015, pp. 6289–6296. Doi: 10.4238/2015.June.11.2.

[36] B. He, Y. Pan, Y. Xu, Q. Deng, H. Sun, T. Gao, and S. Wang, "Associations of polymorphisms in microRNAs with female breast cancer risk in Chinese population", TumourBiol, vol. 36, no. 6, 2015, pp. 4575–82. Doi: 10.1007/s13277-015-3102-2.

[37] F. Ma, P. Zhang, D. Lin, D. Yu, P. Yuan, J. Wang,... and B. Xu, "There is no association between microrna gene polymorphisms and risk of triple negative breast cancer in a Chinese Han population". PLoS One, vol. 8, no. 3, 2013a, e60195. Doi: 10.1371/journal.pone.0060195.

[38] Z. Hu, L. Liang, Z. Wang, T. Tian, X. Zhou, J. Chen,... and H. Shen, "Common genetic variants in pre-microRNAs were associated with increased risk of breast cancer in Chinese women", Hum Mutat, vol. 30, no. 1, 2009,pp. 79–84. Doi: 10.1002/humu.20837.

[39] A.A. Alshatwi, G. Shafi, T.N. Hasan, N.A. Syed, A.A. Al-Hazzani, M.A. Alsaif, and A.A. Alsaif, "Differential expression profile and genetic variants of microRNAs sequences in breast cancer patients", PLoS One, vol. 7, no. 2, 2012, e30049. Doi: 10.1371/journal.pone.0030049.

[40] V.K. Bodal, S. Sangwan, M.S. Bal, M. Kaur, S. Sharma, and B. Kaur, "Association between Microrna 146a and Microrna 196a2 Genes Polymorphism and Breast Cancer Risk in North Indian Women", Asian Pac J Cancer Prev, vol. 18, no. 9, 2017, pp. 2345–2348. Doi:10.22034/APJCP.2017.18.9.2345.

[41] C. Bansal, K.L. Sharma, S. Misra, A.N. Srivastava, B. Mittal, and U.S. Singh, "Common genetic variants in pre-microRNAs and risk of breast cancer in the North Indian population", Ecancermedicalscience, 8, 2014, 473. Doi: 10.3332/ecancer.2014.473.

[42] M., Omrani, M. Hashemi, E. Eskandari-Nasab, S.S. Hasani, M.A. Mashhadi, F. Arbabi, and M. Taheri, "Hsa-mir-499 rs3746444 gene polymorphism is associated with susceptibility to breast cancer in an Iranian population", Biomark Med, vol. 8, no. 2, 2014, pp. 259–267. Doi: 10.2217/bmm.13.118.

[43] S. Mashayekhi, S. H. Saeidi, Z. Salehi, S. Soltanipour, and E. Mirzajani, "Effects of miR-27a, miR-196a2 and miR-146a polymorphisms on the risk of breast cancer", Br J Biomed Sci, vol. 75, no. 2, 2018, pp. 76–81. Doi: 10.1080/09674845.2017.1399572.

[44] S.M. Afsharzadeh, S.M.M. Ardebili, S.M. Seyedi, N.K. Fathi, and M. Mojarrad, "Association between rs11614913, rs3746444, rs2910164 and occurrence of breast cancer in Iranian population", Meta Gene, vol. 11, no. c, 2007, pp. 20–25. Doi: 10.1016/j.mgene.2016.11.004.

[45] A. Nejati-Azar, and M.R. Alivand, "MiRNA 196a2 (rs11614913) & 146a (rs2910164) polymorphisms & breast cancer risk for women in an Iranian population", Per Med, vol. 15, no. 4, 2018, pp. 279–289. Doi: 10.2217/pme-2017-0088.

[46] Z.M. Dai, H.F. Kang, W.G. Zhang, H.B. Li, S.Q. Zhang, X.B. Ma,... and Z.J. Dai, "The associations of single nucleotide polymorphisms in miR196a2, miR-499, and miR-608 with breast cancer susceptibility: a STROBEC ompliant Observational Study", Medicine (Baltimore), vol. 95, no. 7, 2016, e2826. Doi: 10.1097/MD.0000000000002826.

