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A meta-analysis on the susceptibility to the development of bladder cancer in the presence of DNMT3A, DNMT3B, and MTHFR gene polymorphisms

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Abstract

Background: The etiology of bladder cancer is not yet well known. In this study, we want to evaluate the effect of polymorphisms of genes that have an epigenetic effect (*MTHFR, DNMT3A/B*) on the susceptibility to develop bladder cancer (BC).

Methods: A systematic review was performed for MTHFR, *DNMT3A, and DNMT3B*, followed by a meta-analysis conducted for rs1801131, rs1801133, rs2274976, rs1550117, and rs1569686 SNPs. A sensitivity and a subgroup analysis were then used.

Results: 20 studies were included, where no statistically significant association between any of the analyzed SNPs and the occurrence of BC was detected. Subgroup analysis revealed a statistically significant association in North African population with rs1801133: TT *vs*. TC + CC ($P = 0.013$; OR 95% CI = 0.52 [0.311–0.872]); TT *vs*.TC ($P = 0.003$; OR 95% CI = 0.448 [0.261–0.769]) and in North American population with rs1801131: CC *vs*. CA ($P = 0.039$; OR 95% CI = 0.71 [0.523–0.984]). A sensitivity analysis revealed that there is a statistically significant association between rs1801131 and the occurrence of BC (OR = 0.79, 95%CI [0.65–0.97]), (OR = 0.80, 95%CI [0.65–0.98]) and (OR = 0.78, 95%CI [0.63–0.96]) which correspond to CC *vs*. CA + AA; CC *vs.* CA; and CC *vs.* AA genetic models.

Conclusion: This is the first study to assess the effect of *DNMTs* on bladder cancer risk. No statistically significant association was found between polymorphisms of *MTHFR*, *DNMT3A/B* genes and bladder cancer development, except for the North African and the North American populations with rs1801133 and rs1801131, respectively, with a protective effect of rs1801131 based on a sensitivity analysis.

Keywords: Bladder cancer (BC), DNMT3A/B, Meta-analysis, MTHFR, Polymorphism

1 Background

According to GLOBOCAN data, bladder cancer (BC) holds the 10th place among the most frequently diagnosed cancers in the world, with approximately 573,000 new cases and 213,000 deaths in 2020. Men are more likely to develop bladder cancer than women, with incidences and mortality rates of 9.5 and 3.3 per 100,000 for men worldwide, about four times higher than for women [1].

The etiology of bladder cancer is not yet well known. However, there are risk factors associated with the disease, including environmental factors such as smoking and occupational exposure to some types of chemicals

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[2]. Furthermore, among people exposed to the same environment, only a small fraction develop bladder cancer, which implies the role of genetic as well as epigenetic factors in bladder carcinogenesis [3].

The term epigenetics refers to inherited changes in gene expression that are not induced by changes in the DNA sequence itself. The DNA methylation mechanism is one of the earliest and most extensively studied types of epigenetic regulation [4]. Its association with developmental processes, aging, and carcinogenesis through mechanisms such as hypermethylation of tumor suppressor genes and hypomethylation of oncogenes is well known [5].

There are several genes classified as having an epigenetic effect, including the Methylene Tetra Hydrofolate Reductase (*MTHFR*) gene. It belongs to the one-carbon metabolic chain (OCM) and has an essential role in the release of free methyl groups (CH3) during the irreversible reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate [6].

In the process of DNA methylation, the methyl group (CH3) is added to the 5-carbon of cytosine, leading to the formation of 5-methylcytosine (5-mC) through enzymes of the DNA methyltransferase (*DNMTs*) family. Two main methylation pathways are found: the establishment pathway and the maintenance pathway. They take place during embryonic development via *DNMT3A* and *DNMT3B*, and during DNA replication via *DNMT1* [7]. By means of these enzymes, DNA methylation patterns are established and inherited throughout the subsequent cell generations. It is therefore a mechanism of cellular memory and it is linked to critical information on how gene expression is programmed [8].

Ren et al. suggest that the *MTHFR* gene rs1801133 is associated with global DNA hypomethylation, which might consequently contribute to quantitative alterations at the genetic level and thus to susceptibility to cancer development [9]. In addition, possible associations between SNPs of *DNMTs* and the predisposition to different types of cancers have been reported: *DNMT3A* with gastric cancer [10], *DNMT3B* with breast cancer [11], and lung cancer [12].

In light of these findings, we set out to evaluate the impact of five SNPs in the *MTHFR* and *DNMT* genes on bladder cancer susceptibility, both qualitatively and quantitatively.

2 Methods

2.1 Research strategy

A literature search was performed on PubMed and Google Scholar databases in order to identify relevant studies published until November 6th, 2021. We used the same search strategy for the three genes, changing only the gene names each time. As an example, in the search strategy for the *MTHFR* gene on PubMed:((Bladder) AND (cancer)) AND (*MTHFR*), ((Urothelial carcinoma) OR (Bladder cancer)) AND (MTHFR), (Urothelial carcinoma) AND (*MTHFR*), (Transitional cell carcinoma) AND (*MTHFR* gene), (Urothelial carcinoma) AND (*MTHFR* polymorphism), (*MTHFR* polymorphism) AND (Transitional cell carcinoma), (Bladder cancer) AND (*MTHFR* polymorphism), (Transitional cell carcinoma) AND (*MTHFR* polymorphism). See Appendix A for *DNMT3A's* research strategy. The working language was limited to English.

2.2 Selection process

All included studies in the present analysis fulfilled the following inclusion criteria: studies that examined the association between SNPs of *DNMTs* and *MTHFR* with susceptibility to the development of bladder cancer in humans; case control studies; and availability of genotypic frequencies. The exclusion criteria were: papers or studies with overlapping data, duplicate studies, lack of full text, not a case/control study, not related to bladder Cancer, Review/ Meta-analysis. Data and SNPs are not available.

