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RESEARCH ARTICLE

Association between NQO1 C609T polymorphism and bladder cancer susceptibility: a systemic review and meta-analysis

Min Gong · Qingtong Yi · Weiming Wang

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Abstract There is growing evidence for the important roles of genetic factors in the host's susceptibility to bladder cancer. NAD(P)H:quinone oxidoreductase 1 (NQO1) is a cytosolic enzyme that catalyzes the two-electron reduction of quinoid compounds into hydroquinones. Since the NQO1 C609T polymorphism is linked to enzymatic activity of NQO1, it has also been hypothesized that NQO1 C609T polymorphism may affect the host's susceptibility to bladder cancer by modifying the exposure to carcinogens. There were many studies carried out to assess the association between NQO1 C609T polymorphism and bladder cancer risk, but they reported contradictory results. We conducted a meta-analysis to examine the hypotheses that the NQO1 C609T polymorphism modifies the risk of bladder cancer. Eleven case–control studies with 2,937 bladder cancer cases and 3,008 controls were included in the meta-analysis. Overall, there was no obvious association between NQO1 C609T polymorphism and bladder cancer susceptibility (for T versus C: odds ratio (OR) = 1.12, 95 % confidence interval (95 %CI) 0.99–1.26, P_{OR} = 0.069; for TT versus CC: OR = 1.31, 95 %CI 0.95–1.81, P_{OR} = 0.100; for TT/CT versus CC: OR = 1.06, 95 %CI 0.95–1.18, P_{OR} = 0.304; for TT versus CT/CC: OR = 1.29, 95 %CI 0.94–1.77, P_{OR} = 0.112). After adjusting for heterogeneity, meta-analysis of those left 10 studies showed that there was an obvious association between NQO1 C609T polymorphism and bladder cancer susceptibility (for T versus C: OR = 1.18, 95 %CI 1.06–1.31, P_{OR} = 0.003; for TT versus CC: OR = 1.47, 95 %CI 1.14–1.90, P_{OR} = 0.003; for TT/CT versus CC: OR = 1.16, 95 %CI 1.01–1.34, P_{OR} = 0.036; for TT versus CT/CC: OR = 1.39, 95 %CI 1.10–1.75, P_{OR} = 0.006). There was low risk of publication bias. Therefore, our meta-analysis suggests that NQO1 C609T polymorphism is associated with bladder cancer susceptibility.

Keywords NQO1 · Polymorphism · Bladder cancer · Meta-analysis

M. Gong · Q. Yi (✉)
Department of Urology, Shanghai Pudong Hospital, Fudan University Pudong Medical Center, 2800 Gongwei Road, Huinan Town,
Shanghai 201399, China
e-mail: tongqingshangh@126.com

W. Wang
Department of Urology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China

Introduction

Bladder cancer is one of the most common malignant diseases around the world [1, 2]. Previous studies have suggested that bladder cancer results from many exogenous and endogenous factors, such as cigarette smoking and occupational exposures to chemicals [2]. Though there have been increasingly intensive researches on bladder cancer over the past two decades, there are little considerable advances in the understanding of the pathogenesis of bladder cancer [2, 3]. There is growing evidence for the important roles of genetic factors in the host's susceptibility to bladder cancer [4, 5]. NAD(P)H:quinine oxidoreductase 1 (NQO1) is a cytosolic flavoenzyme that catalyzes the two-electron reduction of quinoid compounds into hydroquinones, and it has been described as an anticancer enzyme [6, 7]. The NQO1 gene is located on chromosome 16q22, and there are many single-nucleotide polymorphisms discovered in this gene [8, 9]. NQO1 C609T (dbSNP ID: rs1800566) polymorphism is a nonsynonymous single-nucleotide polymorphism at nucleotide position 609 [8]. NQO1 C609T polymorphism is a C-to-T transition and results in a proline to serine amino acid substitution at codon

187 in the protein [8]. The variant allele of NQO1 C609T polymorphism can result in reduced enzymatic activity [10]. Compared with the wild type (CC) of NQO1 C609T polymorphism, the homozygous variant (TT) has only 2 to 4 % of the quinone reductase activity [10, 11]. Since the NQO1 C609T polymorphism is linked to enzymatic activity of NQO1, it has also been hypothesized that NQO1 C609T polymorphism may affect the host's susceptibility to bladder cancer by modifying the exposure to carcinogens [6–8]. There were many studies carried out to assess the association between NQO1 C609T polymorphism and bladder cancer risk, but they reported contradictory results [12–22]. In this study, we conducted a meta-analysis to examine the hypotheses that the NQO1 C609T polymorphism modifies the risk of bladder cancer.

