Arch Toxicol (2016) 90:1917–1927
DOI 10.1007/s00204-015-1590-x

TOXICOGENOMICS

Polymorphisms of human 8-oxoguanine DNA glycosylase 1 and 8-hydroxydeoxyguanosine increase susceptibility to arsenic methylation capacity-related urothelial carcinoma

Chao-Yuan Huang[1] · Yeong-Shiau Pu[1] · Horng-Sheng Shiue[2] · Wei-Jen Chen[3] · Ying-Chin Lin[4,5,6] · Yu-Mei Hsueh[3,7]

Received: 15 May 2015 / Accepted: 31 August 2015 / Published online: 10 September 2015
© Springer-Verlag Berlin Heidelberg 2015

Abstract Arsenic causes oxidative stress in cultured animal and human cells, and it is a well-documented human carcinogen. We conducted a hospital-based case–control study including 167 cases of urothelial carcinoma (UC) and 334 age- and gender-matched healthy controls to evaluate the relationships between urinary arsenic profiles, urinary 8-hydroxydeoxyguanosine (8-OHdG) levels, and human 8-oxoguanine DNA glycosylase (hOGG1) genotypes and UC. The urinary arsenic species were analyzed by high-performance liquid chromatography and hydride generator-atomic absorption spectrometry. Genotyping for *hOGG1* (Ser326Cys) and *hOGG1* (−15C>G) was performed using the Sequenom MassARRAY platform with iPLEX Gold chemistry. Urinary 8-OHdG was measured with high-sensitivity enzyme-linked immunosorbent assay kits. The results indicated that the *hOGG1* 326 Cys/Cys genotype and the *hOGG1* −15C>G G/G genotype were associated with an increased risk of UC (OR [95 % CI] 1.57 [1.04–2.35] and 1.57 [1.04–2.35], respectively). Participants with high urinary total arsenic, regardless of the haplotype of *hOGG1* Ser326Cys and the −15C>G polymorphism, had significantly higher urinary 8-OHdG compared to participants with low urinary total arsenic. This is the first study to investigate the joint effects of high urinary total arsenic or inefficient arsenic methylation capacity indices, and the high-risk G–G haplotype of *hOGG1* on the risk of UC. The findings are especially meaningful for participants with risk factors such as high urinary total arsenic, inefficient arsenic methylation indices, high urinary 8-OHdG, and the high-risk G–G haplotype of *hOGG1* which are all associated with an increased UC risk.

Keywords Arsenic · Methylation · 8-Hydroxydeoxyguanosine · 8-Oxoguanine DNA glycosylase · Haplotype · Urothelial carcinoma

✉ Yu-Mei Hsueh
ymhsueh@tmu.edu.tw

[1] Department of Urology, National Taiwan University Hospital, College of Medicine National Taiwan University, Taipei, Taiwan

[2] Department of Chinese Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan

[3] School of Public Health, College of Public Health and Nutrition, Taipei Medical University, Taipei, Taiwan

[4] Department of Family Medicine, Shung Ho Hospital, Taipei Medical University, Taipei, Taiwan

[5] Department of Health Examination, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

[6] Division of Family Medicine, School of Medicine, Taipei Medical University, Taipei, Taiwan

[7] Department of Public Health, School of Medicine, College of Medicine, Taipei Medical University, No. 250 Wu-Hsing Street, Taipei 110, Taiwan

Introduction

Urothelial carcinoma (UC) can arise from the urothelium of the lower urinary tract, which includes the urinary bladder, or the upper urinary tract, which includes the renal pelvis and ureter (Liang et al. 2012). UC accounts for more than 90 % of cases of bladder cancer and the incidence of UC ranks seventh in men and seventeenth in women among cancers worldwide (Jemal et al. 2010). Environmental and occupational risk factors such as cigarette smoking and arsenic exposure are well-known risk factors for urothelial bladder cancer (Burger et al. 2013).

Worldwide, more than 200 million people are exposed to arsenic in drinking water at levels exceeding the World Health Organization's guideline of 10 µg/L (WHO 2008). Several epidemiological studies in Taiwan have demonstrated that 2 to 3 decades of chronic exposure to high concentrations of arsenic in drinking water is associated with high risks of skin, bladder, kidney, liver, lung, and prostate cancers (Chen et al. 1988), as well as high risks of peripheral vascular disease (Tseng 2008), cardiovascular and cerebrovascular disease (Chiou et al. 1997), diabetes mellitus, and hypertension (Chen et al. 2007). Our previous study also showed that subjects who have an unfavorable urinary arsenic profile have an increased risk of UC even at low arsenic exposure levels (Pu et al. 2007).

Arsenic induces oxidative stress and generates reactive oxygen species (ROS), such as the superoxide anion, hydrogen peroxide, and the hydroxyl radical, which play an important role in arsenic toxicity (Flora 2011). One report showed that a high concentration of arsenic produced 8-hydroxy-2′-deoxyguanosine (8-OHdG), which is a biomarker of arsenic-induced oxidative DNA damage (Roy et al. 2011). Our previous study showed that urinary 8-OHdG levels were significantly correlated with urinary total arsenic concentrations. Also, our study showed that UC patients had significantly higher 8-OHdG levels (7.48 ± 0.97 ng/mg creatinine) than healthy controls (5.95 ± 0.21 ng/mg creatinine) (Chung et al. 2008). We also found that urinary 8-OHdG levels were significantly related to urinary total arsenic levels and that levels of urinary 8-OHdG were significantly associated with the odds ratio (OR) of renal cell carcinoma (RCC) in a dose–response relationship after multivariate adjustment (Huang et al. 2012).