2.3 Data extraction

Two authors independently examined the records. While one author extracted the data (first author, year of publication, study population, genotyping methods, genes, SNPs, number of cases and controls, and Hardy–Weinberg equilibrium (HWE), the second author was consulted in cases where the data was uncertain. After a number of discussions, a common agreement has finally been reached regarding each uncertain data point. Three authors were contacted to obtain either additional information or to request the full text of the article. No feedback has been received yet.

2.4 Quality control

In the quantitative analysis, each study included was scored according to the quality assessment criteria used by Li et al., with overall quality scores ranging from 0 to 15. Thus, studies with a score of ≥ 9 are considered to be of high quality; otherwise, they are classified as being of low quality [13].

2.5 Statistical analysis

In this meta-analysis, Hardy–Weinberg equilibrium (HWE) was recalculated in controls. *p* values and FDR-adjusted p values greater than 0.05 were considered to be in HWE. The OR (95% CI) and *p*-values calculation of the quantitative analysis of *MTHFR* and *DNMT*s gene polymorphisms was performed with the statistical methods

Inverse Variance and DerSimonian-Laird, which correspond, respectively, to the fixed-effect and random-effect analysis models. A p-value less than 0.05 was considered significant. Calculations were performed using MetaGenyo [14] https://metagenyo.genyo.es/.

3 Results

3.1 Literature search

A total of 394 records were identified through the database search. After removing duplicates, 143 records were analyzed based on their titles and abstracts. There were 98 publications excluded because: they did not evaluate the polymorphism of interest (29), were not related to bladder cancer (42), were systematic reviews and/or meta-analyses (24), or had no relation to our genes of interest (3).

After that, 45 full-text articles were still evaluable according to the eligibility criteria, 11 of which were excluded because of: duplication (4), absence of the required data (4), missing of the full-text (2), and indetermination of the polymorphisms (1). After cotenant verification, 14 more articles were excluded because: studies were not related to bladder cancer (2), they were reviews/meta-analyses (3), they were not case/control studies (7), and finally, one study was found to be overlapping.

Finally, we end up with 20 eligible studies, from which 4723 BC cases and 5784 healthy controls were included in the current meta-analysis [15–34]. Figure 1 depicts the selection process based on the «PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only» [35].

3.2 Study characteristics

Table 1 describes the main characteristics of the included studies. Four studies were conducted in Taiwan, three in the USA, two in China, two in Tunisia, and one study for each of the following populations: Turkey, Argentina, Germany, Sweden, India, Spain, Algeria, Pakistan, and Iran. The quality of the 20 studies included in the meta-analysis was calculated with scores found to range from two to 11. We achieved a score of ≥ 9 (high quality) in 20% of the included papers. All studies included in the present meta-analysis are in Hardy–Weinberg equilibrium with adjusted p values greater than 0.05.

3.3 Meta-analysis

MTHFR rs1801133, rs1801131, and rs2274976 were investigated, as were *DNMT3A* rs1550117 and *DNMT3B* rs1569686. The following genetic models were used: allele contrast, recessive, dominant, as well as homozygous and heterozygous models. Table 2 shows the heterogeneity tests (*P*-value and I^2) and the association tests between the polymorphisms of the *MTHFR* and *DNMTs* genes with the occurrence of bladder cancer. No significant associations were found among the adopted genetic models. Figures 2 and 3 Represents the result of the 5 SNPs under the allelic contrast model.

No significant heterogeneity was found in the majority of the studies' data included in this analysis ($P > 0.1$), for that *DNMT3A/B* revealed no heterogeneity ($P > 0.1$ and $I^2 = 0\%$) among their tested SNPs, in contrast to the *MTHFR,* which revealed significant heterogeneity for rs1801133 and rs1801131 ($P < 0.1$) in some genetic models (Allele contrast, Recessive, Dominant, and Homozygous). There was no impact of these two SNPs on the risk of developing bladder cancer. The analysis also revealed that there was no significant heterogeneity in the rs2274976 studies ($P > 0.1$; $I^2 < 50\%$) and there was no association with BC.

3.4 Sensitivity and subgroup analysis

The genetic models of rs1801133 showed heterogeneity (Table 2): T *vs.*C ($I^2 = 48\%$, *P*-Het = 0.013); TT *vs.* TC + CC ($I^2 = 32\%$, *P*-Het = 0.093); TT + TC *vs.* CC ($I^2 = 42\%$, *P*-Het = 0.035), TT vs. CC ($I^2 = 42\%$, *P*-Het = 0.032), as well as for rs1801131: C *vs.* A ($I^2 = 74\%$, *p*-Het = 0); CC *vs.* CA + AA ($I^2 = 37\%$, *P*-Het = 0.092); CC + CA *vs.* AA ($I^2 = 74\%$, *p*-Het = 0); CC *vs.* AA ($I^2 = 65\%$, *P*-Het = 0.0008); CA *vs.* AA ($I^2 = 69\%$, *P*-Het = 0.0002). Subsequently, a sensitivity analysis was performed to determine whether any studies had a primary effect on the pooled ORs. For rs1801133, there was no source of heterogeneity caused by the studies included in the meta-analysis. For rs1801131, the heterogeneity was primarily caused by the study of Safarinejad et al. In fact, when the latter was removed, we moved to an association (OR = 0.79, 95% CI [0.65–0.97]), (OR = 0.80, 95% CI [0.65–0.98]) and (OR = 0.78, 95% CI [0.63–0.96]) which correspond to CC *vs.* CA + AA; CC *vs.* CA; and CC *vs.* AA, respectively Fig. 4 [24].