Methods

Publication search

We searched all published studies investigating the association between the NQO1 C609T polymorphism and bladder cancer risk in the PubMed and Wanfang databases. A literature search was conducted using the following search terms: ("NAD(P)H:quinine oxidoreductase 1," "NQO1," or "rs1800566") and ("bladder cancer" or "bladder carcinoma"). Review articles and reference cited in the searched studies were examined to identify additional published articles. Studies included in the meta-analysis were required to meet the following criteria: (1) case–control design with the genotyping of individuals with and without bladder cancer, (2) identification of bladder cancer was confirmed histologically or pathologically, (3) sufficient reported genotypic frequencies in both cases and controls for estimating an odds ratio (OR) with a 95 % confidence interval (95 %CI), and (4) the genotype distribution among the controls was consistent with the Hardy–Weinberg equilibrium (HWE). For studies with overlapping data published by same authors, only the most recent or complete study was included. Conference abstracts, case reports, editorials, review articles, and letters were excluded.

Data extraction

Two separate investigators reviewed and extracted the data from all of the eligible publications independently. The following information was extracted from each study: first author, year of publication, country of study population, genotyping method, genotype frequency, and HWE in the controls. Ethnic backgrounds were categorized as Caucasians, Asians, or others.

Statistical analysis

We evaluated the association between NQO1 C609T polymorphism and bladder cancer risk under the allele contrast model (T versus C), the homozygote model (TT versus CC), the recessive model (TT versus CT/CC), and the dominant model (TT/CT versus CC). HWE was tested using the chi-squared test, and it was considered statistically significant when $P<0.05$. The heterogeneity of these studies was tested by the Q statistic and was considered statistically significant when $P<0.10$ [23]. The pooled OR was estimated using the fixed-effects model when there was less heterogeneity among those studies [24] or random-effects model when there was obvious heterogeneity among those studies [25]. The statistical significance of the overall OR was determined using a Z test, and $P<0.05$ was considered statistically significant. Galbraith plot was also used to spot the outliers as the possible major sources of heterogeneity [26]. Publication bias was assessed by a funnel plot using both funnel plots and Egger's linear regression test [27]. Meta-analysis was performed using Stata version 11.0 (StataCorp LP, College Station, TX).

Results

Characteristics of included studies

Eleven case–control studies with 2,937 bladder cancer cases and 3,008 controls were included in the meta-analysis [12–22]. Among those 11 studies, eight studies were performed in the Caucasian populations [13–18, 20, 22], and the remaining three studies were performed in Asian populations [12, 19, 21]. Most of those 11 studies were hospital-based studies, and all 11 studies were consistent with HWE in the controls. The number of cases varied from 61 to 1,128 (mean 267), and the number of controls varied from 100 to 1,123 (mean 273) [12–22].

Meta-analysis

Table 1 shows the main results in this meta-analysis. Overall, there was no obvious association between NQO1 C609T polymorphism and bladder cancer susceptibility (for T versus C: OR = 1.12, 95 %CI 0.99–1.26, $P_{OR} = 0.069$; for TT versus CC: OR = 1.31, 95 %CI 0.95–1.81, $P_{OR} = 0.100$; for TT/CT versus CC: OR = 1.06, 95 %CI 0.95–1.18, $P_{OR} = 0.304$; for TT versus CT/CC: OR = 1.29, 95 %CI 0.94–1.77, $P_{OR} = 0.112$) (Table 1, Fig. 1). Subgroup analysis by ethnicity suggested that there was no association between NQO1 C609T polymorphism and bladder cancer susceptibility in Caucasians, but there was an obvious association

Table 1 Results in the meta-analysis of the association between NQO1 C609T polymorphism and bladder cancer susceptibility

