Original paper

Germinal polymorphism of methionine synthetase gene in the aspect of red meat consumption and colorectal cancer risk – preliminary report

Polimorfizm genu syntetazy metioniny w zakresie spożycia czerwonego mięsa i ryzyka wystąpienia raka jelita grubego – wstępny raport

Monika Wawszczak-Kasza[1], Piotr Lewitowicz[1], Jarosław Matykiewicz[1], Anna Dziuba[1], Justyna Klusek[2], Łukasz Nawacki[1], Monika A. Kozłowska-Geller[1], Wioletta Adamus-Białek[1], Katarzyna Kubica[1], Julia Dulębska[1], Dorota Kozieł[2], Anna Nasierowska-Guttmejer[3], Stanisław Głuszek[1]

[1]Institute of Medical Sciences, Jan Kochanowski University, Kielce, Poland
[2]Institute of Health Sciences, Jan Kochanowski University, Kielce, Poland
[3]Department of Pathomorphology, State Medical Institute of the Ministry of Interior and Administration in Warsaw, Warsaw, Poland

Medical Studies/Studia Medyczne 2024; 40 (3): 241–247
DOI: https://doi.org/10.5114/ms.2024.143015

Key words: colorectal cancer, red meat consumption, methionine synthetase.

Słowa kluczowe: rak jelita grubego, spożycie czerwonego mięsa, syntetaza metioniny.

Abstract

Introduction: Methionine synthase is a vitamin B_{12}-dependent enzyme involved in cyclic re-synthesis methionine from homocysteine. To date, the research with *MTR* A2756G (rs1805087) variant and risk of cancers brought the opposite results. It was also shown that the relationship with environmental factors such as diet and genetic predisposition play an important role in cancer development, including colorectal cancer (CRC).
Aim of the research: To analyse the association of *MTR* variants with CRC in respect of dietary patterns and health conditions.
Material and methods: The prevalence of *MTR* variants was determined in 191 patients with colorectal cancer and 93 healthy volunteers. The DNA was isolated from blood (MagCore II, RBC Bioscience). Genotypes and allele frequencies were determined in patients and controls using TaqMan SNP genotyping assays (ThermoFischer Scientifics).
Results: There were no cases of *MTR* rs121913582, rs121913580, or rs121913578 mutations in CRC or controls. There is no correlation between CRC occurrence and *MTR* c.2756A>G genotype presence. We confirm that red meat consumption increases the risk of CRC. There was no statistically significant correlation between environmental factors and genetic variants.
Conclusions: Red meat consumption greater than 50 g/day increase the risk of colorectal cancer by approximately 20%. There is no correlation between *MTR* variant and CRC risk as well as CRC localisation.

Streszczenie

Wprowadzenie: Syntetaza metioniny jest enzymem zależnym od witaminy B_{12}, który bierze udział w cyklicznej resyntezie metioniny z homocysteiny. Dotychczasowe analizy wariantu genu *MTR* A2756G (rs1805087) i ryzyka zachorowania na raka przyniosły sprzeczne wyniki. Wykazano również, że czynniki środowiskowe, takie jak dieta i predyspozycje genetyczne, odgrywają ważną rolę w rozwoju raka, w tym raka jelita grubego (CRC).
Cel pracy: Analiza związku wariantów *MTR* z CRC w odniesieniu do wzorców żywieniowych i warunków zdrowotnych.
Materiał i metody: Częstość występowania wariantów *MTR* analizowano u 191 pacjentów z CRC i 93 osób zdrowych. DNA wyizolowano z krwi (MagCore II, RBC Bioscience). Genotypy i częstości alleli określono u pacjentów i osób kontrolnych przy użyciu metody genotypowania SNP TaqMan (ThermoFischer Scientifics).
Wyniki: Nie zidentyfikowano przypadków mutacji *MTR* rs121913582, rs121913580 lub rs121913578 w CRC lub grupach kontrolnych. Nie wykazano korelacji między występowaniem CRC a obecnością genotypu *MTR* c.2756A>G. Potwierdzono, że spożycie czerwonego mięsa zwiększa ryzyko wystąpienia CRC. Nie stwierdzono statystycznie istotnej zależności między czynnikami środowiskowymi a wariantami genetycznymi.
Wnioski: Spożycie czerwonego mięsa w ilości większej niż 50 g/dobę zwiększa ryzyko rozwoju CRC o około 20%. Nie wykazano korelacji między wariantem *MTR* a ryzykiem wystąpienia CRC, a także jego lokalizacją.