In the subgroup analysis, two factors were selected to explain the heterogeneity: geographic regions and genotyping methods (Table 3):

For geographical regions: the North African and North American populations were, respectively, associated with the occurrence of BC via rs1801133 and rs1801131: TT *vs.* TC + CC (*P*-value: 0.013; OR 95% CI = 0.52 [0.311–0.872]), TT vs. TC (*P*-value: 0.003; OR 95% CI = 0.448 [0.261–0.769]). Rs1801131: CC *vs.* CA (*P*-value: 0.039; OR 95% CI = 0.71 [0.523–0.984]). However, for the remaining genetic models, no statistically significant association was considered because of the limited combined studies (< 2).

For genotyping methods, only PCR–RFLP under rs1801133 was found to be associated with BC using the TC *vs.* CC model (*P*-value: 0.040; OR 95% CI = 1.12

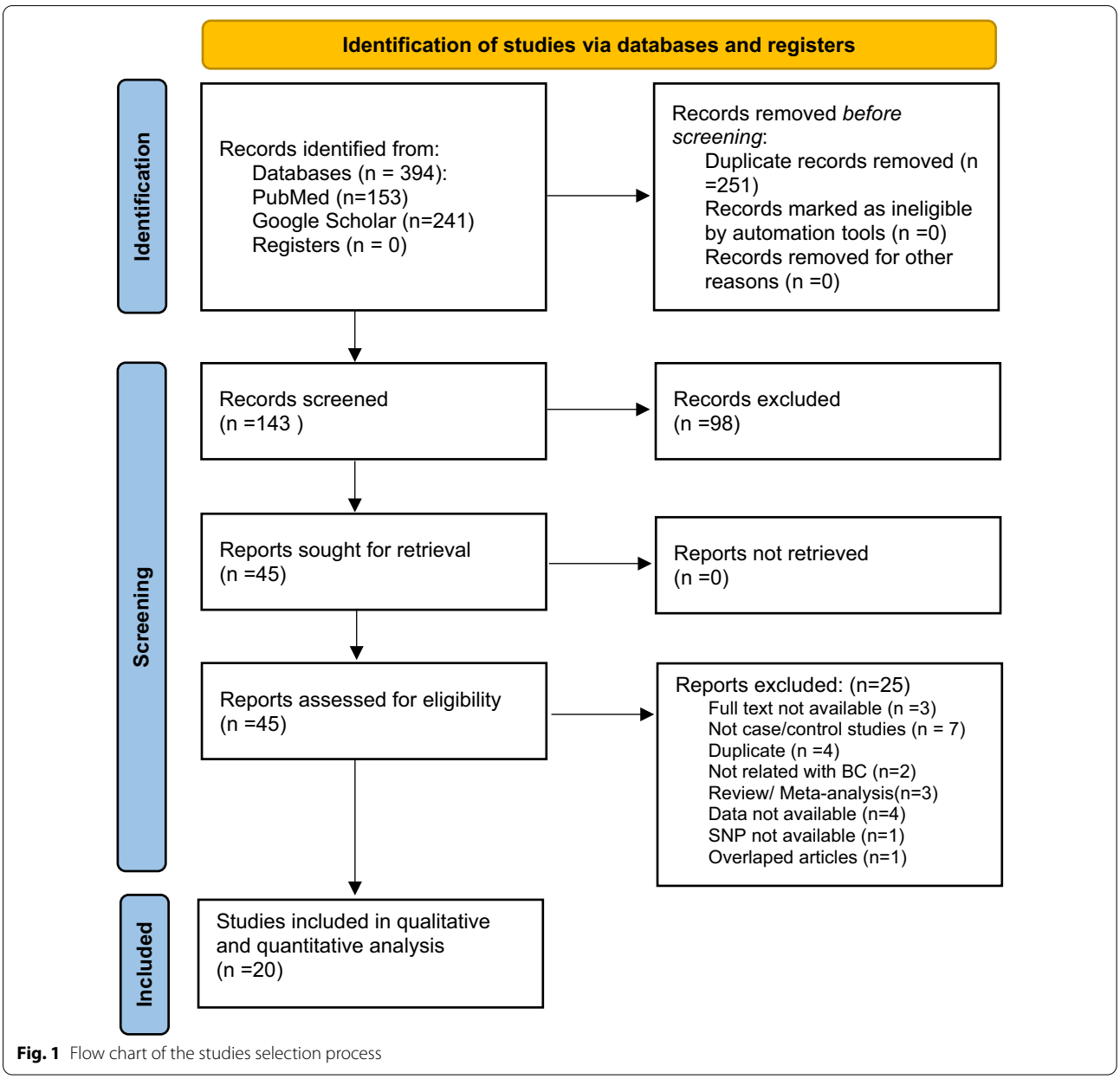

Fig. 1 Flow chart of the studies selection process

[1.005–1.269]). For the other genotyping methods (TaqMan and PCR-Sequencing), no significant association was observed, neither for rs1801133 nor rs1801131.

3.5 Publication bias

Publication bias assessment for each genetic model was performed using a funnel plot , Additional file 1: example of allele contrast and Egger's test (Table 2). For the SNPs *MTHFR* rs2274976, *DNMT3A* rs1550117, and *DNMT3B* rs1569686, numerical results of Egger's test were not available; this could be explained by the limited number of studies. However, according to funnels Plots of the three SNPs (Additional file 1) and the Egger's test, of the other two SNPs (rs 1801133 and rs 1801131), no publication bias was detected among the studies included in the current meta-analysis.

