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Original Article

MDM2 T309G polymorphism and esophageal cancer risk: a meta-analysis

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Abstract: Murine double minute 2 (MDM2) has suggested to play an important role in esophageal cancer. The association between MDM2 T309G polymorphism and esophageal cancer risk was inconclusive. To clarify the possible association, we conducted a meta-analysis. We searched in the PubMed, Embase, and Wanfang databases. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association. A total of 6 studies with 4909 cases and controls were included based on the search criteria. The MDM2 T309G polymorphism was associated with a significantly decreased risk of esophageal cancer (OR=0.88; 95% CI, 0.81-0.96; I^2=22%). When stratified by type of race, a significantly decreased esophageal cancer risk were observed in Asians (OR=0.85; 95% CI, 0.78-0.93; I^2=0%). In conclusion, this meta-analysis suggested that MDM2 T309G polymorphism was associated with a significantly decreased risk of esophageal cancer.

Keywords: Esophageal cancer, MDM2, meta-analysis, polymorphism

Introduction

Esophageal cancer is the fourth most common cause of cancer-related death in China. Esophageal cell carcinoma (ESCC) is by far the most common subtype of esophageal cancer, followed distantly by adenocarcinoma, which accounts for less than 3% of all esophageal cancers in high incidence areas of China [1]. Recent studies have suggested that a variety of genes may be associated with susceptibility to esophageal cancer, including murine double minute 2 (MDM2) gene.

The protein encoded by the MDM2 gene plays a key role in cell cycle control as a regulator of p53 activity (the protein coded for by the TP53 gene). It also interacts with several other major proteins involved in cell cycle control and growth arrest, such as pRb and E2F1 [2]. The importance of MDM2 function is illustrated by the fact that Mdm2 knock-out leads to early embryonic death in mice, which can be reversed by concomitant knockout of the TP53 gene [3].

The polymorphism SNP309T>G (rs2279744), located in the MDM2 intronic promoter (P2), has been found to be associated with enhanced Sp1 transcription factor binding, thereby leading to increased MDM2 expression [4]. SNP309G was initially found associated with early cancer onset among individuals carrying TP53 germline mutations (Li-Fraumeni syndrome) and spontaneous soft tissue sarcomas as well as estrogen receptor (ER) rich breast cancer [5]. Subsequent to the initial discovery of SNP309, potential associations between this variant and cancer risk have been studied across many cancer types and ethnic groups. Many investigators have investigated the association between the MDM2 T309G polymorphism and esophageal cancer risk [6-11]. But the results were conflicted and inconclusive. As a single study may lack the power to provide reliable conclusion, we performed this meta-analysis.

Methods

Selection of published studies

We searched in the PubMed, Embase, and Wanfang Medicine databases for studies assessing the association between MDM2

Table 1. Characteristics of the included studies

First author	Year	Country	Ethnicity	Age	Gender	Total number (n)	Hardy-Weinberg equilibrium
Hong	2005	China	Asian	Adult	Mixed	2178	Yes
Cao	2007	China	Asian	Adult	Mixed	993	Yes
Liu	2010	USA	Caucasian	Adult	Mixed	765	Yes
Li	2011	China	Asian	Adult	Mixed	264	Yes
Ma	2012	China	Asian	Adult	Mixed	452	Yes
Er	2012	China	Asian	Adult	Mixed	257	Yes

