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Hsa-miR-499 polymorphism (rs3746444) and cancer risk: A meta-analysis of 17 case–control studies

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ABSTRACT

Introduction: MicroRNAs (miRNAs) are a family of endogenous, small and noncoding RNAs that negatively regulate gene expression by suppressing translation or degrading mRNAs. Recently, many studies investigated the association between hsa-miR-499 rs3746444 polymorphism and cancer risk, which showed inconclusive results.

Methodology/main results: We conducted a meta-analysis of 17 studies that included 7842 cancer cases and 8989 case-free controls and assessed the strength of the association, using odds ratios (ORs) with 95% confidence intervals (CIs). Overall, hsa-miR-499 rs3746444 polymorphism was associated with higher cancer risk in heterozygote model (AG vs AA, OR = 1.15, 95%CI = 1.01–1.30, $P_{heterogeneity} < 0.001$), dominant genetic model (GG/AG vs AA, OR = 1.18, 95% CI = 1.04–1.33, $P_{heterogeneity} < 0.001$) and allele contrast (G vs A, OR = 1.09, 95% CI = 1.01–1.18, $P_{heterogeneity} = 0.021$). In the stratified analyses, we observed that the GG/AG genotype might modulate breast cancer risk (OR = 1.13, 95% CI = 1.01–1.26, $P_{heterogeneity} = 0.111$) comparing with the AA genotype. Moreover, a significantly increased risk was found among Asian populations in heterozygote model (AG vs AA, OR = 1.23, 95% CI = 1.06–1.43, $P_{heterogeneity} < 0.001$), homozygote model (GG vs AA, OR = 1.22, 95% CI = 1.02–1.46, $P_{heterogeneity} = 0.319$), dominant model (GG/AG vs AA, OR = 1.25, 95% CI = 1.06–1.39, $P_{heterogeneity} < 0.001$) and allele contrast (G vs A, OR = 1.14, 95% CI = 1.04–1.25, $P_{heterogeneity} = 0.021$).

Conclusions: These findings supported that hsa-miR-499 rs3746444 polymorphism contributes to the susceptibility of cancers.

1. Introduction

MicroRNAs (miRNAs) are a class of endogenous small non-coding regulatory RNAs, approximately 22 nucleotides in length, which are known to regulate gene expression by repressing translation or decreasing the stability of mRNAs (Bartel, 2009). MiRNAs play important roles in the etiology of many human diseases through post-transcriptionally regulating the expression of approximately one third of all human genes (Lewis et al., 2005). A strong link between miRNA expression profiles and the etiology, classification, progression, and prognosis of multiple human cancers has been established with miRNA acting as either oncogenes or tumor suppressors.

Single nucleotide polymorphisms (SNPs) or mutations occurring in the miRNA gene region are reported to be the novel sources of genetic variation that may contribute to cancer risk via affecting the property of specific miRNA (Chen et al., 2008; Saunders et al., 2007). A T to C polymorphism has been identified in the hsa-miR-499 gene, and this polymorphism is located in the stem region opposite to the mature miR-499 sequence which results in a change from A:U pair to G:U mismatch in the stem structure of miR-499 precursor. (A to G in 3p, but T to C in 5p. We define rs3746444A/G in this meta-analysis) Recently, a large body of reports demonstrate that hsa-miR-499 rs3746444 polymorphisms in precursor were correlated with cancer risk in many cancer types, such as breast cancer (Alshatwi et al., 2012; Hu et al., 2009), lung cancer (Hu et al., 2008; Vinci et al., 2011), Hepatocellular Carcinoma (HCC) (Xiang et al., 2012) and others (Liu et al., 2010; Srivastava et al., 2010; Zhou et al., 2011). However, the results of these studies remain conflicting. Considering the limits of the single study, we performed a meta-analysis on all eligible case–control studies to drive a more powerful estimation of the link between the hsa-miR-499 rs3746444 polymorphisms and cancer risk.

Abbreviations: miRNA, microRNA; SNP, single nucleotide polymorphism; HCC, hepatocellular carcinoma; OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism; HRMA, high-resolution melting analysis; NBN, nijmegen breakage syndrome protein; BCL2L14, apoptosis regulator Bcl-G; CHB, chronic hepatitis B; HB, hospital-based; PB, population-based; SCCHN, squamous cell carcinoma of the head and neck; BC, bladder cancer; CSCC, cervical squamous cell carcinoma; GC, gastric cancer.

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Table 1
Characteristics of literatures included in the meta-analysis.

