RESEARCH ARTICLE

C1420T Polymorphism of Cytosolic Serine Hydroxymethyltransferase and Risk of Cancer: a Meta-analysis

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Abstract

A series of studies have explored the role of cytosolic serine hydroxymethyltransferase (SHMT1) C1420T polymorphism in cancer risk, but their results were conflicting rather than conclusive. To derive a more precise estimation of the association between C1420T and cancer risk, the present meta-analysis of 28 available studies with 15,121 cases and 18,023 controls was conducted. The results revealed that there was no significant association between the polymorphism and cancer risk overall. In stratified analysis by cancer type (breast cancer, gastrointestinal cancer, leukemia, lymphoma, and others), the results showed that 1420T allele was associated with decreased risk in leukemia (CT vs. CC: OR= 0.825, 95% CI =0.704-0.966; and CT+TT vs. CC: OR= 0.838, 95% CI = 0.722-0.973), but the same results were not present for other cancer types. When subgroup analysis was performed by source of control (population-based [PB] and hospital-based [HB]), a borderline inverse association was observed for the HB subgroup (CT vs. CC: OR= 0.917, 95% CI = 0.857-0.982) but not for the PB subgroup. Stratifying by geographic area (America, Asia and Europe), significant inverse association was only found in Asia subgroup (CT vs. CC: OR= 0.674, 95% CI = 0.522-0.870). In summary, the findings suggest that SHMT1 C1420T polymorphism is not associated with overall cancer development, but might decrease cancer susceptibility of Asians as well as reduce leukemia risk. Large well-designed epidemiological studies will be necessary to validate the risk identified in the current meta-analysis.

Keywords: Cancer - meta-analysis - C1420T - SHMT1 – polymorphism - susceptibility

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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., 2013). Now, the mechanism of carcinogenesis is poorly understood. It has been suggested that susceptibility genes combining with environmental factors may be important in the development of cancer (Lichtenstein et al., 2000). Epidemiologic studies indicate that folate metabolism imbalance can lead to reduced S-adenosylmethionine (SAM) production and modification of DNA methylation profile promoting stimulation of proto-oncogene and inactivation of tumor growth suppressor genes. Serine hydroxymethyltransferase (SHMT) is a key enzyme controlling folate metabolism. It catalyzes the reversible conversion of serine and tetrahydrofolate (THF) to glycine and methylene THF to provide one-carbon units for the synthesis of SAM, purine, and thymidine. SHMT1 is one of SHMT isoenzymes, which plays a crucial role in generating one-carbon units for purine, thymidylate, and methionine synthesis in the cytoplasm (Girgis et al., 1997). It is reported that a polymorphism in 1420 C>T (rs1979277) can convert the codon for leucine to phenylalanine, resulting in a lower plasma and red blood cell folate levels in 1420CC individuals (Heil et al., 2001). Consequently, the cancer risk might be different in the mutation carriers. A series of studies have explored the role of SHMT1 C1420T polymorphism in cancer risk, but their results are conflicting rather than conclusive. Therefore, we performed a meta-analysis of all studies available now to derive a more precise estimation of the association between SHMT1 C1420T polymorphism and cancer risk.

Materials and Methods

Publication search

In order to identify all previously published studies on the association of SHMT1 C1420T polymorphism with cancer, PubMed, Embase, and Web of Science were searched with following keywords and subject terms: "Cytosolic serine hydroxymethyltransferase", "cSHMT", "SHMT1", and "polymorphism" by two independent investigators (last search update: October 8,

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Table 1. Characteristics of the Studies Involvd in SHMT1 C1420T Polymorphism and Cancer Risk

