Int J Clin Exp Med 2015;8(11):20236-20244
www.ijcem.com /ISSN:1940-5901/IJCEM0015280

Original Article

The association between rs9642880 gene polymorphism and bladder cancer risk: a meta-analysis

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Received August 30, 2015; Accepted October 27, 2015; Epub November 15, 2015; Published November 30, 2015

Abstract: Previous studies had researched the relationship between rs9642880 gene polymorphism and bladder cancer risk, but the results remained unclear. The comprehensive meta-analysis was performed to clarify this possible association. Relevant articles were searched from Pubmed, Embase and web of science. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated to assess the strength of the association. The assessment of publication bias was conducted by Begg's funnel plots and Egger's regression test. A total of 7 case-control studies involving 4072 cases and 4898 controls were included in our study. Overall, an obvious relationship between rs9642880 polymorphism and increased risk of bladder cancer were detected in all models. Besides, the positive results were observed among both Caucasians and Asians when stratified by ethnicity. Moreover, when stratified by genotyping method, the significant results were detected in all genotyping methods except Sequenom. In addition, in the subgroup analysis by source of control, significant results were detected in both population and hospital based controls. This present meta-analysis with accurate and reliable results indicated that the T allele of SNP rs9642880 confers susceptibility to bladder cancer in both Asian and Caucasian populations.

Keywords: MYC, rs9642880, gene polymorphism, bladder cancer, meta-analysis

Introduction

Bladder cancer, as one of the most common malignant cancers, has a large amount of estimated cases and deaths of approximately 386,300 and 150,200 respectively worldwide [1]. The etiology of bladder cancer is complicated, while two major known risk factors are smoking and occupational exposures [2]. Besides, it has been clarified that genetic polymorphisms are likely to play an important role in the occurrence of bladder cancer [3]. Recently, single-nucleotide polymorphisms (SNPs) have been demonstrated to be associated with bladder cancer risk by genome-wide association studies (GWAS) in European populations [4-8].

As an oncogene, MYC is implicated in the carcinogenesis and tumor progression [9-11]. MYC is a nuclear protein which connects with a small protein called MAX to act as a sequence-specific, DNA-binding transcription factor that regulates various genes involved in cell cell growth, proliferation and apoptosis [12]. Rs9642880 polymorphism is located 30 kb upstream of MYC gene at the 8q24 region [13]. Recently, it has been clarified that rs9642880 GT/TT polymorphism was associated with the enhanced expression of MYC in both mRNA and protein levels in bladder tissues [14], which might play an important role in bladder carcinogenesis.

So far, a growing number of studies have investigated the relevance between rs9642880 polymorphism and bladder cancer susceptibility [15-23]. However, the results are still unclear with limited sample size. Furthermore, lack of stratified analysis prevented comprehensive understanding of the association in current studies. We thereby conducted a meta-analysis to clarify the real association.

Materials and methods

The database PubMed, EMbase and Web of Science were searched for relevant studies until March 31, 2015. The following keywords

Table 1. Characteristics of individual studies included in the meta-analysis

rs9642880							Case (n)			Control(n)		
Year	Surname	Ethnicity	SOC	Genotyping	Case	Control	GG	GT	TT	GG	GT	TT
2014	Wang	Asian	PB	Taqman	1210	1008	550	536	124	514	389	105
2013	Yates	Caucasian	HB	Taqman	231	264	64	114	53	84	130	50
2013	Ma	Asian	PB	Sequenom	171	962	74	74	23	489	371	102
2013	Ali	Asian	PB	PCR-RFLP	200	200	33	84	83	48	90	62
2012	Roupret	Caucasian	HB	Taqman	261	261	69	119	73	81	130	50
2012	Schwender	Caucasian	HB	Taqman	1584	1738	391	767	426	486	876	376
2009	Wang	Asian	HB	PCR-RFLP	415	465	149	203	63	223	192	50

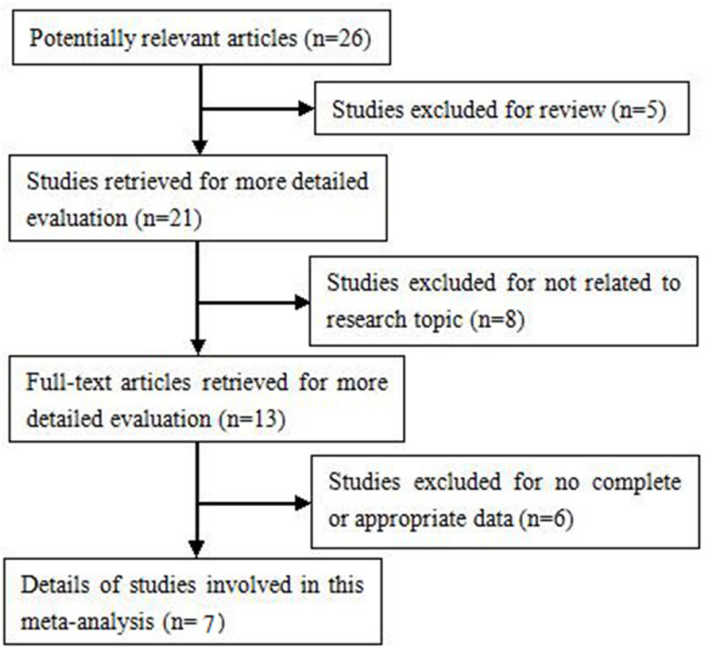

Figure 1. Flow diagram of literature search and selection process.

were utilized for searching: "MYC", "polymorphism" or "rs9642880" and "bladder caner". Only the latest or the largest sample size was included in studies with partly overlapping. Additional eligible studies were hand-searched from reference of original studies or reviews.

