Research Article

The potential role of *MGMT* rs12917 polymorphism in cancer risk: an updated pooling analysis with 21010 cases and 34018 controls

Zhiguo Sheng¹, Meini Kang² and Hao Wang³

¹Department of Neurosurgery, The First Center Hospital of Tianjin, Tianjin Medical University First Center Clinical College, Tianjin 300192, P.R. China; ²Department of Family Medicine, Tianjin United Family Hospital, Tianjin 300221, P.R. China; ³Department of Neurosurgery, Shenzhen People’s Hospital, The Second Clinical Medical College of Jinan University, Shenzhen 518020, P.R. China

Correspondence: Hao Wang (hwmai1979@163.com)

In the present study, we aimed at determining the potential role of rs12917 polymorphism of the O-6-methylguanine-DNA methyltransferase (*MGMT*) gene in the occurrence of cancer. Based on the available data from the online database, we performed an updated meta-analysis. We retrieved 537 articles from our database research and finally selected a total of 54 case–control studies (21010 cases and 34018 controls) for a series of pooling analyses. We observed an enhanced risk in cancer cases compared with controls, using the genetic models T/T compared with C/C (P-value of association test <0.001; odds ratio (OR) = 1.29) and T/T compared with C/C+C/T (P<0.001; OR = 1.32). We detected similar positive results in the subgroups ‘Caucasian’, and ‘glioma’ (all P<0.05; OR > 1). However, we detected negative results in our analyses of most of the other subgroups (P>0.05). Begg’s and Egger’s tests indicated that the results were free of potential publication bias, and sensitivity analysis suggested the stability of the pooling results. In summary, the T/T genotype of *MGMT* rs12917 is likely to be linked to an enhanced susceptibility to cancer overall, especially glioma, in the Caucasian population.

**Introduction**

In humans, the O-6-methylguanine-DNA methyltransferase (*MGMT*) protein, encoded by the *MGMT* gene located on chromosome 10 (10q26) [1], is involved in the DNA repair process [2,3]. By means of methyl transfer, MGMT removes alkylating agents from the DNA direct reversal repair pathway and thus repairs the DNA [2,3]. Two potential functional polymorphisms have been identified in the *MGMT* gene, namely rs12917 (Leu84Phe) and rs2308321 (Ile143Val) [4,5]. In addition, the promoter methylation status of the gene is reportedly correlated with several clinical diseases, such as glioblastoma [6,7], gastric cancer [8], and oral carcinoma [9].

Both genetic and environmental factors contribute to the occurrence and progression of clinical cancers [10,11]. A number of studies have been conducted on the potential genetic effect of *MGMT* rs12917 polymorphism on its susceptibility to cancer, but the results were inconclusive. Before 2013, only three relative meta-analyses investigated the potential role of this polymorphism in the overall risk for cancer [12–14]. Based on the currently available data, we performed an updated meta-analysis to reassess the genetic relationship between *MGMT* rs12917 polymorphism and cancer risk. We enrolled a total of 54 case–control studies for the study.
Materials and methods

Database searching strategy
To identify potential publications, we searched four online electronic databases (PubMed, Embase, Cochrane Library, and WANFANG) up through August 2018. We used the terms 'MeSH (Medical Subject Headings)' and 'Entry Terms' to search PubMed and Cochrane Library, and 'Emtree' and 'Synonyms' for Embase. The search string we used for PubMed was as follows: (((((((((((((((O(6)-Methylguanine-DNA Methyltransferase [MeSH Terms]) OR Methylated-DNA-Protein-Cysteine S-Methyltransferase) OR Methylated DNA Protein Cysteine S Methyltransferase) OR S-Methyltransferase, Methylated-DNA-Protein- Cysteine) OR O(6)-Methylguanine Methyltransferase) OR O(6)-Alkylguanine-DNA Alkyltransferase) OR O(6)-MeG-DNA Methyltransferase) OR O(6)-Methylguanine DNA Transmethylase) OR Guanine-O(6)-Alkyltransferase) OR O(6)-AGT) OR DNA Repair Methyltransferase II) OR DNA Repair Methyltransferase I) OR MGMT)) AND ((((((((Polymorphism, Genetic [MeSH Terms]) OR Polymorphisms, Genetic) OR Genetic Polymorphisms) OR Genetic Polymorphism) OR Polymorphism (Genetics)) OR Polymorphisms)) AND (((((Neoplasms [MeSH Terms]) OR Neoplasia) OR Neoplasms) OR Neoplasm) OR Tumor) OR Cancer) OR Cancers) OR Malignant Neoplasms) OR Neoplasm, Malignant) OR Neoplasm, Malignant) OR Malignancy) OR Malignancies) OR Benign Neoplasms) OR Neoplasms, Benign) OR Benign Neoplasm) OR Neoplasm, Benign).

Article screening strategy
We designed our inclusion and exclusion criteria according to Patient, Intervention, Comparison and Outcome and Study design (PICOS) principles. We ruled out duplicates and screened improper articles. Exclusion criteria were as follows: (P), non-cancer patients; (I), other variants, gene expression or methylation; (C), lack of study controls or $P$-value of Hardy–Weinberg equilibrium (HWE) $< 0.05$; (O), lack of full genotype frequency data; (S), review, meta, poster or meeting abstract. Eligible articles had to be designed as case–control studies, targeting the genetic relationship between $MGMT$ rs12917 and cancer risk and containing the full genotype (C/C, C/T, T/T) frequencies in both cancer cases and negative controls.