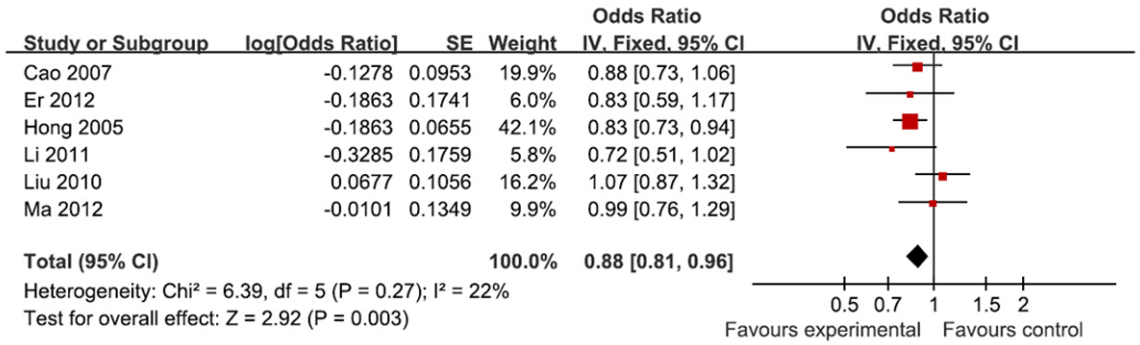

Figure 1. Forest plot of MDM2 T309G polymorphism and esophageal cancer.

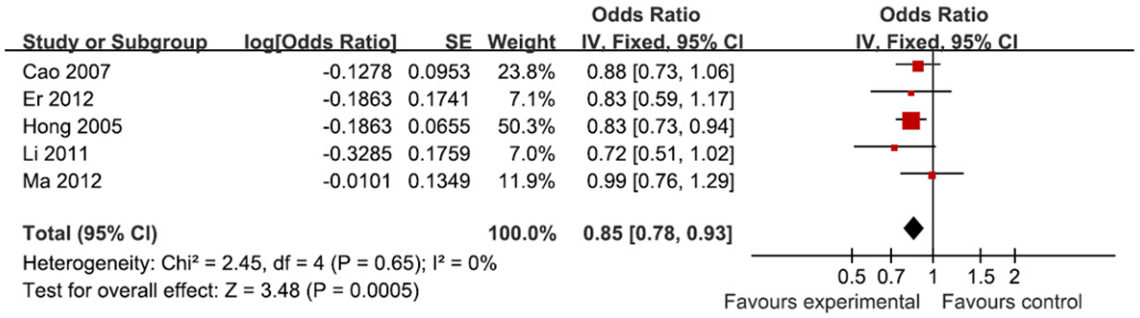

Figure 2. Forest plot of MDM2 T309G polymorphism and esophageal cancer in Asians.

T309G polymorphism and esophageal cancer risk. The literature strategy used the following keywords: ("murine double minute 2", "MDM2") and ("esophageal cancer" or "esophageal tumor"). The references of the retrieved articles were also hand searched at the same time to identify additional published articles. The references of eligible studies and relevant reviews were also checked for other literature not indexed into common databases. There was no language restriction applied in this meta-analysis. The inclusion criteria of eligible studies were as following: (1) Case-control or cohort study; (2) The cases were patients with esophageal cancer; (3) The controls were cancer-free individuals; (4) Reported the frequencies of MDM2 T309G polymorphism in both cases and controls or the odds ratio (OR) and its 95% confidence interval (95% CI) of the association between MDM2 T309G polymorphism and esophageal cancer risk. Family-based studies and studies containing overlapping data were all excluded.

Data extraction

Relevant data were extracted from all the eligible studies independently by two reviewers, and disagreements were settled by discussion and the consensus among all reviewers. The

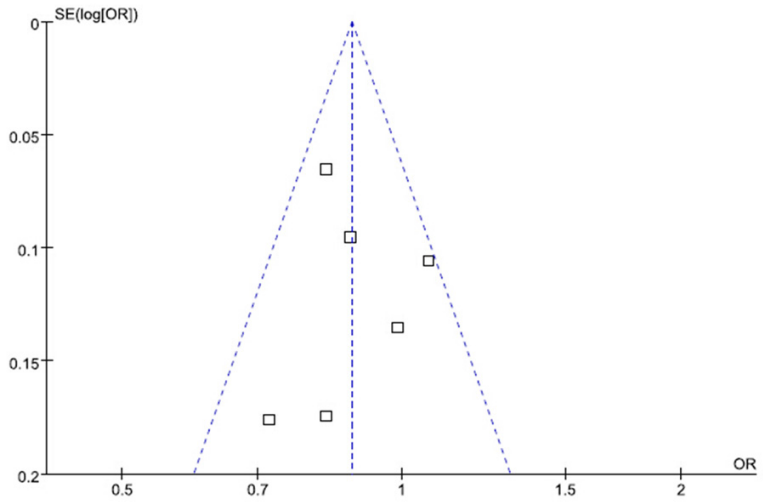

Figure 3. Funnel plot of MDM2 T309G polymorphism and esophageal cancer.

