A comprehensive review of microRNA-related polymorphisms in gastric cancer

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ABSTRACT. MicroRNAs (miRNAs) are a class of small non-coding RNA molecules of about 22 nucleotides in length. miRNAs are highly conserved in both plants and animals, and function as gene regulators by binding to the 3'-untranslated region of target mRNAs for cleavage and/or translational repression. miRNA biogenesis, stability, and regulation of expression are strongly sequence dependent. Sequence variants, such as single nucleotide polymorphisms (SNPs) in pri-miRNA, pre-miRNA, promoter regions, or miRNA-target sites, can influence miRNA function, thereby contributing to the pathological features of human disease. In this review, we focus on miRNA-related SNPs in gastric cancer and comprehensively analyze some commonly studied SNPs.

Key words: MicroRNA; Polymorphism; Gastric cancer; Review

INTRODUCTION

MicroRNAs (miRNAs) are a class of small non-coding RNA molecules of about 22 nucleotides in length. The first miRNA (lin-4) was discovered by Lee et al. (1993) who reported that lin-4 can control the timing of *Caenorhabditis elegans* larval development. Subsequently, more than 1000 miRNAs have been identified, which can regulate nearly 30% of human genes. miRNAs are first transcribed by RNA polymerase II in the nucleus, forming primary miRNAs (pri-miRNAs). pri-miRNAs are then cleaved into hairpin loops (70-100 nucleotides) of precursor structure (pre-miRNA) by the Drosha-DGCR8 complex (Lee et al., 2003). pre-miRNAs are transported to the cytoplasm by exportin 5/Ran GTP, where pre-miRNAs are cleaved by the RNase III enzyme Dicer, resulting in mature miRNAs (Lund and Dahlberg, 2006). miRNAs are highly conserved in both plants and animals, and they function as gene regulators by binding to the 3'-untranslated region (3'-UTR) of target mRNAs for cleavage and/or translational repression (Lee et al., 1993).

miRNA biogenesis, stability, and regulation of expression are strongly sequence dependent (Leshkowitz et al., 2013). Sequence variants, such as single nucleotide polymorphisms (SNPs) in pri-miRNA, pre-miRNA, promoter regions, or miRNA target sites, can influence miRNA function, thereby contributing to the pathological features of human disease (Sethupathy et al., 2007). Sethupathy et al. (2007) reported an SNP (rs5186) in the 3'-UTR of angiotensin II receptor type 1 (*AGTR1*), where the rs5186 C allele abrogates an existing miR-155 binding site and induces elevated expression of *AGTR1*, which is implicated in hypertension. In view of the potential roles of miRNA-related SNPs, large numbers of studies have been carried out to identify disease-associated miRNA polymorphisms. In this review, we focus on miRNA-related SNPs in gastric cancer and comprehensively analyze some commonly studied SNPs.

MATERIAL AND METHODS

miRNA-related polymorphisms in gastric cancer

He et al. (2005) provided the first evidence that miRNA-related polymorphisms can change the expression of miRNAs and their target genes, which may contribute to carcinogenesis. Subsequently, miRNA-related polymorphisms were regarded as a gold mine for molecular epidemiology and a large number of studies have been done to assess the association of genetic polymorphisms with cancer risk. In this study, we review miRNA-related polymorphisms and gastric cancer. We searched PubMed using the following terms: “miRNA”, “polymorphism”, and “gastric cancer” (last search update: April 2, 2015). From this search, 64 records were identified and, after reading the full text, 45 studies reporting the relationship of SNPs with gastric cancer risk were included in this study.

The overview of miRNA-related polymorphisms evaluated in gastric cancer is shown in Table 1. According to SNP location, four groups were formed: pri-miRNA, pre-miRNA, promoter of miRNA, and 3'-UTR of target transcript. Overall, these are involved in more than 100 miRNAs, including miR-146a, miR-196a2, and miR-499a/b/c.

Table 1. Overview of microRNA-related polymorphisms evaluated in gastric cancer.

