Association between Hsa-Mir-499 rs3746444 Polymorphism and Cancer Risk: Evidence from Current Studies

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Abstract

Epidemiologic findings concerning the association between the hsa-mir-499 rs3746444 A>G polymorphism and cancer risk have yielded mixed results. We aimed to investigate the association by performing a meta-analysis of all available studies. We searched PubMed and EMBASE for studies published up to November 2014, using odds ratios (ORs) with 95% confidence intervals (CIs) to assess the strength of any association. The Benjamini-Hochberg (BH) method was used to correct the p values for multiple comparisons. We included 39 studies, including 14,136 cases and 16,937 controls. The results of overall meta-analysis suggested a borderline association between hsa-mir-499 rs3746444 polymorphism and cancer susceptibility (AG+GG vs. AA: OR=1.15, 95% CI=1.04-1.26, corrected p value=0.04). After removing studies not conforming to Hardy–Weinberg equilibrium (HWE), however, this association disappeared (AG+GG vs AA: OR=1.18, 95% CI=1.03-1.34, corrected p value=0.21). When stratified analysis by ethnicity, cancer type or HWE in controls, although some associations between hsa-mir-499 rs3746444 polymorphism and cancer susceptibility were detected, these associations no longer existed after adjustment using BH method. In conclusion, our meta-analysis suggests that hsa-mir-499 rs3746444 A>G polymorphism is not associated with risk of cancer based on current evidence.

Keywords: Cancer - meta-analysis - hsa-mir-499 - polymorphism - susceptibility

Introduction

Cancer is a major public health problem all over the world. In the United States, one in four deaths is due to cancer (Siegel et al., 2014). The etiology of cancer is still not fully understood. It has been suggested that genetic factors play a significant role in cancer development. MicroRNAs (miRNAs, miRs) are a class of small non-coding RNAs with 18-25 nucleotides (Kutanzi et al., 2011) that negatively control gene expression at the mRNA and protein level (He and Hannon, 2004). It has been demonstrated that miRNAs are master regulators of key genes implicated in important biological processes, such as embryonic development, cell proliferation, differentiation, migration, apoptosis and signal transduction, etc (Anglicheau et al., 2010; Kutanzi et al., 2011). It has also been reported that miRNAs play key roles in tumor formation. Recently, single nucleotide polymorphisms (SNPs) in miRNAs have been paid much more attention. Studies have reported that miRNA SNPs could alter expressions or functions of miRNAs thus affecting cancer risk. An important SNP in the hsa-mir-499 with an A to G change (rs3746444) was identified. A series of studies have explored the role of hsa-mir-499 rs3746444 polymorphism in cancer risk, but their results are conflicting rather than conclusive. Many meta-analyses have examined the association of the polymorphism with cancer risk and the last one (Ma et al., 2013) suggested that hsa-mir-499 rs3746444 polymorphism was a risk factor for cancer development. Since the latest meta-analysis had been performed, nineteen case-control studies (Ling et al., 2011; Ahn et al., 2013; Lv et al., 2013; Shan et al., 2013; Umar et al., 2013; Wu et al., 2013; Zou and Zhao, 2013; Bansal et al., 2014; Chu et al., 2014; Du et al., 2014; Gutierrez-Camino et al., 2014; Hasani et al., 2014; Hou et al., 2014; Hu et al., 2014; Ma et al., 2014; Omrani et al., 2014; Pu et al., 2014; Qi et al., 2014; Wang et al., 2014) have been published. Therefore, we performed a meta-analysis of all studies available now to derive a more precise estimation of the association between hsa-mir-499 rs3746444 polymorphism and cancer risk.

Materials and Methods

Publication search

We searched PubMed (from 2009 to present) and Embase (from 2009 to present) for studies in humans of the association between hsa-mir-499 rs3746444 polymorphism and risk of cancer. The search strategy used the terms “rs3746444 or miR-499” and “cancer OR
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The latest date of this search was November 2014. Reference lists were examined manually to further identify potentially relevant studies. All studies matching the eligible criteria listed below were included in our meta-analysis, without language restriction.

Inclusion criteria

The following inclusion criteria were used in selecting literature for further meta-analysis: (a) evaluation of hsa-mir-499 rs3746444 polymorphism and cancer risk; (b) a case-control design; and (c) sufficient published data for calculating odds ratios (ORs) with their 95% confidence intervals (95% CIs).