Author	Year	County	Ethnicity	Cancer type	Source of control	Genotyping	Matching criteria	Case	Control	HWE
Alshatwi	2012	Saudi	Asian	Breast cancer	PB	Taqman	NA	100	89	Y
Catucci	2010	Germany	Caucasian	Breast cancer	PB	Taqman DNA sequencing	Age	823	925	Y
		Italy	Caucasian	Breast cancer	PB	Taqman DNA sequencing	Age	756	1242	Y
Hu[1]	2009	China	Asian	Breast cancer	PB	PCR-RFLP	Age; residential	1009	1093	Y
Zhou[2]	2012	China	Asian	HCC	HB	PCR-RFLP DNA sequencing	Age	186	483	Y
Xiang	2012	China	Asian	HCC	HB	PCR-RFLP DNA sequencing	Age; sex	100	200	N
Akkiz	2011	Turkey	Asian	HCC	HB	PCR-RFLP	Age; sex; smoking; alcohol status	222	222	Y
Vinsi	2011	Italy	Caucasian	Lung cancer	HB	HRMA	Age; sex	101	129	Y
Tian	2009	China	Asian	Lung cancer	PB	PCR-RFLP	Sex; age; residential	1058	1035	Y
Hu[1]	2008	China	Asian	Lung cancer	HB	PCR-RFLP	NA	556	223	Y
Geroge	2011	India	Asian	Prostate	HB	PCR-RFLP	Age	159	230	Y
Liu	2010	USA	Caucasian	SCCHN	PB	PCR-RFLP	Age; sex	1109	1130	Y
Mittal	2011	India	Asian	BC	HB	PCR-RFLP	Age; sex; ethnicity;	212	250	N
Zhou[2]	2011	China	Asian	CSCC	HB	PCR-RFLP	Age	226	309	Y
Okubo	2010	Japan	Asian	GC	HB	PCR-RFLP	NA	552	697	N
Stivastava	2010	India	Asian	Gallbladder	PB	PCR-RFLP	Age; sex	230	230	Y
Min	2011	Korean	Asian	Colorectal cancer	HB	PCR-RFLP DNA sequencing	NA	446	502	Y

[1]The same author with different article.
[2]Different author with the same last name.
HCC: Hepatocellular Carcinoma; SCCHN; Squamous Cell Carcinoma of the Head and Neck; BC: bladder cancer; CSCC: Cervical Squamous Cell Carcinoma; GC: gastric cancer; PCR-RFLP, Polymerase Chain Reaction–restriction Fragment Length Polymorphism; HRMA, high-resolution melting analysis; PB, Population Based; HB, Hospital Based; NA, not available.

2. Materials and methods

2.1. Publication search

We carried out a search in Pubmed and other public domains with a combination of the following keywords: “microRNA/miR-499”, “rs3746444”, “polymorphism” and “cancer” (last search was updated on 10 May 2012). The search was limited to English language papers. We evaluated potentially relevant publications by examining their titles and abstracts and all studies matching the eligible criteria were retrieved.

2.2. Inclusion criteria

Studies included in the current meta-analysis had to meet all the following criteria: (a) evaluation of the hsa-miR-499 rs3746444 polymorphism and cancer risks, (b) study designed as case–control, and (c) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI).

2.3. Data extraction

Data were independently extracted in duplicate by two investigators (Wang and Yang) using a standard protocol and data-collection form according to the inclusion criteria listed above. The following characteristics were included from each study: the name of the first author, the year of publication date, country origin, ethnicity, cancer type, the source of control, genotyping methods, matching criteria, total number of cases and controls. (Table 1) For one study including subjects of different countries of origin group, we extracted data

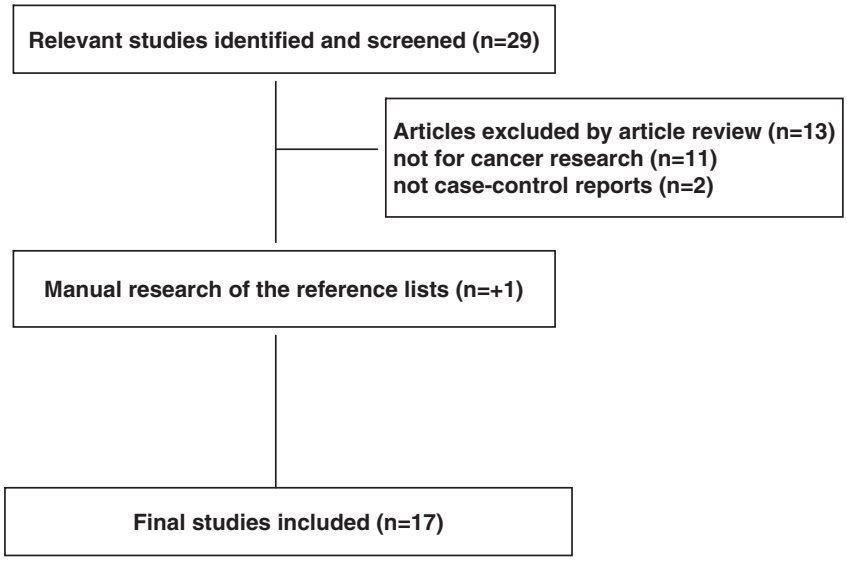

Fig. 1. Studies identified with criteria for inclusion and exclusion.