SNP location	miRNA	rs number	References
pri-miRNA	let-7a-1	rs10739971	(Xu et al., 2014a,c)
	let-7a-2	rs629367, rs1143770	(Xu et al., 2014a)
	let-7f-2	rs17276588	
	miR-124	rs531564	(Zhou et al., 2012b; Xu et al., 2015)
	miR-26a-1	rs7372209	(Zhou et al., 2012b; Stenholm et al., 2013; Xu et al., 2015)
	miR-938	rs2505901	(Arisawa et al., 2012)
pre-miRNA	miR-146a	rs2910164	(Okubo et al., 2010; Zeng et al., 2010; Hishida et al., 2011; Wang et al., 2012; Zhou et al., 2012a,b; Ahn et al., 2013; Ma et al., 2013; Stenholm et al., 2013; Wu et al., 2013a; Dikeakos et al., 2014; Kupcinskas et al., 2014; Li et al., 2014b; Parlayan et al., 2014; Pu et al., 2014; Tahara et al., 2014; Xu et al., 2014d, 2015)
	miR-196a2	rs11614913	(Okubo et al., 2010; Peng et al., 2010; Ahn et al., 2013; Ma et al., 2013; Stenholm et al., 2013; Wang et al., 2013a; Dikeakos et al., 2014; Kupcinskas et al., 2014; Parlayan et al., 2014; Pu et al., 2014; Tahara et al., 2014; Xu et al., 2015)
	miR-149	rs2292832	(Zhang et al., 2012; Ahn et al., 2013; Ma et al., 2013; Dikeakos et al., 2014; Pu et al., 2014; Xu et al., 2015)
	miR-499	rs3746444	(Okubo et al., 2010; Ahn et al., 2013; Ma et al., 2013; Pu et al., 2014; Tahara et al., 2014; Xu et al., 2015)
	miR-27a	rs895819	(Zhou et al., 2012b; Ma et al., 2013; Stenholm et al., 2013; Kupcinskas et al., 2014; Xu et al., 2015)
	miR-492	rs2289030	(Zhou et al., 2012b; Kupcinskas et al., 2014)
	miR-608	rs4919510	(Kupcinskas et al., 2014)
	miR-423	rs6505162	(Zhou et al., 2012b; Stenholm et al, 2013)
	miR-605	rs2043556	(Zhang et al., 2012)
Promoter of miRNA	miR-34b/c	rs4938723	(Yang et al., 2014; Pan et al., 2015)
	miR-196a2	rs35010275	(Xu et al., 2014b)
3'-UTR of target transcript	miR-200c-3p	rs12904	(Li et al., 2014a)
	miR-498	rs699517	
	miR-92a-3p	rs1042542	
	let-7	rs712	(Li et al., 2013a)
	miR-181a	rs12537, rs1460008, rs10954213	(Lin et al., 2012)
	miR-214, miR-3120, miR-199a-2	rs17277008, rs2819531, rs10911101	
	miR-29c, miR-29b-2	rs2724377, rs1474742, rs7523273	
	miR-215, miR-194-1	rs1124763, rs17007135	
	miR-10b	rs1348807, rs6736786	
	miR-375	rs452985, rs398926, rs359975	
	let-7g	rs1767, rs7614727	
	miR-15b, miR-16-2	rs4680580, rs10936201, rs17236424	
	miR-449a, miR-449b, miR-449c	rs353294, rs3733846, rs353291	
	miR-146a	rs4921141, rs883517, rs3096021, rs4921142	
	miR-218	rs6918659, rs6455468, rs9455927, rs6900844, rs7764535	
	miR-25, miR-93, miR-106b	rs4729575, rs4928, rs13242458, rs1534309, rs2070215	
	miR-29a, miR-29b-1	rs17186418, rs11980951, rs7349991, rs157907, rs157908, rs731730, rs157910	
	let-7f-1, let-7d	rs10512231, rs10512232	
	miR-23b, miR-27b, miR-3074, miR-24-1	rs10491560, rs10821447	
	miR-107	rs11185772, rs7095066, rs17124306, rs2038921, rs10509577	
	miR-125b-1	rs947893, rs2241490, rs512932, rs17126105, rs4121975	
	let-7a-2, miR-100	rs564649, rs564037, rs629367, rs638742, rs17126230, rs1895718, rs1816158	
	let-7i	rs11174557, rs7953138, rs12357, rs1056340, rs10877888, rs12818198, rs10877889	
	miR-16-1, miR-15a	rs2066557, rs9535416	
	miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR-92a-1	rs7322734, rs17642969, rs769040	
	miR-493, miR-337, miR-665, miR-431, miR-433, miR-127, miR-432, miR-136	rs1077411, rs6575805, rs3825569	
	miR-376a-1,miR-300, miR-381, miR-1185-1, miR-1185-2, miR-539, miR-487b, miR-889, miR-544, miR-655, miR-487a, miR-382, miR-134, miR-668, miR-485	rs11621499, rs2281610, rs7161441, rs4525426	
	miR-132, miR-212	rs1131600, rs12451788, rs1051322, rs11870150, rs8065878, rs4239071, rs903158, rs1048483	
	miR-10a	rs2555111, rs2288278, rs4793943	
	miR-301	rs9303403, rs7502947	
	miR-21	rs7213697, rs1292037, rs1295927	
	miR-24-2, miR-27a, miR-23a	rs3745453, rs1531212	
	miR-99b, let-7e, miR-125a	rs11672944, rs2034576, rs11670215, rs8111742, rs4239495	
	miR-371a, miR-371b, miR-372, miR-373	rs12983508, rs3859501, rs12983273, rs8103186, rs3859503, rs17305227, rs10403709	
	miR-296, miR-298	rs2282131, rs4815628	
	let-7c	rs17276117, rs17276124	
	miR-125b-2	rs7279730, rs2823902	
	miR-155	rs1893650	
	miR-301b, miR-130b	rs374659	
	let-7a-3, miR-4763, let-7b	rs11090909, rs4823529, rs5768746	
	miR-221, miR-222	rs2858070, rs1016588, rs2858060, rs980878	
	miR-223	rs1044165	
	miR-363,miR-92a-2,miR-19b-2, miR-20b, miR-18b, miR-106a	rs916698, rs17317628	