Relevant studies were selected by the following inclusion criteria: (1) Case-control studies were designed; (2) The number of each genotype was available for estimating the odds ratio (OR) and the corresponding 95% confidence interval (95% CI); (3) The diagnosis of patients was confirmed pathologically and the controls were confirmed as free from any cancer. In addition, the major exclusion criterion was as follows: (1) without control series; (2) not available of genotype frequency data; (3) review articles; (4) duplicates of previous publication.

Data extraction

Two authors (Tang J and Li X) reviewed the studies carefully and independently identify the eligible ones. A consensus was reached on all items and the disagreement would be solved by a discussion. The data was extracted independently and the following data was extracted from each study: first author's name, year of publication, ethnicity, source of controls (SOC), genotyping method, number of cases and controls, genotype frequency of rs9642880 polymorphism in cases and controls respectively and the results of the Hardy-Weinberg equilibrium (HWE) test.

Statistical analysis

To evaluate the strength of association between rs9642880 polymorphism and bladder cancer risk, the pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The fixed-effects model (a Mantel-Haenszel method) and the random-effects model (a DerSimonian-Laird method) were respectively utilized to pool the data [24]. If the significant heterogeneity was observed, the random-effects model was applied preferentially. Sensitivity analysis was carried out to evaluate the stability of the results by omitting each study at a time. Then, subgroups analysis was further conducted by ethnicity, genotyping methods and source of control (SOC).

Table 2. Meta-analysis results of association between rs9642880 polymorphism and bladder cancer risk

			GT vs. GG		TT vs. GG		GT/TT vs. GG		TT vs. GT/GG	
	N[a]	Sample Size	OR (95% CI)*	P[b]	OR (95% CI)*	P[b]	OR (95% CI)*	P[b]	OR (95% CI)*	P[b]
Total	7	8970	1.23 (1.11-1.35)	0.406	1.42 (1.25-1.62)	0.362	1.28 (1.17-1.41)	0.505	1.31 (1.17-1.46)	0.358
Ethnicity										
Caucasian	3	4339	1.36 (1.19-1.55)	0.690	1.44 (1.22-1.70)	0.752	1.20 (1.05-1.37)	0.961	1.36 (1.18-1.56)	0.624
Asian	4	4631	1.09 (0.95-1.26)	0.966	1.40 (1.15-1.71)	0.113	1.36 (1.20-1.55)	0.347	1.23 (1.02-1.47)	0.177
Genotyping										
Taqman	4	6557	1.17 (1.04-1.30)	0.565	1.35 (1.16-1.56)	0.386	1.22 (1.10-1.35)	0.973	1.27 (1.12-1.44)	0.157
Sequenom	1	1133	1.32 (0.93-1.87)	--	1.49 (0.89-2.49)	--	1.36 (0.98-1.88)	--	1.31 (0.81-2.13)	--
PCR-RFLP	2	1280	1.53 (1.19-1.97)	0.620	1.91 (1.36-2.67)	0.928	1.63 (1.29-2.07)	0.920	1.53 (1.15-2.04)	0.834
SOC										
PB	3	3751	1.30 (1.12-1.51)	0.979	1.29 (1.02-1.62)	0.167	1.29 (1.12-1.49)	0.622	1.17 (0.95-1.43)	0.148
HB	4	5219	1.18 (1.04-1.34)	0.159	1.49 (1.28-1.75)	0.593	1.27 (1.13-1.44)	0.228	1.37 (1.20-1.57)	0.774

[a]Number of studies; [b]*P* value of Q test for heterogeneity; *Fixed-effects model was used because all *P* value for heterogeneity test >0.1.

Publication bias between the studies was examined by Begg's funnel plots and Egger's linear regression test. It was considered statistically significant when P<0.05 [25]. HWE was estimated by the goodness-of-fit chi-square test and it was regarded as a significantly selective bias when P<0.05 [26]. All statistical analysis was carried out by the STATA software (version 12.0; StataCorp LP, College Station, TX). All tests were two-sided and it was considered statistically significant when P<0.05.

Results

Characteristics of the studies

Finally, a total of 7 case-control studies including 4072 cases and 4898 controls were involved in the current meta-analysis [15-21] as listed in **Table 1**. All studies showed that the genotype distribution of control groups was consistent with HWE. The flowchart of literature search and identification process is presented in **Figure 1**.

