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A literature review of MTHFR (C677T and A1298C polymorphisms) and cancer risk

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Abstract 5,10-Methlenetetrahydrofolate reductase (MTHFR) is one of the most important enzymes for folate metabolism. This enzyme is mapped on chromosome 1, which is located at the end of the short arm (1p36.3). The C677T and A1298C are MTHFR polymorphisms that decrease in vitro MTHFR enzyme activity. Folate metabolism plays a key role in cell metabolism. These reactions are associated with purine–pyrimidine synthesis: DNA, RNA, and protein methylation. Polymorphism is also a factor in biodiversity, and be affected by ethnic heritage and geographic locale. In the case of unknown outcomes, not only should all geographical regions be investigated to ascertain biodiversity, but all populations as well to fully understand the variations in the effect. PUBMED was searched from January 2006 to December 2011 to develop an investigatory pursuit strategy. MTHFR, cancer, C677T, A1298C, and polymorphisms were key words used to focus the search. The literature review included all published relevant cancer types and MTHFR polymorphisms for that 5 years period. All selected polymorphisms data for cancer types was listed in tables for easy access and retrieval.

Keywords Cancer · MTHFR · C677T polymorphism · A1298C polymorphism

Introduction

The 5,10-methlenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism and its catalysis creates an irreversible reduction in 5,10-methlenetetrahydrofolate (THF); which is converted into 5-methyl-THF during the process. MTHFR has been described as being located at the branch point in directing folate metabolites toward remethylation of homocysteine and away from DNA and RNA biosynthesis [1]. The MTHFR enzyme gene is located at the end of the short arm of chromosome 1 (1p36.3) [2]. The DNA sequence of this gene is approximately 2.2 kilobases (kb), which includes 11 exons [3]. The MTHFR gene consists of two well described polymorphisms: C677T and A1298C. Other reported polymorphisms are T1317C and G1793A. The C677T polymorphism is located in exon 4 and results in an alanine conversion to valine at codon 222. This region is the base binding site for the MTHFR cofactor, flavin adenine dinucleotide (FAD). It is reported that the MTHFR C677T genotype decreases by 30 percent the in vitro MTHFR enzyme activity compared with the wild type. The second MTHFR polymorphism is A1298C, which lies on exon 7 and results in a glutamate being transformed into alanine at codon 429. This polymorphism is situated in the *S*-adenosyle methionine (SAM) regulatory domain of the enzyme. It causes conformational changes within the MTHFR enzyme that alter enzymatic activity [4, 5].

Folate is one of the most important (lead off) precursor substrates for cell metabolism. One task of folate is to act as the carrier of single carbon fragments. This reaction is required for the synthesis of purine–pyrimidine, DNA, RNA, and protein methylation. Previous research has shown that low folate levels result in uracil disincorporation during DNA replication, which causes double-strand breaks to increase during uracil excision repair [1]. Folate deficiency has also been linked to an increased risk for a number of cancers. Several cancer researchers have suggested that the level of MTHFR activity is another

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important factor that influences the risk for developing some the types of cancer. Other disease risks include cardiovascular disease, diabetes, birth defects, ischemia, venous thrombosis, hypotonia, leukemia, migraine, schizophrenia, depression, preeclampsia, Alzheimer disease, congenital heart defects, Down syndrome, and cleft palate [5–11].

Genetic polymorphisms are influenced by ethnic backgrounds and geographical differences. In this article, I completed a comprehensive examination of polymorphism studies that investigated MTHFR polymorphism, C677T and A1298C, for association with cancer. Further, I have included articles on MTHFR polymorphism, C677T and A1298C, covering geographical and ethnic backgrounds for cancer types for the last 5 years.

Materials and methods

A PUBMED search was completed for the key words "methylenetetrahydrofolate reductase", "MTHFR", "cancer", "C677T polymorphism," and "A1298C polymorphism". The literature published studies were extracted from articles written from January 2006 to December 2011. I assessed the literature as significant or non significant which was indicated by manuscript's author. I did not approach these data statistically.