4 Discussion

Throughout a systematic review, we found a total of 5 SNPs belonging to 3 different genes that were intensively analyzed for their association to BC occurrence: *MTHFR* (rs1801133, rs1801131 and rs2274976), *DNMT3A* (rs1550117) and *DNMT3B* (rs1569686). Hence, we used them in the present meta-analysis. No statistically

Table 1 The main characteristics of the 20 studies included in the meta-analysis

Study ID	Study population	Geographic region	Source of control	Genotyping Techniques	Gene	SNPs	Cases/controls	HWE		Quality score
								*P-value	**Adjusted P- value	
Chung 2014a[17]	Tawian	East Asian	HB	PCR–RFLP PCR–RFLP	*DNMT3A* *DNMT3B*	rs1550117 rs1569686	170/ 331 163/ 328	0.7901 0.5699	0.8426 0.5699	8
Chung 2014b [16]	Taiwan	East Asian	HB	PCR–RFLP	*DNMT3B*	rs1569686	159/308	0.0912	0.1824	5
Karagas et al. 2005[15]	New Hamsphire /USA	North American	PB	PCR–RFLP	*MTHFR*	rs1801133 rs1801131	350/543 350/542	0.7019 0.3333	0.8523 0.5259	11
Izmirli et al. 2011[18]	Turkey	West Asian	HB	PCR–RFLP	*MTHFR*	rs1801133 rs1801131	54/50 47/50	0.2497 0.1952	0.6226 0.4228	2
Ouerhani et al. 2009 [19]	Tunisia	North African	NA	PCR–RFLP	*MTHFR*	rs1801133	90/110	0.4167	0.7084	4
Cai et al. 2009 [20]	China	East Asian	HB	PCR–RFLP	*MTHFR*	rs1801133 rs1801131	312/325 312/325	0.0755 0.5043	0.3808 0.6052	7
Ouerhani et al. 2007 [21]	Tunisia	North African	NA	PCR–RFLP	*MTHFR*	rs1801133 rs1801131	111/131 111/131	0.5502 0.0891	0.7258 0.4032	4
Beebe-Dimmer et al. 2012 [22]	Southeastern-Michigen / USA	North American	PB	Taqman SNP genotyping assays	*MTHFR*	rs1801133 rs1801131	219/273 218/272	0.9281 0.2114	0.9281 0.4228	8
Lin et al. 2004 [23]	USA	North American	HB	PCR–RFLP	*MTHFR*	rs1801133 rs1801131	410/410 410/409	0.0896 0.3506	0.3808 0.5259	8
Safarinejad et al. 2011 [24]	Iran	South Asian	HB	PCR–RFLP	*MTHFR*	rs1801133 rs1801131 rs2274976	158/316 158/316 158/316	0.555 0.4601 0.4276	0.7258 0.6052 0.8552	8
Moore et al. 2004 [25]	Argentina	South American	PB	NA	*MTHFR*	rs1801133 rs1801131	106/109 106/108	0.293 0.7708	0.6226 0.7708	7
Kimura et al. 2001 [26]	Germany	Western Europe	HB	NA	*MTHFR*	rs1801133	165/150	0.1695	0.5763	3
Chung et al. 2010 [27]	Taiwan	East Asian	HB	PCR–RFLP	*MTHFR*	rs1801133	150/300	0.2564	0.6226	8
Sanyal et al. 2004 [28]	Sweden	Northern Europe	PB	PCR–RFLP	*MTHFR*	rs1801133 rs1801131	309/246 311/245	0.8225 0.6005	0.9125 0.6551	7
Gautam et al. 2019 [29]	India	South Asian	NA	PCR-Sequencing	*MTHFR*	rs1801133 rs1801131	232/250 232/250	0.3982 0.1008	0.7084 0.4032	7
Wang et al. 2009 [30]	China	East Asian	HB	PCR–RFLP	*MTHFR*	rs1801133 rs1801131	239/250 239/250	0.0665 0.1869	0.3808 0.4228	9
Tsai et al. 2014 [31]	Taiwan	East Asian	NA	PCR–RFLP	*DNMT3A*	rs1550117	168/332	0.8426	0.8426	5
Moore et al. 2007 [32]	Spain	Southern Europe	HB	NA	*MTHFR*	rs1801133	1041/1049	0.4807	0.7258	9
Kherouatou-Chaoui et al. 2015[33]	Algeria	North African	NA	PCR–RFLP	*MTHFR*	rs1801133	95/109	0.0282	0.3808	5
Ali 2012 [34]	Pakistan	South Asian	PB	PCR–RFLP	*MTHFR*	rs1801133 rs1801131 rs2274976	200/200 200/200 200/200	0.8588 0.0113 0.9368	0.9125 0.1356 0.9368	10

PB population based, *HB* hospital based, *HWE* Hardy–Weinberg equilibrium; *Unadjusted HWE *p*-values; **Adjusted HWE *p*-values by FDR method. *NA* not available, *DNMT3A* DNA (cytosine-5)-methyltransferase 3 alpha, *DNMT3B* DNA (cytosine-5-)-methyltransferase 3 beta, *PCR–RFLP* polymerase chain reaction-restriction fragment length polymorphism, *MTHFR*: 5,10-méthylènetétrahydrofolate reductase, *SNP* single nucleotide polymorphism

Table 2 Meta-analysis of the association between polymorphisms of genes *MTHFR, DNMTs* and bladder cancer susceptibility