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Introduction

Epidemiology and aetiology of colorectal cancer

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide [1, 2]. According to the World Health Organisation (WHO) in 2020 a total of 1,931,590 new cases were diagnosed and there were 935,173 deaths, which ranks colorectal cancer in second place in terms of lethality [3]. Worldwide, the areas with higher prevalence of CRC per 100,000 citizens are in central Europe [4]. The highest overall rates of colorectal cancer equals were observed in Hungary and Slovakia reaching 45.3/100 000 and 43.9/100 000 citizens, respectively [5]. It was also shown that there is a higher incidence of cancer located in the colon than in the rectum [6]. Moreover, it was also observed that the risk of CRC development increases in the fourth decade of life, and the peak of incidence occurs after the age of 80 years [7]. Over the past 20 years, research has been presented analysing the impact of diet and lifestyle on the development of CRC. World Cancer Research Fund International (WCRF) provided evidence that tobacco smoking and alcohol consumption significantly increase the risk of CRC [8]. Additionally, low physical activity, obesity, and metabolic syndrome increases the risk of cancer. Also, the dietary habits are the main factor predisposing to CRC development. A diet that is low in fibre, rich in red meat, poor in antioxidants, and rich in saturated fat plays a crucial role [9–12]. It is believed that high consumption of myoglobin could increase the risk of CRC via methylation [13, 14].

Approximately 5% of CRC cases are driven by germline mutations [15]. The germline mutations classified as CRC susceptibility genes are predominantly identified in the mismatch repair (MMR) genes, adenomatous *Polyposis coli* (*APC*) gene, and *E. coli* MutY homologue (*MUTYH*) [15, 16]. Over the past few years, the development of next generation sequencing (NGS) has enabled analysis of the whole gene panel. As a result, the new genes are classified as CRC susceptibility genes. It was also suggested that mutations in gene-encoded enzymes involved in folate metabolism may play an important role in CRC development [17].

Methionine synthetase in methylation process

The methionine synthetase (*MTR*) gene is located on 1q43. The enzyme catalyses the remethylation of homocysteine to methionine [17]. Methionine metabolism is crucial for many biochemical processes including gene silencing, proliferation through DNA, protein, and phospholipid methylation [18]. The 2 most common patterns of DNA methylation-dependent carcinogenesis are gene-specific hypermethylation and entire DNA hypomethylation [19]. Foliate metabolism is predominantly based on regulation of DNA synthesis and methylation. The role of the methionine synthase (MTR) is catalysing the remethylation of homocysteine to methionine in a cobalamine-dependent reaction, which utilises methylenetetrahydrofolate reductase (MTHFR) as a methyl donor. Mutations in *MTR* and other links of this metabolic pathway like *MTHFR*, 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (*MTRR*), and serine hydroxymethyltransferase (*SHMT*) are gaining increasing prominence in numerous clinical trials investigating the etiopathogenesis of colon cancer [20]. It has already been shown that polymorphism resulting in a change of aminoacidic glycine to aspartic acid – NM_000254.3(MTR):c.2756A>G (p.Asp919Gly), (rs1805087) – leads to lower enzyme activity. The consequence of the amino acid change is homocysteine elevation and DNA hypomethylation [21]. It is considered that variant c.2756A>G of the *MTR* gene is associated with the risk and course of various cancers (e.g. breast, colorectal, or thyroid) [22–24]. The aim of the study was to analyse the association of *MTR* variants with CRC in respect of dietary patterns and health conditions.

Study population and sample collection

This multicentre study was based on cases selected in Holy Cross Cancer Centre, Kielce, Poland and the Regional Hospital in Kielce, Poland. Healthy controls were selected at the Regional Hospital in Kielce, Poland. All CRC diagnoses were recoded according to the eighth edition UICC classification. Moreover, all sampling was conducted from 2014 to 2017. Finally, 191 patients diagnosed with CRC and 93 controls comprised the study cohort.