Result

The literature review for 2006–2012 covered all cancer types (i.e., breast cancer; gastrointestinal and digestive system cancers; leukemia–lymphoma; head and neck; pulmonary, neurological, and genitourinary) with each cancer assessed for MTHFR gene polymorphisms: C677T and A1298C (see Tables 1, 2, 3, 4, 5, 6). The investigations were designated as significant, non-significant, and unstudied investigations were indicated by the imprinted symbol ∅. As an additional measure, studies were grouped for display and presented in alphabetical order; however, group classifications and the status of drug use was not included as a measurement criterion. Rather, groupings were used to merely increase clarity discussing real data.

For breast cancer, according to Table 1, there were 17 significant investigations and 17 non-significant investigations at MTHFR gene C677T polymorphism. In the case of A1298C polymorphism, eight studies were significant and 11 studies were non-significant in populations with breast cancer (Table 1).

Table 2 cancers were associated with C677T and A1298C polymorphisms of the MTHFR gene in the gastrointestinal and digestive systems. There were four studies that mentioned polymorphisms of the MTHFR gene in hepatic cancer. Three of these were significant; one study was non-significant for C677T polymorphism. For the second polymorphism, there was only one study, in it, puisne mortgage was non-significant. In one of the three studies, significance for C677T polymorphism of the MTHFR gene was observed in pancreatic cancer. Two studies were non-significant for both polymorphisms. For the A1298C polymorphism, no studies were identified for assessment during the 5 years under review in regards to gastrointestinal and digestive cancers. The characteristics of the MTHFR polymorphisms in gastrointestinal system cancer are presented (Table 2). According to this data, four studies were significant and three studies were non-significant for C677T polymorphism in esophageal cancer. For A1298C polymorphism, there was only one non-significant study. For C677T polymorphism in the gastric cancer, significant study data was found in 11 investigations and non-significant data in four. All investigations about A1298C polymorphism were non-significant. For colon cancer, there were 13 investigations. Eight investigations were significant and five non-significant for C677T polymorphism. There were six significant investigations and three non-significant investigations for A1298C polymorphism in colon cancer studies (Table 2).

Table 3 cancers were associated with C677T and A1298C polymorphisms of MTHFR gene regionally located in the head and neck, and respiratory system. These studies included 11 significant and three non-significant investigations for C677T polymorphism in head and neck cancer. For the A1298C polymorphisms of MTHFR gene, there were four significant and two non-significant studies also for head and neck cancer. In addition, Table 3 presented C677T and A1298C polymorphisms of the MTHFR gene in lung cancer. For the first polymorphism, seven investigations were significant and two were non-significant. On the other hand, one study was significant and two studies were non-significant for the A1298C polymorphisms.

For the polymorphisms of the MTHFR gene in leukemia exhibited in Table 4, 22 studies were significant and the others are non-significant for C677T polymorphism. In A1298C polymorphism for leukemia, 12 studies were significant and 14 were non-significant. For lymphoma, there were three significant and three non-significant investigations for C677T polymorphism. There were also three significant studies and one non-significant study for A1298C polymorphism (Table 4).

Table 5 was concerned with C677T and A1298C polymorphisms of MTHFR gene in nervous system cancer. There were four studies about these two polymorphisms of MTHFR gene. For A1298C polymorphisms in MTHFR gene, two studies were significant but in the case of C677T polymorphism two studies were non-significant (Table 5).