[47] A. Doulah, A. Salehzadeh, and M. Mojarrad, "Association of single nucleotide polymorphisms in miR- 499 and miR-196a with susceptibility to breast cancer", Tropi J Pharma Res, vol. 17, no. 2, 2018, pp. 319–323. Doi: 10.4314/tjpr.v17i2.17.

[48] S. Kabirizadeh, M. Azadeh, M. Mirhosseini, K. Ghaedi, and H.M. Tanha, "The SNP rs3746444 within miR-499a is associated with breast cancer risk in Iranian population", J Cell Immnother, vol. 2, no. 2, 2016, pp.95–97. Doi: 10.1016/j.jocit.2016.08.003.

[49] N. Zhang, Q. Huo, X. Wang, X. Chen, L. Long, L. Jiang,... snd Q. Yang, "A genetic variant in pre-miR-27a is associated with a reduced breast cancer risk in younger Chinese population", Gene, vol. 529, no. 1, 2013, pp.125–30. Doi: 10.1016/j.gene.2013.07.041.

[50] M. Zhang, M. Jin, Y. Yu, S. Zhang, Y. Wu, H. Liu,... and K. Chen, "Associations of miRNA polymorphisms and female physiological characteristics with breast cancer risk in Chinese population", Eur J Cancer Care (Engl), vol. 21, no. 2, 2012, pp. 274–280. Doi: 10.1111/j.1365-2354.2011.01308.x.

[51] H.C. Rah, H.S. Kim, S.H. Cha, Y.R. Kim, W.S. Lee, J.J. Ko, and N.K. Kim, "Association of breast cancer-related microRNA polymorphisms with idiopathic primary ovarian insufficiency", Menopause, vol. 22, no. 4, 2015, pp. 437–443. Doi: 10.1097/gme.0000000000000325.

[52] H. Zhao, A. Gao, Z. Zhang, R. Tian, A. Luo, M. Li,... and Z. Zhu, "Genetic analysis and preliminary function study of miR-423 in breast cancer", TumourBiol, vol. 36, no. 6, 2015, pp. 4763–71. Doi: 10.1007/s13277-015-3126-7.

[53] R. Mir, I.A.A. Balawi, and F.M. Abu Duhier, "Involvement of microRNA-423 Gene Variability in Breast Cancer Progression in Saudi Arabia", Asian Pac J Cancer Prev, vol. 19, no. 9, 2018, pp. 2581–2589. Doi: 10.22034/APJCP.2018.19.9.2581.

[54] A.J. Huang, K.D. Yu, J. Li, L. Fan, and Z.M. Shao, "Polymorphism rs4919510: C > G in mature sequence of human microRNA-608 contributes to the risk of HER2-positive breast cancer but not other subtypes", PLoS One, vol. 7, no. 5, 2012, e35252. Doi: 10.1371/journal.pone.0035252.

[55] M. Hashemi, S. Sanaei, M. Rezaei, G. Bahari, S.M. Hashemi, M.A. Mashhadi,... and S. Ghavami, "MiR-608 rs4919510 C>G polymorphism decreased the risk of breast cancer in an Iranian subpopulation", ExpOnco, vol. 38, 2016, pp. 57–59.

[56] R. Yang, B. Schlehe, K. Hemminki, C. Sutter, P. Bugert, B. Wappenschmidt,... and B. Burwinkel "A genetic variant in the pre-miR-27a oncogene is associated with a reduced familial breast cancer risk", Breast Cancer Res Treat, vol. 121, no. 3, 2010, pp. 693–702. Doi: 10.1007/s10549-009-0633-5.

