Association between the *hMSH2* IVS12-6 T>C polymorphism and cancer risk: A meta-analysis

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Abstract. The *hMSH2* gene, a member of the mismatch repair (MMR) pathway, plays a key role in the maintenance of genomic integrity. The common sequence variation in *hMSH2*, IVS12-6 T>C, has been implicated in cancer risk. However, the results of published studies on this polymorphism remain conflicting. Hence, we conducted a meta-analysis to clarify the role of the *hMSH2* IVS12-6 T>C polymorphism in cancer. We performed a comprehensive literature search updated to March 2011 of studies on the associations between the *hMSH2* IVS12-6 T>C polymorphism and cancer risk. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the associations. Thirteen studies involving 7,527 patients and 8,762 control subjects were included in this meta-analysis. The overall results indicated no major influence of the polymorphism on cancer risk. However, stratified analysis by cancer types showed that the *hMSH2* IVS12-6 polymorphism increased the risk for non-Hodgkin's lymphomas (heterozygote comparison: OR=1.62; 95% CI 1.06-2.47). When stratified by the source of controls, significant associations were observed in hospital-based populations (heterozygote comparison: OR=1.28; 95% CI 1.02-1.61). These results indicate that the polymorphism of *hMSH2,* IVS12-6, may cause a different effect in different types of cancers. To draw more comprehensive conclusions, further prospective studies with larger numbers of participants worldwide are required to examine the associations between this polymorphism and cancer risk.

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Introduction

During the last decade, a number of important genes responsible for the genesis of various types of cancers have been discovered, at the same time their mutations have been precisely established, and the pathway through which they act has been characterized (1). The mismatch repair (MMR) pathway, first described in bacteria, is involved in the maintenance of genomic integrity by repairing DNA replication errors (2), and MMR proteins correct base substitution mismatches and small insertion-deletion mismatches generated during DNA replication (3). The MMR system is well conserved from *Escherichia coli* to mammals, and the *E. coli* MMR system, where MutS, MutL and MutH complexes function, has been well analyzed. In mammalian cells, heterodimers of MutS homologues (*MSH2-MSH6* and *MSH2-MSH3*) recognize replication errors, and the heterodimer of the MutL homologue (*MLH1-PMS2*) interacts with MutS homologues and recruits further repair proteins (4).

Seven MMR genes exist in humans: *MLH1, MLH3, PMS1, PMS2, MSH2, MSH3* and *MSH6* (5). The inactivation of these genes leads to increased genetic instability, which in turn results in an increased rate of mutation in 'gatekeeper' genes that regulate human cell proliferation and death (6). A role for *hMSH2* in cancer has been firmly established in hereditary nonpolyposis colorectal cancer (HNPCC) (7-9). Several single nucleotide polymorphisms (SNPs), IVS12-6 T>C (rs2303428), G23A (rs4987188) and IVS10+12 A>G (rs3732183) were identified in the *hMSH2* gene and among them, only the IVS12-6 T>C polymorphism was reported functional and therefore has been extensively studied in recent years (3,10-21).

The IVS12-6 T>C is a common polymorphism located at position -6 of the intronic splice acceptor site of exon 13 of *hMSH2*. Although the genetic function of this polymorphism has not been well determined, its variant type may result in alternative splicing and deficiency of *hMSH2* protein (22,23).

To date, many studies have investigated the role of this polymorphism in the etiology of cancers of various organs including the lung, colon, rectum, ovary, and others (3,10-21). However, the results of these studies remain conflicting rather than conclusive. Considering the extensive role of *hMSH2* in

the carcinogenic process, we performed a meta-analysis on all eligible case-control studies to estimate the overall cancer risk of this polymorphism and to quantify the potential between-study heterogeneity.