RESULTS AND DISCUSSION

To date, the most commonly studied polymorphisms are rs2910164, rs11614913, rs2292832, and rs3746444, which are located in pre-miR-146a, pre-miR-196a2, pre-miR-149, and pre-miR-499, respectively. These polymorphisms were first reported by Hu et al. (2008), who found that rs11614913 might be used as prognostic biomarker for non-small cell lung cancer. Regarding the first report of the polymorphism in gastric cancer, Zeng et al. (2010) found that subjects with pre-miR-146a rs2910164 GC/GG genotypes had a 1.58-fold elevated risk of gastric cancer compared to carriers of the CC genotype [95% confidence interval (CI) = 1.11-2.20; P = 0.009]. For SNPs in pri-miRNA, Xu et al. (2014b) reported an rs629367 polymorphism located in pri-let-7a-2 and the CC genotype was associated with an increased risk

of gastric cancer [odds ratio (OR) = 1.83; 95%CI = 1.00-3.32] and poorer survival [hazard ratio (HR) = 4.48; 95%CI = 1.60-12.60]. Arisawa et al. (2012) reported a polymorphism (rs2505901) in pri-miR-938 and the CC genotype was associated with a decreased risk of gastric cancer (OR = 0.73; 95%CI = 0.55-0.99). Stenholm et al. (2013) reported that the variant allele of rs7372209 in pri-miR-26a1 was associated with a worse prognosis of advanced gastric cancer. In our previous study, we found that a polymorphism (rs4938723) in the promoter of miR-34b/c was associated with a decreased risk of gastric cancer (OR = 0.66; 95%CI = 0.45-0.97) (Pan et al., 2015). Our result was confirmed by another study (Yang et al., 2014). Moreover, Xu et al. (2014a) reported a similarly decreased effect of rs35010275 in the promoter of miR-196a2 on gastric cancer (adjusted OR = 0.85; 95%CI = 0.77-0.94). Besides SNPs in pri-miRNA, pre-miRNA, and promoters of miRNA, SNPs in the 3'-UTR of miRNA target genes have also been studied widely. For example, our other previous study showed that the rs712 polymorphism in the 3'-UTR of let-7 was associated with an increased risk of gastric cancer (adjusted OR = 3.05; 95%CI = 1.53-6.08) (Li et al., 2013b). Li et al. (2014a) reported that the rs12904 polymorphism in the 3'-UTR of miR-200c was significantly associated with risk of gastric cancer (OR = 0.65; 95%CI = 0.50-0.85), and the rs12904 A allele may abrogate miR-200c binding, inducing elevated levels of its target gene ephrin-A1. Lin et al. (2012) reported that the rs12537 CT/TT genotypes in the miR-181a binding site were associated with a significantly increased risk of gastric cancer (adjusted OR = 1.72; 95%CI = 1.36-2.16) and poor overall survival (HR = 1.38; 95%CI = 1.03-1.83). Further analysis showed that the rs12537 CT genotype carriers had lower expression of the miR-181a target gene myotubularin-related protein 3.