Contrast model	Studies	OR (95 %CI)	P_{OR}	P_H
Total studies				
T versus C	11	1.12 (0.99–1.26)	0.069	0.099
TT versus CC	11	1.31 (0.95–1.81)	0.100	0.052
TT+CT versus CC	11	1.06 (0.95–1.18)	0.304	0.124
TT versus CT+CC	11	1.29 (0.94–1.77)	0.112	0.038
Adjusting for heterogeneity				
T versus C	10	1.18 (1.06–1.31)	0.003	0.467
TT versus CC	10	1.47 (1.14–1.90)	0.003	0.249
TT+CT versus CC	10	1.16 (1.01–1.34)	0.036	0.269
TT versus CT+CC	10	1.39 (1.10–1.75)	0.006	0.133
Caucasians				
T versus C	8	1.02 (0.93–1.13)	0.656	0.271
TT versus CC	8	0.99 (0.75–1.30)	0.932	0.122
TT+CT versus CC	8	1.04 (0.92–1.17)	0.545	0.382
TT versus CT+CC	8	0.98 (0.75–1.28)	0.869	0.117
Asians				
T versus C	3	1.22 (1.04–1.44)	0.018	0.129
TT versus CC	3	1.66 (1.19–2.33)	0.003	0.519
TT+CT versus CC	3	1.14 (0.70–1.87)	0.601	0.027
TT versus CT+CC	3	1.51 (1.13–2.01)	0.005	0.205

OR odds ratio, *95%CI* 95 % confidence interval, P_{OR} *P* value of OR, P_H *P* value of heterogeneity

between NQO1 C609T polymorphism and bladder cancer susceptibility in Asians (Table 1).

The heterogeneity results in the meta-analysis were also shown in Table 1. There was obvious heterogeneity under all comparison models of this meta-analysis, and all *P* values were less than 0.10 (Table 1). Galbraith plot in the meta-analysis under the homozygote model showed that Figueroa's study was the outlier and may be the possible major source of heterogeneity in this meta-analysis (Fig. 2). After omitting Figueroa's study, there was no heterogeneity under all comparison models of this meta-analysis (Table 1).

After omitting Figueroa's study, meta-analysis of those remaining 10 studies showed that there was an obvious association between NQO1 C609T polymorphism and bladder cancer susceptibility (for T versus C: OR = 1.18, 95 %CI 1.06–1.31, P_{OR} = 0.003; for TT versus CC: OR = 1.47, 95 %CI 1.14–1.90, P_{OR} = 0.003; for TT/CT versus CC: OR = 1.16, 95 %CI 1.01–1.34, P_{OR} = 0.036; for TT versus CT/CC: OR = 1.39, 95 %CI 1.10–1.75, P_{OR} = 0.006) (Table 1, Fig. 3).

Publication bias

Funnel plots and Egger's test were performed to estimate the risk of publication bias in this meta-analysis. It is difficult for us to assess the asymmetry of the funnel plot under the allele contrast model (Fig. 4). However, the *P* value of Egger's test was 0.092 and was more than 0.05, which provided statistical evidence for the symmetry of the funnel plot. Thus, the results above suggested that there was a low risk of publication bias.