Materials and methods

Identification and eligibility of relevant studies. We searched the electronic literature PubMed for all relevant reports (the last search update was March 22, 2011), using the key words '*MSH2*' or '*hMSH2*', 'cancer' and 'polymorphism'. The search was limited to English language manuscripts. In addition, studies were identified by a manual search of the reference lists of reviews and retrieved studies. Studies were selected when there were available data for the *hMSH2* IVS12-6 T>C polymorphism with cancer risk in a case-control design. Additional studies were identified by a hand search of the references of the original studies. We also used the PubMed option 'Related Citations' in each research article to search potentially relevant articles. In our meta-analysis, the studies had to meet the following criteria: i) was a study of the *hMSH2* IVS12-6 T>C polymorphism and cancer risk, ii) used a case-control design and iii) contained available genotype frequency.

Data extraction. Two of the authors independently extracted data and reached a consensus on all of the items. For each study, the following information was sought: the first author's last name, year of publication, country of origin, ethnicity, source of control groups (population- or hospital-based controls), numbers of genotyped cases and controls, genotyping methods, and cancer type. Different ethnic descents were categorized as Caucasian, Asian and mixed (composed of an admixture of different ethnic groups). For studies including subjects of different ethnic groups, data were extracted separately for each ethnic group whenever possible.

Statistical analysis. For the control group of each study, the observed genotype frequencies of *hMSH2* IVS12-6 T>C were assessed for Hardy-Weinberg equilibrium using the χ^2 test. The strength of the association between *hMSH2* IVS12-6 T>C and cancer risk was measured by odds ratios (ORs) with 95% confidence intervals (CIs). We first estimated the risks of the CC and CT genotypes on cancers, compared with the wild-type TT homozygote, and then evaluated the risks of (CC/CT) vs. TT and CC vs. (CT/TT) on cancers, assuming dominant and recessive effects of the variant C allele, respectively. In order to evaluate the ethnicity-specific effect, subgroup analyses were performed by ethnic group. In consideration of the possibility of heterogeneity across the studies, a statistical test for heterogeneity was performed based on the Q-test. When the P-value was >0.10 in the Q-test which indicates a lack of heterogeneity among studies, the summary OR estimate of each study was calculated by the fixed-effects model of Mantel-Haenszel (24). Otherwise, the random-effects model of DerSimonian and Laird (25) was used. An estimate of potential publication bias was carried out by the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggested a possible publication bias. All statistical tests were performed with Stata software (version 10.0; Stata Corporation, College Station, TX, USA).

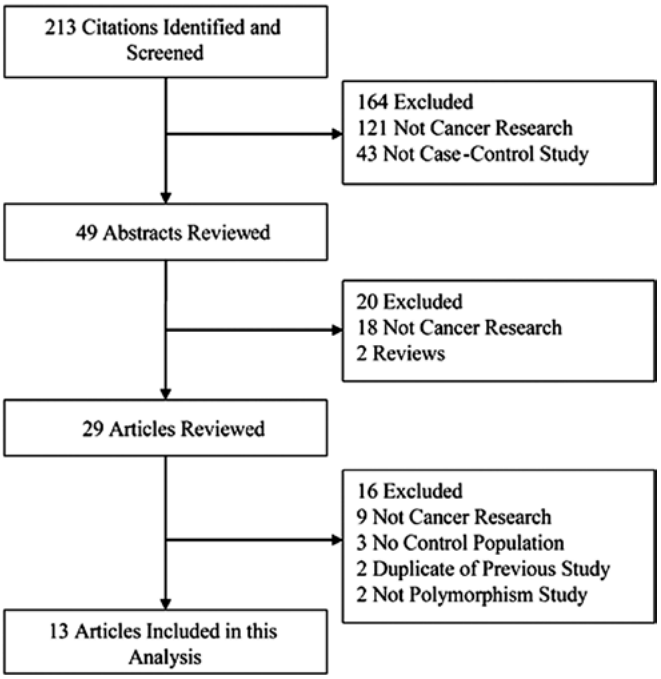

Figure 1. Studies identified with criteria for inclusion and exclusion.