Quantitative synthesis

The results of the relationship between rs9642880 polymorphism and bladder cancer risk is listed in **Table 2**. In general, the pooled OR was 1.23 (95% CI: 1.11-1.35) for heterozygote model, 1.42 (95% CI: 1.25-1.62) for homozygote model, 1.28 (95% CI: 1.17-1.41) for dominant model and 1.31 (95% CI: 1.17-1.46) for recessive model (**Figure 2A**). Overall, there was an obvious connection between rs9642880 polymorphism and increased risk of bladder cancer. Moreover, the positive results were observed among both Caucasians and Asians when stratified by ethnicity (**Figure 2B**). Furthermore, when stratified by genotyping method, the significant results were detected in all genotyping methods except Sequenom (**Figure 2C**). In addition, in the subgroup analysis by SOC, significant results were detected in both population and hospital based controls (**Figure 2D**).

Test of heterogeneity and sensitivity

No significant heterogeneity was observed in all kinds of models, which was confirmed by the analysis of Galbraith (**Figure 3**). Sensitivity analysis was performed to evaluate the effect of each study on the pooled OR by omitting one single study at a time. The results of the sensitivity analysis demonstrated that no individual study significantly affected the pooled OR (**Figure 4**). All these indicated the stability of our results.

Publication bias

Begg's funnel plot and Egger's test were utilized to assess the publication bias of the literature. No obvious asymmetry was seen from the shape of the Begg's funnel plot (**Figure 5**), indicating there was no significant publication bias and our results were robust. The same result was found in the Egger's test.

Discussion

The 8q24 region, where rs9642880 polymorphism located at, is a gene desert. Various enhancers regulate transcription are found in this region that can regulate the transcription of MYC [27-29]. Moreover, this region interacts

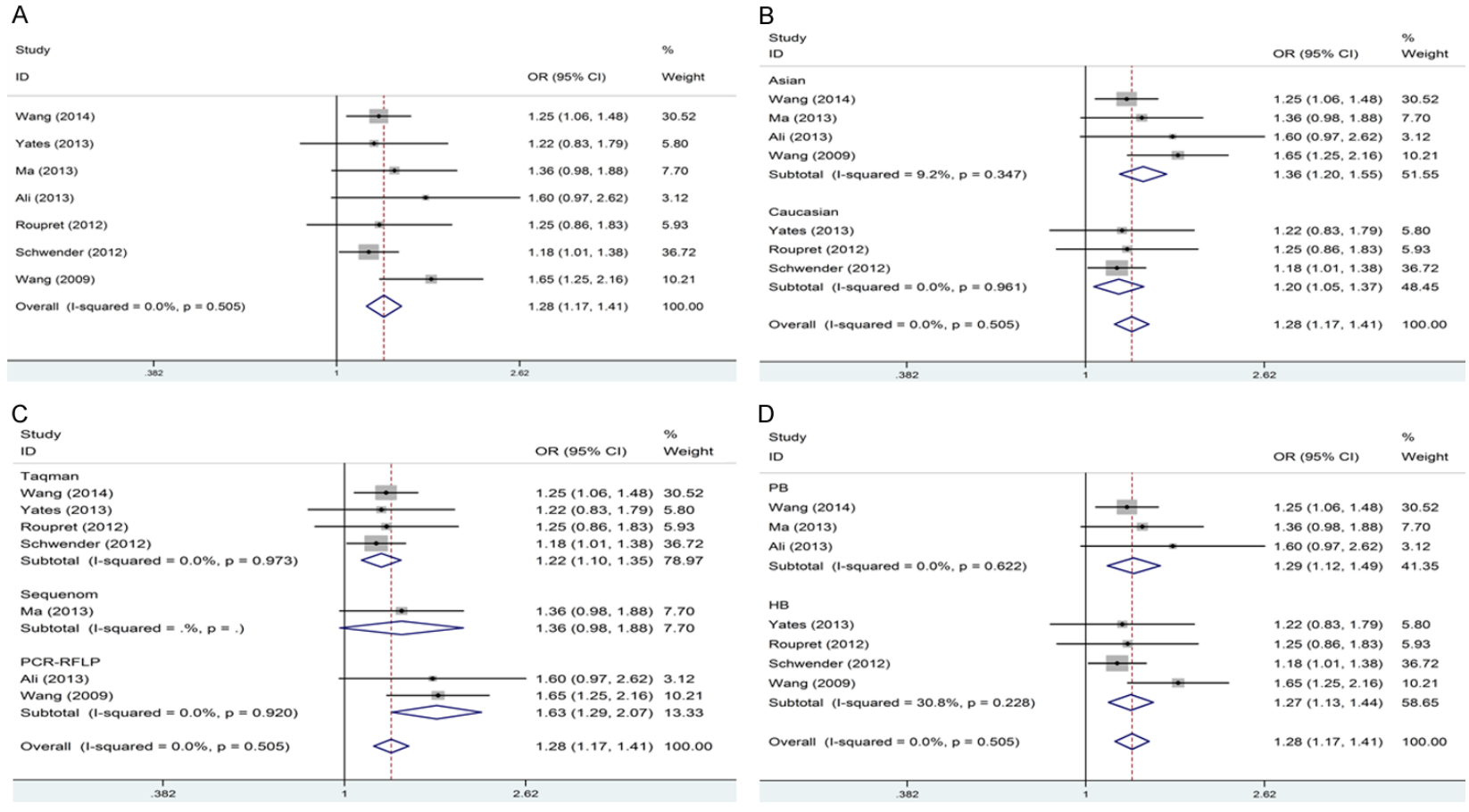

Figure 2. Forest plots of association between rs9642880 polymorphism and bladder cancer risk in dominant model. A: Overall results; B: Stratified by ethnicity; C: Stratified by genotyping method; D: Stratified by SOC.