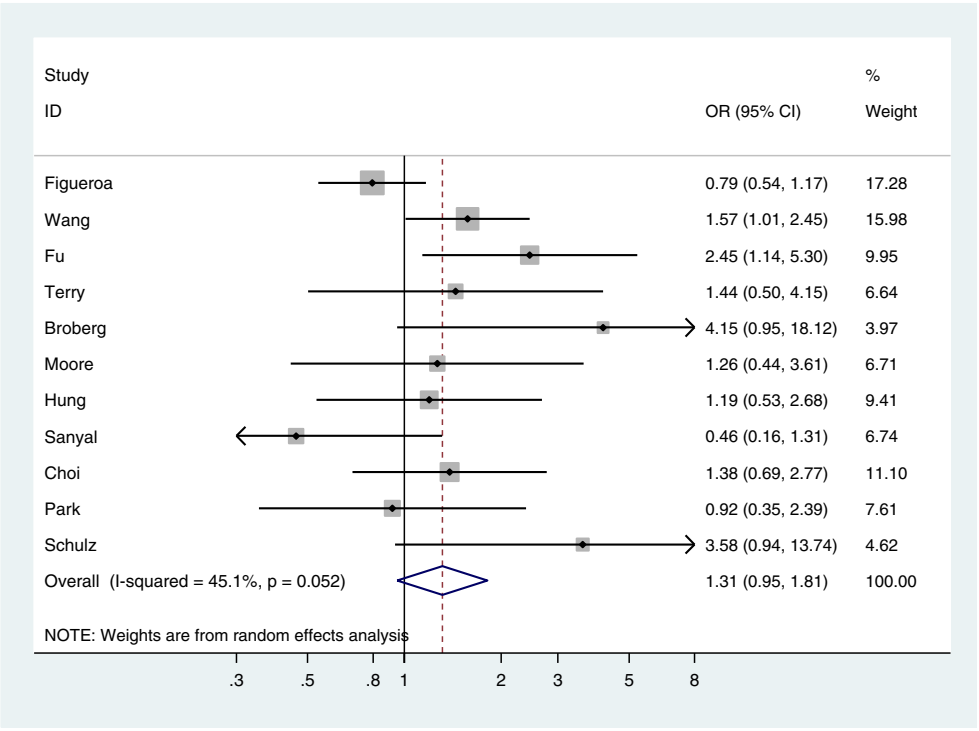

Fig. 1 Meta-analysis of the association between NQO1 C609T polymorphism and bladder cancer susceptibility under the homozygote model (random-effects model)

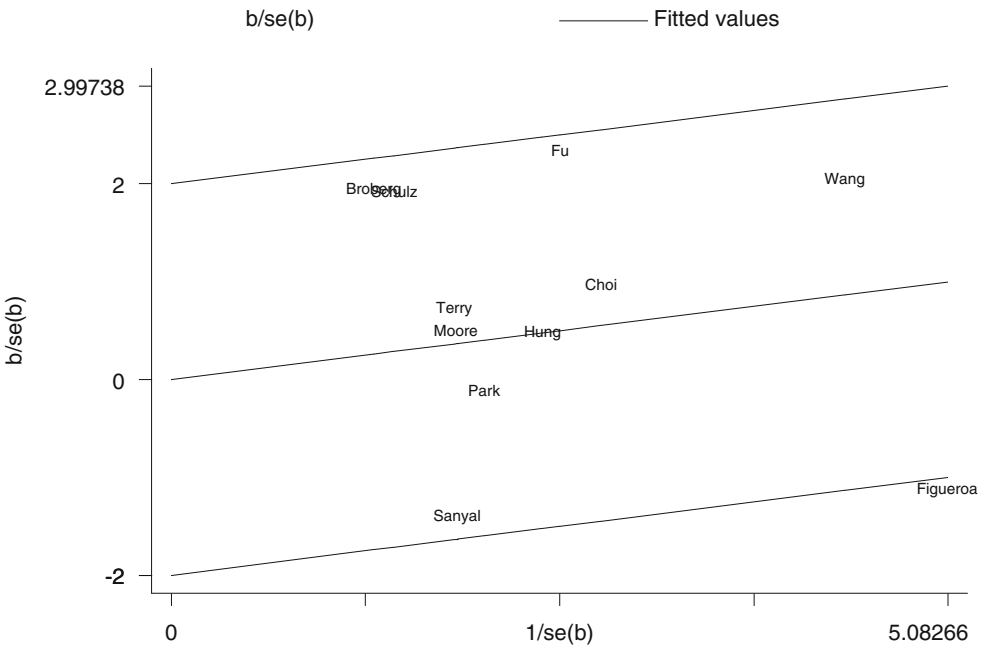

Fig. 2 Galbraith plot in the meta-analysis of the association between NQO1 C609T polymorphism and bladder cancer susceptibility under the homozygote model (each name represented a different study included into meta-analysis)

Discussion

There is growing evidence for the important roles of genetic factors in the host's susceptibility to bladder cancer [3, 5, 28]. NQO1 is a cytosolic enzyme that catalyzes the two-electron reduction of quinoid compounds into hydroquinones [12, 19]. Since the NQO1 C609T polymorphism is linked to enzymatic activity of NQO1, it has also been hypothesized that NQO1 C609T polymorphism may affect the host's susceptibility to bladder cancer by modifying the exposure to carcinogens. Since the original identification of the NQO1 C609T polymorphism, a number of studies have been published to assess the genetic effect of this polymorphism on susceptibility to bladder cancer, but they reported contradictory results [12–22]. Considering these inconsistent findings, we performed a meta-analysis on those published studies to quantify those data and generate a robust estimate of the effect of the association between NQO1 C609T polymorphism and susceptibility to bladder cancer.