Table 1 MTHFR polymorphisms in breast cancer

Breast cancer	Study groups	Geographical region	MTHFR			
			C677T		A1298C	
			Significant	Non-significant	Significant	Non-significant
Breast cancer	Qiu et al. [12]	China (Shanghai)	∅			✔
	Mohammad et al. [13]	India (Hyderabad)	✔		∅	
	Huang et al. [14]	Taiwan (Kaohsiung)	✔		∅	
	Alshatwi et al. [15]	Saudi Arabia	✔		∅	
	Perel'muter et al. [16]	Russia	✔		∅	
	Suzuki T [17]	Japon (Nagoya)	✔		∅	
	Maruti et al. [18]	USA (Seattle)	✔		∅	
	Ericson et al. [19]	Sweden	✔		∅	
	Batschauer et al. [20]	Brazil (Belo Horizonte)		✔	∅	
	Prasad et al. [21]	India (Hyderabad)		✔	∅	
	Eroglu et al. [22]	Turkey (Ankara)		✔	∅	
	Ziva Cerne et al. [23]	Slovenia		✔	∅	
	Knechtel et al. [24]	Austria (Graz)		✔		
	Xu et al. [25]	USA (New York)		✔		
	Lewis et al. [26]	Unitad Kingdom (Bristol)		✔		
	Hekim et al. [27]	Turkey (Istanbul)		✔		
	Yu et al. [28]	Taiwan (Taipei)		✔		
	Sangrajrang et al. [29]	Thailand (Bangkok)		✔	✔	
	Tao et al. [30]	USA (Buffalo)		✔		✔
	Martin et al. [31]	USA (Mayo Clinic)		✔		✔
	Vainer et al. [32]	Russia		✔		✔
	Ma et al. [33]	Japon (Tokyo)		✔		✔
	Ferroni et al. [34]	Italy (Rome)		✔		✔
	Beetstra et al. [35]	South Australia		✔		✔
	Kotsopoulos et al. [36]	Canada (Toronto)		✔		✔
	Mir et al. [37]	India (Kashmir)	✔			✔
	Guilem et al. [38]	Spain (Valancia)	✔		✔	
	Martin et al. [39]	USA (Bethesda)	✔		✔	
	Jakubowska et al. [40]	Poland (Szczecin)	✔		✔	
	Chou et al. [41]	Taiwan (Taipei)	✔		✔	
	Stevens et al. [42]	USA (Atlanta)	✔		✔	
	Pepe et al. [43]	Italy (Pısa)	✔		✔	
	Ericson et al. [44]	Sweden (Malmö)	✔		✔	
	Gao et al. [45]	China (Nanjing)	✔			✔
	Papandreou et al. [46]	Greece(Laricca)	✔			✔

MTHFR polymorphisms associated with genitourinary system cancers were listed in Table 6. Four of whole investigations were significant and seven investigations were non-significant for C677T polymorphism. On the other hand, one study was significant and seven studies were non-significant for A1298C polymorphism in female genital organ cancer. For male genitourinary organ cancer; significant data was available in four studies and non-significant data in three studies for C677T polymorphism. For the A1298C polymorphism in males, three data were significant and the others were non-significant. Genitourinary system cancers also included bladder cancer for which eight studies were located for the relevant 5 years covering MTHFR gene C677T and A1298C polymorphisms. For C677T polymorphism, five of these investigations were significant, the others non-significant were found. Four investigations were found to be significant and two were non-significant for A1298C polymorphism. For C677T polymorphism in renal cancer, there were four significant studies and are not non-significant. All of studied