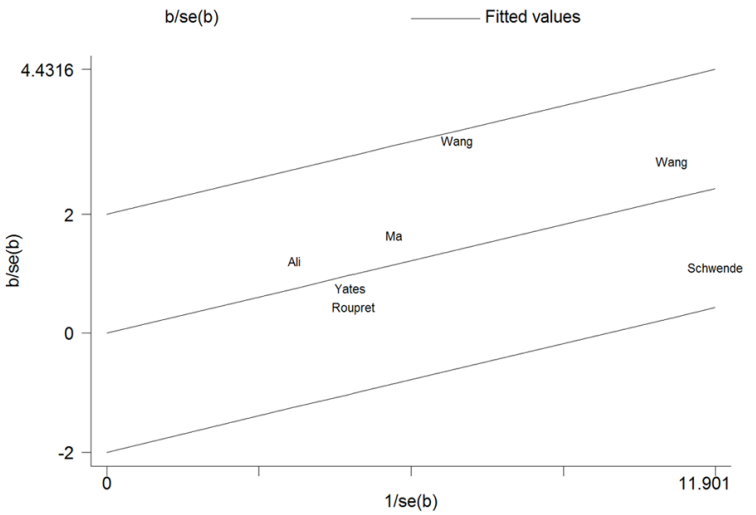

Figure 3. The analysis of Galbraith to assess the heterogeneity.

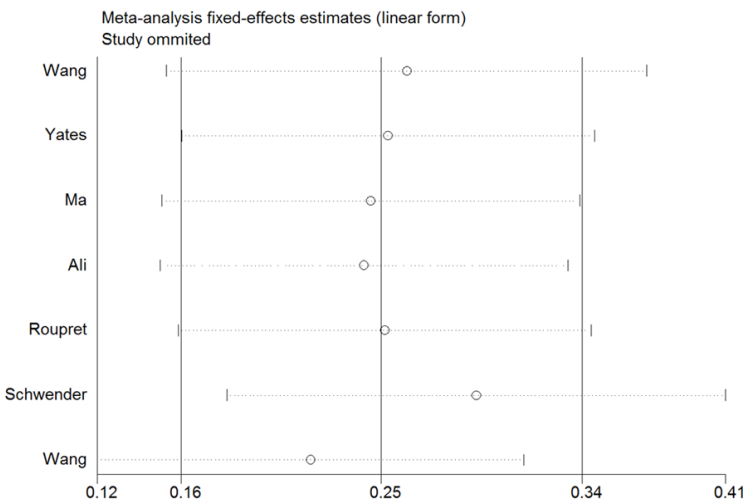

Figure 4. Sensitivity analysis under the dominant model.

with the MYC protooncogene by a chromatin loop [30]. Meanwhile, it has been demonstrated that T allele of rs9642880 polymorphism was related with the overexpression of MYC mRNA and protein in bladder tissues [14], implying this polymorphism may contribute to the occurrence of bladder cancer through regulating the expression of MYC.

MYC is overexpressed in various tumors, which confers a proliferative advantage to tumor cells both in vitro and in vivo [31, 32], regulating cell function associated with tumorgenesis. In addition, Fu et al. [13] found that synthetic artificial microRNAs targeting MYC could inhibit the malignant phenotypes of bladder cancer. Furthermore, it has been shown down-regulating the MYC expression could increase the antitumor activity in gemcitabine-resistant bladder cancer [33], indicating MYC is a potential regulator of chemotherapy resistance.

In 2008, Kiemeney et al. [34] identified rs9642880 polymorphism as the risk locus for bladder cancer. Since then, increasing studies have investigated the association between this polymorphism and bladder cancer risk [15-21]. Nevertheless, the outcomes remained unclear without sufficient support from larger population. Moreover, further studies by different stratified analysis were not carried out. As a powerful tool, meta-analysis can provide more reliable results than individual study and comprehensive information through different subgroup analysis [35]. Therefore, we utilized meta-analysis to illustrate the possible association between rs9642880 polymorphism and bladder cancer risk. In the present meta-analysis, our results indicated the T allele of rs9642880 could increase bladder cancer susceptibility.