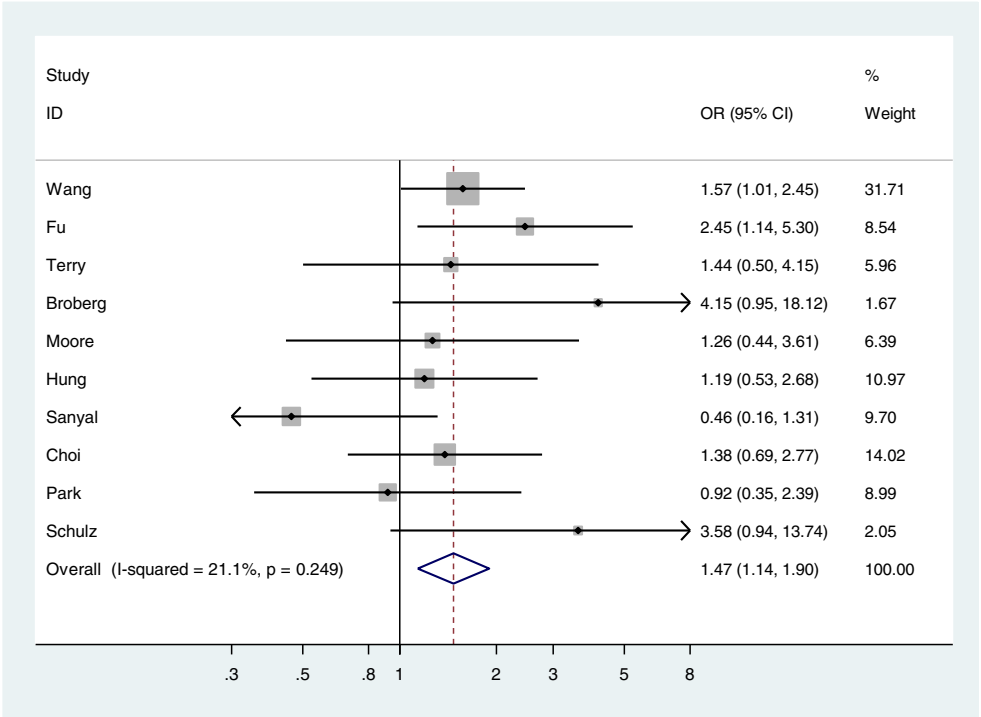

Fig. 3 Meta-analysis of the association between NQO1 C609T polymorphism and bladder cancer susceptibility under the homozygote model after adjusting for heterogeneity (fixed-effects model)

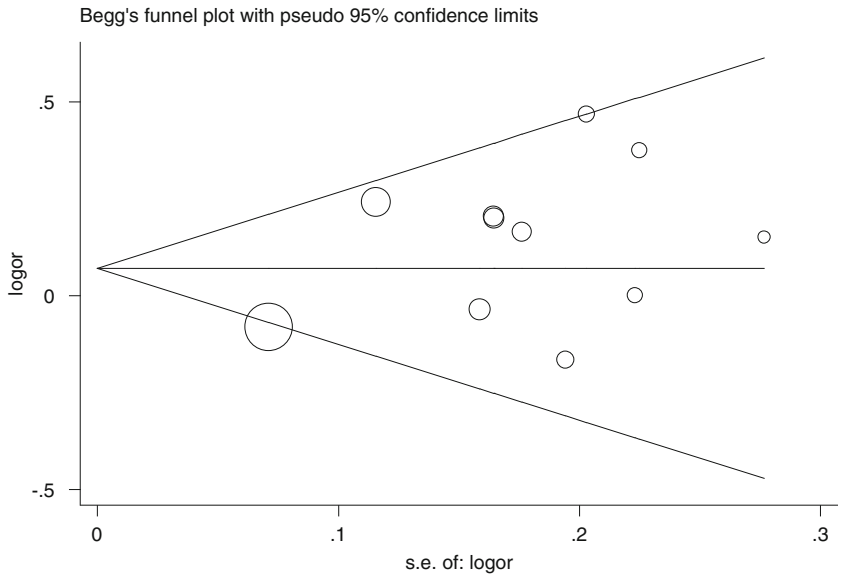

Fig. 4 Funnel plot for assessing the publication bias risk under the allele contrast model (T versus C, P_{Egger}=0.092)

Eleven case–control studies with 2,937 bladder cancer cases and 3,008 controls were included in the meta-analysis [12–22]. Overall, there was no obvious association between NQO1 C609T polymorphism and bladder cancer susceptibility (Table 1, Fig. 1). After adjusting for heterogeneity, meta-analysis of those remaining 10 studies showed that there was an obvious association between NQO1 C609T polymorphism and bladder cancer susceptibility (Table 1, Fig. 3). Therefore, our meta-analysis suggests that NQO1 C609T polymorphism is associated with bladder cancer susceptibility.