Data extraction and quality assessment
After extracting usable data, we listed the basic information in tables. We assessed methodological quality via the Newcastle–Ottawa Scale (NOS) [15]. High-quality articles with NOS score $> 5$ were regarded as eligible and included in our statistical analysis.

Statistical analysis
We used STATA software version 12.0-SE (StataCorp, College Station, TX) to perform our analyses. We first assessed the inter-study heterogeneity using Cochran’s $Q$ statistic and the $I^2$ test. A $P$-value of Cochran’s $Q$ statistic $< 0.1$ or $I^2$ value $> 50\%$ was considered to show a high level of heterogeneity. We thus used the DerSimonian–Laird association test with a random-effects model. Otherwise, we used the Mantel–Haenszel association test with a fixed-effects model. The $P$-value of association test, summary odds ratio (OR), along with the corresponding 95% confidence interval...
(CI) could be obtained for the allele (T compared with C), homozygous (T/T compared with C/C), recessive (T/T compared with C/C+C/T), heterozygous (C/T compared with C/C), dominant (C/T+T/T compared with C/C), and carrier (T compared with C) models.

We performed subgroup analyses by race, cancer type, and control source. Additionally, we assessed possible publication bias by means of Begg’s and Egger’s tests and evaluated the robustness of the results through sensitivity analysis.

Results

Eligible case–control studies

Figure 1 depicts the flowchart for the identification of eligible case–control studies. We initially obtained a total of 537 articles by searching four databases, including PubMed (245 articles), Cochrane Library (1 article), Embase (241 articles), and WANFANG (50 articles). We then excluded 233 duplicates plus another 258 articles based strictly on our screening strategy. Finally, we identified 46 full-text articles for inclusion [4,5,16–59]. After data extraction and quality evaluation, we enrolled a total of 54 case–control studies free of poor quality (all NOS score > 5) in our pooling analyses. The basic information and genotype frequency distribution are presented in Supplementary Table S1 and Table 1, respectively.

Meta-analysis data

First, we studied the association between the MGMT rs12917 polymorphism and cancer risk via an overall meta-analysis. As shown in Table 2, we included a total of 54 case–control studies with 21010 cases and 34018 controls under the genetic models of allele T compared with C, C/T compared with C/C, C/T+C/T compared with C/C, and carrier T compared with C; meanwhile, we included 50 studies with 20716 cases and 33608 controls under the models of T/T compared with C/C and T/T compared with C/C+C/T. For the homozygous, recessive and carrier genetic models, we performed a Mantel–Haenszel association test with a fixed-effects model, and we observed no high degree of heterogeneity (Table 2; all P-values of heterogeneity > 0.1; I² < 50%). For other models (all P-values of heterogeneity < 0.001), we performed a DerSimonian–Laird association test with a random-effects model. Pooling data (Table 2) indicated an increased risk of cancer in cases compared with controls for the T/T compared with C/C genetic model (P-value of association test < 0.001; OR = 1.39) and T/T compared with C/C+C/T (P < 0.001; OR = 1.32) genetic models. Nevertheless, we failed to detect any statistical difference between cancer cases and negative controls under other genetic models (Table 2; all P > 0.05). Forest plot data are shown in Figure 2 and Supplementary Figures S1–S5; they revealed that the T/T genotype of the MGMT rs12917 polymorphism was likely to be associated with an increased susceptibility to cancer.

Subgroup analysis data

Next, we carried out four subgroup analyses by race, cancer type, and control source. For the T/T compared with C/C model (Table 3), the association test data showed an increased cancer risk in the subgroups ‘Caucasian’ (P < 0.001; OR = 1.35), ‘glioma’ (P = 0.022; OR = 1.70), ‘population-based control (PB)’ (P < 0.001; OR = 1.32) and ‘hospital-based control (HB)’ (P < 0.030; OR = 1.39). Figure 3 and Supplementary Figures S6–S7 present the forest plot data.

For the T/T compared with C/C+C/T model (Table 4), we also observed positive correlations in the subgroups ‘Caucasian’ (P < 0.001; OR = 1.37), ‘Asian’ (P = 0.036; OR = 1.37), ‘glioma’ (P = 0.026; OR = 1.68), ‘PB’ (P < 0.001; OR = 1.32), and ‘HB’ (P = 0.004; OR = 1.52). Supplementary Figures S8–S10 present the forest plot data.

We did not detect positive results for the other genetic models (Supplementary Tables S2–S5; P < 0.05) except for the subgroups ‘colorectal cancer’ (Supplementary Table S3; P = 0.041; OR = 0.79), ‘HB’ (Supplementary Table S3; P = 0.027; OR = 0.86) under the C/T compared with C/C model; and the subgroup ‘head and neck cancer’ (Supplementary Table S5; P = 0.020; OR = 0.92) under the carrier T compared with C model. Thus, the T/T genotype of MGMT rs12917 may have been associated with an increased risk of cancer in cases, especially the glioma cases, in the Caucasian population.

Publication bias and sensitivity analysis

Begg’s and Egger’s tests indicated that results were free of possible publication bias (Supplementary Table S6; P > 0.05 for Begg’s test, > 0.05 for Egger’s test). A Begg’s funnel plot with pseudo–95% confidence limits under the T/T compared with C/C model is shown in Figure 4. In addition, we observed the same stable results in our subsequent sensitivity analysis; data from this analysis under the homozygous model (Figure 5) are presented as an example.