main data extracted from the eligible studies were as following: the first author, year of publication, country, ethnicity, age and gender of the cases, total numbers of cases and controls.

Statistical analysis

The strength of the association was measured by ORs with 95% CIs. The ORs with corresponding 95% CIs from individual studies were pooled using fixed or random effects models according to the heterogeneity. When the *P* value for Cochran's Q statistic was less than 0.1, and a significant heterogeneity existed across the included studies, the random effects model (DerSimonian and Laird method) was used for meta-analysis, or else the fixed effects model (Mantel-Haenszel method) was used. Sensitivity analysis was further performed by excluding single study in turn to assess the impact of individual study on the pooled estimate. Subgroup analyses were stratified by ethnicity. Funnel plots was undertaken to assess the potential publication bias. Data analysis was performed using Revman 5.1.

Results

Study characteristics

A total of 6 studies with 4909 cases and controls were included based on the search criteria [6-11]. All these studies were conducted in Asians but one was performed in Caucasians. All the studies were in Hardy-Weinberg equilibrium. The main study characteristics are summarized in **Table 1**.

Meta-analysis results

The MDM2 T309G polymorphism was associated with a significantly decreased risk of esophageal cancer (OR=0.88; 95% CI, 0.81-0.96; I^2=22%; **Figure 1**). When stratified by type of race, a significantly decreased esophageal cancer risk were observed in Asians (OR=0.85; 95% CI, 0.78-0.93; I^2=0%; **Figure 2**).

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs, and the corresponding pooled ORs were not materially altered (data not shown).

Funnel plot was performed to assess the publication bias of literatures. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (**Figure 3**).

Discussion

Previous studies on the association between MDM2 T309G polymorphism and esophageal cancer risk reported inconclusive results. To clarify the possible association, we conducted a meta-analysis of a total of 6 studies with 4909 individuals. Overall, MDM2 T309G polymorphism was significantly associated with decreased risk of esophageal cancer, respectively. Significant association was also found in Asian patients. However, this association should be confirmed in Caucasians, since only one study used Caucasians.

Carcinoma of the esophagus has diverse incidence patterns and risk factors [12]. The etiology of this cancer is incompletely understood, like many other malignancies. Although the biological mechanisms underlying these factors are not fully understood, one of the proposed mechanisms represents the involvement of oxidative DNA damage which can induce mutations leading to cancers [13]. The MDM2 regulation of disorders is associated with the development of cancer, which is confirmed by the

evidence that MDM2 was over-expressed in some human cancers [14]. MDM2 single nucleotide polymorphism SNP (T309G) has already been described as being associated with several types of cancer [15], and also with accelerated tumorigenesis and poor prognosis [16]. This polymorphism is located in position 309 in the first intron of the MDM2 oncogene, which serves as a transcriptional enhancer region. When T is replaced with G, this increases the affinity of the Sp1 transcription factor and it has been shown that cells carrying the T309G genotype have a 2-3-fold increase in MDM2 mRNA and protein synthesis. This leads to the abrogation of p53 tumor suppressor activity and the development of cancer [4].

In conclusion, this meta-analysis suggested that MDM2 T309G polymorphism was significantly associated with decreased risk of esophageal cancer.

Disclosure of conflict of interest

None.

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References

[1] Wang LD, Zhou Q, Yang CS. Esophageal and gastric cardia epithelial cell proliferation in northern Chinese subjects living in a high-incidence area. J Cell Biochem Suppl 1997; 28-29: 159-65.