Since gastric cancer is a complex disease with multiple factors involved, gene-gene and gene-environment analyses were also evaluated. Xu et al. (2014c) reported an increased interaction effect of the pri-let-7a-1 rs10739971 polymorphism with *ERCC6* rs1917799 on gastric cancer (OR = 2.59; 95%CI = 1.12-5.97). Zhang et al. (2012) reported that smokers carrying pre-miR-149 rs2292832 CT/CC genotypes and pre-miR-605 rs2043556 AG/GG genotypes had an increased risk of gastric cancer (OR = 1.87; 95%CI = 1.03-3.42), and tea drinkers with the pre-miR-149 rs2292832 CT/CC genotypes were protected from gastric cancer (OR = 0.47; 95%CI = 0.29-0.77).

Association of the pre-miR-146a rs2910164 polymorphism with risk of gastric cancer

Over the past several years, the association of the pre-miR-146a rs2910164 polymorphism with risk of gastric cancer has been extensively investigated (Okubo et al., 2010; Zeng et al., 2010; Hishida et al., 2011; Wang et al., 2012; Zhou et al., 2012a,b; Ahn et al., 2013; Ma et al., 2013; Stenholm et al., 2013; Wu et al., 2013a; Dikeakos et al., 2014; Kupcinskas et al., 2014; Li et al., 2014b; Parlayan et al., 2014; Pu et al., 2014; Tahara et al., 2014; Xu et al., 2014d, 2015). In total, 18 studies were involved, including 10 case-control studies, 6 meta-analyses, and 2 case-only studies. As shown in Table 2, most of the studies were conducted in Asia, mainly in China, and only 3 studies were done in Europe. In case-control studies, some authors reported a positive result (Okubo et al., 2010; Zeng et al., 2010; Zhou et al., 2012a; Kupcinskas et al., 2014) and others reported a negative result (Hishida et al., 2011; Ahn et al., 2013; Dikeakos et al., 2014; Parlayan et al., 2014). To make the results more precise, some authors performed meta-analyses by combining all the data together (Ma et al.,

2013; Wu et al., 2013a; Li et al., 2014b; Xu et al., 2014d, 2015), which improved the statistical power. However, conflicting results were still present. For example, Li et al. (2013a) reported that the miR-146a rs2910164 polymorphism was significantly associated with a decreased risk of gastric cancer under the allele model (OR = 0.87; 95%CI = 0.81-0.93) and recessive model (OR = 0.81; 95%CI = 0.72-0.90). Xu et al. (2015) reported that the miR-146a rs2910164 polymorphism was not associated with gastric cancer risk. Although it is difficult to decipher the exact reason for the inconsistent results, sample size, study design, and ethnicity should be considered. If the sample size is not large enough, the power is insufficient and false-negative results may occur. If the study design is hospital-based, selection bias cannot be ruled out and the results may be unreliable. Moreover, it is well known that genetic variants are diverse in different ethnicities. Therefore, further population-based association studies with large sample sizes are valuable to identify the real effect of the pre-miR-146a rs2910164 polymorphism on risk of gastric cancer.

Table 2. Association of the pre-miR-146a rs2910164 polymorphism with risk of gastric cancer.