© 2018 The Author(s). This is an open access article published by Portland Press Limited on behalf of the Biochemical Society and distributed under the Creative Commons Attribution License 4.0 (CC BY).
Table 1 Genotype and allele frequency of MGMT rs12917 in the enrolled case–control studies

| Authors          | Year | Genotype (case) | Allele (case) | Cancer type (case) | Genotype (control) | Allele (control) | HWE (control) |
|------------------|------|-----------------|---------------|-------------------|-------------------|-----------------|--------------|
|                  |      | C/C C/T T/T     | C/T           |                   | C/C C/T T/T       | C/T            | x² P         |
| Agalliu et al.   | 2010 | 949 269 32 32   | 2167 333      | Prostate cancer    | 916 298 23 23     | 2130 344 0.05 0.83 |
|                  |      | 106 35 6 6      | 247 47        | Prostate cancer    | 60 20 1 1         | 140 22 0.22 0.64 |
| Akbari et al.    | 2009 | 142 53 1 1     | 337 55        | Esophageal cancer  | 185 63 2 2        | 433 67 1.84 0.17 |
| Betti et al.     | 2011 | 95 36 2 2      | 226 40        | MPM                | 179 64 8 4        | 422 80 0.59 0.44 |
| Bye et al.       | 2011 | 225 111 10 10  | 561 131       | Esophageal cancer  | 300 155 14 15     | 755 183 1.28 0.26 |
|                  |      | 120 65 11 11   | 305 87        |                   |                   |                 |              |
| Chae et al.      | 2006 | 344 84 4 4     | 772 92        | Lung cancer        | 341 81 10 10      | 763 101 3.65 0.06 |
| Chuang et al.    | 2011 | 1105 307 43 43 | 2517 393      | Head and neck cancer| 2256 823 81 82   | 5335 985 0.33 0.57 |
| Doecke et al.    | 2007 | 416 136 14 14  | 968 164       | Esophageal cancer  | 1029 281 27 23    | 2339 335 2.25 0.13 |
| Felini et al.    | 2007 | 289 84 6 6     | 662 96        | Glioma             | 369 84 6 6        | 822 96 0.24 0.63 |
| Feng et al.      | 2008 | 96 58 47 47    | 250 152       | Esophageal cancer  | 87 85 29 25       | 259 143 1.20 0.27 |
| Gu et al.        | 2009 | 152 60 2 2     | 364 64        | Melanoma           | 168 43 1 1        | 379 45 1.01 0.31 |
| Hall et al.      | 2007 | 548 193 38 38  | 1289 269      | UADT               | 730 281 23 23     | 1741 327 0.44 0.51 |
| Han et al.       | 2006 | 344 82 8 8     | 770 98        | Endometrial cancer | 822 242 21 21     | 1886 284 0.42 0.52 |
| Han et al.       | 2006 | 964 279 33 33  | 2207 345      | Breast cancer       | 1,306 382 26      | 2994 434 0.10 0.75 |
| Hu et al.        | 2013 | 389 130 24 24  | 908 178       | Glioma             | 405 84 6 6        | 894 96 0.48 0.49 |
| Hu et al.        | 2007 | 418 77 5 5     | 913 87        | Lung cancer         | 421 93 3 3        | 905 99 0.78 0.38 |
| Huang et al.     | 2007 | 76 12 2 2      | 164 16        | Glioma             | 75 14 1 1         | 164 16 0.14 0.71 |
| Huang et al.     | 2007 | 372 156 11 11  | 900 178       | Cervical cancer     | 592 198 10 10     | 1382 218 2.12 0.15 |
| Huang et al.     | 2010 | 151 25 0 2     | 327 25        | Oral cancer         | 89 21 0            | 199 21 1.22 0.27 |
| Huang et al.     | 2005 | 190 82 8 8     | 462 98        | Gastric cancer      | 279 99 9 9        | 657 117 0.00 0.95 |
| Huang et al.     | 2005 | 386 117 11 11  | 889 139       | Head and neck cancer| 529 204 21 21     | 1262 248 0.06 0.80 |
| Inoue et al.     | 2003 | 55 18 0 0      | 128 18        | Primary brain cancer| 160 55 9           | 375 73 2.24 0.13 |
| Kiczmer          | 2018 | 49 11 9 9      | 109 29        | Head and neck cancer| 168 66 5           | 402 76 0.25 0.61 |
| Kietthubthaw et al.| 2006 | 84 21 1 1   | 189 23        | Oral cancer         | 130 33 1 1        | 293 35 0.50 0.48 |
| Li et al.        | 2005 | 132 34 1 1     | 298 36        | Bladder cancer      | 173 28 3 3        | 374 34 2.11 0.15 |
| Liu et al.       | 2007 | 53 7 0 0      | 113 7         | Lung cancer         | 89 11 0            | 189 11 0.34 0.56 |
| Liu et al.       | 2002 | 21 3 0 0      | 45 3          | Gynecologic tumor   | 89 11 0            | 189 11 0.34 0.56 |
|                  |      | 28 8 0 0      | 60 8          | Digestive system cancer| 89 11 0           | 189 11 0.34 0.56 |
| Liu et al.       | 2006 | 82 16 2 2     | 180 20        | Esophageal cancer   | 57 8 0             | 122 8 0.28 0.60 |
| Liu et al.       | 2009 | 299 62 8 8    | 660 78        | Glioma             | 267 89 7 7         | 623 103 0.02 0.89 |
| Loh et al.       | 2011 | 146 37 5 5    | 329 47        | Cancer              | 894 212 14 14     | 2000 240 0.13 0.72 |
| Lu et al.        | 2006 | 142 45 4 4    | 329 53        | Gastric cancer      | 186 59 6           | 431 71 0.26 0.61 |
| McKeown-Cowdin et al. | 2009 | 774 204 20 20 | 1752 244      | Glioblastoma        | 1,480 453 35       | 3413 523 0.00 0.96 |