First author	Year	Country	Ethnicity	Cancer type	Source of controls	Cases	Controls	P_{HWE}
Skibola	2002	UK	Caucasian	ALL	HB	71	114	0.578
Hishida	2003	Japan	East Asian	Lymphoma	HB	108	494	0.106
Skibola	2004	USA	Mixed	NHL	PB	333	729	0.509
Chen	2004	USA	Mixed	CRC	PB	271	458	0.793
Lightfoot	2005	USA	Caucasian	NHL	PB	589	754	0.181
Zhang	2005	USA	Caucasian	SCCHN	HB	721	1234	0.261
Niclot	2006	France	Caucasian	FL	HB	169	205	0.547
Lissowska	2007	Poland	Caucasian	Breast	PB	1959	2257	0.259
van den Donk	2007	Netherlands	Caucasian	CRA	HB	743	697	0.724
Moore	2007	Spain	Caucasian	Bladder	HB	1092	1011	0.909
Hazra	2007	USA	Mixed	CRA	HB	521	519	0.446
Lim	2007	USA	Mixed	NHL	PB	270	240	0.065
Wang	2007	USA	Mixed	Lung	HB	1032	1145	0.318
Steck	2008	USA	African	Colon	PB	239	322	0.168
Guerreiro	2008	Portugal	Caucasian	CRC	HB	196	200	0.067
Cheng	2008	China	East Asian	Breast	HB	354	534	0.719
de Jonge	2009	Netherlands	Caucasian	ALL	HB	244	497	0.764
Berglund	2009	Sweden	Caucasian	NHL	Not State	258	241	0.63
Komlosi	2010	Hungary	Caucasian	Colon	HB	476	461	0.11
Komlosi	2010	Hungary	Caucasian	Rectal	HB	479	478	0.143
Lightfoot	2010	UK	Caucasian	Leukemia	PB	896	761	0.131
Vainer	2010	Russia	Caucasian	Breast	PB	830	809	0.895
Weiner	2011	Russia	Caucasian	NHL	HB	141	504	0.357
Yang	2011	China	East Asian	ALL	PB	361	367	0.845
Kasperzyk	2011	USA	Mixed	HL	HB	443	338	0.146
Weiner	2012	Russia	Caucasian	Prostatic	HB	371	284	0.806
Carvalho Barbosa Rde	2012	Brazil	Mixed	Breast	HB	120	120	0.958
Liu	2012	USA	Mixed	Colon	PB	1414	1774	0.819
Li	2013	USA	Mixed	NHL	PB	420	476	0.059

P_{HWE}, P value of the Chi square goodness-of-fit test for Hardy–Weinberg equilibrium in controls; PB, population-based; HB, hospital-based; ALL, acute lymphocytic leukemia; NHL, non-Hodgkin lymphoma; CRC, colorectal cancer; SCCHN, squamous cell carcinoma of the head and neck; FL, follicular lymphoma; CRA, colorectal adenoma; HL; Hodgkin lymphoma

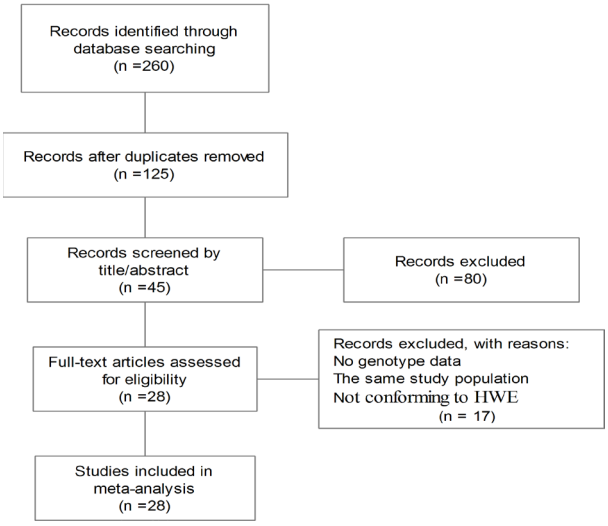

Figure 1. Flow Chart of the Selection of Publications Included in the Meta-analysis

2013). 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. When more than one of the same subject population was included in several publications, only the most recent population was used in this meta-analysis.

Inclusion criteria

The following inclusion criteria were used in selecting literature for further meta-analysis: (1) evaluation of SHMT1 C1420T polymorphism and cancer risk; (2) a case-control design; (3) sufficient published data for calculating odds ratios (ORs) with their 95% confidence intervals (95% CIs); (4) genotype frequencies in controls conform to Hardy-Weinberg equilibrium (HWE).