First author	Publication year	Country (region)	Ethnicity	Study design	Case/control	Case		Control		Results		
						CC	CG	GG	CC	CG	GG	
Zeng	2010	China (Nanjing)	Asian	Case-control	304/304	89	153	62	119	132	53	Association
Okubo	2010	Japan (Toyoake)	Asian	Case-control	552/697	236	243	73	322	254	121	Association
Hishida	2011	Japan (Nagoya)	Asian	Case-control	583/1637	230	271	82	633	775	229	No association
Zhou	2012b	China (Hefei)	Asian	Case-control	331/336	-	-	-	-	-	-	No association
Zhou	2012a	China (Yixing)	Asian	Case-control	1686/1895	286	822	578	393	951	551	Association
Ahn	2013	South Korea (Seongnam)	Asian	Case-control	461/477	159	231	71	164	221	62	No association
Kupcinskas	2014	Lithuania (Kaunas)	European	Case-control	363/351	16	94	252	16	108	223	Association
Parlayan	2014	Japan (Tokyo)	Asian	Case-control	160/524	-	-	-	-	-	-	No association
Pu	2014	China (Chengdu)	Asian	Case-control	197/513	65	96	36	143	274	96	No association
Dikeakos	2014	Greece (Athens)	European	Case-control	163/480	105	45	13	307	149	24	No association
Stenholm	2013	Germany (Aachen)	European	Case only	487/-	-	-	-	-	-	-	No association
Tahara	2014	Japan (Toyoake)	Asian	Case only	130/-	67	47	16	-	-	-	No association
Wang	2012	China (Jinan)	-	Meta-analysis	1439/2688	555	667	217	1074	1211	403	No association
Ma	2013	China (Shanghai)	-	Meta-analysis	3125/4533	841	1489	795	1467	2112	954	No association
Wu	2013a	China (Shanghai)	-	Meta-analysis	1439/2638	555	667	217	1074	1161	403	No association
Li	2014b	China (Hangzhou)	-	Meta-analysis	3003/3343	770	1449	784	998	1558	787	Association
Xu	2014d	China (Guiyang)	-	Meta-analysis	4607/6736	1293	2101	1213	2224	3079	1433	No association
Xu	2015	China (Shenyang)	-	Meta-analysis	4048/5876	1212	1911	925	2065	2697	1114	No association

Association of the pre-miR-196a2 rs11614913 polymorphism with risk of gastric cancer

Overall, 13 studies reported the association between the pre-miR-196a2 rs11614913 polymorphism with risk of gastric cancer (Table 3) (Okubo et al., 2010; Peng et al., 2010; Ahn et al., 2013; Ma et al., 2013; Stenholm et al., 2013; Wang et al., 2013a,b; Dikeakos et al., 2014; Kupcinskas et al., 2014; Parlayan et al., 2014; Pu et al., 2014; Tahara et al., 2014; Xu et al., 2015). Among them, 8 were case-control studies, 3 were meta-analyses, and 2 were case-only studies. Similar to the pre-miR-146a rs2910164 polymorphism, most of the studies were conducted in Asian populations (Okubo et al., 2010; Peng et al., 2010; Ahn et al., 2013; Wang et al., 2013b; Parlayan et al., 2014; Pu et al., 2014; Tahara et al., 2014). The phenomenon of conflicting results is also observed with this polymorphism, even in the same population. Peng et al. (2010) reported that the pre-miR-196a2 rs11614913 CC genotype was associated with a significantly increased risk of gastric cancer in a Chinese population (OR = 1.57; 95%CI = 1.03-2.39). However, Pu et al. (2014) did not find any significant difference between cases and controls in another Chinese population. Similarly, meta-analysis was used to assess whether the pre-miR-196a2 rs11614913 polymorphism contributed to the risk of gastric cancer. No significant association was found between the pre-miR-196a2 rs11614913 polymorphism and gastric cancer risk by 3 independent groups (Ma et al., 2013; Wang et al., 2013a; Xu et al.,

2015), suggesting that the pre-miR-196a2 rs11614913 polymorphism may not be a risk factor for the development of gastric cancer.

Table 3. Association of the pre-miR-196a2 rs11614913 polymorphism with risk of gastric cancer.