[57] I. Catucci, R. Yang, P. Verderio, S. Pizzamiglio, L. Heesen, K. Hemminki, ... and P. Peterlongo, "Evaluation of SNPs in miR-146a, miR196a2 and miR-499 as low-penetrance alleles in German and Italian familial breast cancer cases", Hum Mutat, vol. 31, no. 1, 2010, pp. E1052–E1057. Doi: 10.1002/humu.21141.

[58] I. Catucci, P. Verderio, S. Pizzamiglio, L. Bernard, V. Dall'olio, D. Sardella,... and P. Peterlongo, "The SNP rs895819 in miR-27a is not associated with familial breast cancer risk in Italians", Breast Cancer Res Treat, vol. 133, no. 2, 2012, pp. 805–807. Doi: 10.1007/s10549-012-2011-y.

[59] C. Pastrello, J. Polesel, L.D. Puppa, A. Viel, and R. Maestro, "Association between hsa-miR-146a genotype and tumor age-of-onset in BRCA1/BRCA2-negative familial breast and ovarian cancer patients", Carcinogenesis, vol. 31, no. 12, 2010, pp. 2124–2126. Doi: 10.1093/carcin/bgq184.

[60] R.A. Smith, D.J. Jedlinski, P.N. Gabrovska, S.R. Weinstein, L. Haupt, and L.R. Griffiths, "A genetic variant located in miR-423 is associated with reduced breast cancer risk", Cancer GenoProteo, vol. 9, no. 3, 2012, pp. 115–118.

[61] A. Upadhyaya, R.A. Smith, D. Chacon-Cortes, G. Revêchon, C. Bellis, R.A. Lea,... and L.R. Griffiths, "Association of the microRNA-Single Nucleotide Polymorphism rs2910164 in miR146a with sporadic breast cancer susceptibility: a case control study", Gene, vol. 576, no. 1Pt 2, 2016, pp. 256–260. Doi: 10.1016/j.gene.2015.10.019.

[62] S. Morales, F. Gulppi, P. Gonzalez-Hormazabal, R. Fernandez-Ramires, T. Bravo,... , and L. Jara, "Association of single nucleotide polymorphisms in pre-miR-27a, pre-miR-196a2, pre-miR-423, miR-608 and pre-miR-618 with breast cancer susceptibility in a South American population", BMC Genet, vol. 17, no. 1, 2016, pp. 109. Doi: 10.1186/s12863-016-0415-0.

[63] S. Morales, T.D. Mayo, F.A. Gulppi, P. Gonzalez-Hormazabal, V. Carrasco, J.M. Reyes,... and L. Jara, "Genetic Variants in pre-miR-146a, pre-miR-499, pre-miR-125a, pre-miR-605, and pri-miR-182 Are Associated with Breast Cancer Susceptibility in a South American Population", Genes (Basel), vol. 9, no. 9, 2018, pp. 1–18. Doi: 10.3390/genes9090427.

[64] Z.J. Dai, Y.P. Shao, X.J. Wang, D. Xu, H. F. Kang, H.T. Ren,... and Z.J. Song, "Five common functional polymorphisms in microRNAs (rs2910164, rs2292832, rs11614913, rs3746444, rs895819) and the susceptibility to breast cancer: evidence from 8361 cancer cases and 8504 controls", Curr Pharm Des, vol. 21, no. 12, 2015, pp.1455–1463. Doi: 10.2174/1381612821666141208143533.

[65] F. Wang, G. Sun, Y. Zou, Y. Li, L. Hao, and F. Pan, "Association of microRNA-499 rs3746444 polymorphism with cancer risk: evidence from 7188 cases and 8548 controls", PLoS One, vol. 7, no. 9, 2012d, e45042. Doi:10.1371/journal.pone.0045042.

[66] P.Y. Wang, Z.H. Gao, Z.H. Jiang, X.X. Li, B.F. Jiang, and S.Y. Xie, "The associations of single nucleotide polymorphisms in miR-146a, miR-196a and miR-499 with breast cancer susceptibility", PLoS One, vol. 8, no. 9, 2013, e70656. Doi: 10.1371/journal.pone.0070656.