Continued over
Table 1 Genotype and allele frequency of MGMT rs12917 in the enrolled case–control studies (Continued)

| Authors          | Year | Genotype (case) | Allele (case) | Cancer type               | Genotype (control) | Allele (control) | HWE (control) |
|------------------|------|----------------|---------------|---------------------------|--------------------|-----------------|---------------|
| O'Mara et al.    | 2011 | 889 261 4 2039 307 | Endometrial cancer | 810 270 19 | 1890 308 0.42 | 0.52 |
| Rajaraman et al. | 2010 | 2100 777 24 2277 31 | Gastric cancer | 395 131 11 | 921 153 0.00 | 0.97 |
| Palli et al.     | 2010 | 265 77 9 607 95 | Gloma | 348 117 12 | 813 141 0.33 | 0.57 |
| Shirahata et al. | 2010 | 102 23 4 227 31 | Meningioma | 348 117 12 | 813 141 0.33 | 0.57 |
| O'Mara et al.    | 2005 | 132 6 2 282 40 | Prostate cancer | 213 32 1 | 458 34 0.03 | 0.86 |
| Palli et al.     | 2007 | 46 11 1 106 4 | Esophageal cancer | 57 20 0 | 134 20 1.72 | 0.19 |
| Shen et al.      | 2005 | 778 265 21 | Breast cancer | 824 263 20 | 1911 303 0.03 | 0.85 |
| Shie et al.      | 2007 | 432 112 11 | NHL | 373 110 12 | 856 134 1.27 | 0.26 |
| Stern et al.     | 2007 | 253 47 3 553 53 | AML | 459 91 4 | 1009 99 0.05 | 0.82 |
| Tranah et al.    | 2006 | 147 33 6 327 45 | Colorectal cancer | 1634 471 32 | 3739 535 0.09 | 0.77 |
| Wang et al.      | 2006 | 832 259 30 | Lung cancer | 872 272 19 | 2016 310 0.18 | 0.67 |
| Yang et al.      | 2009 | 33 14 1 | NHL | 289 58 5 | 636 68 1.10 | 0.29 |
| Zienoldiny et al.| 2005 | 132 6 2 | 282 40 | 458 34 0.03 | 0.86 |
| Palli et al.     | 2007 | 46 11 1 | 110 12 | 200 20 0.03 | 0.86 |
| Shen et al.      | 2005 | 778 265 21 | Breast cancer | 824 263 20 | 1911 303 0.03 | 0.85 |
| Shie et al.      | 2007 | 432 112 11 | NHL | 373 110 12 | 856 134 1.27 | 0.26 |
| Stern et al.     | 2007 | 253 47 3 | 553 53 | 1009 99 0.05 | 0.82 |
| Tranah et al.    | 2006 | 147 33 6 | 327 45 | 3739 535 0.09 | 0.77 |
| Wang et al.      | 2006 | 832 259 30 | Lung cancer | 872 272 19 | 2016 310 0.18 | 0.67 |
| Yang et al.      | 2009 | 33 14 1 | NHL | 289 58 5 | 636 68 1.10 | 0.29 |
| Zienoldiny et al.| 2005 | 132 6 2 | 282 40 | 458 34 0.03 | 0.86 |

Abbreviations: AML, acute myeloid leukemia; MPM, malignant mesothelioma; NHL, non-Hodgkin’s lymphoma; UADT, upper aerodigestive tract.

Table 2 Meta-analysis of the association between MGMT rs12917 and cancer susceptibility

| Models          | Sample size | Heterogeneity | Association |
|-----------------|-------------|---------------|-------------|
| Allele T compared with C | 54 | 21010 | 34018 | 50.1% | 0.001 | Random | 0.354 |
| T/T compared with C/C | 50 | 20716 | 33608 | 4.5% | 0.384 | Fixed | <0.001 | 1.29 (1.14–1.46) |
| T/T compared with C/C+C/T | 50 | 20716 | 33608 | 3.2% | 0.410 | Fixed | <0.001 | 1.32 (1.17–1.49) |
| C/T compared with C/C | 54 | 21010 | 34018 | 46.1% | <0.001 | Random | 0.442 |
| C/T+T/T compared with C/C | 54 | 21010 | 34018 | 47.7% | <0.001 | Random | 0.976 |
| Carrier T compared with C | 54 | 21010 | 34018 | 20.0% | 0.104 | Fixed | 0.642 |

Discussion

We observed conflicting conclusions about the genetic role of MGMT rs12917 polymorphism in its susceptibility to different cancers. For instance, the polymorphism seems to be associated with the risk of esophageal cancer in the Chinese population [41], but not in the Kashmiri population [50]. This merits a quantitative synthesis via the meta-analytic approach. Although there were already three meta-analyses of the MGMT rs12917 polymorphism and its role in the overall risk for cancer [12–14], expanding the sample size and employing a distinct analysis strategy led to better results in our updated pooling analysis.
Table 3 Data of subgroup analysis under T/T compared with C/C model

