Tumor Biol. (2014) 35:10723–10729
DOI 10.1007/s13277-014-2346-6

RESEARCH ARTICLE

NBS1 Glu185Gln polymorphism and susceptibility to urinary system cancer: a meta-analysis

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Received: 4 June 2014 / Accepted: 10 July 2014 / Published online: 30 July 2014

Abstract A number of studies have investigated the association between the *NBS1* Glu185Gln (rs1805794, 8360 G>C) polymorphism and risk for urinary system cancer including bladder cancer, prostate cancer, and renal cell cancer; however, the findings are conflicting. We conducted a meta-analysis focusing on eight published studies with 3,542 cases and 4,210 controls to derive a more precise evaluation of the relationship between the *NBS1* Glu185Gln polymorphism and urinary system cancer susceptibility. Overall, the *NBS1* Glu185Gln polymorphism was significantly related to increased risk for urinary system cancer (homozygous model: odds ratio (OR)=1.23, 95 % confidence interval (95 % CI)=1.05–1.44, p=0.011; heterozygous model: OR=1.14, 95 % CI=1.04–1.26, p=0.008; dominant model: OR=1.16, 95 % CI=1.05–1.27, p=0.002; and Gln vs. Glu: OR=1.12, 95 % CI=1.04–1.20, p=0.002) and further stratification analysis indicated an increased risk for bladder cancer (heterozygous model: OR=1.13, 95 % CI=1.02–1.26, p=0.022; dominant model: OR=1.14, 95 % CI=1.03–1.26, p=0.014; and Gln vs. Glu: OR=1.09, 95 % CI=1.01–1.18, p=0.023) and Caucasian populations (homozygous model: OR=1.33, 95 % CI=1.11–1.59, p=0.002; heterozygous model: OR=1.16, 95 % CI=1.04–1.30, p=0.009; dominant model: OR=1.19, 95 % CI=1.07–1.32, p=0.001; and Gln vs. Glu: OR=1.15, 95 % CI=1.06–1.25, p<0.001). Despite some limitations, this meta-analysis established some solid statistical evidence for the association between *NBS1* Glu185Gln polymorphism and increased risk for urinary system cancer, especially for bladder cancer, but more well-designed prospective studies are needed to further verify our findings.

Keywords *NBS1* · Glu185Gln · Urinary system cancer · Meta-analysis

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Background

Cancer is a kind of commonly encountered disease which severely threatens people's health and life. Based on the GLOBOCAN 2008, an estimated about 12.7 million new cancer cases and 7.6 million cancer-related deaths occurred in 2008 [1]. DNA damage may lead to increase the risk for cancer [2]. However, DNA damage would be caused by environmental factors including UV, ionizing radiation, cigarette smoke, and dietary factors and mostly by endogenous mutagens such as water, reactive oxygen species, and

chemical agents [2, 3]. DNA double-strand breaks (DSBs) are the most destructive form of DNA damage; if defectively repaired or unrepaired, it will cause genomic breakage and thus leading to carcinogenesis [4, 5], while these serious harms are counteracted by two different pathways in the repair of DSBs: homologous recombination and nonhomologous end-joining [6, 7]. The MRE-RAD50-NBS1 complex (MRN), as an initial step to recognize DSBs, plays an important role in the two DSBs repair pathways [8, 9]. Nijmegen breakage syndrome 1 (NBS1) is a component and the key regulator of MRN complex. If DSBs are generated, NBS1 promotes the assembly of MRN complex, activates its function to recognize the site of DSBs and finally, repairs the damage [10–12].

Human *NBS1* gene is mapped on chromosome 8q21and comprises about 50 kb encoding 754 amino acids protein [13, 14]. Studies in animal suggested that heterozygous *NBS1* knockout mice developed tumors affecting the liver, lung, prostate, lymphomas, and mammary gland [15, 16]. In addition, there is growing evidence that variants in the *NBS1* gene contribute to the increased risk of human cancer [17, 18]. There are at least 106 reported coding SNPs in the *NBS1* gene (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=4683). Among all these *NBS1* coding SNPs, Glu185Gln (rs1805794, 8360 G>C), which is the common polymorphism, has been investigated in relation to several types of cancer [18–23], including urinary system cancer such as bladder cancer [24–29], prostate cancer [30], and renal cell cancer [31]. However, the findings remain inconclusive. Hence, to provide an updated, more precise estimation of the association between *NBS1* Glu185Gln polymorphism and risk for urinary system cancer, a meta-analysis with all eligible case–control studies was conducted.