[67] K. Mu, Z.Z. Wu, J.P. Yu, W. Guo, N. Wu, L.J. Wei,... and J.T. Liu, "Meta-analysis of the association between three microRNA polymorphisms and breast cancer susceptibility", Oncotarget, vol. 8, no. 40, 2017, pp. 68809–68824. Doi: 10.18632/oncotarget.18516.

[68] H. Zhang, Y. Zhang, W. Yan, W. Wang, X. Zhao, X. Ma,... and S. Zhang, "Association between three functional microRNA polymorphisms (miR-499 rs3746444, miR-196a rs11614913 and miR-146a rs2910164) and breast cancer risk: a meta-analysis", Oncotarget, vol. 8, no. 1, 2017a, pp. 393–407. Doi:

10.18632/oncotarget.13426.

[69] W. Yan, X. Gao, and S. Zhang, "Association of miR-196a2 rs11614913 and miR-499 rs3746444 polymorphisms with cancer risk: a meta-analysis". Oncotarget, vol. 8, no. 69, 2017, pp. 114344–114359.

[70] Q.H. Chen, Q.B. Wang, and B. Zhang, "Ethnicity modifies the association between functional microRNA polymorphisms and breast cancer risk: a HuGE meta-analysis", TumourBiol, vol. 35, no. 1, 2014, pp. 529–543. Doi: 10.1007/s13277-013-1074-7.

[71] R. Chen, Y. Zheng, L. Zhuo, and S. Wang, "The association between miR-423 rs6505162 polymorphism and cancer susceptibility: a systematic review and meta-analysis", Oncotarget, vol. 8, no. 25, 2017, pp. 40204-40213. Doi: 10.18632/oncotarget.16319.

[72] J. Wu, Y. Wang, L. Shang, L. Qi, and M. Song, "Five Common Functional Polymorphisms in microRNAs and Susceptibility to Breast Cancer: An Updated Meta-Analysis", GENETIC TESTING AND MOLECULAR BIOMARKERS, Vol. 22, no. 6, 2201, pp. 350–358. DOI: 10.1089/gtmb.2017.0270.

[73] C. Fan, C. Chen, and D. Wu, "The association between common genetic variant of microRNA-499 and cancer susceptibility: A meta-analysis", MolBiol Rep, vol. 40, no. 4, 2013, pp. 3389–3394. Doi: 10.1007/s11033-012-2416-z.

[74] X.P. Ma, T. Zhang, B. Peng, L. Yu, and D.K. Jiang, "Association between microRNA polymorphisms and cancer risk based on the findings of 66 case-control studies", PLoS One, vol. 8, no. 11, 2013b, e79584. Doi: 10.1371/journal.pone.0079584.

[75] H. Sun, Q. Li, T. Yang, and W. Wang, "Quantitative assessment of the association between microRNA-499 rs3746444 A/G polymorphism and cancer risk", TumourBiol, vol. 35, no. 3, 2014, pp. 2351–2358. Doi: 10.1007/s13277-013-1407-6.

[76] S.C. Tan, P.Y. Lim, J. Fang, M.F.M. Mokhtar, E.A.M. Hanif, and R. Jamal, "Association between MIR499A rs3746444 polymorphism and breast cancer susceptibility: a meta-analysis", Sci Rep, vol. 10no. 3508, 2020. Doi: https://doi.org/10.1038/s41598-020-60442-3.

[77] P. Chen, J. Zhang, and F. Zhou, "MiR-499 rs3746444 polymorphism is associated with cancer development among Asians and related to breast cancer susceptibility", MolBiol Rep, vol. 39, no. 12, 2012, pp. 10433–10438. Doi: 10.1007/s11033-012-1922-3.

[78] K. Srivastava, and K. Srivastava, "Comprehensive Review of Genetic Association Studies and Meta-Analyses on miRNA Polymorphisms and Cancer Risk", PLoS One, vol. 7, no. 11, 2012, e50966. Doi: 10.1371/journal.pone.0050966.