SNPs	Association test			Heterogeneity			Publication bias
Genetic models	**OR**	**95% CI**	***p*-value**	**Effect model**	***P*-value***	I^2	****Egger's test *p*-value**
***MTHFR* rs1801133**							
T *vs.* C[a]	1.021	[0.927–1.124]	0.666	REM	0.013	0.485	0.630
TT *vs.* TC + CC[b]	0.962	[0.802–1.154]	0.682	REM	0.093	0.328	0.936
TT + TC *vs.* CC[c]	1.057	[0.936–1.194]	0.366	REM	0.035	0.420	0.397
TT vs. CC[d]	0.988	[0.798–1.223]	0.914	REM	0.032	0.427	0.869
TT *vs.* TC[e]	0.949	[0.826–1.092]	0.470	FEM	0.203	0.215	0.825
TC *vs.* CC[f]	1.058	[0.966–1.158]	0.219	FEM	0.118	0.299	0.394
***MTHFR* rs1801131**							
C *vs.* A[a]	1.029	[0.870–1.215]	0.736	REM	0	0.741	0.787
CC *vs.* CA + AA[b]	0.889	[0.689–1.147]	0.368	REM	0.092	0.373	0.926
CC + CA *vs.* AA[c]	1.083	[0.867–1.354]	0.480	REM	0	0.745	0.867
CC *vs.* AA [d]	0.922	[0.637–1.334]	0.667	REM	8e−04	0.653	0.991
CC *vs.*CA [e]	0.845	[0.694–1.029]	0.094	FEM	0.557	0	0.594
CA *vs.* AA [f]	1.115	[0.902–1.380]	0.311	REM	2e−04	0.695	0.814
***MTHFR* rs2274976**							
A *vs.* G[a]	1.044	[0.714–1.528]	0.820	FEM	0.77	0	–
AA *vs.* AG + GG[b]	2.020	[0.365–11.157]	0.419	FEM	–	–	–
AA + AG *vs.* GG[c]	1.007	[0.671–1.512]	0.972	FEM	0.87	0	–
AA *vs.* GG[d]	2.012	[0.363–11.140]	0.423	FEM	–	–	–
AA *vs.* AG[e]	2.058	[0.353–11.988]	0.421	FEM	–	–	–
AG *vs.* GG[f]	0.971	[0.641–1.470]	0.889	FEM	0.97	0	–
DNMT3A rs1550117							
A *vs.* G[a]	0.804	[0.632–1.021]	0.074	FEM	0.712	0	–
AA *vs.* AG + GG[b]	0.720	[0.344–1.507]	0.384	FEM	0.773	0	–
AA + AG *vs.* GG[c]	0.780	[0.590–1.030]	0.080	FEM	0.744	0	–
AA *vs.* GG[d]	0.668	[0.317–1.407]	0.289	FEM	0.746	0	–
AA *vs.* AG[e]	0.842	[0.392–1.810]	0.660	FEM	0.826	0	–
AG *vs.* GG[f]	0.794	[0.595–1.059]	0.116	FEM	0.800	0	–
DNMT3B rs1569686							
G *vs.* T[a]	0.882	[0.614–1.267]	0.499	FEM	0.984	0	–
GG *vs.* GT + TT[b]	0.245	[0.030–1.971]	0.186	FEM	0.890	0	–
GG + GT *vs.* TT[c]	0.949	[0.649–1.390]	0.791	FEM	0.944	0	–
GG *vs.* TT [d]	0.246	[0.030–1.979]	0.187	FEM	0.893	0	–
GG *vs.* GT[e]	0.237	[0.028–1.958]	0.181	FEM	0.872	0	–
GT *vs.* TT [f]	1.026	[0.698–1.507]	0.896	FEM	0.875	0	–

REM random effect model, *FEM* fixed effect model

*REM if *p*-value < 0.1, FEM if otherwise

***p*-value > 0.05 indicate that there is no publication bias

[a] Allele contrast

[b] Recessive model

[c] Dominant model

[d] Homozygote model (homozygous rare vs. homozygous frequent allele)

[e] Homozygous rare vs. Heterozygous

[f] Heterozygote model (heterozygous vs. homozygous frequent allele)

significant associations were found except for rs1801133, which showed a significant association in the North African population [TT *vs.* TC + CC, TT *vs.* TC], and for rs1801131 in the North American population [CC *vs.* CA]. On the other hand, sensitivity analysis revealed

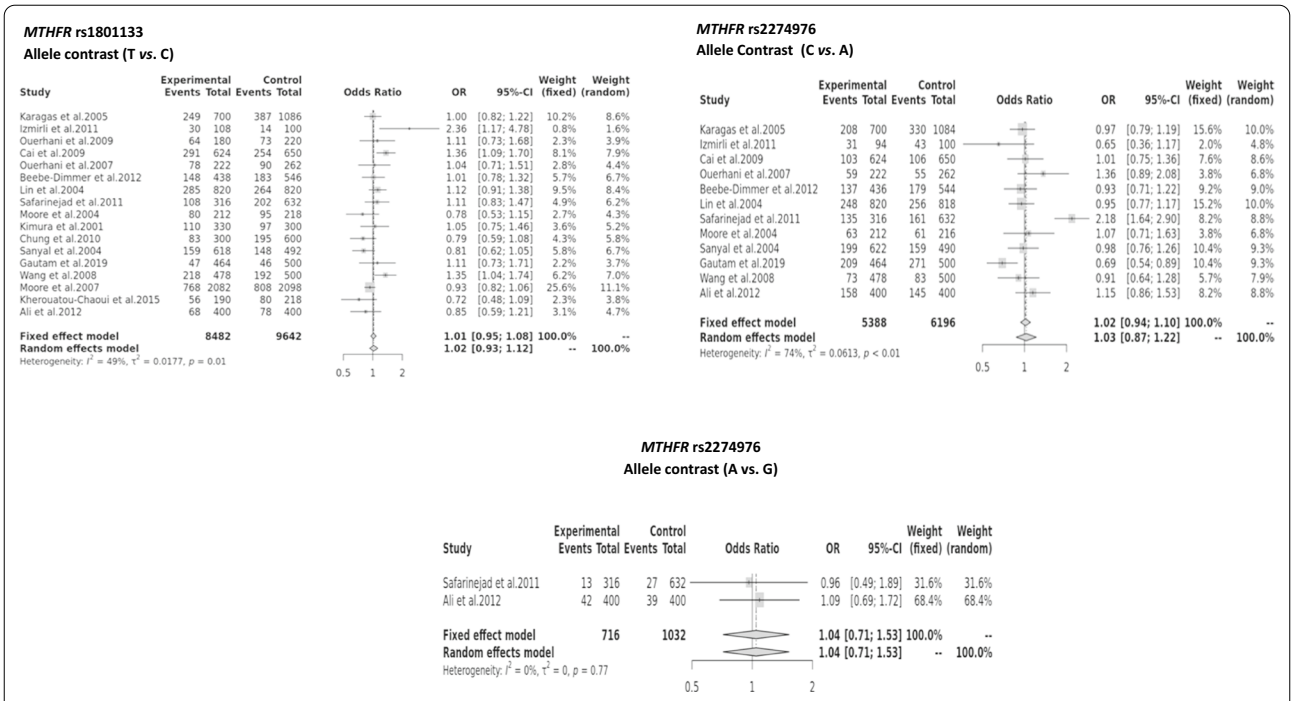

Fig. 2 Forest-plot for *MTHFR* polymorphisms under the allele contrast genetic model