Material and methods

Identification and eligibility of relevant studies

We performed a comprehensive literature search in MEDLINE, EMBASE, and Chinese Biomedical (CBM) database using the following search terms: "NBS1 or NBN," "polymorphism or variant," and "cancer or tumor or carcinoma or neoplasm" (prior to February 28, 2014). No language restriction was imposed. Furthermore, additional studies were screened manually for all eligible original publications, review articles, and other relevant studies.

Inclusion criteria in this final analysis were as follows: (1) evaluating the association between the *NBS1* Glu185Gln polymorphism and urinary system cancer risk, (2) using a case–control design, (3) sufficient data for estimating odds ratio (OR) with their 95 % confidence interval (95 % CI), (4) no overlapping data or same subjects, and (5) genotype frequencies in the controls must be in Hardy–Weinberg equilibrium (HWE).

Data extraction

Data were extracted from all the publications independently by two investigators for compliance with the inclusion criteria mentioned above. For any disagreement, a final consensus was reached on all items after a discussion between the two investigators. The following data was collected from each study: first authors, year of publication, country of origin, ethnicity, cancer type, control source (hospital-based or population-based), and numbers of cases and controls with the *NBS1* Glu185Gln polymorphism.

Statistical analysis

The strength of the association between the *NBS1* Glu185Gln polymorphism and urinary system cancer risk was measured by crude ORs with their corresponding 95 % CIs. The pooled ORs were performed for homozygous model (CC vs. GG), heterozygous model (GC vs. GG), recessive model (CC vs. GC+GG), and dominant models (GC+CC vs. GG) as well as allele comparison (C vs. G). Heterogeneity was assessed by using chi-square-based Q test. A p value >0.10 for the Q test indicated a lack of heterogeneity among studies, so we chose the fixed-effects model (the Mantel–Haenszel method) [32]. Otherwise, the random-effects model (the DerSimonian and Laird method) was applied [33]. Additionally, the between-studies heterogeneity was also calculated with I^2 statistics; the higher score suggests the greater degree of heterogeneity [34]. Subgroup analyses were performed by cancer type, ethnicity, control source, and sample size (<500 and ≥500). A potential publication bias was verified by the funnel plot, in which the standard error of log (OR) for each investigation was plotted against its log (OR). We assessed the asymmetry of the funnel plot by Egger's linear regression test ($p<0.05$ indicated a significant publication bias) [35]. Statistical analysis was performed using STATA (version 11.0; Stata Corporation, College Station, TX). All p values were two-sided and $p<0.05$ was considered significant.

Results

Study characteristics

As shown in Fig. 1, a total of 131 articles were found using the literature search terms. Based on our inclusion criteria, only 10 studies were preliminarily identified after each abstracts and full texts were assessed. Among them, one was excluded for no case–control studies [36].

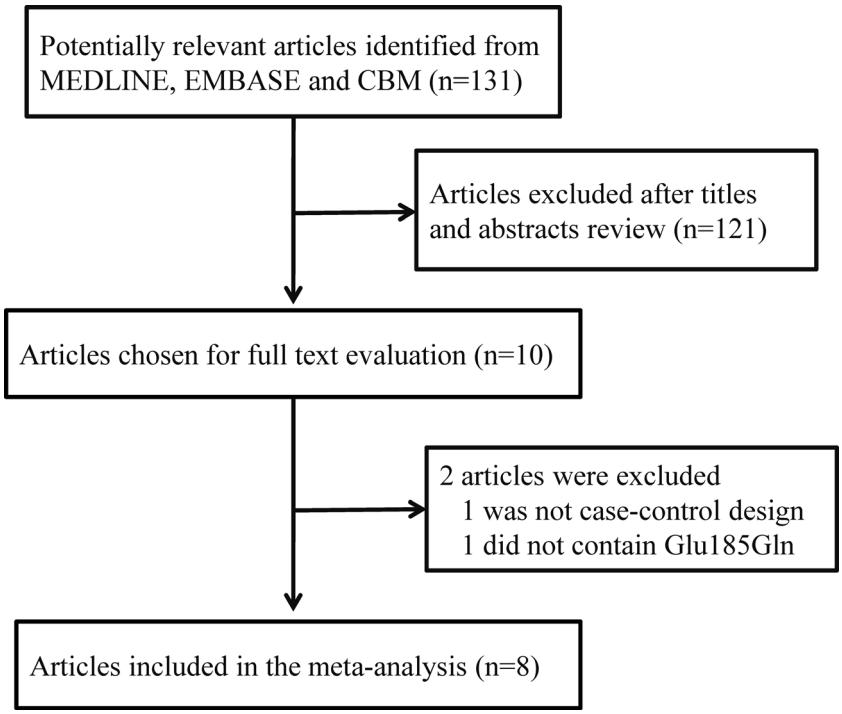

Fig. 1 Flow diagram of included studies

Another one did not contain the *NBS1* Glu185Gln polymorphism for further evaluation [17]. Finally, eight publications were included in this meta-analysis (Table 1).