Due to various genetic backgrounds, different ethnic populations may have different incidence of gene polymorphisms [36]. As a result, subgroup analysis by ethnic was performed and the positive results were observed among both Asian and Caucasian. When stratified by SOC, both the population and hospital based controls showed significant results. However, in subgroup analysis by genotyping method, the positive results were detected in Taqman and PCR-RFLP method, instead of sequenom. The difference may be caused as only one study take sequenom method, which increased the inaccuracy of the results. In addition, different genotyping methods have specialty in different aspects, so the results would be more reliable and accurate if the same appropriate genotyp-

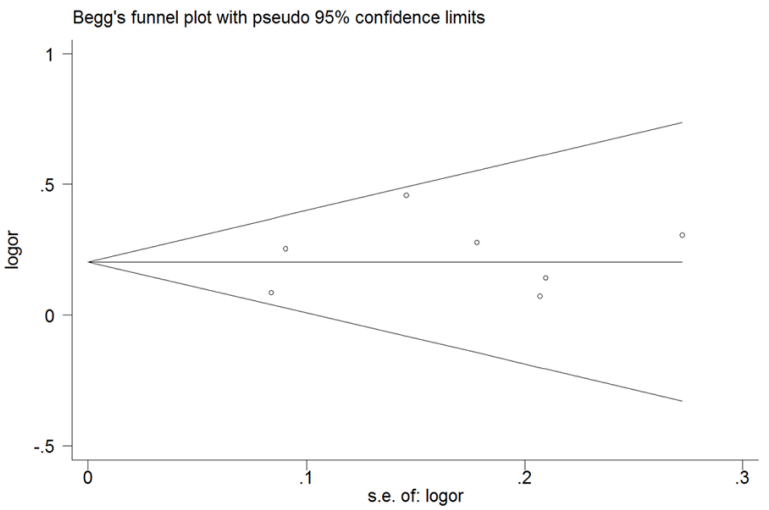

Figure 5. Begg's funnel plot for publication bias test.

ing method was applied in different studies. In this meta-analysis, no significant heterogeneity was detected and the sensitivity analysis showed the results were stable. In summary, all these analysis suggested rs9642880 polymorphism played an important role in the risk of bladder cancer.

Though the results of this meta-analysis were identified by sufficient statistical evidence, some limitations must be noticed. Firstly, only 7 researches included in the meta-analysis met inclusion criterion, which required more high-quality studies to provide more sufficient evidence. Secondly, the number in some subgroups is relatively small, which limits the statistical power to reveal the real association. Furthermore, bladder cancer susceptibility might result from interactions of various genetic and environmental factors instead of one single gene. Thereby, future studies should focus on the combined effects of different factors.

In summary, this present meta-analysis with accurate and reliable results indicated the T allele of rs9642880 polymorphism confers susceptibility to bladder cancer both in Asian and Caucasian populations. Future studies on combined effects of different gene polymorphisms are required to explore the etiology and provide an early diagnosis of bladder cancer.

Disclosure of conflict of interest

None.

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References

[1] Aly M, Wiklund F, Xu J, Isaacs WB, Eklund M, D'Amato M, Adolfsson J, Gronberg H. Polygenic risk score improves prostate cancer risk prediction: results from the Stockholm-1 cohort study. Eur Urol 2011; 60: 21-28.

[2] Murta-Nascimento C, Schmitz-Drager BJ, Zeegers MP, Steineck G, Kogevinas M, Real FX, Malats N. Epidemiology of urinary bladder cancer: from tumor development to patient's death. World J Urol 2007; 25: 285-295.

[3] Murta-Nascimento C, Silverman DT, Kogevinas M, Garcia-Closas M, Rothman N, Tardon A, Garcia-Closas R, Serra C, Carrato A, Villanueva C, Dosemeci M, Real FX, Malats N. Risk of bladder cancer associated with family history of cancer: do low-penetrance polymorphisms account for the increase in risk? Cancer Epidemiol Biomarkers Prev 2007; 16: 1595-1600.

[4] Kiemeney LA, Thorlacius S, Sulem P, Geller F, Aben KK, Stacey SN, Gudmundsson J, Jakobsdottir M, Bergthorsson JT, Sigurdsson A, Blondal T, Witjes JA, Vermeulen SH, Hulsbergen-van de Kaa CA, Swinkels DW, Ploeg M, Cornel EB, Vergunst H, Thorgeirsson TE, Gudbjartsson D, Gudjonsson SA, Thorleifsson G, Kristinsson KT, Mouy M, Snorradottir S, Placidi D, Campagna M, Arici C, Koppova K, Gurzau E, Rudnai P, Kellen E, Polidoro S, Guarrera S, Sacerdote C, Sanchez M, Saez B, Valdivia G, Ryk C, de Verdier P, Lindblom A, Golka K, Bishop DT, Knowles MA, Nikulasson S, Petursdottir V, Jonsson E, Geirsson G, Kristjansson B, Mayordomo JI, Steineck G, Porru S, Buntinx F, Zeegers MP, Fletcher T, Kumar R, Matullo G, Vineis P, Kiltie AE, Gulcher JR, Thorsteinsdottir U, Kong A, Rafnar T, Stefansson K. Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. Nat Genet 2008; 40: 1307-1312.

[5] Wu X, Ye Y, Kiemeney LA, Sulem P, Rafnar T, Matullo G, Seminara D, Yoshida T, Saeki N, Andrew AS, Dinney CP, Czerniak B, Zhang ZF,

Kiltie AE, Bishop DT, Vineis P, Porru S, Buntinx F, Kellen E, Zeegers MP, Kumar R, Rudnai P, Gurzau E, Koppova K, Mayordomo JI, Sanchez M, Saez B, Lindblom A, de Verdier P, Steineck G, Mills GB, Schned A, Guarrera S, Polidoro S, Chang SC, Lin J, Chang DW, Hale KS, Majewski T, Grossman HB, Thorlacius S, Thorsteinsdottir U, Aben KK, Witjes JA, Stefansson K, Amos CI, Karagas MR, Gu J. Genetic variation in the prostate stem cell antigen gene PSCA confers susceptibility to urinary bladder cancer. Nat Genet 2009; 41: 991-995.