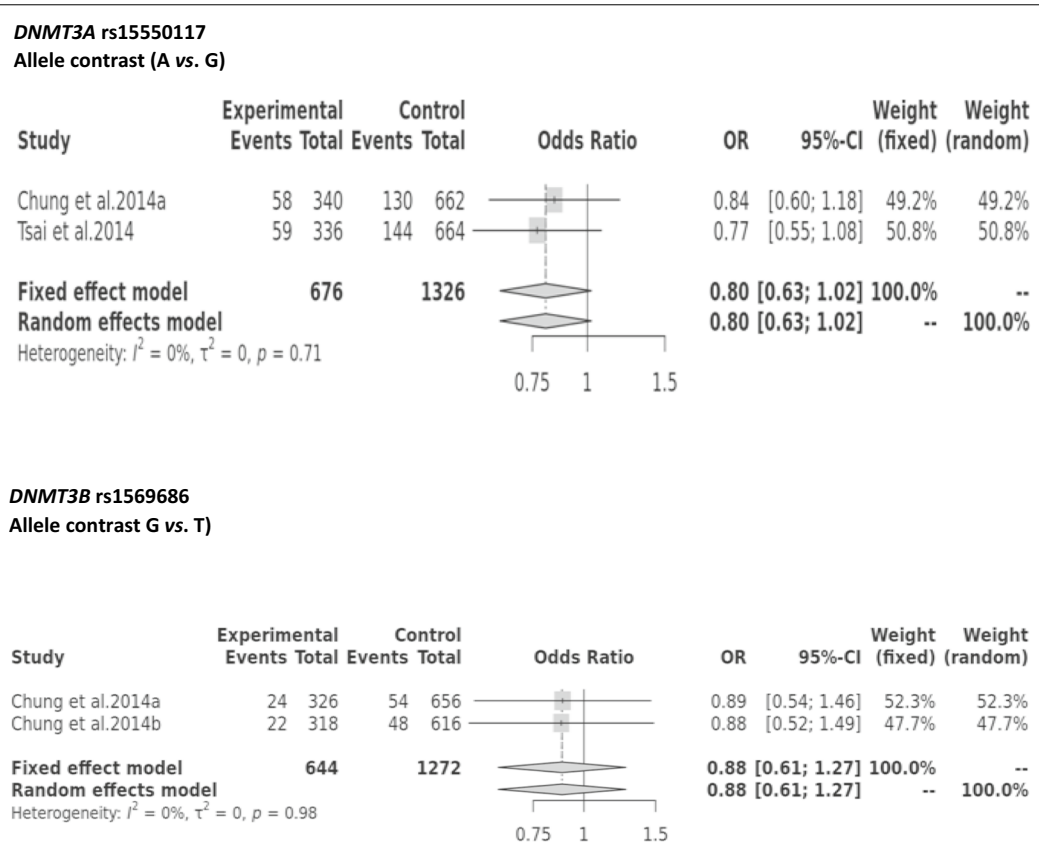

Fig. 3 Forest-plot for *DNMTs* polymorphisms under the allele contrast genetic model