Table 2 MTHFR polymorphisms in gastrointestinal and digestive system cancers

Gastrointestinal and digestive system cancers	Study groups	Geographical region	MTHFR			
			C677T		A1298C	
			Significant	Non-significant	Significant	Non-significant
Hepatic cancer	Kwak et al. [47]	South Korea (Seongnam)		✔	✔	
	Cui et al. [48]	China (Qingdao)	✔		∅	
	Mu et al. [49]	China (Shanghai)	✔		∅	
	Zhu et al. [50]	China (Shanghai)	✔			
Pancreatic cancer	Suzuki et al. [51]	Japan (Nagoya)		✔	∅	
	Nisevic et al. [52]	Serbia (Belgrade)		✔	∅	
	Wang et al. [53]	China (Beijing)	✔		∅	
Esophageal cancer	Qin et al. [54]	China (Xinjiang Uygur Region)	✔		∅	
	Liu et al. [55]	China (Chengdu)	✔		∅	
	Qin et al. [56]	China (Shihezi)	✔		∅	
	Li et al. [57]	China (Jinan)	✔		∅	
	Umar et al. [58]	India (Lucknow)		✔	∅	
	Lu et al. [59]	China (Nanjing)		✔	∅	
	Zeybek et al. [60]	Turkey (Istanbul)		✔		✔
Gastric cancer	Boccia et al. [61]	Italy (Rome)	✔			✔
	Li et al. [62]	China (Nanjing)	✔			✔
	Mu et al. [63]	China (Shanghai)	✔			✔
	Zhang et al. [64]	USA (Maryland)		✔		✔
	Neves Filho et al. [65]	Brazil (Fortaleza)		✔	∅	
	Götze et al. [66]	Germany (Munich)		✔	∅	
	Zuniga-Noriega et al. [67]	Mexico (Nevivo Leon)		✔	∅	
	DeRe et al. [68]	Italy (Aviano)	✔		∅	
	Lin et al. [69]	China (Beijing)	✔		∅	
	Wang et al. [70]	China (Nanjing)	✔		∅	
	Cui et al. [71]	South Korea (Gwangiu)	✔		∅	
	Wang et al. [72]	China (Hebei)	✔		∅	
	Ko et al. [73]	South Korea (Seongnam)	✔		∅	
	Graziano et al. [74]	Italy (Urbino)	✔		∅	
	Lacasana-Navarro et al. [75]	Mexico (Morelos)	✔			
Colon cancer	Prompthet et al. [76]	Thailand (Khon Kaen)	✔		✔	
	Haghighi et al. [77]	Iran (Tehran)	✔		✔	
	Levine et al. [78]	USA (L. Angeles)	✔		✔	
	El Awady et al. [79]	Egypt (Cairo)	✔		✔	
	Osian et al. [80]	Romania (Cluj-Napoca)	✔		✔	
	Chang et al. [81]	Taiwan (Taipei)		✔		✔
	Zeybek et al. [60]	Turkey (Istanbul)		✔		✔
	Cao et al. [82]	China (Nanjing)		✔		✔
	Wang et al. [83]	Japan (Nagoya)		✔	✔	
	Iacopetta et al. [84]	Australia	✔		∅	
	Prasad et al. [21]	(The Netherlands)	✔		∅	
	Komlosi et al. [85]	India (Hyderabad)	✔		∅	
	Derwinger et al. [86]	Sweden (Gottenburg)		✔	∅	

Table 3 MTHFR polymorphisms in head-neck and respiratory system cancer

Head-neck and respiratory system cancers	Study groups	Geographical region	MTHFR			
			C677T		A1298C	
			Significant	Non-significant	Significant	Non-significant
Head and neck cancer	Prasad et al. [21]	India (Hyderabad)		✔	∅	
	Rodrigues et al. [87]	Brazil		✔	∅	
	Fard-Esfahani et al. [88]	Iran (Tehran)	✔		∅	
	Supic et al. [89]	Serbia (Belgrade)	✔		∅	
	Solomon et al. [90]	India (Madurai)	✔		∅	
	Suzuki et al. [91]	Japan (Nagoya)	✔		∅	
	Vairaktaris et al. [92]	Greece (Athens)	✔		∅	
	Sailasree et al. [93]	India (Kerala)	✔		∅	
	Tsai et al. [94]	Taiwan	✔		∅	
	Boccia et al. [95]	Italy (Rome)	✔		✔	
	Galbiatti et al. [96]	Brazil (Sao Paulo)	✔		✔	
	Cao et al. [97]	China (Guangzhou)	✔		✔	
	Ni et al. [98]	China (Beijing)	✔			✔
	Krsuszyna et al. [99]	Italy (Rome)		✔		✔
	Siraj et al. [100]	Saudi Arabia (Riyadh)	✔		✔	
Lung cancer	Liu et al. [101]	Taiwan (Taichung)		✔	∅	
	Arslan et al. [102]	Turkey (Sivas)		✔		
	Liu et al. [103]	China (Shanghai)	✔			✔
	Suzuki et al. [104]	Japan (Nagoya)	✔			✔
	Kiyohara et al. [105]	Japan	✔		✔	
	Matakidou et al. [106]	United Kingdam (Surrey)	✔		∅	
	Hung et al. [107]	France (Lyon Cedex)	✔		∅	
	Cui et al. [108]	China (Qingdao)	✔		∅	
	Gemignani et al. [109]	Italy (Pisa)	✔		∅	

investigations about A1298C polymorphism are significant in renal cancer (Table 6).