[2] Martin K, Trouche D, Hagemeier C, Sørensen TS, La Thangue NB, Kouzarides T. Stimulation of E2F1/DP1 transcriptional activity by MDM2 oncoprotein. Nature 1995; 375: 691-4.

[3] Jones SN, Roe AE, Donehower LA, Bradley A. Rescue of embryonic lethality in Mdm2-deficient mice by absence of p53. Nature 1995; 378: 206-8.

[4] Bond GL, Hu W, Bond EE, Robins H, Lutzker SG, Arva NC, Bargonetti J, Bartel F, Taubert H, Wuerl P, Onel K, Yip L, Hwang SJ, Strong LC, Lozano G, Levine AJ. A single nucleotide polymorphism in the MDM2 promoter attenuates the p53 tumor suppressor pathway and accelerates tumor formation in humans. Cell 2004; 119: 591-602.

[5] Bond GL, Hirshfield KM, Kirchhoff T, Alexe G, Bond EE, Robins H, Bartel F, Taubert H, Wuerl P, Hait W, Toppmeyer D, Offit K, Levine AJ. MDM2 SNP309 accelerates tumor formation in a gender-specific and hormone-dependent manner. Cancer Res 2006; 66: 5104-10.

[6] Hong Y, Miao X, Zhang X, Ding F, Luo A, Guo Y, Tan W, Liu Z, Lin D. The role of P53 and MDM2 polymorphisms in the risk of esophageal squamous cell carcinoma. Cancer Res 2005; 65: 9582-7.

[7] Ma J, Zhang J, Ning T, Chen Z, Xu C. Association of genetic polymorphisms in MDM2, PTEN and P53 with risk of esophageal squamous cell carcinoma. J Hum Genet 2012; 57: 261-4.

[8] Liu G, Cescon DW, Zhai R, Zhou W, Kulke MH, Ma C, Xu W, Su L, Asomaning K, Heist RS, Wain JC, Lynch TJ, Christiani DC. p53 Arg72Pro, MDM2 T309G and CCND1 G870A polymorphisms are not associated with susceptibility to esophageal adenocarcinoma. Dis Esophagus 2010; 23: 36-9.

[9] Li R, Zhang L, Liu Z. Correlation of MDM2 gene polymorphisms and risk of esophageal squamous cell carcinoma in southwest Shandong Han nationality. Xinxiang Yi Xue Yuan Xue Bao 2011; 28: 437-42.

[10] Cao YY, Zhang XF, Guo W, Wang R, Ge H, Zhang JH. Association of the MDM2 polymorphisms with susceptibility of esophageal squamous cell carcinoma and that of gastric cardiac adenocarcinoma. Tumor 2007; 27: 628-32.

[11] Er LM, Zhang LW, Niu W. Relevance of MDM2 polymorphisms with esophageal squamous cell carcinoma, gastric adenocarcinoma and double primary cancers in esophagus and stomach. Xian Dai Yu Fang Yi Xue 2012; 39: 3342-4.

[12] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108.

[13] Fearon ER. Human cancer syndromes: clues to the origin and nature of cancer. Science 1997; 278: 1043-50.

[14] Chen X, Sturgis EM, Lei D, Dahlstrom K, Wei Q, Li G. Human papillomavirus seropositivity synergizes with MDM2 variants to increase the risk of oral squamous cell carcinoma. Cancer Res 2010; 70: 7199-208.

[15] Joshi AM, Budhathoki S, Ohnaka K, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Maekawa T, Yasunami Y. TP53 R72P and MDM2 SNP309 polymorphisms and colorectal cancer risk: the Fukuoka Colorectal Cancer Study. Jpn J Clin Oncol 2011; 41: 232-8.

[16] Hirata H, Hinoda Y, Kikuno N, Kawamoto K, Suehiro Y, Tanaka Y, Dahiya R. MDM2 SNP309 polymorphism as risk factor for susceptibility and poor prognosis in renal cell carcinoma. Clin Cancer Res 2007; 13: 4123-9.