| Factor       | Subgroup        | Sample size | Heterogeneity | Association | OR (95% CI) |
|--------------|-----------------|-------------|---------------|-------------|-------------|
|              |                 | Study size  | Case | Control | $I^2$ | $P$ | $P$ | OR (95% CI) |
| Race         | Caucasian       | 27          | 13158 | 20678 | 0.0% | 0.573 | <0.001 | 1.35 (1.15, 1.58) |
|              | African         | 3           | 796   | 1104  | 0.0% | 0.538 | 0.560 | - |
|              | Asian           | 16          | 4031  | 6152  | 28.6% | 0.136 | 0.088 | - |
| Cancer type  | Urinary system cancer | 4           | 1725  | 1768  | 0.0% | 0.526 | 0.174 | - |
|              | Esophageal cancer | 8           | 2131  | 3907  | 0.0% | 0.781 | 0.069 | - |
|              | Lung cancer     | 4           | 2357  | 2475  | 40.7% | 0.167 | 0.155 | - |
|              | Head and neck cancer | 14         | 5983  | 10581 | 39.5% | 0.064 | 0.138 | - |
|              | Gastric cancer  | 3           | 762   | 1175  | 0.0% | 0.692 | 0.881 | - |
|              | Blood cancer    | 3           | 906   | 1401  | 0.0% | 0.702 | 0.882 | - |
|              | Colorectal cancer | 3           | 735   | 3732  | 38.5% | 0.197 | 0.416 | - |
|              | Brain cancer    | 9           | 2996  | 5030  | 17.4% | 0.288 | 0.106 | - |
|              | Gloma           | 5           | 1735  | 1884  | 37.9% | 0.168 | 0.022 | 1.70 (1.08, 2.68) |
| Control source | PB             | 39          | 16526 | 26488 | 6.3%  | 0.358 | <0.001 | 1.32 (1.14, 1.52) |
|              | HB              | 8           | 2482  | 4148  | 3.2%  | 0.405 | 0.030 | 1.39 (1.03, 1.86) |

-, OR (95% CI) data were not provided, when $P$-value of association > 0.05.

We did our best to gather candidate articles from four online databases. After screening them based on strict inclusion and exclusion criteria, we enrolled only the case–control studies that were of high quality and those that followed HWE. We ultimately included a total of 46 articles in our updated meta-analysis. After data extraction, we enrolled 54 case–control studies with 21010 cases and 34018 controls in the meta-analysis. We used the carrier, allele,
Table 4 Data of subgroup analysis under T/T compared with C/C+C/T model

| Factor       | Subgroup       | Sample size | Heterogeneity | Association |
|--------------|----------------|-------------|---------------|-------------|
|              |                | Study       | Case          | Control     | % | Weight |
| Race         | Caucasian      | 27          | 13158         | 20678       | 0.0% | 0.528 | <0.001 | 1.37 (1.17, 1.60) |
|              | African        | 3           | 796           | 1104        | 0.0% | 0.542 | 0.535 | -            |
|              | Asian          | 16          | 4031          | 6152        | 27.2% | 0.150 | 0.036 | 1.37 (1.02, 1.83) |
| Cancer type  | Urinary system cancer | 4 | 1725        | 1768        | 0.0% | 0.527 | 0.152 | -            |
|              | Esophageal cancer | 8          | 2131          | 3907        | 0.0% | 0.725 | 0.021 | -            |
|              | Lung cancer    | 4           | 2357          | 2475        | 40.0% | 0.467 | 0.174 | -            |
|              | Head and neck cancer | 14       | 5863          | 10581       | 37.5% | 0.077 | 0.064 | -            |
|              | Gastric cancer | 3           | 762           | 1175        | 0.0% | 0.718 | 0.815 | -            |
|              | Blood cancer   | 3           | 906           | 1401        | 0.0% | 0.769 | 0.901 | -            |
|              | Colorectal cancer | 3          | 735           | 3732        | 39.6% | 0.191 | 0.105 | -            |
|              | Brain cancer   | 9           | 2998          | 5030        | 3.0%  | 0.410 | 0.088 | -            |
|              | Glioma         | 5           | 1735          | 1884        | 23.7% | 0.263 | 1.68 (1.07, 2.65) |
| Control source | PB            | 39          | 16526         | 26488       | 2.5%  | 0.426 | <0.001 | 1.32 (1.15, 1.52) |
|              | HB             | 8           | 2482          | 4148        | 11.0% | 0.344 | 0.004 | 1.52 (1.14, 2.03) |

-, OR (95% CI) data was not provided, when P-value of association > 0.05.
Bioscience Reports (2018) 38 BSR20180942
https://doi.org/10.1042/BSR20180942

Figure 4. Begg’s funnel plot with pseudo-95% confidence limits (T/T compared with C/C model)

Figure 5. Sensitivity analysis result (T/T compared with C/C model)

homozygous, recessive, heterozygous, and dominant genetic models, and also confirmed the stability of the statistical results via sensitivity analysis.

In 2010, Zhong et al. [12] performed the first meta-analysis on this topic, reviewing 28 case-control studies from 26 articles [4,5,20,22,23,26–28,31,33–35,37,38,42,45,49,51,52,54,55,59–63]. Another 24 case-control studies [16–19,21,24,25,29,30,32,36,39–41,43,44,46–48,50,53,54–58] were included in our study. We excluded three studies not in-line with the HWE principle [61–63] and one that focussed only on colorectal adenomatous or hyperplastic polyps but not on colorectal cancer [60]. In 2013, Du et al. [14] enrolled 41 case-control studies with 16643 cancer cases and 26720 negative controls from 37 articles [5,16–20,22–24,26–28,31–34,37–41,43,44,46,47,49–59,64] in a meta-analysis. We excluded one of these studies [64] from our meta-analysis because it did not meet the requirement of full genotype frequency in both case and control groups. Finally, we enrolled another ten case-control studies [4,21,25,29,30,35,36,42,45,48]. In addition, when compared with another meta-analysis of Liu et al. (2013) [13], which consisted of 44 case-control studies from 37 articles [4,5,16,17,19,20,22,23,25–27,31–33,35,37,38,42,43,45–47,49,51,52,54–63,65,66], we excluded four studies that were not in HWE [61–63,66], one that did not analyze colorectal cancer [60], and one that included other genetic variants [65]. We also added another 15 new case-control studies [18,21,24,28–30,34,36,39–41,44,48,50,53] for the analysis.