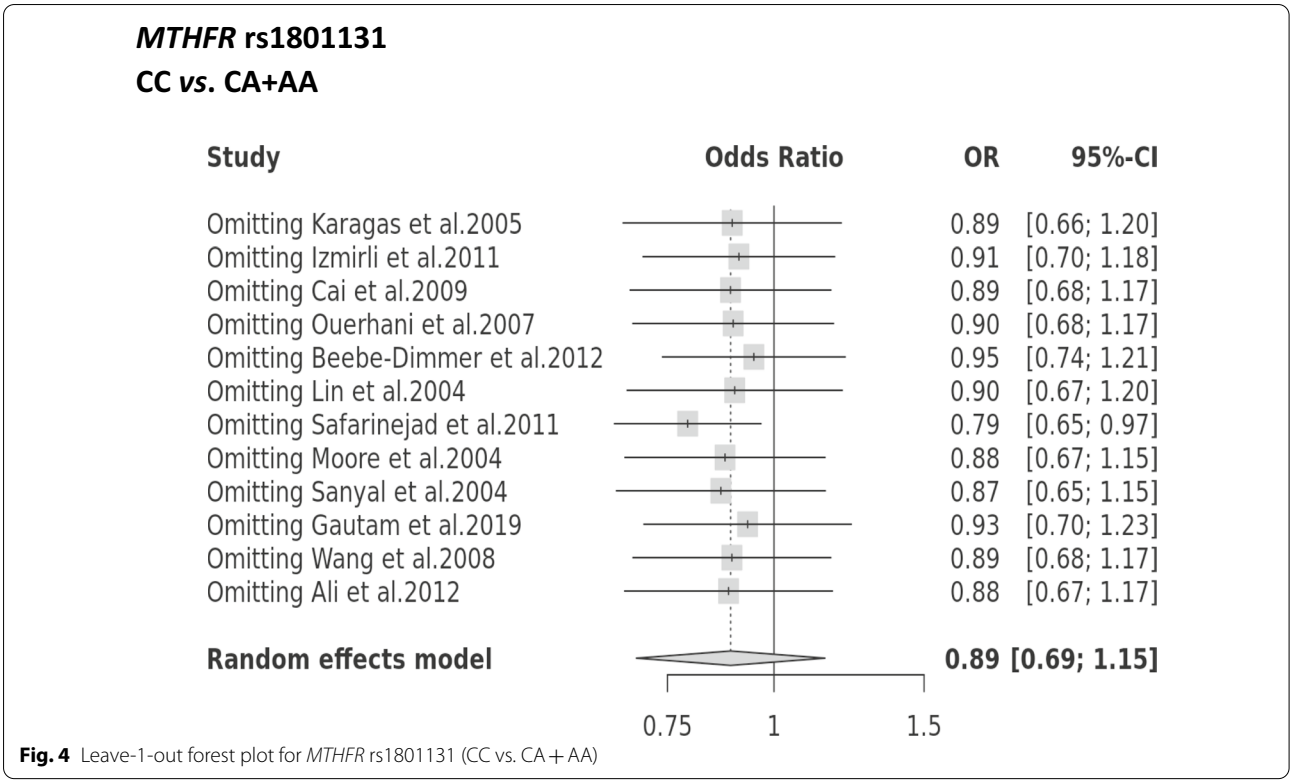

Fig. 4 Leave-1-out forest plot for *MTHFR* rs1801131 (CC vs. CA + AA)

Table 3 Subgroup analysis of MTHFR polymorphisms rs1801133 and rs1801131

SNPs	Genetic model	Group	Number of studies	Asso *P*-val	OR 95% CI
Rs1801133		*Geographic region*			
	T vs. C	Western Asia	1	0.016	2.36 [1.168–4.779]
	TT vs. TC + CC	**North African**	**3**	**0.013**	**0.52 [0.311–0.872]**
	TT + TC vs. CC	South America	1	0.046	0.56 [0.320–0.990]
		Western Asia	1	0.036	2.38 [1.055–5.400]
		South America	1	0.033	0.556 [0.323–0.956]
	TT vs. TC	**North African**	**3**	**0.003**	**0.448 [0.261–0.769]**
	TC vs. CC	South America	1	0.026	0.506 [0.277–0.923]
		Genotyping methods			
	TC vs. CC	**PCR–RFLP**	**12**	**0.040**	**1.12 [1.005–1.269]**
Rs1801131		*Geographic region:*			
	CC + CA vs. AA	North African	1	0.047	1.68 [1.006–2.832]
	CC vs. CA	**North American**	**3**	**0.039**	**0.71 [0.523–0.984]**
	CA vs. AA	North African	1	0.025	1.86 [1.079–3.210]
		Genotyping methods			
	C vs. A	PCR-Sequencing	1	0.004	0.69 [0.537–0.892]
	CC vs. CA + AA	Taqman SNP genotyping assays	1	0.027	0.48 [0.250–0.920]
	CC + CA vs. AA	PCR-Sequencing	1	0.003	0.53 [0.347–0.815]
	CC vs. AA	PCR-Sequencing	1	0.003	0.45 [0.269–0.777]
	CC vs. CA	Taqman SNP genotyping assays	1	0.011	0.419 [0.213–0.824]
	CA vs. AA	PCR-Sequencing	1	0.013	0.56 [0.364–0.890]

The bolds pointed to models that had statistically significant associations with BC

an association between rs1801131 and bladder cancer occurrence Fig. 4.

As for the PCR–RFLP genotyping method, it has been found to be the most widely used technique that has revealed an association between bladder cancer and rs1801133 [TC *vs.* CC]. However, this technique has some limitations, particularly in detecting heterozygotes, which is not the case for TaqMan real-time PCR and sequencing.

4.1 *MTHFR*

4.1.1 rs1801133

No significant association was found in the overall analysis of the association of rs1801133 polymorphism with susceptibility to BC development. This result is in agreement with Xu's research [36], and in discordance with other studies where it was found to be a risk factor for lung cancer [37], and esophageal cancer [38].

Subgroup analysis revealed a statistically significant association with a protective effect of SNP rs1801133 against bladder cancer in the North African population. This result correlates with the study of You et al. [39] and with a meta-analysis of Kennedy et al. for colorectal cancer [40]. Inconsistency in results could be explained in part by differences in allele distribution frequencies of the C677T SNP across ethnic groups.

Association studies between the *MTHFR* rs1801133 polymorphism and susceptibility to the development of BC have revealed conflicting results. A protective effect has been found in various studies, which may result from the spontaneous deamination of cytosine and 5-methylcytosine residues to uracil and thymine, respectively. If not repaired, spontaneous deamination results in G:C > A:T transitions. These kinds of alterations represent about 37% of the mutations affecting the TP53 tumor suppressor gene in BC [41]. Plus, several studies have shown that nearly half of MIBC (Muscle Invasive Bladder Cancer) samples had a mutation in TP53, with function inactivation in 76% of samples [42].

In the 1-carbon cycle, there is a balance in the use of 5,10-CH2-THF between methionine and purine synthesis. This balance depends on the presence of the thermolabile variant 677 T.

The enzyme activity of heterozygous and homozygous mutant individuals is at 67% and 25%, respectively, as compared to wild type CC [43].

Consequently, in the presence of an adequate amount of folate, the T allele preferentially diverts the content of the 1-carbon cycle to DNA synthesis at the expense of the methionine cycle.

At the same time, the rs1801133 variant can also lead to reduced availability of methyl groups for CpG methylation, which can lead to hypomethylated DNA [44], thus improving DNA stability, which suggests a new mechanism by which *MTHFR* variants may reduce cancer risk [45].