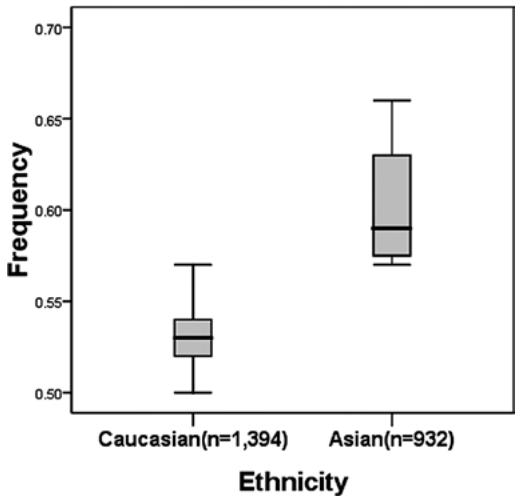

Figure 2. Frequencies of the variant alleles among controls stratified by ethnicity.

Results

Characteristics of the studies. Thirteen eligible publications were identified on the association between the *hMSH2* IVS12-6 T>C polymorphism and cancer risk including 7,527 cancer cases and 8,762 controls (3,10-21). The selected study characteristics are listed in Table I and the criteria for inclusion and exclusion are shown in Fig. 1. All studies were case-control studies. There were six studies in populations of Caucasian descent, four of Asian origin and three of mixed race. A classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was conducted in four of the 13 studies. In addition, other methods were utilized to detect genotypes. The genotype distributions among the

Table I. Characteristics of the eligible studies included in the meta-analysis.

First author	Year	Country/Region	Ethnicity	Cancer type	Source of controls	Genotyping method	Cases	Controls	HWE
Goessl	1997	Germany	Caucasian	Colorectal cancer	PB	FLUPD	106	125	0.540
Paz-y-mino	2002	Ecuador	Mixed	Non-Hodgkin's lymphomas	HB	PCR-SSCP	22	50	0.009
Paz-y-mino	2003	Ecuador	Mixed	Lymphoma and leukemia	HB	PCR-SSCP	181	50	0.009
Hishida	2003	Japan	Asian	Non-Hodgkin's lymphomas	HB	PCR-RFLP	103	487	0.942
Kim	2004	Korea	Asian	Colorectal cancer	PB	TaqMan	107	330	0.091
Jung	2006	Korea	Asian	Lung cancer	PB	PCR-RFLP	432	432	0.613
Beiner	2006	Canada	Caucasian	Endometrial cancer	PB	MALDI-TOF	665	654	0.000
Song	2006	UK, Denmark, USA	Caucasian	Ovarian cancer	PB	TaqMan	1325	2044	0.411
Hsu	2007	Taiwan	Asian	Lung cancer	PB	PCR-RFLP	156	235	0.493
Raptis[a]	2007	Canada	Caucasian	Colorectal cancer	PB	TaqMan	929	1098	0.444
Raptis[a]	2007	Canada	Caucasian	Colorectal cancer	PB	TaqMan	430	275	0.195
Koessler	2008	UK	Caucasian	Colorectal cancer	PB	TaqMan	2294	2279	0.752
Tulupova	2008	Czech	Caucasian	Colorectal cancer	HB	TaqMan	611	608	0.689
Demokan	2010	Turkey	Mixed	Head and neck cancer	HB	PCR-RFLP	166	95	0.054

[a]Different populations existed in one study. HWE, Hardy-Weinberg equilibrium. PB, population-based; HB, hospital-based. FLUPD, fluorescent-labeled universal primer; PCR, polymerase chain reaction; SSCP, single-strand conformation polymorphism; RFLP, restriction fragment length polymorphism; MALDI-TOF, matrix assisted laser desorption/ionization time-of-flight.

Table II. Stratified analyses of the *hMSH2* IVS12-6 T>C polymorphism on cancer risk.