Our updated pooling analysis data demonstrated that cases had an overall enhanced risk for cancer when compared with negative controls under the T/T compared with C/C and T/T compared with C/C+C/T genetic models, especially in the European-descended population, which is partly consistent with the data of previous analyses [12–14]. Moreover, we observed that the MGMT rs12917 polymorphism is likely to be associated with the susceptibility to
glioma, which is partly in-line with the two studies on the association between DNA repair gene polymorphisms and glioma risk [67,68]. Nevertheless, owing to the limitation of sample size, the previous three meta-analyses of the overall risk for cancer did not conduct subgroup analyses of ‘glioma’ [12–14]. Some of the limitations to our meta-analysis are as follows:

(1) Although the sample sizes enrolled were quite large (21010 cases and 34018 controls), genotype data were very limited in many subgroup analyses. For instance, we used only three case–control studies in our analyses of the subgroups for gastric [33,44,47], blood [52,53,56], and colorectal [54,55] cancers. Even for the subgroup analysis of ‘glioma’, with positive correlations under the T/T compared with C/C and T/T compared with C/C+C/T models, only five case–control studies [23,29,30,42,48] were included.

(2) We did not investigate the genetic effects of the MGMT rs12917 polymorphism in combination with other variants, such as rs2308321 of MGMT, rs25487 of X-ray cross-complementing group 1 (XRCC1), and rs13181 of xeroderma pigmentosum complementation group D (XPD), in certain specific cancers.

(3) We extracted certain demographic information such as the mean age at diagnosis and the sex of subject, but not other confounding factors such as lifestyle and clinical features. Moreover, we did not perform the relevant stratified meta-analyses due to lack of sufficient usable data.

(4) We detected significant heterogeneity amongst studies under the allele T compared with C, C/T compared with C/C, C/T+T/T compared with C/C, and carrier T compared with C genetic models. Complicating factors such as race and cancer type may be sources of inter-study heterogeneity. For instance, we detected decreased levels of heterogeneity in the ‘Caucasian’ and ‘esophageal cancer’ subgroups. Although we observed a positive conclusion in the ‘glioma’ subgroup, we failed to detect reduced inter-study heterogeneity. Only five case–control studies [23,29,30,42,48] were enrolled.

(5) There may be other undetected or unpublished articles containing potential eligible case–controls in other geographical locations or languages; in other words, our study may suffer from selection bias.

(6) Last but most important, our meta-analysis found a positive conclusion between MGMT rs12917 and the risk of cancer in general for the T/T compared with C/C and T/T compared with C/C+C/T models. Considering the distinct etiopathogenesis or pathogenesis of different kinds of cancers, more studies of large-scale populations of different ethnicities are required for a more scientific elucidation of MGMT rs12917’s functional role in each particular cancer type.

To sum up, our updated pooling analysis offered additional evidence that MGMT rs12917 polymorphism is likely to be associated with an enhanced susceptibility to cancer overall, especially glioma, in the Caucasian population.

Author contribution
Z.S. and H.W. conceived and designed the study. Z.S. and M.K. were responsible for the data extraction and statistical analysis. Z.S. wrote the manuscript and H.W. revised the manuscript.

Competing interests
The authors declare that there are no competing interests associated with the manuscript.

Funding
This work was supported by grants from the key program of Tianjin health Bureau (Grant NO.14KG104).

Abbreviations
HB, hospital-based control; HWE, Hardy–Weinberg equilibrium; MeSH, Medical Subject Heading; MGMT, O-6-methylguanine-DNA methyltransferase; NOS, Newcastle–Ottawa scale; OR, odds ratio; PB, population-based control.