DNA sampling

The peripheral vain blood was placed into EDTA-coated tubes. Then, the material was stored at –80°C and biobanked. The genomic DNA was extracted from blood samples using the automatic nucleic acid extractor and genomic DNA whole blood kit (Magcore®, RBC BioScience, New Taipei City, Taiwan). Purity and concentration of isolated DNA were evaluated spectrophotometrically (DeNovix, DeNovix Inc.).

Genotype analysis of the *MTR*

For genotyping of *MTR* c.2756A>G (rs1805087), c.3518C>T (rs121913578), c.1753C>T (rs121913580), and c.1228G>C (rs121913582) variant TaqMan SNP Genotyping assays (Thermo Fischer Scientific) were used. The amplification and detection procedure were carried out in a total reaction volume of 10 µl, containing 5 µl TaqPathTM ProAmpTM Master Mix (Applied Biosystems), 0.5 µl TaqMan® SNP genotyping assay (20´) (Thermo Fischer Scientific), 1.5 µl genomic DNA (10 ng), and 3.5 µl nuclease-free water (Thermo Fischer Scientific). The PCR amplification was conducted using Rotor-Gene Q (Qiagen)

with an initial step of 95°C for 10 min followed by 40 cycles of 95°C for 15 s and 60°C for 60 s.

Dietary assessment

The frequency of red meat consumption was assessed with the food frequency questionnaire (FFQ-6) [https://www.uwm.edu.pl/edu/lidiawadolowska/html/ffq6.html] used in our previous research [25]. The questions concerned the usual frequency of red meat consumption, including the method of preparation (roasting, frying, braising, grilling). The questionnaire was completed independently by the patients after prior instructions from a nurse trained to participate in the project. We analysed the frequency of the consumption (meal per week) as well as the estimated quantity of meat consumption (g/day) estimated based on the weight of standard dietary portions.

Statistical analysis

Categorical data were expressed as number and percentage distributions. The presented results were prepared using adequate statistical tests of Statistica version 13.3 (TIBCO Software Inc.), and $p < 0.05$ meant statistically significant. The normality of the distribution was checked with the Shapiro-Wilk test. In the case of a skewed distribution and variables on a quantitative scale, the Mann-Whitney *U* test was used. For variables on a nominal scale, the χ^2 test (chi-square test) was used with the Benjamini-Hochberg procedure when necessary. The Hardy-Weinberg equilibrium assumption was assessed by comparing the genotype frequencies with those expected based on the observed frequencies. The visualisation was prepared in GraphPad Prism 6 Ink.

Results

The DNA samples from CRC patients (n = 191) and healthy volunteers (n = 93) were analysed. In both groups, diet (red meat consumption) and genotype (*MTR* rs1805087, rs121913578, rs121913580, rs121913582) were included in the study. The demographic distribution including age, gender, weight, and BMI is shown in Table 1.

In both groups (patients and controls), the distribution of variants in *MTR* gene was analysed. There were no cases of *MTR* rs121913582, rs121913580, or rs121913578 mutations in both groups. There was no statistically significant relationship between the occurrence of *MTR* c.2756A>G polymorphism and risk of colorectal cancer ($p > 0.05$; χ^2 test). The genotype frequencies of the study group were in agreement with the Hardy-Weinberg equilibrium for the *MTR* c.2756A>G. The data are shown in Table 2.

Table 1. The demographic characteristics of study group, *n* – number of cases

Characteristic	Case CRC (n = 191)	Control (n = 93)
Age, mean ± (SD); median	64.40 (0.61); 65	61.10 (1.20); 63
Gender, *n* (%):		
Male	114 (59.69)	38 (49.86)
Female	77 (40.31)	55 (59.14)
Weight, mean ± (SD); median	78.63 (1.15); 78	76.65 (1.60); 78
BMI, mean ± (SD); median	27.72 (0.34); 27.08	27.39 (0.51); 27.02

Table 2. Allele and genotype frequencies of MTR 2756A>G polymorphism among patients and controls. a – allele and genotype frequencies in patients and controls were compared using χ^2 test; *n* – number of subjects; $p < 0.05$ was considered as statistically significant

Variable	Controls (n = 93) *n* (%)	Patients (n = 191) *n* (%)	Frequency *f*	OR	*P*-value
Alleles (rs1805087):					
A	144 (77.42)	302 (79.06)	0.79	1.00 (Reference)	
G	42 (22.58)	80 (20.94)	0.21	0.91	> 0.05
Genotypes (rs1805087):					
AA	53 (56.99)	118 (61.78)	nt	1.00 (Reference)	
AG	38 (40.86)	66 (34.55)	nt	0.78	> 0.05
GG	2 (2.15)	7 (3.66)	nt	1.57	> 0.05

nt – not tested.