			CT vs. TT		CC vs. TT		CC/CT vs. TT (dominant)		CC vs. CT/TT (recessive)	
Variables	n	Cases/controls	OR (95% CI)	P-value[a]	OR (95% CI)	P-value[a]	OR (95% CI)	P-value[a]	OR (95% CI)	P-value[a]
Total	14	7527/8762	1.10 (0.94-1.28)[b]	0.002	0.92 (0.74-1.15)	0.881	1.07 (0.93-1.23)[b]	0.003	0.89 (0.72-1.10)	0.892
Cancer types										
Lung cancer	2	588/667	1.15 (0.90-1.46)	0.392	1.02 (0.70-1.46)	0.818	1.11 (0.89-1.40)	0.477	0.93 (0.66-1.30)	0.878
NHL	2	125/537	**1.62 (1.06-2.47)**	0.173	0.98 (0.43-2.27)	0.948	1.50 (1.00-2.27)	0.247	0.81 (0.36-1.81)	0.951
Colorectal cancer	6	4477/4715	1.02 (0.82-1.28)[b]	0.008	1.00 (0.68-1.45)	0.896	1.03 (0.83-1.28)[b]	0.008	1.04 (0.71-1.51)	0.867
Other cancers	4	2337/2843	1.09 (0.77-1.55)[b]	0.031	0.68 (0.42-1.09)	0.261	1.03 (0.73-1.44)[b]	0.027	0.67 (0.42-1.08)	0.319
Ethnicities										
Asian	4	798/1484	1.11 (0.92-1.34)	0.114	1.04 (0.76-1.41)	0.981	1.09 (0.91-1.31)	0.243	0.96 (0.72-1.29)	0.792
Caucasian	7	6360/7083	1.07 (0.88-1.28)[b]	0.002	0.87 (0.63-1.20)	0.809	1.06 (0.88-1.27)[b]	0.002	0.87 (0.63-1.20)	0.863
Mixed	3	369/195	1.78 (0.64-4.94)[b]	0.080	0.25 (0.05-1.14)	0.637	1.43 (0.57-3.64)[b]	0.080	0.25 (0.05-1.12)	0.694
Source of controls										
Hospital-based	5	1083/1290	**1.28 (1.02-1.61)**	0.214	0.78 (0.40-1.51)	0.444	1.22 (0.98-1.52)	0.223	0.70 (0.37-1.33)	0.520
Population-based	9	6444/7472	1.04 (0.88-1.23)[b]	0.003	0.94 (0.74-1.19)	0.899	1.03 (0.88-1.20)[b]	0.004	0.92 (0.73-1.15)	0.900

[a]P-value of the Q-test for heterogeneity test. [b]Random-effects model was used when the P-value for heterogeneity test was <0.10; otherwise, the fix-effects model was used.

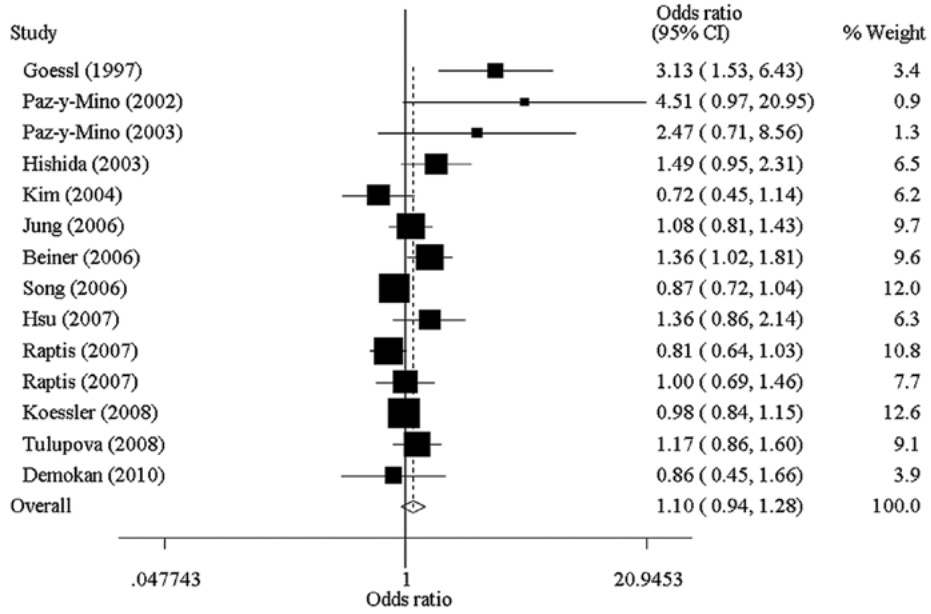

Figure 3. Forest plot of the cancer risk associated with *hMSH2* IVS12-6 T>C (CT vs. TT). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

controls of all studies were in agreement with Hardy-Weinberg equilibrium for all except three studies (16,17,21).