First author	Publication year	Country (region)	Ethnicity	Study design	Case/control	Case			Control			Results
						TT	CT	CC	TT	CT	CC	
Peng	2010	China (Shenyang)	Asian	Case-control	213/213	43	94	76	50	107	56	Association
Okubo	2010	Japan (Toyoake)	Asian	Case-control	552/697	166	281	105	223	350	124	No association
Ahn	2013	South Korea (Seongnam)	Asian	Case-control	461/477	119	242	100	128	232	87	No association
Wang	2013b	China (Nanjing)	Asian	Case-control	1689/1946	519	851	319	524	940	482	Association
Kupcinskas	2014	Lithuania (Kaunas)	European	Case-control	363/351	35	184	144	46	145	159	Association
Parlayan	2014	Japan (Tokyo)	Asian	Case-control	160/524	-	-	-	-	-	-	Association
Pu	2014	China (Chengdu)	Asian	Case-control	159/511	25	95	39	86	324	101	No association
Dikeakos	2014	Greece (Athens)	European	Case-control	163/480	15	46	102	79	229	172	Association
Stenholm	2013	Germany (Aachen)	European	Case only	487/-	-	-	-	-	-	-	Association
Tahara	2014	Japan (Toyoake)	Asian	Case only	130/-	37	63	30	-	-	-	No association
Wang	2013a	China (Hefei)	-	Meta-analysis	765/910	209	375	181	273	457	180	No association
Ma	2013	China (Shanghai)	-	Meta-analysis	765/910	209	375	181	273	457	180	No association
Xu	2015	China (Shenyang)	-	Meta-analysis	3078/3783	862	1514	702	1004	1858	921	No association

Association of the pre-miR-149 rs2292832 polymorphism with risk of gastric cancer

The association of the pre-miR-149 rs2292832 polymorphism with risk of gastric cancer is presented in Table 4. In total, 6 studies were performed, including 4 case-control studies and 2 meta-analyses (Zhang et al., 2012; Ahn et al., 2013; Ma et al., 2013; Dikeakos et al., 2014; Pu et al., 2014; Xu et al., 2015). Zhang et al. (2012) reported that male subjects with the pre-miR-149 rs2292832 CT genotype had a decreased susceptibility for gastric cancer in an Asian population (OR = 0.58; 95%CI = 0.37-0.93). Duplicate studies did not find the positive result in another two Asian populations (Ahn et al., 2013; Pu et al., 2014). The null result was also observed in meta-analyses (Ma et al., 2013; Xu et al., 2015). Nevertheless, Dikeakos et al. (2014) reported that the pre-miR-149 rs2292832 polymorphism was associated with an increased risk of gastric cancer in a European population under a homozygote comparison (OR = 2.29; 95%CI = 1.25-4.22), dominant genetic model (OR = 1.47; 95%CI = 1.03-2.10), and recessive genetic model (OR = 2.00; 95%CI = 1.12-3.57). Taken together, these findings indicate that the pre-miR-149 rs2292832 polymorphism may have different roles in diverse ethnicities with respect to gastric cancer risk.

Table 4. Association of the pre-miR-149 rs2292832 polymorphism with risk of gastric cancer.

First author	Publication year	Country (region)	Ethnicity	Study design	Case/control	Case			Control			Results
						TT	CT	CC	TT	CT	CC	
Zhang	2012	China (Hangzhou)	Asian	Case-control	274/269	132	101	41	114	120	35	Association
Ahn	2013	South Korea (Seongnam)	Asian	Case-control	461/477	241	176	44	220	187	40	No association
Pu	2014	China (Chengdu)	Asian	Case-control	187/459	134	31	22	308	103	48	No association
Dikeakos	2014	Greece (Athens)	European	Case-control	163/480	69	73	21	249	198	33	Association
Ma	2013	China (Shanghai)	-	Meta-analysis	274/269	132	101	41	114	120	35	No association
Li	2013a	China (Chongqing)	-	Meta-analysis	735/716	373	277	85	334	307	75	No association
Xu	2013	China (Nanjing)	-	Meta-analysis	735/716	373	277	85	334	307	75	No association
Xu	2015	China (Shenyang)	-	Meta-analysis	898/1196	442	350	106	583	505	108	No association

Association of the pre-miR-499 rs3746444 polymorphism with risk of gastric cancer

The association of the pre-miR-499 rs3746444 polymorphism with risk of gastric cancer is summarized in Table 5. In total, 7 studies were performed, including 4 case-control studies, 2 meta-analyses, and 1 case-only study (Okubo et al., 2010; Ahn et al., 2013; Ma et

al., 2013; Wu et al., 2013b; Pu et al., 2014; Tahara et al., 2014; Xu et al., 2015). All the studies were performed in Asian populations. Tahara et al. (2014) reported that the pre-miR-499 rs3746444 polymorphism was associated with overall survival and progression-free survival among gastric cancer cases of neoadjuvant chemotherapy. Cox's regression model revealed that the pre-miR-499 rs3746444 A allele was a predictive factor for better overall survival (HR = 0.33; 95%CI = 0.18-0.75), indicating that the pre-miR-499 rs3746444 polymorphism may be used as a biomarker for prognosis of advanced gastric cancer treated with chemotherapy (Tahara et al., 2014).