[6] Rothman N, Garcia-Closas M, Chatterjee N, Malats N, Wu X, Figueroa JD, Real FX, Van Den Berg D, Matullo G, Baris D, Thun M, Kiemeney LA, Vineis P, De Vivo I, Albanes D, Purdue MP, Rafnar T, Hildebrandt MA, Kiltie AE, Cussenot O, Golka K, Kumar R, Taylor JA, Mayordomo JI, Jacobs KB, Kogevinas M, Hutchinson A, Wang Z, Fu YP, Prokunina-Olsson L, Burdett L, Yeager M, Wheeler W, Tardón A, Serra C, Carrato A, García-Closas R, Lloreta J, Johnson A, Schwenn M, Karagas MR, Schned A, Andriole G Jr, Grubb R 3rd, Black A, Jacobs EJ, Diver WR, Gapstur SM, Weinstein SJ, Virtamo J, Cortessis VK, Gago-Dominguez M, Pike MC, Stern MC, Yuan JM, Hunter DJ, McGrath M, Dinney CP, Czerniak B, Chen M, Yang H, Vermeulen SH, Aben KK, Witjes JA, Makkinje RR, Sulem P, Besenbacher S, Stefansson K, Riboli E, Brennan P, Panico S, Navarro C, Allen NE, Bueno-de-Mesquita HB, Trichopoulos D, Caporaso N, Landi MT, Canzian F, Ljungberg B, Tjonneland A, Clavel-Chapelon F, Bishop DT, Teo MT, Knowles MA, Guarrera S, Polidoro S, Ricceri F, Sacerdote C, Allione A, Cancel-Tassin G, Selinski S, Hengstler JG, Dietrich H, Fletcher T, Rudnai P, Gurzau E, Koppova K, Bolick SC, Godfrey A, Xu Z, Sanz-Velez JI, D García-Prats M, Sanchez M, Valdivia G, Porru S, Benhamou S, Hoover RN, Fraumeni JF Jr, Silverman DT, Chanock SJ. A multi-stage genome-wide association study of bladder cancer identifies multiple susceptibility loci. Nat Genet 2010; 42: 978-984.

[7] Kiemeney LA, Sulem P, Besenbacher S, Vermeulen SH, Sigurdsson A, Thorleifsson G, Gudbjartsson DF, Stacey SN, Gudmundsson J, Zanon C, Kostic J, Masson G, Bjarnason H, Palsson ST, Skarphedinsson OB, Gudjonsson SA, Witjes JA, Grotenhuis AJ, Verhaegh GW, Bishop DT, Sak SC, Choudhury A, Elliott F, Barrett JH, Hurst CD, de Verdier PJ, Ryk C, Rudnai P, Gurzau E, Koppova K, Vineis P, Polidoro S, Guarrera S, Sacerdote C, Campagna M, Placidi D, Arici C, Zeegers MP, Kellen E, Gutierrez BS, Sanz-Velez JI, Sanchez-Zalabardo M, Valdivia G, Garcia-Prats MD, Hengstler JG, Blaszkewicz M, Dietrich H, Ophoff RA, van den Berg LH, Alexiusdottir K, Kristjansson K, Geirsson G, Nikulasson S, Petursdottir V, Kong A, Thorgeirsson T, Mungan NA, Lindblom A, van Es MA, Porru S, Buntinx F, Golka K, Mayordomo JI, Kumar R, Matullo G, Steineck G, Kiltie AE, Aben KK, Jonsson E, Thorsteinsdottir U, Knowles MA, Rafnar T, Stefansson K. A sequence variant at 4p16.3 confers susceptibility to urinary bladder cancer. Nat Genet 2010; 42: 415-419.

[8] Rafnar T, Vermeulen SH, Sulem P, Thorleifsson G, Aben KK, Witjes JA, Grotenhuis AJ, Verhaegh GW, Hulsbergen-van de Kaa CA, Besenbacher S, Gudbjartsson D, Stacey SN, Gudmundsson J, Johannsdottir H, Bjarnason H, Zanon C, Helgadottir H, Jonasson JG, Tryggvadottir L, Jonsson E, Geirsson G, Nikulasson S, Petursdottir V, Bishop DT, Chung-Sak S, Choudhury A, Elliott F, Barrett JH, Knowles MA, de Verdier PJ, Ryk C, Lindblom A, Rudnai P, Gurzau E, Koppova K, Vineis P, Polidoro S, Guarrera S, Sacerdote C, Panadero A, Sanz-Velez JI, Sanchez M, Valdivia G, Garcia-Prats MD, Hengstler JG, Selinski S, Gerullis H, Ovsiannikov D, Khezri A, Aminsharifi A, Malekzadeh M, van den Berg LH, Ophoff RA, Veldink JH, Zeegers MP, Kellen E, Fostinelli J, Andreoli D, Arici C, Porru S, Buntinx F, Ghaderi A, Golka K, Mayordomo JI, Matullo G, Kumar R, Steineck G, Kiltie AE, Kong A, Thorsteinsdottir U, Stefansson K, Kiemeney LA. European genome-wide association study identifies SLC14A1 as a new urinary bladder cancer susceptibility gene. Hum Mol Genet 2011; 20: 4268-4281.