Heterogeneity analysis is an important part for a good meta-analysis. We used the classical Q statistic, and heterogeneity was considered statistically significant when $P<$ 0.10 [23]. The heterogeneity analysis in the meta-analysis showed that there was obvious heterogeneity under all comparison models of this meta-analysis, and all P values were less than 0.10 (Table 1). In addition, Galbraith plot in the meta-analysis under the homozygote model showed that Figueroa's study was the outlier and may be the possible major source of heterogeneity in this meta-analysis (Fig. 2). So we excluded Figueroa's study and reanalyzed the remaining data. After omitting Figueroa's study, there was no heterogeneity under all comparison models of this meta-analysis (Table 1), which further identified Figueroa's study as the major source of heterogeneity in this meta-analysis.

Subgroup analysis by ethnicity suggested that there was no association between NQO1 C609T polymorphism and bladder cancer susceptibility in Caucasians, but there was an obvious association in Asians (Table 1). The results above suggested that a race-specific effect may exist in the association between NQO1 C609T polymorphism and bladder cancer susceptibility. However, there were only three studies from Asians and there were no studies from Africans. In addition, the negative findings in Caucasians may result from the relative small effect of NQO1 C609T polymorphism on bladder cancer risk in Caucasians, and the data currently available were not big enough to produce a precise estimation. Therefore, more studies with large samples are needed to a more precise estimation on the effect of NQO1 C609T polymorphism on bladder cancer risk in different ethnicities.

It is well established that bladder carcinogenesis is a result of the interactions between environmental factors and genetic factors [29–31]. Apart from the role of genetic variants, environmental factors also have a major effect on the development of bladder cancer [32, 33], and there are some gene–environment interactions in the association between NQO1 C609T polymorphism and bladder cancer susceptibility. But the usable data from those 11 studies were limited and we did not analyze the possible gene–environment interactions in the association between NQO1 C609T polymorphism and bladder cancer susceptibility. Therefore, further analyses are needed to provide a precise estimation on the gene–environment interactions.

In conclusion, the findings from our meta-analysis suggest that NQO1 C609T polymorphism is associated with bladder cancer susceptibility. Bedsides, more studies with large samples are needed to a more precise estimation on the effect of NQO1 C609T polymorphism on bladder cancer risk in different ethnicities.

Conflicts of interests None

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.