Discussion

The etiology of cancer is not well understood, but research has linked risk to certain genes. MTHFR is one such gene, but this association requires consideration of environmental factors such as geographical region. The studies identified in the aforementioned tables provide a snapshot of investigations associated with C677T and A1298C polymorphisms of the MTHFR gene. I focused this literature review on the 5 year covering 2006–2012. During that time, the most studied cancers were breast cancer and leukemia for these polymorphisms. The least investigated cancer types were from the nervous, endocrine, and renal systems. In examining all cancers under this genetic coding, A1298C polymorphism has been studied less than C677T polymorphism. However, the effect of the MTHFR polymorphisms for susceptibility by is still unexplored for entire geographic regions and ethnic groups. These factors are extremely important in fully understanding risk and developing treatments related to polymorphism. Therefore, I conclude that every attempt should be made to sample people from every geographic region and every ethnicity to population to capture biodiversity. Scientists widely acknowledge that these two factors underpin the disparities for populations and are intensified by region with regard to understanding risk and response to drug treatment regimes.

This literature review was designed to identify studies of cancers related to C677T and A1298C polymorphisms in folate metabolism and to characterize those studies as being significant, nonsignificant or not studied. To better understand polymorphism, I recommend further studies that include more diverse populations and attempt to link etiology, ethnic group, and geographic region.

Table 4 MTHFR polymorphisms in leukemia and lymphoma

Leukemia and lymphoma	Study groups	Geographical region	MTHFR			
			C677T		A1298C	
			Significant	Non-significant	Significant	Non-significant
Leukemia	Ruiz-Argiulles et al. [110]	Mexico (Puebla)		✔	∅	
	Giovannetti et al. [111]	The Netherland (Amsterdam)	✔		∅	
	Tong et al. [112]	China (Nanjing)	✔		∅	
	Pietrzyk et al. [113]	Poland (Krakow)	✔		∅	
	Alcasabas et al. [114]	Philippines (Manila)	✔		∅	
	Kim et al. [115]	Korea (Jeollanamdo)	✔		∅	
	Imanishi et al. [116]	Japan (Kobe)	✔		∅	
	Chen et al. [117]	China (Nanjing)	✔		∅	
	Bolufer et al. [118]	Spain (Valencia)	✔		✔	
	Robien et al. [119]	USA (Washington)	✔		✔	
	Zanrasso et al. [120]	Canada (Quebec)	✔		✔	
	Reddy et al. [121]	India (Hyderabad)	✔		✔	
	Koppen et al. [122]	The Netherlands (Amsterdam)	✔		✔	
	Krull et al. [123]	USA (Houston)	✔		✔	
	Thomas et al. [124]	South Australia (Adelaide)	✔		✔	
	Zintzaras et al. [125]	Greece (Larissa)	✔		✔	
	Yang et al. [126]	China (Tianjin)	✔			✔
	Damnjanovic et al. [127]	Serbia (Belgrade)	✔			✔
	Tantawy et al. [128]	Egypt (Cairo)	✔			✔
	Pereira et al. [129]	Brazil (Sao Paulo)	✔			✔
	Sood et al. [130]	India (Chandigarh)	✔			✔
	de Jonge et al. [131]	The Netherlands (Rotterdam)	✔			✔
	Yan et al. [132]	USA (Houston)	✔			✔
	Benetatos et al. [133]	Greece (Ioannina)		✔		✔
	Karathananis et al. [134]	Greece (Crete)		✔		✔
	Sadananda Adiga et al. [135]	India (Bangalore)		✔		✔
	Kamel et al. [136]	Egypt (Cairo)		✔		✔
	Oh et al. [137]	South Korea (Seongnam)		✔		✔
	Amorim et al. [138]	Brazil (Rio de Janeiro)		✔		✔
	Kim et al. [139]	South Korea (Pochon)		✔	✔	
	Lv et al. [140]	China (Shanghai)		✔	✔	
	Moon et al. [141]	South Korea (Seoul)		✔	✔	
	Hur et al. [142]	South Korea (Seoul)		✔	✔	
	Azhar et al. [143]	Iran (Kermanshah)		✔		✔
Lymphoma	Lee et al. [144]	USA (Bethesda)	✔		∅	
	Seidemann et al. [145]	Germany (Hannover)	✔		∅	
	Kurzwelly et al. [146]	Germany (Bonn)		✔	✔	
	Ismail et al. [147]	Jordan (Amman)		✔	✔	
	Kim et al. [148]	Korea (Jeollanamdo)	✔		✔	
	Kasperzyk et al. [149]	USA (Massachussetts)		✔		✔