[9] Ben-David E, Bester AC, Shifman S, Kerem B. Transcriptional dynamics in colorectal carcinogenesis: new insights into the role of c-Myc and miR17 in benign to cancer transformation. Cancer Res 2014; 74: 5532-5540.

[10] Fonseca-Alves CE, Rodrigues MM, de Moura VM, Rogatto SR, Laufer-Amorim R. Alterations of C-MYC, NKX3.1, and E-cadherin expression in canine prostate carcinogenesis. Microsc Res Tech 2013; 76: 1250-1256.

[11] Xiao W, Wang J, Ou C, Zhang Y, Ma L, Weng W, Pan Q, Sun F. Mutual interaction between YAP and c-Myc is critical for carcinogenesis in liver cancer. Biochem Biophys Res Commun 2013; 439: 167-172.

[12] Patel JH, Loboda AP, Showe MK, Showe LC, McMahon SB. Analysis of genomic targets reveals complex functions of MYC. Nat Rev Cancer 2004; 4: 562-568.

[13] Fu X, Liu Y, Zhuang C, Liu L, Cai Z, Huang W. Synthetic artificial microRNAs targeting UCA1-MALAT1 or c-Myc inhibit malignant phenotypes of bladder cancer cells T24 and 5637. Mol Biosyst 2015; 11: 1285-9.

[14] Wang M, Wang M, Zhang W, Yuan L, Fu G, Wei Q, Zhang Z. Common genetic variants on 8q24

contribute to susceptibility to bladder cancer in a Chinese population. Carcinogenesis 2009; 30: 991-996.
[15] Wang P, Ye D, Guo J, Liu F, Jiang H, Gong J, Gu C, Shao Q, Sun J, Zheng SL, Yu H, Lin X, Xia G, Fang Z, Zhu Y, Ding Q, Xu J. Genetic score of multiple risk-associated single nucleotide polymorphisms is a marker for genetic susceptibility to bladder cancer. Genes Chromosomes Cancer 2014; 53: 98-105.
[16] Yates DR, Roupret M, Drouin SJ, Audouin M, Cancel-Tassin G, Comperat E, Bitker MO, Cussenot O. Genetic polymorphisms on 8q24.1 and 4p16.3 are not linked with urothelial carcinoma of the bladder in contrast to their association with aggressive upper urinary tract tumours. World J Urol 2013; 31: 53-59.
[17] Ma Z, Hu Q, Chen Z, Tao S, Macnamara L, Kim ST, Tian L, Xu K, Ding Q, Zheng SL, Sun J, Xia G, Xu J. Systematic evaluation of bladder cancer risk-associated single-nucleotide polymorphisms in a Chinese population. Mol Carcinog 2013; 52: 916-921.
[18] Ali SHB, Younis M, Bangash KS, Rauf A, Anwar K, Khurram R, Khawaja MA, Qureshi AA, Akhter S, Azam M, Kiemeney LA, Qamar R. Common Variants at 8q24 Confer Susceptibility to Urothelial Bladder Cancer in the Pakistani Population. PAK J ZOOL 2013; 45: 1501-1509.
[19] Roupret M, Drouin SJ, Cancel-Tassin G, Comperat E, Larre S, Cussenot O. Genetic variability in 8q24 confers susceptibility to urothelial carcinoma of the upper urinary tract and is linked with patterns of disease aggressiveness at diagnosis. J Urol 2012; 187: 424-428.
[20] Schwender H, Selinski S, Blaszkewicz M, Marchan R, Ickstadt K, Golka K, Hengstler JG. Distinct SNP combinations confer susceptibility to urinary bladder cancer in smokers and non-smokers. PLoS One 2012; 7: e51880.
[21] Golka K, Hermes M, Selinski S, Blaszkewicz M, Bolt HM, Roth G, Dietrich H, Prager HM, Ickstadt K, Hengstler JG. Susceptibility to urinary bladder cancer: relevance of rs-9642880[T], GSTM1 0/0 and occupational exposure. Pharmacogenet Genomics 2009; 19: 903-906.
[22] Figueroa JD, Ye Y, Siddiq A, Garcia-Closas M, Chatterjee N, Prokunina-Olsson L, Cortessis VK, Kooperberg C, Cussenot O, Benhamou S, Prescott J, Porru S, Dinney CP, Malats N, Baris D, Purdue M, Jacobs EJ, Albanes D, Wang Z, Deng X, Chung CC, Tang W, Bas Bueno-de-Mesquita H, Trichopoulos D, Ljungberg B, Clavel-Chapelon F, Weiderpass E, Krogh V, Dorronsoro M, Travis R, Tjønneland A, Brenan P, Chang-Claude J, Riboli E, Conti D, Gago-Dominguez M, Stern MC, Pike MC, Van Den Berg D, Yuan JM, Hohensee C, Rodabough R, Cancel-Tassin G, Roupret M, Comperat E, Chen C, De Vivo I, Giovannucci E, Hunter DJ, Kraft P, Lindstrom S, Carta A, Pavanello S, Arici C, Mastrangelo G, Kamat AM, Lerner SP, Barton Grossman H, Lin J, Gu J, Pu X, Hutchinson A, Burdette L, Wheeler W, Kogevinas M, Tardón A, Serra C, Carrato A, García-Closas R, Lloreta J, Schwenn M, Karagas MR, Johnson A, Schned A, Armenti KR, Hosain GM, Andriole G Jr, Grubb R 3rd, Black A, Ryan Diver W, Gapstur SM, Weinstein SJ, Virtamo J, Haiman CA, Landi MT, Caporaso N, Fraumeni JF Jr, Vineis P, Wu X, Silverman DT, Chanock S, Rothman N. Genome-wide association study identifies multiple loci associated with bladder cancer risk. Hum Mol Genet 2014; 23: 1387-1398.
[23] Cortessis VK, Yuan J, Van Den Berg D, Jiang X, Gago-Dominguez M, Stern MC, Castelao JE, Xiang Y, Gao Y, Pike MC, Conti DV. Risk of Urinary Bladder Cancer Is Associated with 8q24 Variant rs9642880[T] in Multiple Racial/Ethnic Groups: Results from the Los Angeles-Shanghai Case-Control Study. Cancer Epidem Biomar 2010; 19: 3150-3156.
[24] DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007; 28: 105-114.
[25] Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
[26] Guo SW, Thompson EA. Performing the exact test of Hardy-Weinberg proportion for multiple alleles. Biometrics 1992; 48: 361-372.
[27] Lavenu A, Pournin S, Babinet C, Morello D. The cis-acting elements known to regulate c-myc expression ex vivo are not sufficient for correct transcription in vivo. Oncogene 1994; 9: 527-536.
[28] Hallikas O, Palin K, Sinjushina N, Rautiainen R, Partanen J, Ukkonen E, Taipale J. Genome-wide prediction of mammalian enhancers based on analysis of transcription-factor binding affinity. Cell 2006; 124: 47-59.
[29] Jia L, Landan G, Pomerantz M, Jaschek R, Herman P, Reich D, Yan C, Khalid O, Kantoff P, Oh W, Manak JR, Berman BP, Henderson BE, Frenkel B, Haiman CA, Freedman M, Tanay A, Coetzee GA. Functional enhancers at the gene-poor 8q24 cancer-linked locus. PLoS Genet 2009; 5: e1000597.
[30] Sotelo J, Esposito D, Duhagon MA, Banfield K, Mehalko J, Liao H, Stephens RM, Harris TJ, Munroe DJ, Wu X. Long-range enhancers on 8q24 regulate c-Myc. Proc Natl Acad Sci U S A 2010; 107: 3001-3005.
[31] Adams JM, Harris AW, Pinkert CA, Corcoran LM, Alexander WS, Cory S, Palmiter RD, Brinster RL. The c-myc oncogene driven by im-