[79] B. He, Y. Pan, W.C. Cho, Y. Xu, L. Gu, Z. Nie,... and S. Wang, "The association between four genetic variants in micrornas (rs11614913, rs2910164, rs3746444, rs2292832) and cancer risk: evidence from published studies, " PLoS One, vol. 7, no. 11, 2012, e49032. Doi: 10.1371/journal.pone.0049032.

[80] Y. Xu, L. GU, Y. Pan, R. Li, T. Gao, G., Song,... and B. He, "Different effects of three polymorphisms in MicroRNAs on cancer risk in Asian population: evidence from published literatures", PLoS One, vol. 8, no. 6, 2013a, e65123. Doi: 10.1371/journal.pone.0065123.

[81] X. Yang, X. Li, and B. Zhou, "A Meta-Analysis of miR-499 rs3746444 Polymorphism for Cancer Risk of Diferent Systems: Evidence From 65 Case-Control Studies". Front. Physiol, vol. 9, no. 737, 2018. Doi: 10.3389/fphys.2018.00737.

[82] I. Torruella-Loran, H. Laayouni, B. Dobon, A. Gallego, I. Balcells, E. Garcia-Ramallo, and Y. Espinosa-Parrilla, "MicroRNA Genetic Variation: From Population Analysis to Functional Implications of Three Allele Variants Associated with Cancer", Hum Mutat, vol. 37, no. 10, 2016, pp. 1060–1073. Doi: 10.1002/humu.23045.

[83] J. Zhou, R. Lv, X. Song, D. Li, X. Hu, B. Ying,... and L. Wang, "Association between two genetic variants in miRNA and primary liver cancer risk in the Chinese population", DNA Cell Biol, vol. 31, no. 4, 2012, pp. 524–530. Doi: 10.1089/dna.2011.1340.

[84] L.B. Gao, P. Bai, X.M. Pan, J. Jia, L.J. Li, W.B. Liang,... and L Zhang, "The association between two polymorphisms in pre-miRNAs and breast cancer risk: a meta-analysis", Breast Cancer Res Treat, vol. 125, no. 2, 2011, pp. 571–574. Doi: 10.1007/s10549-010-0993-x.

[85] J. Wang, J. Bi, X. Liu, K. Li, J. Di, and B. Wang, "Has-miR-146a polymorphism (rs2910164) and cancer risk: a meta-analysis of 19 case-control studies", MolBiol Rep, vol. 39, no. 4, 2012a, pp. 4571–4579. Doi: 10.1007/s11033-011-1247-7.

[86] J. Wang, Q. Wang, H. Liu, N. Shao, B. Tan, G. Zhang,... and Y. Cheng, "The association of miR-146a rs2910164 and miR-196a2 rs11614913 polymorphisms with cancer risk: a meta-analysis of 32 studies", Mutagenesis, vol. 27, no. 6, 2012b, pp. 779–788. Doi: 10.1093/mutage/ges052.

[87] A.X. Wang, B. Xu, N. Tong, S.Q. Chen, Y. Yang, X.W. Zhang, ... and M. Chen, "Meta analysis confirms that a common g/c variant in the pre-mir-146a gene contributes to cancer susceptibility and that ethnicity, gender and smoking status are risk factors", Genet Mol Res, vol. 11, no. 3, 2012c, pp. 3051–3062. Doi: 10.4238/2012.August.31.2.

[88] H. Lian, L. Wang, and J. Zhang, "Increased risk of breast cancer associated with CC genotype of has-miR-146a rs2910164 polymorphism in Europeans", PloS One, vol. 7, no. 2, 2012, e31615. Doi: 10.1371/journal.pone.0031615.

[89] R.P. Bai, Y. Weng, L.L. Su, M.J. Jin, Z.P. Xu, L.Q. Lu, and G.D. Chen, "Association of a premiR-27a polymorphism with cancer risk: an updated meta-analysis", Asian Pac J Cancer P, vol. 15, no. 23, 2014, pp. 10107–14. Doi: 10.7314/apjcp.2014.15.23.10107.