Quantitative synthesis. There was a wide variation in the C allele frequency of the *hMSH2* IVS12-6 T>C polymorphism among the controls across different ethnicities. For Asian populations, the IVS12-6 C allele frequency was 0.60 (95% CI 0.54-0.67), which was significantly higher than that in Caucasian populations (0.53; 95% CI 0.51-0.55; P=0.003) (Fig. 2).

As shown in Table II, no significant association was found in any genetic model among studies of these cancers. Forest plot of heterozygote comparison was given (Fig. 3). In the stratified analysis by cancer type, significant increased risks were observed for non-Hodgkin's lymphoma patients (heterozygote comparison: OR=1.62; 95% CI 1.06-2.47) (Table II). According to the source of the controls, a significant effect was observed in hospital-based studies (heterozygote comparison: OR=1.28; 95% CI 1.02-1.61). Among studies of lung cancer, colorectal cancer and other cancers, no significant associations were found in any genetic model, in neither Asian nor Caucasian individuals (Table II).

Test of heterogeneity. There was significant heterogeneity for the heterozygote comparison (CT vs. TT, P=0.001) and dominant model comparison (CC/CT vs. TT, P=0.002). We then assessed the source of heterogeneity for the heterozygote comparison (CT vs. TT) by cancer type, ethnicity and source of controls. As a result, the source of controls (χ^2=4.11, df=1, P=0.043), but not cancer type (χ^2=6.21, df=3, P=0.102) or ethnicity (χ^2=1.85, df=2, P=0.396) was found to contribute to the substantial heterogeneity.

Publication bias. Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature studies.

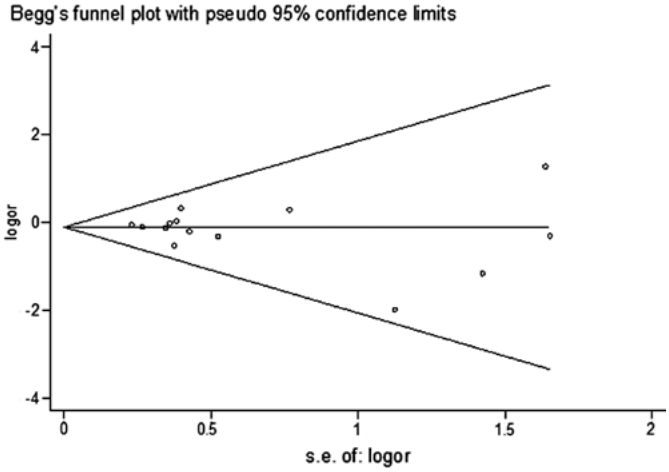

Figure 4. Begg's funnel plot for publication bias test (CC vs. TT). Each point represents a separate study for the indicated association. Log[or], natural logarithm of odds ratio. Horizontal line, mean effect size.

The shapes of the funnel plots did not reveal any evidence of obvious asymmetry. The Egger's test was subsequently used to provide statistical evidence of funnel plot symmetry. The results did not show any evidence of publication bias (t=0.83, P=0.423 for CC vs. TT) (Fig. 4).