Data extraction

Two investigators independently extracted the data. Discrepancies were solved by discussion until consensus was achieved on every item. From each of included articles the following information was abstracted: the name of first author, year of publication, country origin, ethnicity, cancer type, source of controls, total number of cases and controls, the number of cases and controls with hsa-mir-499 rs3746444 polymorphism genotypes and p value for Hardy-Weinberg equilibrium (HWE), respectively. Only controls randomly selected from general population were defined as population-based (PB) otherwise hospital-based (HB).

Statistical methods

For the controls of each study, HWE was assessed using the chi-square goodness-of-fit test and a P<0.05 was considered representative of a departure from HWE. The OR and its 95% CI were used to assess the strength of association between hsa-mir-499 rs3746444 polymorphism and cancer risk. The pooled ORs were performed for allelic comparison (G vs A), homozygote comparison (GG vs AA), heterozygote comparison (GA vs AA), recessive model (GG vs AA+AG) and dominant model (AG+GG vs AA), respectively. Summary estimates of OR and 95% CIs were obtained using a random effects model where the restricted maximum likelihood estimator was used to evaluate the inter-study heterogeneity (Viechtbauer, 2005; Raudenbush, 2009). Subgroup analyses were performed based on ethnicity (Asian and Caucasian), HWE in controls (yes/no) and cancer type (acute lymphoblastic leukemia, breast cancer, lung cancer, hepatocellular carcinoma, colorectal cancer, squamous cell carcinoma of the head and neck, gastric cancer, esophageal cancer, renal cell carcinoma, prostate cancer, gallbladder cancer, bladder cancer and cervical squamous cell carcinoma. There were fifteen studies of caucasian descent and twenty-four studies of Asian descent. The genotype distributions in the controls of fourteen studies were not conforming to HWE (p<0.05) (Okubo et al., 2010; Akkiz et al., 2011; Ling et al., 2011; Mittal et al., 2011; Vinci et al., 2011; Zhou et al., 2011; Alshatwi et al., 2012; Chu et al., 2012; Kim et al., 2012; Min et al., 2012; Xiang et al., 2012; Zhou et al., 2012; Ahn et al., 2013; Lv et al., 2013; Shan et al., 2013; Song et al., 2013; Umar et al., 2013; Vinci et al., 2013; Wei et al., 2013; Wu et al., 2013; Zou and Zhao, 2013; Bansal et al., 2014; Chu et al., 2014; Du et al., 2014; Gutierrez-Camino et al., 2014; Hasani et al., 2014; Hou et al., 2014; Hu et al., 2014; Ma et al., 2014; Omrani et al., 2014; Pu et al., 2014; Qi et al., 2014; Wang et al., 2014). Table 1 presents the main characteristics of each study included in the meta-analysis. The cancer type includes acute lymphoblastic leukemia, breast cancer, lung cancer, hepatocellular carcinoma, colorectal cancer, squamous cell carcinoma of the head and neck, gastric cancer, esophageal cancer, renal cell carcinoma, prostate cancer, gallbladder cancer, bladder cancer and cervical squamous cell carcinoma.

Results

Characteristics of the studies

Figure 1 outlines the search strategy used to obtain relevant literature. One hundred and three titles and abstracts were identified and screened and forty-two studies were reviewed in detail. One study was excluded as it was not associated with hsa-mir–499 rs3746444 A>G (Kucipinskas et al., 2012). After further excluding two abstracts (Hu et al., 2009; Hwang et al., 2010), thirty-nine case-control studies involving 14,136 cases and 16,937 controls were selected for meta-analysis (Hu et al., 2009; Tian et al., 2009; Catucci et al., 2010; Liu et al., 2010; Okubo et al., 2010; Srivastava et al., 2010; Akkiz et al., 2011; George et al., 2011; Ling et al., 2011; Mittal et al., 2011; Vinci et al., 2011; Zhou et al., 2011; Alshatwi et al., 2012; Chu et al., 2012; Kim et al., 2012; Min et al., 2012; Xiang et al., 2012; Zhou et al., 2012; Ahn et al., 2013; Lv et al., 2013; Shan et al., 2013; Song et al., 2013; Umar et al., 2013; Vinci et al., 2013; Wei et al., 2013; Wu et al., 2013; Zou and Zhao, 2013; Bansal et al., 2014; Chu et al., 2014; Du et al., 2014; Gutierrez-Camino et al., 2014; Hasani et al., 2014; Hou et al., 2014; Hu et al., 2014; Ma et al., 2014; Omrani et al., 2014; Pu et al., 2014; Qi et al., 2014; Wang et al., 2014). Table 1 presents the main characteristics of each study included in the meta-analysis. The cancer type includes acute lymphoblastic leukemia, breast cancer, lung cancer, hepatocellular carcinoma, colorectal cancer, squamous cell carcinoma of the head and neck, gastric cancer, esophageal cancer, renal cell carcinoma, prostate cancer, gallbladder cancer, bladder cancer and cervical squamous cell carcinoma. There were fifteen studies of caucasian descent and twenty-four studies of Asian descent. The genotype distributions in the controls of fourteen studies were not conforming to HWE (p<0.05) (Okubo et al., 2010; Akkiz et al., 2011; Ling et al., 2011; Mittal et al., 2011; Zhou et al., 2011; Xiang et al., 2012; Shan et al., 2013; Vinci et al., 2013; Wei et al., 2013; Zou and Zhao, 2013; Bansal et al., 2014; Ma et al., 2014; Omrani et al., 2014; Wang et al., 2014).