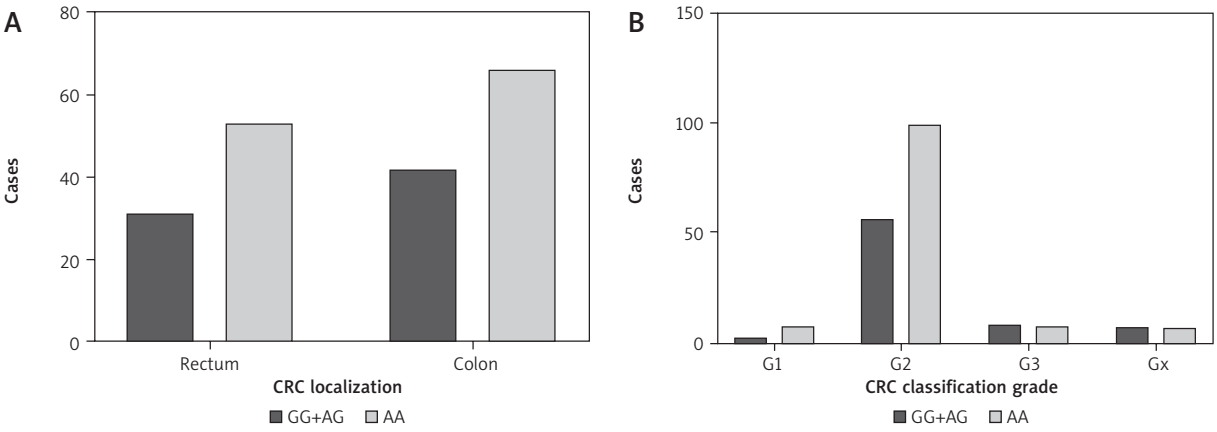

Figure 1. The localisation of the cancer and cancer grade was analysed in respect of the genotype. CRC – colorectal cancer

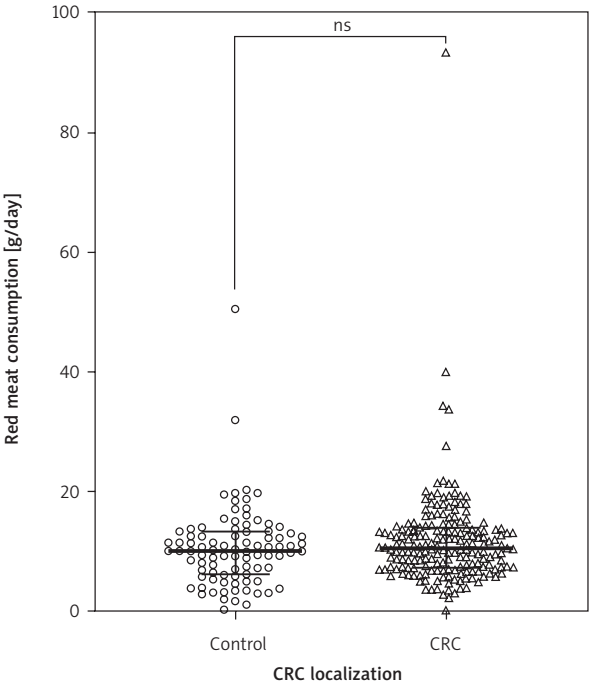

Figure 2. Daily red meat consumption in both groups – controls and colorectal cancer patients (CRC) ($p > 0.05$; U Mann-Whitney test), ns – not statistically significant

The localisation of the cancer and cancer grade were analysed in respect of the genotype, and no statistically significant differences were shown (Figures 1 A, B) ($p > 0.05$; χ^2 test; $p > 0.05$; χ^2 test with Benjamini Hochberg's procedure, respectively).