There were six publications focusing on bladder cancer [24–29], one for prostate cancer [30] and one for renal cell cancer [31]. We combined these types of cancer into urinary system cancer. Overall, eight studies of 3,542 cases and 4,210 controls were included in this final meta-analysis evaluating the association between the *NBS1* Glu185Gln polymorphism and risk for urinary system cancer. There were seven studies on Caucasians and one study on mixed ethnicity. As for source of control, four were population-based, three were hospital-based, and one was mixed. Of all studies, five studies with sample size less than 500 and three studies with sample size no less than 500.

Meta-analysis results

As listed in Table 2 and Fig. 2, the overall data showed that there was a significant association between the *NBS1* Glu185Gln polymorphism and risk for urinary system cancer (homozygous model: OR=1.23, 95 % CI=1.05–1.44, p=0.011; heterozygous model: OR=1.14, 95 % CI=1.04–1.26, p=0.008; dominant model: OR=1.16, 95 % CI=1.05–1.27, p=0.002; and Gln vs. Glu: OR=1.12, 95 % CI=1.04–1.20, p=0.002). In the subgroup analysis by cancer type, a statistically significant increased risk was found for bladder cancer (heterozygous model: OR=1.13, 95 % CI=1.02–1.26, p=0.022; dominant model: OR=1.14, 95 % CI=1.03–1.26, p=0.014; and Gln vs. Glu: OR=1.09, 95 % CI=

Table 1 Characteristics of studies included in the meta-analysis

Surname	Year	Country	Ethnicity	Cancer type	Control source	No. of cases				No. of controls				MAF
						All	GG	GC	CC	All	GG	GC	CC	
Sanyal	2004	Sweden	Caucasian	Bladder	HB	299	114	140	45	278	116	134	28	0.34
Broberg	2005	Sweden	Caucasian	Bladder	PB	61	21	36	4	154	63	67	24	0.37
Wu	2006	USA	Caucasian	Bladder	HB	604	254	283	67	595	282	259	54	0.31
Hebbring	2006	Finland	Caucasian	Prostate	PB	321	112	157	52	200	89	79	32	0.36
Matullo	2006	Italy	Caucasian	Bladder	PB	101	43	47	11	842	404	350	88	0.31
Figueroa	2007	Spain	Caucasian	Bladder	HB	1,086	516	449	121	1,020	511	407	102	0.30
Choudhury	2008	UK	Mixed	Bladder	HB/PB	748	347	332	69	788	375	330	83	0.31
Margulis	2008	USA	Caucasian	Renal cell	PB	322	137	142	43	333	152	160	21	0.30

HB hospital-based, *PB* population-based, *MAF* minor allele frequency

Table 2 Meta-analysis of the association between Glu185Gln polymorphism and urinary system cancer