munoglobulin enhancers induces lymphoid malignancy in transgenic mice. Nature 1985; 318: 533-538.

[32] Land H, Parada LF, Weinberg RA. Tumorigenic conversion of primary embryo fibroblasts requires at least two cooperating oncogenes. Nature 1983; 304: 596-602.

[33] Seo HK, Ahn KO, Jung NR, Shin JS, Park WS, Lee KH, Lee SJ, Jeong KC. Antitumor activity of the c-Myc inhibitor KSI-3716 in gemcitabine-resistant bladder cancer. Oncotarget 2014; 5: 326-337.

[34] Kiemeney LA, Thorlacius S, Sulem P, Geller F, Aben KK, Stacey SN, Gudmundsson J, Jakobsdottir M, Bergthorsson JT, Sigurdsson A, Blondal T, Witjes JA, Vermeulen SH, Hulsbergen-van de Kaa CA, Swinkels DW, Ploeg M, Cornel EB, Vergunst H, Thorgeirsson TE, Gudbjartsson D, Gudjonsson SA, Thorleifsson G, Kristinsson KT, Mouy M, Snorradottir S, Placidi D, Campagna M, Arici C, Koppova K, Gurzau E, Rudnai P, Kellen E, Polidoro S, Guarrera S, Sacerdote C, Sanchez M, Saez B, Valdivia G, Ryk C, de Verdier P, Lindblom A, Golka K, Bishop DT, Knowles MA, Nikulasson S, Petursdottir V, Jonsson E, Geirsson G, Kristjansson B, Mayordomo JI, Steineck G, Porru S, Buntinx F, Zeegers MP, Fletcher T, Kumar R, Matullo G, Vineis P, Kiltie AE, Gulcher JR, Thorsteinsdottir U, Kong A, Rafnar T, Stefansson K. Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. Nat Genet 2008; 40: 1307-1312.

[35] Munafo MR, Flint J. Meta-analysis of genetic association studies. Trends Genet 2004; 20: 439-444.

[36] Hirschhorn JN, Lohmueller K, Byrne E, Hirschhorn K. A comprehensive review of genetic association studies. Genet Med 2002; 4: 45-61.