Data extraction

Two investigators independently extracted the data. Discrepancies were adjudicated by third investigator 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 C1420T polymorphism genotypes, and P value for HWE, respectively.

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 odds ratio (OR) and its 95% confidence interval (95% CI) were used to assess the strength of association between SHMT1 C1420T polymorphism and cancer risk. The pooled ORs were performed for allelic comparison (T vs. C), homozygote comparison (TT vs. CC), heterozygote comparison (CT vs. CC), recessive

Table 2. Stratified Analyses of the SHMT1 C1420T Polymorphism on Cancer Risk

Variable	Study, n	Cases/Controls	T vs. C		TT vs. CC		CT vs. CC		TT vs. CC+CT		CT+TT vs. CC	
			OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Overall	29	15121/18023	0.990 (0.943-1.039)	0.010	1.028 (0.922-1.146)	0.017	0.968 (0.924-1.015)	0.150	1.040 (0.937-1.155)	0.014	0.971 (0.918-1.027)	0.078
Cancer type												
Breast	4	3263/3720	0.994 (0.813-1.216)	0.004	1.077 (0.912-1.271)	0.178	0.943 (0.725-1.225)	0.006	1.063 (0.909-1.243)	0.442	0.970 (0.744-1.265)	0.003
GI	8	4339/4909	0.963 (0.905-1.026)	0.508	0.889 (0.769-1.027)	0.219	1.001 (0.918-1.091)	0.864	0.886 (0.771-1.017)	0.202	0.979 (0.902-1.062)	0.799
Lymphoma	9	2731/3981	1.026 (0.949-1.110)	0.108	1.135 (0.874-1.475)	0.059	0.990 (0.888-1.102)	0.154	1.138 (0.859-1.507)	0.017	1.009 (0.911-1.118)	0.225
Leukemia	4	1572/1739	0.861 (0.696-1.065)	0.080	0.871 (0.675-1.123)	0.110	0.825 (0.704-0.966)	0.366	0.957 (0.750-1.222)	0.169	0.838 (0.722-0.973)	0.167
Others	4	3216/3674	1.027 (0.954-1.104)	0.467	1.121 (0.954-1.317)	0.371	0.962 (0.869-1.065)	0.949	1.145 (0.982-1.335)	0.391	0.993 (0.902-1.093)	0.793
Source of control												
PB	11	7582/8947	1.008 (0.961-1.056)	0.682	1.001 (0.900-1.115)	0.285	1.018 (0.953-1.088)	0.579	0.994 (0.897-1.101)	0.172	1.016 (0.954-1.081)	0.727
HB	17	7281/8835	0.956 (0.880-1.039)	0.001	1.024 (0.858-1.223)	0.009	0.917 (0.857-0.982)	0.119	1.056 (0.896-1.245)	0.015	0.918 (0.837-1.008)	0.026
Geographic area												
America	12	6373/8109	1.022 (0.972-1.075)	0.339	1.062 (0.913-1.236)	0.094	1.020 (0.951-1.094)	0.431	1.047 (0.903-1.215)	0.070	1.025 (0.959-1.095)	0.481
Asia	3	823/1395	0.737 (0.477-1.139)	0.060	1.045 (0.421-2.595)	0.539	0.674 (0.522-0.870)	0.103	1.134 (0.456-2.821)	0.587	0.698 (0.446-1.093)	0.069
Europe	14	7925/8519	0.970 (0.906-1.038)	0.048	0.998 (0.843-1.182)	0.013	0.948 (0.888-1.012)	0.653	1.037 (0.881-1.220)	0.012	0.956 (0.898-1.017)	0.372