References
1 Natarajan, A.T., Vermeulen, S., Darroudi, F., Valentine, M.B., Brent, T.P., Mitra, S. et al. (1992) Chromosomal localization of human O6-methylguanine-DNA methyltransferase (MGMT) gene by in situ hybridization. Mutagenesis 7, 83–85, https://doi.org/10.1093/mutage/7.1.83
2 Christmann, M., Verbeek, B., Roos, W.P. and Kaina, B. (2011) O(6)-Methylguanine-DNA methyltransferase (MGMT) in normal tissues and tumors: enzyme activity, promoter methylation and immunohistochemistry. Biochim. Biophys. Acta 1816, 179–190
33 Huang, W.Y., Chow, W.H., Rothman, N., Lisowska, J., Liaca, V., Yeager, M. et al. (2005) Selected DNA repair polymorphisms and gastric cancer in Poland. Carcinogenesis 26, 1354–1359, https://doi.org/10.1093/carcin/bgI084
34 Huang, W.Y., Olshan, A.F., Schwartz, S.M., Berndt, S.I., Chen, C., Liaca, V. et al. (2005) Selected genetic polymorphisms in MGMT, XRCC1, XPD, and XRCC3 and risk of head and neck cancer: a pooled analysis. Cancer Epidemiol Biomarkers Prev. 14, 1747–1753, https://doi.org/10.1158/1055-9965.EPI-05-0162
35 Inoue, R., Iso, M., Abe, M., Abe, T. and Kobayashi, H. (2003) A genotype of the polymorphic DNA repair gene MGMT is associated with de novo glioblastoma. Neurosci. Res 25, 875–879, https://doi.org/10.1016/S0168-6942(03)00078-6
36 Kiczmer, P., Prawdzic Senkowska, A., Strzelczyk, J.K., Szydlo, B., Biernacki, K., Osadnik, T. et al. (2018) The role of MGMT polymorphisms rs12917 and rs11016879 in head and neck cancer risk and prognosis. Acta Biochim. Pol. 65, 87–92, https://doi.org/10.18388/abp.2017.1613
37 Kietthubthaw, S., Sriplung, H., Au, W.W. and Ishida, T. (2006) Polymorphism in DNA repair genes and oral squamous cell carcinoma in Thailand. Int. J. Hyg. Environ. Health 209, 21–29, https://doi.org/10.1016/j.ijheh.2005.06.002
38 Li, C., Liu, J., Li, A., Qian, L., Wang, X., Wei, Q. et al. (2005) Exon 3 polymorphisms and haplotypes of O6-methylguanine-DNA methyltransferase and risk of bladder cancer in southern China: a case-control analysis. Cancer Lett. 227, 49–57, https://doi.org/10.1016/j.canlet.2003.04.035
39 Liu, R.Q. and Zhuang, Z.X. (2002) Single-nucleotide polymorphisms of human O6-methylguanine-DNA methyltransferase (MGMT) gene in lung cancer patients from south china. Wei Sheng Du Xue Za Zhi 16, 1–5
40 Liu, R.Q., Zhuang, Z.X., He, C.H. and He, Y. (2002) Relationship between genetic polymorphisms of human O6-methylguanine-DNA methyltransferase (MGMT) gene and gastric cancer hereditary susceptibility. J. Bing Kong Zhi Za Zhi 10, 222–225
41 Liu, S.H., Su, M., Cheng, L., Sun, B.L. and Lu, Z.H. (2006) Polymorphisms of O6-methylguanine-DNA methyltransferase gene in Chinese Chaoshan esophageal cancer patients. Ai Zheng Ji Jian Tu Bian 14, 101–106
42 Liu, Y., Xu, Y.C., Shen, J., Yu, R.B., Niu, J.Y. and Guo, J.T. (2006) Study on the association between the role of polymorphisms of the O6-methylguanine-DNA methyltransferase gene and gastric cancer hereditary susceptibility. J. Bing Kong Zhi Za Zhi 10, 222–225
43 McClean-Cowdin, R., Bamholtz-Sloan, J., Inskip, P.D., Ruder, A.M., Butler, M., Rajaraman, P. et al. (2009) Associations between polymorphisms in DNA repair genes and glioblastoma. Cancer Epidemiol Biomarkers Prev. 18, 1118–1126, https://doi.org/10.1158/1055-9965.EPI-08-1078
44 O’Marra, T.A., Ferguson, K., Fahey, P., Marquart, L., Yang, H.P., Lisowska, J. et al. (2011) CHEK2, MGMT, SULT1E1 and SULT1A1 polymorphisms and endometrial cancer risk. Twin Res. Hum. Genet. 14, 328–332, https://doi.org/10.1375/twin.14.4.328
45 Oh, Y.H., Mitrou, P.N., Wood, A., Luben, R.N., McGavigan, A., Khaw, K.T. et al. (2011) SMAD7 and MGMT genotype variants and cancer incidence in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Study. Cancer Epidemiol. 35, 369–374, https://doi.org/10.1016/j.canep.2010.09.011
46 Palil, D., Polidoro, S., D’Errico, M., Saiava, C., Guarrera, S., Cagnaggi, A.S. et al. (2010) Polymorphic DNA repair and metabolic genes: a multigenic study on gastric cancer. Mutagenesis 25, 569–575, https://doi.org/10.1039/mutage/gpp042
47 Rajaraman, P., Hutchinson, A., Wichner, S., Black, P.M., Fine, H.A., Loeffler, J.S. et al. (2010) DNA repair gene polymorphisms and risk of adult meningioma, glioma, and acoustic neuroma. Neuro Oncol. 12, 37–48, https://doi.org/10.1093/neuonc/nop012
48 Ritchey, J.D., Huang, W.Y., Chokkalingam, A.P., Gao, Y.T., Deng, J., Levine, P. et al. (2005) Genetic variants of DNA repair genes and prostate cancer: a population-based study. Cancer Epidemiol Biomarkers Prev. 14, 1703–1709, https://doi.org/10.1158/1055-9965.EPI-04-0809
49 Shah, M.A., Shaff, S.M., Lone, G.N. and Jan, S.M. (2012) Lack of influence of MGMT codon Leu84Phe and codon ileu143Val polymorphisms on esophageal cancer risk in the Kashmir valley. Asian Pac. J. Cancer Prev. 13, 3047–3052, https://doi.org/10.7314/APJCP.2012.13.7.3047
50 Shen, J., Terry, M.B., Gammon, M.D., Gaudet, M.M., Teitelbaum, S.L., Eng, S.M. et al. (2005) MGMT genotype modulates the associations between cigarette smoking, dietary antioxidants and breast cancer risk. Carcinogenesis 26, 2131–2137, https://doi.org/10.1038/sj.bjc.6604179
51 Shen, M., Purdie, M.P., Kricker, A., Lan, Q., Grulich, A.E., Vajdic, C.M. et al. (2007) Polymorphisms in DNA repair genes and risk of non-Hodgkin’s lymphoma in New South Wales, Australia. Haematologica 92, 1180–1185, https://doi.org/10.3324/haematol.11324
52 Shi, J.Y., Ren, Z.H., Jiao, B., Xiao, R., Yun, H.Y., Chen, B. et al. (2011) Genetic variations of DNA repair genes and their prognostic significance in patients with acute myeloid leukemia. Int. J. Cancer 128, 233–238, https://doi.org/10.1002/ijc.25318
53 Stern, M.C., Conti, D.V., Siegel, R., Bueno, L., Yun, J.M., Koh, W.P. et al. (2007) DNA repair single-nucleotide polymorphisms in colorectal cancer and their role as modifiers of the effect of cigarette smoking and alcohol in the Singapore Chinese Health Study. Cancer Epidemiol Biomarkers Prev. 16, 2363–2372, https://doi.org/10.1158/1055-9965.EPI-06-1728
54 Tranah, G.J., Bugnì, F., Giovannucci, E., Ma, J., Fuchs, C., Hines, L. et al. (2006) O6-methylguanine-DNA methyltransferase Leu84Phe and Ile143Val polymorphisms and risk of colorectal cancer in the Nurses’ Health Study and Physicians’ Health Study (United States). Cancer Epidemiol Biomarkers Prev. 15, 2222–2225, https://doi.org/10.1158/1055-9965.EPI-05-0270
55 Yang, F., Shi, J.Y., Xu, L., Ren, J.L., Zhang, G.H., Zhao, W.L. et al. (2009) Genetic susceptibility of single nucleotide polymorphism in MGMT to non-Hodgkin lymphoma. Zhonghua Xue Ye Xue Za Zhi 30, 622–625
56 Zhang, M., Huang, W.Y., Andretti, G., Gao, Y.T., Rashid, A., Chen, J. et al. (2008) Variants of DNA repair genes and the risk of biliary tract cancers: a population-based study in China. Cancer Epidemiol Biomarkers Prev. 17, 2123–2127, https://doi.org/10.1158/1055-9965.EPI-07-2735
57 Zhang, Z., Wang, L., Chen, C., Liu, Z., Wang, L.E., Sturgis, E.M. et al. (2010) Polymorphisms of the DNA repair gene MGMT and risk and progression of head and neck cancer. DNA Repair (Amst.) 9, 558–566, https://doi.org/10.1016/j.dnarep.2010.02.006
58 Zienolddiny, S., Bampi, D., Lind, H., Ryberg, D., Skau, V., Stangeland, L. et al. (2006) Polymorphisms of DNA repair genes and risk of non-small cell lung cancer. Carcinogenesis 27, 560–567, https://doi.org/10.1038/sj.bjc.6606232
59 Bigler, J., Ulrich, C.M., Kawashima, T., Whitton, J. and Potter, J.D. (2005) DNA repair polymorphisms and risk of colorectal adenomatous or hyperplastic polyps. Cancer Epidemiol. Biomarkers Prev. 14, 2501–2508, https://doi.org/10.1158/1055-9965.EPI-05-0270
61 Jiao, L., Bondy, M.L., Hassan, M.M., Wolff, R.A., Evans, D.B., Abbruzzese, J.L. et al. (2006) Selected polymorphisms of DNA repair genes and risk of pancreatic cancer. Cancer Detect. Prev. 30, 284–291, https://doi.org/10.1016/j.cdp.2006.05.002