Table 5. Association of the pre-miR-499 rs3746444 polymorphism with risk of gastric cancer.

First author	Publication year	Country (region)	Ethnicity	Study design	Case/control	Case			Control			Results
						AA	AG	GG	AA	AG	GG	
Okubo	2010	Japan (Toyoake)	Asian	Case-control	552/697	364	151	37	466	198	33	No association
Ahn	2013	South Korea (Seongnam)	Asian	Case-control	461/477	323	123	15	299	134	14	No association
Wu	2013b	China (Xuzhou)	Asian	Case-control	200/211	149	47	4	166	42	3	No association
Pu	2014	China (Chengdu)	Asian	Case-control	196/504	141	50	5	366	121	17	No association
Tahara	2014	Japan (Toyoake)	Asian	Case only	130/-	81	38	11	-	-	-	Association
Ma	2013	China (Shanghai)	-	Meta-analysis	552/697	364	151	37	466	198	33	No association
Li	2013a	China (Chongqing)	-	Meta-analysis	1013/1144	687	274	52	765	332	47	No association
Xu	2015	China (Shenyang)	-	Meta-analysis	1213/1355	836	321	56	931	374	50	No association

Association of the pre-miR-27a rs895819 polymorphism with risk of gastric cancer

It has been identified that miR-27a functions as an oncogene and is upregulated in gastric cancer, with higher expression resulting in significantly worse overall survival. Downregulation of miR-27a may inhibit proliferation of gastric cancer cells and drug resistance, indicating that miR-27a plays a key role in the carcinogenesis of gastric cancer. Sun et al. (2010) reported that a polymorphism (rs895819) within miR-27a might contribute to gastric cancer susceptibility by modulating the expression of miR-27a and its target gene zinc finger and BTB domain containing 10. Duplication studies in Asian populations found the same results (Zhou et al., 2012b). However, Kupcinskas et al. (2014) failed to find any association between the pre-miR-27a rs895819 polymorphism and risk of gastric cancer in a European population (Table 6). Since only one case-control study was performed in Europe, further investigations are warranted to confirm these results.

Table 6. Association of the pre-miR-27a rs895819 polymorphism with risk of gastric cancer.

First author	Publication year	Country (region)	Ethnicity	Study design	Case/control	Case			Control			Results
						TT	CT	CC	TT	CT	CC	
Sun	2010	China (Wuxi)	Asian	Case-control	304/304	115	135	54	145	119	40	Association
Zhou	2012b	China (Hefei)	Asian	Case-control	295/413	166	122	7	214	167	32	Association
Stenholm	2013	Germany (Aachen)	European	Case only	487/-	-	-	-	-	-	-	Association
Kupcinskas	2014	Lithuania (Kaunas)	European	Case-control	363/351	181	144	38	156	164	30	No association
Song	2014	China (Yantai)	Asian	Case-control	278/278	105	124	49	131	111	36	Association
Ma	2013	China (Shanghai)	-	Meta-analysis	599/717	281	257	61	359	286	72	No association
Xu	2015	China (Shenyang)	-	Meta-analysis	761/1018	366	328	67	528	396	94	Association

In this study, we reviewed miRNA-related polymorphisms in gastric cancer. In total, 45 studies reported the relationship of SNPs with gastric cancer risk. Among them, the most frequently studied polymorphisms were rs2910164, rs11614913, rs2292832, rs3746444, and rs895819, which are located in pre-miR-146a, pre-miR-196a2, pre-miR-149, pre-miR-499, and pre-miR-27a, respectively. Except for pre-miR-146a rs2910164 and pre-miR-27a rs895819, the polymorphisms were not associated with risk of gastric cancer. Therefore, functional

polymorphisms for epidemiological research are of great importance to identify susceptibility genes. Moreover, gene-gene and gene-environment analyses will provide more evidence for the better understanding of tumorigenesis in gastric cancer.

Conflicts of interest

The authors declare no conflict of interest.

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