Evidence Synthesis

The main results of present meta-analysis including the heterogeneity test are shown in Table 2. The results of overall meta-analysis suggested a borderline association between hsa-mir–499 rs3746444 polymorphism and cancer susceptibility (AG+GG vs AA: OR=1.15, 95% CI= 1.04-1.26, corrected p value=0.04). After removing studies not conforming to HWE, however, this association disappeared (AG+GG vs AA: OR=1.18, 95% CI= 1.03-1.34, corrected p value=0.21). When stratified analysis by ethnicity, cancer type, or HWE in controls, although some associations between hsa-mir–499 rs3746444 polymorphism and cancer susceptibility were detected, these associations no longer exited after adjustment using BH method.
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Sensitivity Analysis

From the results of the leave-one-out sensitivity analysis, all the results above were not materially altered (data not shown). When limiting the meta-analysis to the 25 studies conforming to HWE (Table 1), all the results without Benjamini-Hochberg correction were not materially affected, but the several significance associations found in Asian subgroup (G vs A: OR=1.15, 95% CI= 0.98-1.34 and AG+GG vs AA: OR=1.17, 95% CI= 0.99-1.38) and other cancer subgroup (G vs A: OR=1.10, 95% CI= 0.94-1.30; AG vs AA: OR=1.34, 95% CI= 0.83-2.18; and AG+GG vs AA: OR=1.27, 95% CI= 0.88-1.84) no longer existed (Table 2). We further explored the source of heterogeneity by sample size, ethnicity, HWE in controls, cancer type, publication year and genotyping method with meta-regression. However, the results revealed that none of them contributed to the source of heterogeneity.