We also analysed daily [g/day] red meat consumption in both groups. Analysing the raw data, there were no significant differences in red meat consumption ($p > 0.05$; U Mann-Whitney test) (Figure 2). Therefore, we divided the meat consumption into 4 levels: low (0–50 g/day), medium (51–100 g/day), high (101–150 g/day), and very high (> 151 g/day). There was a significant difference between all classes compared to low daily red meat consumption ($p < 0.05$; χ^2 test with Benjamini Hochberg's procedure). The odds ratio (OR) was also determined. The data are shown in Table 3. Meat consumption in relation to the genotype in patients and the study group is shown in Table 4.

Discussion

The gene expression can be modified epigenetically or by DNA mutations. The main epigenetic modifications are DNA methylation and histone modification, which change the DNA accessibility and chromatin structure, thereby regulating patterns of gene ex-

Table 3. Daily red meat consumption in controls and CRC group classified as Low, Medium, High, and Extremely High. Statistical test: χ^2 test with Benjamini-Hochberg; $p < 0.05$ was considered as statistically significant

Daily red meat consumption	Controls (n = 93) n (%)	Patients (n = 191) n (%)	OR	P-value
Low	20 (60.61%)	13 (39.39%)	Reference	
Medium	25 (26.88%)	68 (73.12%)	0.239	> 0.05
High	25 (29.76%)	59 (70.24%)	0.275	> 0.05
Extremely High	23 (31.08%)	51 (68.92%)	0.293	> 0.05

Table 4. The red meat consumption in both group

Daily red meat consumption	Controls (n = 93) n (%)		Patients (n = 191) n (%)	
	AA	AG+GG	AA	AG+GG
Low n = 33	12 (60%)	8 (40)	10 (76.92)	3 (23.08)
Medium n = 93	19 (76%)	6 (24%)	35 (51.47%)	33 (48.53%)
High n = 84	17 (68%)	8 (32%)	36 (61.02%)	23 (38.98%)
Extremely high n = 74	11 (47.83%)	12 (52.17)	31 (60.78%)	20 (39.22)

pression [26]. It was already shown that methionine metabolism plays a crucial role in DNA methylation via the addition of a methyl group to the fifth carbon of cysteine residues that are linked by a phosphate to a guanine nucleotide (CpG nucleotide). The mutations in the *MTR* gene, which encodes one of the proteins involved in folate metabolism, may contribute to various diseases, including cardiovascular diseases, cancers, foetus malformation, and other congenital anomalies [27]. A lack of folates in the diet may increase the risk of colorectal cancer, as well as red meat consumption [25]. The mechanism of the latter is still unknown. It has been suggested that the red meat compound may act as a mutagenic and/or carcinogenic compound [28]. On the other hand, cancers are multifactorial diseases, in which the initial molecular hit could provoke the start and progression of cell proliferation. In our study we analysed a known factor that may predispose to CRC – red meat consumption and genetic factor – the *MTR* variant (rs1805087). Polymorphisms in genes involved in metabolic pathways of foliate, methionine, and homocysteine metabolism have been seen with different frequencies, depending on the population and geographic origin. The NM_000254.3(MTR):c.2756A>G (p.Asp919Gly) polymorphism appeared in the European population with a frequency of f = 0.2 according to the Varsome website (https://varsome.com/). In our study the allele frequency was the same (f = 0.21) (Table 2). The frequencies of the genotype were also correlated with CRC localisation and grade (Figure 1), but no correlation was found. Colorectal cancer is more often localised in the colon than in the rectum, but there is no known genetic factor to explain this observation. The genetic factor may play a different role, the known prognostic factors in CRC are the mutations in *APC*, *KRAS*, and *TP53* associated with microsatellite instability [29].