Although, genetic and environmental risk factors are experientially recognized as sharing a role in increasing the risk for certain types of cancers, there is very limited data on gene-environment interactions. Therefore, the need for more polymorphisms studies to examine genes, ethnicity, and region is evident.

Table 5 MTHFR gene polymorphisms in nerves system cancers

Nerves system cancer	Study groups	Geographical region	MTHFR			
			C677T		A1298C	
			Significant	Non-significant	Significant	Non-significant
Nerves system cancers	Da Costa et al. [150]	Brazil (Ceara)	✔			∅
	Bethke et al. [151]	United Kingdom (Surrey)	✔		✔	
	Sirachainan et al. [152]	Thailand (Bangkok)		✔	✔	
	Kafadar et al. [153]	Turkey (Istanbul)		✔		∅

Table 6 MTHFR polymorphisms in urogenital system cancers

Urogenital system	Study groups	Geographical region	MTHFR			
			C677T		A1298C	
			Significant	Non-significant	Significant	Non-significant
Female genital organ cancers	Shekari et al. [154]	India (Chandigarh)	✔		∅	
	Tong et al. [155]	Korea (Seoul)	✔		∅	
	Kohaar et al. [156]	India (Noida)		✔		✔
	Uvuz et al. [157]	Turkey (Ankara)		✔		✔
	Tong et al. [158]	Korea (Seoul)		✔		✔
	Xu et al. [159]	China		✔		✔
	Delgado-Enciso et al. [160]	Spain		✔		✔
	Piyathilake et al. [161]	USA (Alabama)		✔		✔
	Rao et al. [162]	USA (Dallas)		✔		✔
	Nandan et al. [163]	India (New Delhi)	✔		✔	
	Prasad et al. [21]	India (Hyderabad)	✔		∅	
Male genital organ cancers	Johansson et al. [164]	Sweden (Umea)		✔	∅	
	Wu et al. [165]	Taiwan (Taichung)	✔			✔
	Marchal et al. [166]	Spain (Malaga)	✔			✔
	Saferinejad et al. [167]	Iran (Tehran)	✔		✔	
	Van Guelpen et al. [168]	Sweden (Umea)	✔		✔	
	Cai et al. [169]	China (Shenyang)		✔		✔
	Muslumanoglu et al. [170]	Turkey (Eskisehir)		✔	✔	
Bladder cancer	Chung et al. [171]	Taiwan (Taipei)	✔		∅	
	Manuguerra et al. [172]	Italy (Torino)		✔	∅	
	Cai et al. [169]	China (Shenyang)	✔		✔	
	Rouissi et al. [173]	Tunusia (Tunis)	✔		✔	
	Safarinejad et al. [174]	Iran (Tehran)	✔		✔	
	Moore et al. [175]	USA (Rockville)	✔		✔	
	Sanyal et al. [176]	Sweden (Stockholm)		✔		✔
	Izmirli et al. [177]	Turkey (Adana)		✔		✔
Renal cancer	Saferinejad et al. [178]	Iran (Tehran)	✔		✔	
	Sakano et al. [179]	Japan (Ube)	✔		✔	
	Ferrara et al. [180]	Italy (Naples)	✔		∅	
	Moore et al. [181]	USA (Bethesda)	✔		∅	

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