Table 1. Characteristics of Studies Included in The Meta-Analysis

| First author | Year | Country | Ethnicity | Cancer type | Source of control | Genotyping method | Cases | Controls | P_HWE |
|--------------|------|---------|-----------|-------------|------------------|-------------------|-------|----------|-------|
| Hu           | 2009 | China   | Asian     | Breast      | PB               | PCR-RFLP          | 707   | 258      | 0.06  |
| Tian         | 2009 | China   | Asian     | Lung        | PB               | PCR-RFLP          | 781   | 253      | 0.40  |
| Catucci      | 2010 | Italy   | Caucasian | Breast      | HB               | Sequencing        | 950   | 545      | 0.28  |
| Liu          | 2010 | USA     | Caucasian | Breast      | HB               | PCR-RFLP          | 364   | 154      | 0.05  |
| Srivastava   | 2010 | India   | Caucasian | Gallbladder | PB               | PCR-RFLP          | 112   | 97       | 0.57  |
| Akkiz        | 2011 | Turkey  | Caucasian | Prostate    | HB               | PCR-RFLP          | 48    | 98       | 0.07  |
| George       | 2011 | India   | Caucasian | Bladder     | HB               | PCR-RFLP          | 95    | 25       | 0.02  |
| Mittal       | 2011 | India   | Caucasian | Bladder     | HB               | PCR-RFLP          | 284   | 131      | 0.00  |
| Vinci        | 2011 | Italy   | Caucasian | Lung        | HB               | HRM               | 53    | 41       | 0.50  |
| Zhou         | 2011 | China   | Asian     | CSCC        | HB               | PCR-RFLP          | 134   | 84       | 0.01  |
| Alshatwi     | 2012 | Saudi   | Caucasian | Breast      | HB               | TaqMan            | 30    | 62       | 0.23  |
| Chu          | 2012 | China   | Asian     | Oral        | HB               | PCR-RFLP          | 339   | 119      | 0.98  |
| Kim          | 2012 | Korea   | Asian     | CRC         | HB               | PCR-RFLP          | 109   | 47       | 0.07  |
| Min          | 2012 | Korea   | Asian     | CRC         | HB               | PCR-RFLP          | 292   | 142      | 0.45  |
| Xiang        | 2012 | China   | Asian     | CRC         | HB               | PCR-RFLP          | 36    | 40       | 0.03  |
| Zhou         | 2012 | China   | Asian     | HCC         | HB               | PCR-RFLP          | 141   | 41       | 0.10  |
| Ahn          | 2013 | Korea   | Asian     | Gastric     | HB               | PCR-RFLP          | 323   | 123      | 0.83  |
| Lv           | 2013 | China   | Asian     | CRC         | HB               | PCR-RFLP          | 256   | 86       | 0.08  |
| Shan         | 2013 | China   | Asian     | CRC         | HB               | PCR-RFLP          | 128   | 37       | 0.01  |
| Song         | 2013 | USA     | Caucasian | OSCC        | HB               | PCR-RFLP          | 184   | 141      | 0.49  |
| Umar         | 2013 | India   | Caucasian | ESCC        | HB               | PCR-RFLP          | 155   | 122      | 0.09  |
| Vinci        | 2013 | Italy   | Caucasian | CRC         | HB               | HRM               | 93    | 32       | 0.03  |
| Wei          | 2013 | China   | Asian     | ESCC        | HB               | MassARRAY         | 291   | 61       | 0.11  |
| Wu           | 2013 | China   | Asian     | Gastric     | PB               | PCR-RFLP          | 149   | 47       | 0.85  |
| Zou          | 2013 | China   | Asian     | HCC         | HB               | PCR-RFLP          | 136   | 45       | 0.04  |
| Bansal       | 2014 | India   | Caucasian | Breast      | HB               | PCR-RFLP          | 80    | 30       | 0.10  |
| Chu          | 2014 | China   | Asian     | HCC         | HB               | PCR-RFLP          | 119   | 60       | 0.32  |
| Du           | 2014 | China   | Asian     | RCC         | HB               | TaqMan            | 251   | 94       | 0.59  |
| Gutierrez-Camino | 2014 | Spain   | Caucasian | ALL         | HB               | PCR-RFLP          | 138   | 56       | 0.19  |
| Hasani       | 2014 | Iran    | Caucasian | ALL         | HB               | TARMS-PCR         | 35    | 28       | 0.12  |
| Hou          | 2014 | China   | Asian     | OSCC        | HB               | TaqMan            | 111   | 39       | 0.13  |
| Hu           | 2014 | China   | Asian     | CRC         | HB               | PCR-RFLP          | 157   | 49       | 0.16  |
| Ma           | 2014 | China   | Asian     | HCC         | HB               | MassARRAY         | 724   | 241      | 0.00  |
| Omrani       | 2014 | Iran    | Caucasian | Breast      | PB               | TARMS-PCR         | 131   | 44       | 0.00  |
| Pu           | 2014 | China   | Asian     | Gastric     | HB               | PCR-RFLP          | 141   | 50       | 0.07  |
| Qi           | 2014 | China   | Asian     | HCC         | HB               | HRM               | 195   | 117      | 0.16  |
| Wang         | 2014 | China   | Asian     | HCC         | HB               | PCR-RFLP          | 98    | 32       | 0.00  |

*SCCHN squamous cell carcinoma of the head and neck, HCC hepatocellular carcinoma, CSCC cervical squamous cell carcinoma, CRC colorectal cancer, OSCC oral squamous cell carcinoma ESCC esophageal cancer, RCC renal cell carcinoma, ALL acute lymphoblastic leukemia, PB population-based, HB hospital-based, PCR-RFLP polymerase chain reaction-restriction fragment length polymorphism, HRM high-resolution melting analysis, TARMS-PCR tetra-primer amplification refractory mutation system-polymerase chain reaction.