2. Kaufman DS, Shipley WU, Feldman AS. Bladder cancer. Lancet. 2009;374:239–49.
3. Mitra AP, Cote RJ. Molecular pathogenesis and diagnostics of bladder cancer. Annu Rev Pathol. 2009;4:251–85.
4. Wu X, Hildebrandt MA, Chang DW. Genome-wide association studies of bladder cancer risk: a field synopsis of progress and potential applications. Cancer Metastasis Rev. 2009;28:269–80.
5. Golka K, Selinski S, Lehmann ML, Blaszkewicz M, Marchan R, Ickstadt K, et al. Genetic variants in urinary bladder cancer: collective power of the "wimp SNPs". Arch Toxicol. 2011;85:539–54.
6. Vasiliou V, Ross D, Nebert DW. Update of the NAD(P)H:quinone oxidoreductase (NQO) gene family. Hum Genomics. 2006;2:329–35.
7. Ross D, Siegel D. NAD(P)H:quinone oxidoreductase 1 (NQO1, DT-diaphorase), functions and pharmacogenetics. Methods Enzymol. 2004;382:115–44.
8. Guha N, Chang JS, Chokkalingam AP, Wiemels JL, Smith MT, Buffler PA. NQO1 polymorphisms and de novo childhood leukemia: a huge review and meta-analysis. Am J Epidemiol. 2008;168:1221–32.
9. Siegel D, Yan C, Ross D. NAD(P)H:quinone oxidoreductase 1 (NQO1) in the sensitivity and resistance to antitumor quinones. Biochem Pharmacol. 2012;83:1033–40.
10. Misra V, Grondin A, Klamut HJ, Rauth AM. Assessment of the relationship between genotypic status of a DT-diaphorase point mutation and enzymatic activity. Br J Cancer. 2000;83:998–1002.
11. Siegel D, McGuinness SM, Winski SL, Ross D. Genotype-phenotype relationships in studies of a polymorphism in NAD(P)H:quinone oxidoreductase 1. Pharmacogenetics. 1999;9:113–21.
12. Wang YH, Lee YH, Tseng PT, Shen CH, Chiou HY. Human NAD(P)H:quinone oxidoreductase 1 (NQO1) and sulfotransferase 1A1 (SULT1A1) polymorphisms and urothelial cancer risk in Taiwan. J Cancer Res Clin Oncol. 2008;134:203–9.
13. Terry PD, Umbach DM, Taylor JA. No association between SOD2 or NQO1 genotypes and risk of bladder cancer. Cancer Epidemiol Biomark Prev. 2005;14:753–4.
14. Schulz WA, Krummeck A, Rosinger I, Eickelmann P, Neuhaus C, Ebert T, et al. Increased frequency of a null-allele for NAD(P)H: quinone oxidoreductase in patients with urological malignancies. Pharmacogenetics. 1997;7:235–9.
15. Sanyal S, Festa F, Sakano S, Zhang Z, Steineck G, Norming U, et al. Polymorphisms in DNA repair and metabolic genes in bladder cancer. Carcinogenesis. 2004;25:729–34.
16. Park SJ, Zhao H, Spitz MR, Grossman HB, Wu X. An association between NQO1 genetic polymorphism and risk of bladder cancer. Mutat Res. 2003;536:131–7.
17. Moore LE, Wiencke JK, Bates MN, Zheng S, Rey OA, Smith AH. Investigation of genetic polymorphisms and smoking in a bladder cancer case–control study in Argentina. Cancer Lett. 2004;211:199–207.
18. Hung RJ, Boffetta P, Brennan P, Malaveille C, Gelatti U, Placidi D, et al. Genetic polymorphisms of MPO, COMT, MnSOD, NQO1, interactions with environmental exposures and bladder cancer risk. Carcinogenesis. 2004;25:973–8.
19. Fu J, Chen BC. Relationship between genetic polymorphism of NQO1 and susceptibility to bladder cancer. J Chin Oncol. 2012;18:561–4.
20. Figueroa JD, Malats N, Garcia-Closas M, Real FX, Silverman D, Kogevinas M, et al. Bladder cancer risk and genetic variation in AKR1C3 and other metabolizing genes. Carcinogenesis. 2008;29:1955–62.
21. Choi JY, Lee KM, Cho SH, Kim SW, Choi HY, Lee SY, et al. CYP2E1 and NQO1 genotypes, smoking and bladder cancer. Pharmacogenetics. 2003;13:349–55.
22. Broberg K, Bjork J, Paulsson K, Hoglund M, Albin M. Constitutional short telomeres are strong genetic susceptibility markers for bladder cancer. Carcinogenesis. 2005;26:1263–71.
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
24. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22:719–48.
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.
26. Galbraith R. A note on graphical presentation of estimated odds ratios from several clinical trials. Stat Med. 1988;7:889–94.
27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.
28. Kiltie AE. Common predisposition alleles for moderately common cancers: bladder cancer. Curr Opin Genet Dev. 2010;20:218–24.
29. Han SS, Rosenberg PS, Garcia-Closas M, Figueroa JD, Silverman D, Chanock SJ, et al. Likelihood ratio test for detecting gene (G)-environment (E) interactions under an additive risk model exploiting G-E independence for case–control data. Am J Epidemiol. 2012;176:1060–7.
30. Boffetta P, Winn DM, Ioannidis JP, Thomas DC, Little J, Smith GD, et al. Recommendations and proposed guidelines for assessing the cumulative evidence on joint effects of genes and environments on cancer occurrence in humans. Int J Epidemiol. 2012;41:686–704.
31. Panagiotakis GI, Papadogianni D, Chatziioannou MN, Lasithiotaki I, Delakas D, Spandidos DA. Association of human herpes, papilloma and polyoma virus families with bladder cancer. Tumour Biol. 2013;34:71–9.
32. Zhang Y, Wang X, Zhang W, Gong S. An association between XPC Lys939Gln polymorphism and the risk of bladder cancer: a meta-analysis. Tumour Biol. 2013;34:973–82.
33. Fan R, Zhong M, Wang S, Zhang Y, Andrew A, Karagas M, et al. Entropy-based information gain approaches to detect and to characterize gene-gene and gene-environment interactions/correlations of complex diseases. Genet Epidemiol. 2011;35:706–21.