4.1.2 rs1801131

Generally, no statistically significant association was observed between the rs1801131 polymorphism and the risk of developing BC. These results are supported by the work of Shi et al. and Xu et al. [46], [47]. On the other hand, it is interesting to highlight that the subgroups' analysis related to geographic regions revealed a protective effect of the rs1801131 allele in the North American population. Similarly, a statistically significant association was found between rs1801131 and BC when the sensitivity analysis is applied to the Safarinejad et al. study, with OR = 0.79 [0.65–0.97] Fig. 4. These results may be due to the difference in the allelic and genotypic frequency distribution of A1298C polymorphism between different populations, such as the Italian population (CC = 8.2%, C = 29.6%) [48], the Korean population (CC = 1.80%, C = 16.3%) [49], and the Russian population (CC = 11%, C = 32%) [50].

The protective role of A1298C can be explained by the fact that the enzymatic activity of *MTHFR* under the homozygous stat 1298C variant is at 61% only [51]. At least, this does not lead to a thermolabile protein [52], as in the case of the 677 T variant. Thus, the 1298CC variant may improve the chances of genomic stability under a changed temperature via the DNA repair system due to a preferential orientation of the 1C cycle towards purine synthesis. Further studies are needed to confirm these findings.

4.1.3 rs2274976

The present quantitative analysis included only two studies, where no statistically significant association between rs2274976 and BC was found. This result is in agreement with You et al. bladder cancer meta-analysis [39], and in disagreement with Haghighi et al.'s works about colorectal cancer [53]. Further studies are needed to either confirm or reject these findings. Because the 1793G > A polymorphism of the *MTHFR* gene in exon 11 is a new site reported, nothing yet has been published about its implication in *MTHFR* activity [54].

4.2 *DNMT3A* rs1550117/*DNMT3B* rs1569686

According to our literature search, this meta-analysis is the first pilot study which discusses a possible association between *dnmt3a/b* SNPs (*DNMT3A* rs1550117/*DNMT3B* rs1569686) and BC occurrence.

There was no association between these two polymorphisms with the risk of bladder carcinogenesis. This result is in contrast to what has been reported on the *DNMT3A* rs1550117 variant, which showed a significantly increased risk of developing non-small cell lung cancer (NSCLC) in the Han Chinese population [55]. While Wang et al. found that the rs1550117 AG/AA genotype was significantly associated with an increased mortality rate compared with individuals carrying the GG genotype, suggesting that *DNMT3a* rs1550117 may be a relevant prognostic element for gastric cancer [56].

There was no statistically significant association between the rs1569686 variant of *DNMT3b* and the risk of bladder cancer, which is in agreement with what was found for gastric cancer. However, it was found that individuals with the TG/GG genotype were significantly associated with a poor prognosis of gastric cancer compared with those carrying the TT genotype [57].

4.3 Advantages and limits

To our knowledge, this is the first meta-analysis to examine the susceptibility of bladder cancer development based on DNMT3A/B gene polymorphisms. Our study's main strengths are its systematic focus on BC with the three main genes, DNMT3A/B and MTHFR, and the use of MetaGenyo, which provides a comprehensive, guided workflow, which facilitated the exclusion of methodological errors in the choice of statistical tests, leading to a lower error rate. Some limitations of our mata-analysis should be noted. First, the number of studies available for rs2274976, rs1550117, and rs1569686 is relatively small. Second, the articles found according to our selection were limited to the English language.

5 Conclusion

A total of 20 studies targeting five SNPs of three epigenetic effect genes, *DNMTs* and *MTHFR,* were identified. No statistically significant association was found between rs1801133, rs1801131, rs2274976, rs1550117, and rs1569686 with the occurrence of BC.

However, subgroup analysis allowed us to find a significant association in the North African and North American populations for SNPs rs1801133 and rs1801131, respectively, along with a protective effect of rs1801131 under sensitivity analysis. Further studies in different populations are needed to prove whether the SNPs selected in the present analysis have an ethnic or geographic-based impact on BC occurrence.

This meta-analysis is the first study to address the effect of *DNMTs* on BC occurrence. However, caution should be taken in interpreting these results because of the small number of studies included. Therefore, further studies are necessary in other populations in order to verify the possible involvement of these SNPs in bladder cancer carcinogenesis.

Appendix A

The search strategy conducted on PubMed included the following key elements:

1. ((Bladder) AND (cancer)) AND (*DNMT3A*)
2. ((Urothelial carcinoma) OR (Bladder cancer)) AND (*DNMT3A*)
3. (Urothelial carcinoma) AND (*DNMT3A*)
4. (Transitional cell carcinoma) AND (*DNMT3A* gene)
5. (Urothelial carcinoma) AND (*DNMT3A* polymorphism)
6. (Transitional cell carcinoma) AND (*DNMT3A* polymorphism)
7. (*DNMT3A* polymorphism) AND (Transitional cell carcinoma)
8. (Bladder cancer) AND (*DNMT3A* polymorphism)

Abbreviations

BC: Bladder cancer; DNA: Deoxyribonucleic acid; *DNMTs*: DNA methyltransferase; SNP: Single nucleotide polymorphism; Rs: Reference SNP cluster ID; HWE: Hardy–Weinberg equilibrium; *P*-Het: *P*-value of heterogeneity; OR: Odd ratio; PCR–RFLP: Polymerase chain reaction-restriction fragment length polymorphism; PB: Population based; HB: Hospital based; HWE: Hardy–Weinberg equilibrium; NA: Not available; *DNMT3A*: DNA (cytosine-5)-methyltransferase 3 alpha; *DNMT3B*: DNA (cytosine-5-)-methyltransferase 3 beta; *MTHFR*: 5,10-Methylenetetrahydrofolate reductase; REM: Random effect model; FEM: Fixed effect model; MIBC: Muscle Invasive Bladder Cancer.

Supplementary Information

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Additional file 1. Example of allele contrast and Egger's test (Table 2).

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Author contributions

Z-TC contributed to conceptualization, methodology, and software. R-K A contributed to methodology and writing—original draft preparation. K B: contributed to resources and writing—review & editing. D-N M contributed to supervision. All authors read and approved the final manuscript.

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Declarations

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Competing interests
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