P_h, P value of Q test for heterogeneity test (Random-effects model was used when P value for heterogeneity test<0.10; otherwise, fix-effects model was used); GI, gastrointestinal cancer; PB, population-based; HB, hospital-based

model (TT vs. CC+CT), and dominant model (CT+TT vs. CC), respectively. The statistical significance of the pooled ORs was determined by Z test, and $P<0.05$ was considered statistically significant. A chisquare-based Q-test was performed to assess the Inter-study heterogeneity. The fixed effect model (the Mantel-Haenszel method) (Mantel et al., 1959) was used to access the pooled ORs if the heterogeneity was not significant ($P>0.1$); otherwise, the random effect model (the DerSimonian and Laird method) (DerSimonian et al., 1986) was used. Subgroup analyses were performed based on cancer type (breast cancer, gastrointestinal cancer, leukemia, lymphoma, and others), source of control (population-based [PB] and hospital-based [HB]), and geographic region (America, Asia and Europe) to explore the source of heterogeneity. Meta-regression (Sharp, 1998) was conducted to further explore the heterogeneity quantitatively for among the studies (the analysis was based on allelic comparison). In addition, sensitivity analyses were performed to reflect the influence of individual data on summary ORs. Finally, Publication bias was evaluated using the Begg's funnel plot and Egger's test (Egger et al., 1997). All statistical analyses were done with Stata software (Version 12; Stata Corporation, College Station, Texas, USA), and all tests were two-sided.

Results

Characteristics of the studies

Figure 1 outlines the search strategy used to obtain relevant literature. A total of 45 publications were achieved by an extensive search. We excluded 17 studies and one population of a study (five subjects were overlapped in other publications (Koushik et al., 2006; Wang et al., 2006; Vainer et al., 2010; Mohammad et al., 2011; Naushad et al., 2011a); genotype frequencies of eight studies were not provided (Lee et al., 2007; Gibson et al., 2011; Metayer et al., 2011; Naushad et al., 2011b; Piskac-Collier et al., 2011; Galbiatti et al., 2012; Lautner-Csorba et al., 2013; Swartz et al., 2013); and four studies (Wang et al., 2007b; Yu et al., 2007; Patino-Garcia et al., 2009; Curtin et al., 2011; Naushad et al., 2012) and one of populations in a study (Steck et al., 2008) did not conform to HWE). A total of 28 case-control studies with 29 populations met our inclusion criteria (Skibola et al., 2002; Hishida et al., 2003; Chen et al., 2004; Skibola et al., 2004; Lightfoot et al., 2005; Zhang et al., 2005; Niclot et al., 2006; Hazra et al., 2007; Lim et al., 2007; Lissowska et al., 2007; Moore et al., 2007; van den Donk et al., 2007; Wang et al., 2007a; Cheng et al., 2008; Guerreiro et al., 2008; Steck et al., 2008; Berglund et al., 2009; de Jonge et al., 2009; Komlosi et al., 2010; Lightfoot et al., 2010; Weiner et al., 2010; Kasperzyk et al., 2011; Weiner et al., 2011; Yang et al., 2011; Carvalho Barbosa Rde et al., 2012; Liu et al., 2012; Weiner et al., 2012; Li et al., 2013), including 15, 121 cases and 18, 023 controls. Table 1 presents the main characteristics of each study in the meta-analysis.

Evidence Synthesis

The main results of present meta-analysis including the heterogeneity test were shown in Table 2. The results of overall meta-analysis did not suggest any associations

between C1420T polymorphism and cancer susceptibility for all genetic models (T vs. C: OR= 0.990, 95% CI = 0.943-1.039; TT vs. CC: OR= 1.028, 95% CI = 0.922-1.146; CT vs. CC: OR= 0.968, 95% CI = 0.924-1.015; TT vs. CC+CT: OR= 1.040, 95% CI = 0.937-1.155; and CT+TT vs. CC: OR= 0.971, 95% CI = 0.918-1.027).

In stratified analysis by cancer type, a decreased risk of cancer was only found in leukemia subgroup (CT vs. CC: OR= 0.825, 95% CI =0.704-0.966; and CT+TT vs. CC: OR= 0.838, 95% CI = 0.722-0.973). Subgroup analysis was performed by source of control, a borderline inverse association was observed for HB subgroup (CT vs. CC: OR= 0.917, 95% CI = 0.857-0.982), but not for PB subgroup. Stratifying by geographic area, significant inverse association was only found in Asia subgroup (CT vs. CC: OR= 0.674, 95% CI = 0.522-0.870). However, no significant association was observed in America subgroup and Europe subgroup.