62 Krzesniak, M., Butkiewicz, D., Samojedny, A., Chorazy, M. and Rusin, M. (2004) Polymorphisms in TDG and MGMT genes - epidemiological and functional study in lung cancer patients from Poland. Ann. Hum. Genet. 68, 300–312, https://doi.org/10.1046/j.1529-8817.2004.00079.x

63 Moreno, V., Gemignani, F., Landi, S., Gioia-Patricola, L., Chabrier, A., Blanco, I. et al. (2006) Polymorphisms in genes of nucleotide and base excision repair: risk and prognosis of colorectal cancer. Clin. Cancer Res. 12, 2101–2108, https://doi.org/10.1158/1078-0432.CCR-05-1363

64 Hung, R.J., Baragatti, M., Thomas, D., McKay, J., Szeszenia-Dabrowska, N., Zardize, D. et al. (2007) Inherited predisposition of lung cancer: a hierarchical modeling approach to DNA repair and cell cycle control pathways. Cancer Epidemiol. Biomarkers Prev. 16, 2736–2744, https://doi.org/10.1158/1055-9965.EPI-07-0494

65 Hazra, A., Chanock, S., Giovannucci, E., Cox, D.G., Niu, T., Fuchs, C. et al. (2008) Large-scale evaluation of genetic variants in candidate genes for colorectal cancer risk in the nurses’ health study and the health professionals’ follow-up study. Cancer Epidemiol. Biomarkers Prev. 17, 311–319, https://doi.org/10.1158/1055-9965.EPI-07-0195

66 Khatami, F., Noorinayer, B., Mohebi, S.R., Ghiasi, S., Mohebi, R., Hashemi, M. et al. (2009) Effects of amino acid substitution polymorphisms of two DNA methyltransferases on susceptibility to sporadic colorectal cancer. Asian Pac. J. Cancer Prev. 10, 1183–1188

67 Adel Fahmideh, M., Schwartzbaum, J., Frumento, P. and Feychting, M. (2014) Association between DNA repair gene polymorphisms and risk of glioma: a systematic review and meta-analysis. Neuro Oncol. 16, 807–814, https://doi.org/10.1093/neuonc/nou003

68 Liu, K. and Jiang, Y. (2017) Polymorphisms in DNA repair gene and susceptibility to glioma: a systematic review and meta-analysis based on 33 studies with 15 SNPs in 9 genes. Cell Mol. Neurobiol. 37, 263–274, https://doi.org/10.1007/s10571-016-0367-y