The *MTR* polymorphism is suggested to be a prognostic factor in cancer surveillance. Sarbia *et al.* [30] suggested that that multimodally treated oesophageal squamous cell carcinoma patients with the *MTR* c.2759 AG/GG genotypes may have better survival than individuals with the *MTR* c.2756 AA genotype. Analysing variants in other genes of foliate metabolism. Jokić *et al.* [31] presented the conclusion that genotypes *MTHFR* c.677C>T and the *MTR* c.2756A>G would have been specific for patients younger than 50 years old. In our study there was no correlation (data not shown), and polymorphism *MTR* c.2756A>G was more common in patients with undifferentiated tumours. According to Guimarães *et al.* [32], individuals with the *MTHFR* c.1298A>C genotype and combination of *MTHFR* c.1298A>C plus *MTRR* c.66A>G were more likely to develop rectal cancer (1.42, 3.07-fold) than those with the *MTHFR* c.677C>T, *MTHFR* c.677C>T plus double-(2R) and triple-repeated (3R) sequences of 5'-untranslated region with thymidylate synthase gene (TS) and higher risk of colon cancer (1.55, 5.39-fold). Simultaneously carries of only one polymorphism (*MTHFR* c.1298A>C, *MTHFR* c.677C>T, *MTR* c.2756A>G, *MTRR* c.66A>G, *TS* R2/R3) polymorphisms present no increased risk of sporadic colorectal adenocarcinoma (SCA) development. Previous literature showed that *MTHFR* c.1298A>C, *MTHFR* c.677C>T, *MTR* c.2756A>G, *TS* 2R/3R, and *MTRR* c.66A>G might play a role in preventing colon carcinogenesis [32, 33]. Wettergren *et al.* [33] found a possible link between germ line polymorphisms in the folate- and methyl-associated genes and p16 hypermethylation. The correlation between tumour-suppressor gene, which acts like a negative regulator of cell growth, and proliferation in the G1 phase of the cell cycle suggest the influence of the foliate metabolism gene and survival. This correlation was not observed in a case of the *MTR* variant.

We also analysed the linkage between genetic factors, red meat consumption, and the risk of colorectal cancer. The analysis indicates a lack of dependency between these factors concomitantly. The study of the influence of red meat consumption confirmed that it is a carcinogenetic factor. According to the instability trail observed in the majority (65–70%) of spontaneous cases of colorectal cancer, the rate of mutations per nucleotide base pair is estimated to be as low as 10^{-9} per cellular generation [31]. The compound of red meat may indicate mutagenesis, and there are several biological mechanisms that may explain the association with colorectal cancer [34]. In our study the daily intake of red meat was the crucial risk factor in carci-

nogenesis. It was shown that red meat consumption classified as medium (51–100 g/day), high (101–150 g/day), and very high (> 151g/day) was associated with higher risk of CRC, and it amounted to 23.9%, 27.7%, and 29.3%, respectively, compared to low meat consumption (< 50 g/day). Similar results were presented worldwide [35–37]. Moreover, the World Cancer Research Fund (WCRF) recommends that the intake of red meat is limited to less than 3 portions weekly, corresponding to approximately 350–500 g of cooked weight [38]. The differences between those levels are related to the number of participants and differences in the East European diet. It should be mentioned that red meat is a valuable source of nutrients, particular protein, iron, zinc, and vitamin B_{12}, which is why the recommendation is not to completely avoid eating meat. It is widely known that colorectal cancer is a multifactor disease, so there is a need to analyse more data like supplementation, dietary habits, physical activity, and genetic factors.

The present study did not find any association between *MTR* c.2756A>G, red meat consumption, and risk of colorectal cancer, but we confirmed that red meat consumption may increase the risk of cancer development.

Study limitations: The relatively small number of respondents in the specific group of cancer grade and TNM classification.

Conclusions

Red meat consumption greater than 50 g/day increases the risk of colorectal cancer by approximately 20%. There is no correlation between *MTR* variant and CRC risk as well as the CRC localisation.

Funding

The study was supported by Jan Kochanowski University grant No SUPS.RN.24.018

Ethical approval

The study was approved on 3 June 2013 by the local Bioethics Commission (No. 5/2013) based on the submitted application with an exact description of the procedure.

Conflict of interest

The authors declare no conflict of interest.

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Address for correspondence:

Monika Wawszczak-Kasza PhD
Institute of Medical Sciences
Jan Kochanowski University
Kielce, Poland
E-mail: wawszczak.monika@gmail.com

Received: 5.05.2024
Accepted: 24.06.2024
Online publication: 16.09.2024