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| Variable                  | G vs A | OR (95% CI) | P      |
|--------------------------|-------|-------------|--------|
| Ethnicity                |       |             |        |
| Asian                    | 24    | 1.16 (1.02-1.31) | 0.03   |
| Caucasian                | 14    | 1.05 (0.94-1.18) | 0.37   |
| Cancer type              |       |             |        |
| ALL                      | 2     | 0.91 (0.46-1.81) | 0.80   |
| Breast                   | 5     | 1.19 (0.77-1.84) | 0.49   |
| Colon                    | 10    | 1.21 (0.62-2.35) | 0.66   |
| CRC                      | 4     | 1.20 (0.75-2.01) | 0.27   |
| Gastric                  | 4     | 1.28 (0.75-2.21) | 0.37   |
| HCC                      | 10    | 1.19 (0.93-1.54) | 0.17   |
| HCC                      | 4     | 1.04 (0.85-1.26) | 0.72   |
| Breast                   | 5     | 1.19 (0.98-1.46) | 0.09   |
| Other                    | 5     | 1.14 (1.00-1.31) | 0.05   |

Values in bold font indicate statistical significance before Benjamini–Hochberg correction (P<0.05).

**Publication bias**

Funnel plot and Egger’s test were used to assess the publication bias of included studies. The graphical funnel plots for all genetic models appeared to be symmetrical. Then, Egger’s test was used to provide statistical evidence of funnel plot symmetry. The results still did not show any evidence of publication bias in the overall meta-analysis (G vs A: t = -1.06, P = 0.30; AG vs AA: t = 1.15, P = 0.26; GG vs AG+AA: t = -1.29, P = 0.20; AG+GG vs AA: t = 1.34, P = 0.19).

**Discussion**

The role of SNPs in miRNAs and the influence on cancer susceptibility have attracted much attention. Recently, the role of mutation presenting in hsa-miR-499 gene in the etiology of cancer development have drawn increasing attention. An important SNP (rs3746444) located in the seed site (nucleotides 2-8) of hsa-miR-499 has been extensively studied. The seed site at the 5’ end of the miRNA is important in miRNA-mRNA binding (Lewis et al., 2005), which may be affected by the SNP thus influencing cancer susceptibility. Up to present, many epidemiologic studies have explored the role of this SNP in cancer risk, but the results of these studies remain conflicting rather than conclusive. Therefore, we performed a meta-analysis of the previously published researches to derive a more precise estimation of the association between hsa-miR-499 rs3746444 A>G polymorphism and cancer risk.

The summary results, as derived from thirty-eight case-control studies, indicated that hsa-miR-499 rs3746444 G allele showed little harmful effect on cancer risk. When limiting the meta-analysis to the 25 studies conforming to HWE, however, this significance association no longer existed (Table 2). Deviation from HWE can be due to laboratory/genotyping errors, population stratification, selection bias in the choice of controls and confounding factors unaccounted for (Zintzaras, 2010). Currently, no consensus is achieved for whether or not to include the studies departing from HWE. But if the results are different before and after removing studies not in HWE, it is suggested that the analysis without studies not conforming to HWE would be more valid (Thakkinastin et al., 2005). When stratified analysis by ethnicity, cancer type, or HWE in controls, no significance association was found in any subgroup after adjustment using BH method. Although a number of meta-analyses have explored the association between hsa-miR-499 rs3746444 A>G polymorphism and cancer risk, none of them adjusted p value for multiple tests. The statistical significance results found in the former meta-analyses might be obtained by accident as a result of multiple...
comparisons. Taking account of all the above-mentioned aspects, we concluded that hsa-mir-499 rs3746444 A>G polymorphism was not associated with risk of cancer based on current evidence.

Some limitations likely affect the objectivity of the conclusions and they should be considered when interpreting the results. First, there is significant heterogeneity among included studies. Although sources of heterogeneity were explored by subgroup analysis and meta-regression, the results showed that sample size, ethnicity, HWE in controls, cancer type, publication year, source of controls and genotyping method did not contribute to the source of heterogeneity. Second, the effect of gene-gene and gene-environment interactions was not addressed in the analysis. Third, in the subgroup analysis, the number of each subgroup was relatively small, not having enough statistical power to explore the real association. Furthermore, the data was not stratified by age, nutrient intake and other suspected factors. Only based well-designed studies with the above factors taken into account, a better, comprehensive understanding of the relationship between the rs3746444 polymorphism and cancer risk is obtained.

In conclusion, our meta-analysis suggests that hsa-mir-499 rs3746444 A>G polymorphism was not associated with risk of cancer based on current evidence. Regarding the significant heterogeneity among included studies, large well-designed epidemiological studies will be necessary to validate the risk identified in the current meta-analysis. Moreover, further studies estimating the effect of gene-environment interactions may eventually provide a better, comprehensive understanding of the associations between the hsa-mir-499 rs3746444 polymorphism and cancer risk.

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