Variables	*N*	Homozygous			Heterozygous			Recessive			Dominant			Allele		
		CC vs. GG			GC vs. GG			CC vs. (GC+GG)			(GC+CC) vs. GG			C vs. G		
		OR (95 % CI)	P^{het}	I^2 (%)	OR (95 % CI)	P^{het}	I^2 (%)	OR (95 % CI)	P^{het}	I^2 (%)	OR (95 % CI)	P^{het}	I^2 (%)	OR (95 % CI)	P^{het}	I^2 (%)
All	8 (3,542/4,210)	*1.23 (1.05–1.44)*	0.125	38.2	*1.14(1.04–1.26)*	0.581	0.0	1.16(0.91–1.47)	0.038	52.9	*1.16(1.05–1.27)*	0.806	0.0	*1.12(1.04–1.20)*	0.637	0.0
Cancer type																
Bladder	6 (2,899/3,677)	1.15 (0.97–1.37)	0.276	20.9	*1.13(1.02–1.26)*	0.829	0.0	1.08(0.86–1.36)	0.154	37.8	*1.14(1.03–1.26)*	0.891	0.0	*1.09(1.01–1.18)*	0.652	0.0
Prostate	1 (321/200)	1.29 (0.77–2.17)	–	–	*1.58(1.07–2.33)*	–	–	1.02(0.63–1.64)	–	–	*1.50(1.04–2.15)*	–	–	1.23(0.95–1.59)	–	–
Renal cell	1 (322/333)	*2.27 (1.28–4.02)*	–	–	0.99(0.71–1.36)	–	–	*2.29(1.33–3.95)*	–	–	1.13(0.83–1.54)	–	–	*1.26(1.00–1.59)*	–	–
Ethnicity																
Caucasian	7 (2,794/3,422)	*1.33(1.11–1.59)*	0.276	20.1	*1.16(1.04–1.30)*	0.497	0.0	1.23(0.95–1.59)	0.074	47.8	*1.19(1.07–1.32)*	0.858	0.0	*1.15(1.06–1.25)*	0.871	0.0
Mixed	1 (748/788)	0.90(0.63–1.28)	–	–	1.09(0.88–1.34)	–	–	0.86(0.62–1.21)	–	–	1.05(0.86–1.28)	–	–	1.00(0.86–1.16)	–	–
Control source																
HB	3 (1,989/1,893)	*1.30(1.05–1.61)*	0.536	0.0	1.12(0.98–1.29)	0.747	0.0	*1.23(1.00–1.51)*	0.513	0.0	*1.16(1.02–1.31)*	0.740	0.0	*1.14(1.03–1.25)*	0.672	0.0
PB	4 (805/1529)	*1.40(1.02–1.93)*	0.108	50.7	*1.25(1.02–1.53)*	0.251	26.8	1.10(0.60–1.99)	0.017	70.5	*1.27(1.05–1.54)*	0.722	0.0	*1.19(1.03–1.37)*	0.701	0.0
HB/PB	1 (748/788)	0.90(0.63–1.28)	–	–	1.09 (0.88–1.34)	–	–	0.86(0.62–1.21)	–	–	1.05(0.86–1.28)	–	–	1.00(0.86–1.16)	–	–
Sample size																
<500	5 (1,104/1,807)	*1.46(1.11–1.92)*	0.178	36.4	*1.20(1.00–1.43)*	0.320	14.8	1.22(0.78–1.91)	0.028	63.4	*1.24(1.05–1.47)*	0.819	0.0	*1.19(1.06–1.35)*	0.839	0.0
≥500	3 (2,438/2,403)	1.12(0.93–1.37)	0.264	24.9	1.12(0.99–1.26)	0.749	0.0	1.07(0.87–1.31)	0.308	15.1	*1.12(1.00–1.25)*	0.548	0.0	1.08(0.99–1.18)	0.342	6.7