Sensitivity Analysis

From the results of the leave-one-out sensitivity analysis, all the results above were not materially altered (data not shown). We further explored the source of heterogeneity by sample size (>800 and ≤800) and ethnicity (African, Caucasian, East Asian, and Mixed) with meta-regression. The results revealed that sample size (P=0.455) and ethnicity (P=0.458) did not contribute to the source of heterogeneity.

Publication bias

Begg's 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 (T vs. C: t= -0.94, P= 0.356; TT vs. CC: t= 0.46, P= 0.651; CT vs. CC: t= -1.94, P= 0.063; TT vs. CC+CT: t= 0.71, P= 0.483; CT+TT vs. CC: t= -1.03, P= 0.313).

Discussion

Polymorphisms in folate-related genes may influence cellular folate metabolism by reducing its uptake, increasing its efflux, and/or shifting its intracellular distribution (Kim 1999). This may influence the risk of cancer through several mechanisms. First, low availability of folates for the thymidylate synthase reaction and DNA synthesis results in uracil misincorporation into DNA, possibly leading to double-strand breaks and chromosomal damage (Blount et al., 1997). Second, decreased availability of folate for the methionine cycle results in reduced transmethylation capacity and DNA hypomethylation/ dysmethylation of proto-oncogenes or tumor suppressor genes (Das et al., 2004). Indeed, DNA hypomethylation and uracil misincorporation have been shown to be important factors in carcinogenesis (Duthie et al., 2002; Lucock 2004).

The present meta-analysis explored the association between SHMT1 C1420T and cancer risk. With a sample size of 33, 144, the main message of this meta-analysis was lack of evidence of an overall association between SHMT1 C1420T and cancer risk. Further analysis stratified by cancer type showed 1420T allele was associated with a minor decreased risk only in leukemia, suggesting 1420T allele might be a protective factor for leukemia. It should be noted that the four relative small studies (Skibola et al., 2002; de Jonge et al., 2009; Lightfoot et al., 2010; Yang et al., 2011) with only 1572 cases and 1739 controls had driven the borderline inverse association, which may be due to selection bias. In stratifying analysis by source of control, the association between 1420T allele and reduced risk of cancer was significant in HB subgroup but not in PB subgroup. The hospital-based controls usually have some biases because such controls may not be representative of the general population very well, particularly when the genotypes under investigation were associated with the disease conditions that the hospital-based controls may have. If considering this, the results should be interpreted with caution. In subgroup analysis by geographic area, significant inverse association was only found in Asia subgroup but not in America subgroup and Europe subgroup. Besides the small sample size of Asia subgroup, many other factors may contribute to the different result for different geographic area. Firstly, different genetic backgrounds may cause the discrepancy. The subjects of America and Europe studies were mostly Caucasians, whose 1420T allele frequency was different from East Asians (31.88% vs. 9.43%, P<0.001). Secondly, different populations may have differences in dietary intake of nutrients, some of which (such as folate, coffee and alcohol) may take part in carcinogenesis. Last, some clinical heterogeneity like age, years from onset and disease severity etc. may also make different contributions. Evidences also suggested that the SNPs in other enzymes controlling folate metabolism implicated in cancer risk (Jiang et al., 2013; Morita et al., 2013; Tan et al., 2013). Therefore, further studies estimating the effect of the SHMT1 C1420T polymorphism and other SNPs in linkage disequilibrium or in the same pathway along with gene-environment interactions may provide a better, comprehensive understanding of the associations.

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 cancer type, geographic region, source of control, sample size, and ethnicity did not contribute to the source of heterogeneity. Second, several eligible studies did not present the genotype data of C1420T; therefore, a bias may have occurred. Third, in the subgroup analysis, the number of each subgroup was relatively small especially for Asia subgroup, not having enough statistical power to explore the real association. Furthermore, the data was not stratified by age, folate 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 C1420T polymorphism and cancer risk is obtained.

In conclusion, our meta-analysis suggests that SHMT1 C1420T polymorphism is not associated with overall cancer development, but might decrease cancer susceptibility of Asians as well as reduce leukemia risk. However, conclusions of the present meta-analysis are based on relatively small numbers of studies and participants, and their interpretation has to be cautious. Large well-designed epidemiological studies will be necessary to validate the risk identified in the current meta-analysis.

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