Discussion

The mismatch repair pathway plays an important role in the maintenance of genome integrity and acts conservatively in species. With its main function to repair mismatches during DNA duplication, the MMR pathway ensures the integrity and stability of the genome (3). Genome point mutations, microsatellite instability (MSI) and loss of heterozygosity (LOH) are all mutation

phenotypes caused by impairment in any component of the MMR pathway (3,26). Studies have revealed the presence of MSI in more than 90% of hereditary non-polyposis colorectal cancer (HNPCC) and in 15% of non-family colorectal cancer cases (27), and mutations of *MLH1, MSH2* and *MSH6* germ cells in more than 95% of HNPCC cases with MSI (28). The presence of MSI has been confirmed in other primary cancers such as prostate (29), endometrial (30), pancreatic (31), gastric (32,33) and others (34). Meanwhile, a few SNPs were found to be involved in the formation and development of solid tumors through the alteration of the biological activities of DNA repairase (35-37); for example, *MLH1* I219V and breast cancer (38), *PMS2* rs7797466 and ovarian cancer (19), and *MLH1* -93 G>A, *MSH2* -118 T>C, *MSH6* G39E and colorectal cancer (18,39). *hMSH2* is the first MMR gene to be associated with HNPCC invasion. Its expression is varied not only in gastric cancer, lung cancer, endometrial cancer and others, but also is also associated with the prognosis of cancers. High expression indicates better repair and low expression is indicative of a worse repair ability (40). Although the genetic function of the *hMSH2* IVS12-6 T>C polymorphism is not clear, its variant type may lead to alternative splicing and deficiency of *hMSH2* protein (22,23).

In the present study, we performed a meta-analysis of published studies based on 13 case-control studies in order to reveal the association between the *hMSH2* IVS12-6 T>C polymorphism and cancer risk. The results indicate that there is no significant association between this polymorphism and cancer risk. In the stratified analyses we found that the C allele was a risk factor for developing non-Hodgkin's lymphoma (NHL). This may be due to the limited number of studies analyzed and the small sample size. The ethnically mixed population in our meta-analysis consisted of only Ecuadorian and Trukese individuals from two continents representing a huge discrimination of human race. Our results also demonstrated that no significant associations were found in any genetic model among studies of lung cancer, colorectal cancer and others. A moderate association was observed in the hospital-based controls, but not in the population-based controls when stratifying the source of controls. This may have resulted from a differential effect of selection criteria in different cancers, which was dictated by the sample size in our meta-analysis, as well as the weight of each study. Other factors such as matched criteria may also have conferred an effect. The above differences may contribute to the inconsistent results. Therefore, it is very important to determine the unified selection criteria and to choose larger sample population studies.

We would like to note the differences in the genetic background and gene-environment interactions in the etiology. The IVS12-6 C allele frequency among the controls in Asian populations was significant higher than that in European populations, suggesting a possible ethnic difference (Fig. 2). Moreover, there is no reported study on African populations. Therefore, additional studies are needed to further validate ethnic differences on the effect of this SNP on cancer risk, particularly in Africans.

Identification of the source of heterogeneity is one of the most important goals of meta-analysis. In this analysis, we found that the source of heterogeneity was from the origin of the controls, suggesting that certain effects of the genetic polymorphism were population-specific.

Various limitations of this meta-analysis should be mentioned. First, the lack of original data of the reviewed studies limited our further evaluation of potential interactions, as interactions between gene-gene or gene-environment may modulate cancer risk. Second, our result was based on unadjusted estimates, while more precise analyses were needed to be performed had individual data been available, which would have allowed for an adjusted estimate by age or gender. However, our present meta-analysis also had advantages. First, a substantial number of cases and controls was pooled from different studies, which greatly increased the statistical power of the analysis. Second, the quality of case-control studies included in this meta-analysis was satisfactory according to our selection criteria.

In conclusion, our meta-analysis suggests that the *hMSH2* IVS12-6 T>C polymorphism is not associated with cancer risk. A significant risk effect on cancer was observed in NHL patients while no statistical results were found for the other cancer types. Human race variation in the distribution of genotypes may have also affected the analysis. The role of this variant in other populations should be investigated by carrying out additional studies including a wider spectrum of subjects particularly African individuals. Further functional studies between the *hMSH2* IVS12-6 T>C polymorphism and cancer risk should be conducted in order to reveal its mechanism. Additional well-designed extensive studies are warranted to validate the association between the *hMSH2* IVS12-6 T>C polymorphism and the susceptibility of cancer.

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