HB hospital-based, *PB* population-based

Statistically significant associations are shown in italics

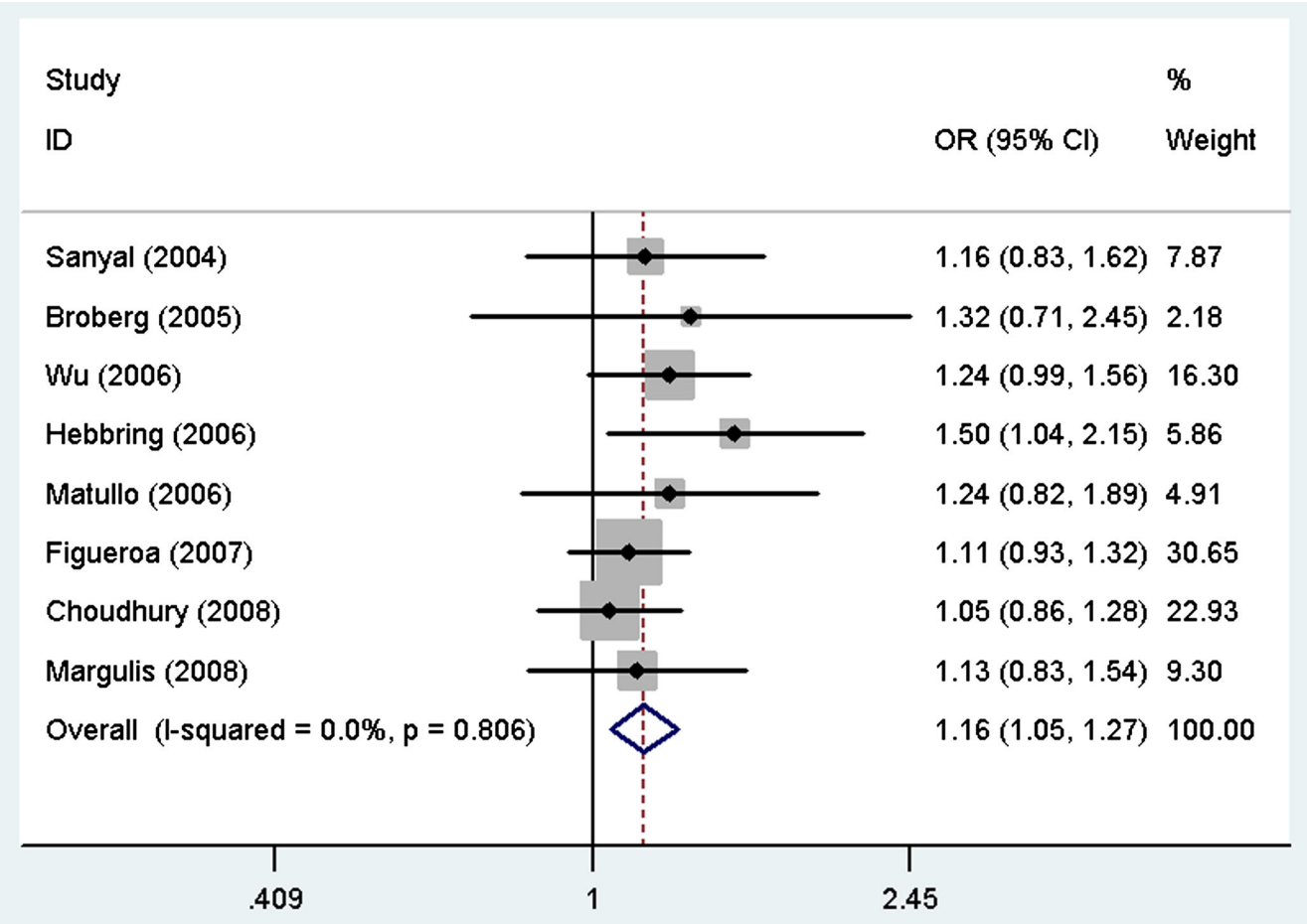

Fig. 2 Forest plot for urinary system cancer risk associated with the NBS1 Glu185Gln polymorphism by dominant model. For each study, the estimates of OR and its 95 % CI are plotted with a *box* and a *horizontal line. White diamond* pooled ORs and its 95 % CIs

1.01–1.18, p=0.023), Caucasian (homozygous model: OR=1.33, 95 % CI=1.11–1.59, p=0.002; heterozygous model: OR=1.16, 95 % CI=1.04–1.30, p=0.009; dominant model: OR=1.19, 95 % CI=1.07–1.32, p=0.001; and Gln vs. Glu: OR=1.15, 95 % CI=1.06–1.25, p<0.001), hospital-based studies (homozygous model: OR=1.30, 95 % CI=1.05–1.61, p=0.017; recessive model: OR=1.23, 95 % CI=1.00–1.51, p=0.048; dominant model: OR=1.16, 95 % CI=1.02–1.31, p=0.025; and Gln vs. Glu: OR=1.14, 95 % CI=1.03–1.25, p=0.009), population-based studies (homozygous model: OR=1.40, 95 % CI=1.02–1.93, p=0.035; heterozygous model: OR=1.25, 95 % CI=1.02–1.53, p=0.034; dominant model: OR=1.27, 95 % CI=1.05–1.54, p=0.015; and Gln vs. Glu: OR=1.19, 95 % CI=1.03–1.37, p=0.017), studies with sample size less than 500 (homozygous model: OR=1.46, 95 % CI=1.11–1.92, p=0.006; heterozygous model: OR=1.20, 95 % CI=1.00–1.43, p=0.045; dominant model: OR=1.24, 95 % CI=1.05–1.47, p=0.011; and Gln vs. Glu: OR=1.19, 95 % CI=1.06–1.35, p=0.005), and with no less than 500 (dominant model: OR=1.12, 95 % CI=1.00–1.25, p=0.049).