[90] Q. Xu, C.Y. He, J.W. Liu, and Y. Yuan, "Pre-miR-27a rs895819 A/G polymorphisms in cancer: a meta-analysis", PLoS One, vol. 8, no. 6, 2013b, e65208. Doi: 10.1371/journal.pone.0065208.

[91] H. Zhang, Y. Zhang, X. Zhao, X. Ma, W. Yan, W. Wang,... and S. Zhang, "Association of two microRNA polymorphisms miR-27 rs895819 and miR-423 rs6505162 with the risk of cancer". Oncotarget, vol. 8, no. 29, 2017b, pp. 46969–46980.doi: 10.18632/oncotarget.16443.

[92] W.G. Cochran, "The effectiveness of adjustment by subclassification in removing bias in observational studies", Biometrics, vol. 24, no. 2, 1968, pp. 295–313. Doi: 10.2307/2528036.

[93] J.P. Higgins, and S.G.Thompson, "Quantifying heterogeneity in a meta-analysis", Stat Med, vol. 21, no. 11, 2002,1539–58. Doi: 10.1002/sim.1186.

[94] N. Mantel, and W. Haenszel, "Statistical aspects of the analysis of data from retrospective studies of disease", J Natl Cancer Inst, vol. 22, no. 4, 1959, pp. 719–748.

[95] R. DerSimonian, and N. Laird, "Meta-analysis in clinical trials", Control Clin Trials, vol. 7, (no. 3, 1986, pp. 177–188.

[96] C.B. Begg, snd M. Mazumdar, "Operating characteristics of a rank correlation test for publication bias". Biometrics, vol. 50, no. 4, 1994, pp. 1088–101.

[97] M. Egger, S.G. Davey, M. Schneider, and C. Minder, "Bias in meta-analysis detected by a simple, graphical test", BMJ, vol. 315, no. 7109, 1997, pp. 629–34. Doi: 10.1136/bmj.315.7109.629.

[98] C. M. Mutshinda, and M. J. Sillanpaa "Swift block-updating EM and pseudo-EM procedures for Bayesian shrinkage analysis of quantitative trait loci", TheorAppl Genet, vol. 125, no. 7, 2012, pp. 1575-1587. doi: 10.1007/s00122-012-1936-1.

[99] D. Cugino, F. Gianfagna, I. Santimone, G. de Gaetano, M.B. Donati, L. Iacoviello, and A. Di Castelnuovo, "Type 2 diabetes and polymorphisms on chromosome 9p21: A meta-analysis", Nutr. MetabCardiovasc Dis, vol. 22, no. 8, 2012, pp. 619–625. Doi: 10.1016/j.numecd.2010.11.010.

[100] V. Vogel, "Approaches to Understanding Breast Cancer. In The Breast"; Bland, K.K.VS., Copeland, EE.M. Gradishar, W.J., Eds.; Elsevier: Amsterdam, Netherlands, 2018, pp. 207–218.

[101] O. Gordon, (2013). "Emery and Rimoin's Principles and Practice of Medical Genetics"; Rimoin, D.P.R., Korf, B., Eds.; Academic Press: Cambridge, MA, USA, 1–31.

[102] D.P. Bartel, "MicroRNAs: Genomics, biogenesis, mechanism, and function", Cell, vol. 116, no. 2, 2004, pp. 281–297. Doi: 10.1016/S0092-8674(04)00045-5.

[103] H. Zheng, F. Song, L. Zhang, D. Yang, P. Ji, Y. Wang,... and K. Chen, "Genetic variants at the miR-124 binding site on the cytoskeleton-organizing IQGAP1 gene confer differential predisposition to breast cancer", Int J Oncol, vol. 38, no. 4, 2011, pp.1153–1161. Doi: 10.3892/ijo.2011.940.