Heterogeneity and sensitivity analyses

There was no significant between-study heterogeneity evaluating the association between the *NBS1* Glu185Gln polymorphism and risk for urinary system cancer in homozygous model (p=0.125), heterozygous model (p=0.581), dominant model (p=0.806), and allele comparing (p=0.637), except for recessive model (p=0.038). The leave-one-out sensitivity analysis indicated that no single investigation had changed the pooled ORs qualitatively.

Publication bias

Begg's funnel plots and Egger's test were used to assess the publication bias of literatures. The shapes of the funnel plots did not reveal any obvious asymmetry. The Egger's test suggested no significant publication bias (p=0.859 for homozygous model, p=0.141 for heterozygous model, p=0.909 for recessive model, p=0.102 for dominant model, and p=0.515 for allele comparing). These results indicated that the publication bias is unlikely to affect the finding of the meta-analysis.

Discussion

Human *NBS1* gene is mapped on chromosome 8q21and comprises about 50 kb encoding 754 amino acids protein [13, 14]. NBS1 is a component and the key regulator of MRE-RAD50-NBS1 complex (MRN) which recognize the sites of double-strand breaks (DSBs) and repair them [8, 9]. Mutation and variants in the *NBS1* gene have been reported to contribute the increased risk of urinary system cancer. However, the findings remain inconclusive. Hence, an updated meta-analysis of all eligible case–control studies was conducted.

In the current meta-analysis, eight eligible case–control studies with 3,542 cases and 4,210 controls were selected to evaluate the association between the *NBS1* Glu185Gln polymorphism and urinary system cancer risk. We found that Glu185Gln polymorphism was significantly related to increased risk for urinary system cancer in the homozygous, heterozygous, dominant, and allele comparing models. From further stratification analysis, the association was also identified in bladder cancer risk and Caucasian ethnicity.

To the best of our knowledge, there is no meta-analysis that has assessed the relationship between the *NBS1* Glu185Gln polymorphism and urinary system cancer risk. In a reported meta-analysis, He et al. [37] focused on testing the association between the *NBS1* Glu185Gln polymorphism and all kinds of cancer risk. The results of their meta-analysis showed no significant association between the *NBS1* Glu185Gln polymorphism and overall cancer risk. Interestingly, after pooling data sets into urinary system cancer, significant association between the *NBS1* Glu185Gln polymorphism and increased risk for urinary system cancer was observed (seven studies). However, as for bladder cancer, the authors found that there was no significant association between the *NBS1* Glu185Gln polymorphism and bladder cancer (four studies). Similarly, no significant association was also observed in another meta-analysis (three studies) [38]. He et al. put one study as two based on unselected and familial prostate cancer. Our update meta-analysis included all of these studies in the previous two studies. We further confirmed that the *NBS1* Glu185Gln polymorphism increase the risk of urinary system cancer. Notably, we found that the *NBS1* Glu185Gln polymorphism was associated with bladder cancer risk. Therefore, there is some new insight to understand the mechanisms of the development of urinary system cancer, especially for bladder cancer. In addition, sample sizes should be enlarged to further investigate the role of this polymorphism.

For Caucasians, we also found a significant association between the *NBS1* Glu185Gln polymorphism and Caucasians. However, most of the reported case–control studies focused on Caucasian populations. Non-Caucasians populations, due to fewer studies, were not involved in this meta-analysis. This single Caucasians ethnicity can lead to one-sidedness of the overall results. In the future studies, more ethnicity populations should be collected to make sure of this association.

Several limitations in the current meta-analysis should be acknowledged. First, the number of reported publications was not sufficiently large for a comprehensive investigation, especially for the subgroup analysis of prostate cancer and renal cell cancer, which may have attenuated the statistical power. Second, there is lacking of original data to adjust estimates of ORs among gene–gene and gene–environment. For example, individual's age, sex, and smoking and drinking status do have effect on the role of the *NBS1* Glu185Gln polymorphism. Third, most of the studies were conducted in Caucasians. In order to elucidate whether the ethnicity can modify the role of Glu185Gln polymorphism, non-Caucasian populations should be engaged to investigate.

Fourthly, we just selected the literatures from MEDLINE, EMBASE, and Chinese Biomedical (CBM), which may miss other relevant articles. In conclusion, this meta-analysis suggested that the *NBS1* Glu185Gln polymorphism was associated with increased risk of urinary system cancer. Moreover, this polymorphism appealed to contribute to the increased risk of bladder cancer and Caucasian populations. Nevertheless, more well-designed prospective studies are needed to further verify our findings.

Conflict of interest None

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