DNA damage and DNA repair may work together to stimulate arsenic-induced carcinogenesis. Our recent study found that *XRCC1* 399 Gln/Gln and 194 Arg/Arg DNA repair genes play important roles in poor arsenic methylation capacity and, as such, increase the risk of UC (Chiang et al. 2014). Other polymorphisms or base excision repair (BER) genes may also be involved in arsenic-induced carcinogenesis. Specifically, the human 8-oxoguanine DNA glycosylase (hOGG1) repair enzyme in the BER pathway removes 8-OHdG, which is an important cause of DNA damage (Zhong et al. 2012a). hOGG1 is located at chromosome 3p26.2; a single-nucleotide polymorphism (SNP) at position 1245 bp in exon 7 of the hOGG1 gene with C→G variation results in an amino acid substitution of serine with cysteine at codon 326 (Ser326Cys) (Zhang et al. 2011). A recent study showed that the *hOGG1* 326 Ser/Cys heterozygous genotype was inversely associated with cancer risk (OR [95 % CI] 0.69 [0.50–0.95]) (Ramaniuk et al. 2014). The variant genotype Cys/Cys of *hOGG1* (Ser326Cys) was associated with a significantly increased risk of bladder cancer compared to the Ser/Ser genotype in a North Indian population (Mittal et al. 2012), and another study reported that the *hOGG1* Ser/Cys + Ser/Ser genotype was associated with a significantly increased risk of bladder cancer (adjusted OR [95 % CI] 1.19 [1.01–1.41]) in a Chinese population (Ma et al. 2012). Conversely, another study found that *hOGG1* Ser326Cys polymorphisms did not contribute to the risk of bladder cancer (Zhong et al. 2012b). Results from epidemiologic studies have been inconsistent, some studies found that the Cys allele of *hOGG1* Ser326Cys was associated with an increased risk of bladder cancer (Ma et al. 2012), while other studies found no association (Zhong et al. 2012b). Additionally, another polymorphism of the *hOGG1* (rs2072668; −15C>G) gene, which is present in intron 4, was reported to be the best polymorphic signature for discriminating between gallbladder cancer cases and controls (Srivastava et al. 2011). Further, the combination of *hOGG1* rs2072668 and *hOGG1* Ser326Cys was reported to be strongly associated with an increased risk of breast cancer (Kim et al. 2013). Therefore, the aim of the present study was to explore whether there was an association between *hOGG1* Ser326Cys and *hOGG1*−15C>G polymorphisms and UC. We also investigated the joint effects of urinary 8-OHdG levels, urinary total arsenic levels, arsenic methylation capacity indices, and *hOGG1* polymorphisms and haplotypes on UC risk.

Materials and methods

Study participants

We conducted a hospital-based case–control study that has been described previously (Pu et al. 2007). Briefly, 167 UC cases and 334 age- and gender-matched healthy controls were recruited from the National Taiwan University Hospital and the Taipei Municipal Wan Fang Hospital from March 2007 to April 2009. All UC cases were diagnosed by histological confirmation, and none of the UC cases presented with other histology, such as squamous cell carcinoma, adenocarcinoma, sarcoma, lymphoma, or benign lesions. The healthy controls had no prior history of cancer. All study participants lived in Taiwan City, which is 200–300 km away from arsenic-contaminated areas. The participants drank tap water supplied by the Taipei Water Department of the Taipei City Government; the average arsenic concentration in tap water in Taiwan City is 0.7 µg/L. The Research Ethics Committee of National Taiwan University Hospital and Taipei Medical University approved this study, and all participants provided written informed consent before the questionnaire interview and biological specimen collection. This study complied with the World Medical Association Declaration of Helsinki.

Questionnaire interview

Well-trained interviewers used a structured questionnaire to collect personal information from all participants, including demographic and socioeconomic characteristics; lifestyle choices such as consumption of alcohol, tea, and coffee and cigarette smoking habits; and family and personal disease histories of diabetes, stroke, and hypertension. Cigarette smoking status was classified as never, former, or current at the time of enrollment. Ever-smokers included former and current smokers.

Determination of urinary 8-OHdG levels

Spot urine samples were collected and placed in 50 mL acid-washed tubes. The samples were immediately transferred to a −20 °C freezer until analysis. To ensure the stability of the samples, 8-OHdG levels were measured within 6 months of collection. Urinary specimens were centrifuged at 1,500 rpm for 10 min to remove particulates. The supernatants were used to measure the enol isomerization of 8-OHdG levels using a competitive in vitro enzyme-linked immunosorbent assay (ELISA) kit (Japan Institute for the Control of Aging, Fukuroi, Japan) (Saito et al. 2000). The detailed procedure was described previously (Chung et al. 2008). The detection range of the ELISA assay was 0.5–200 ng/mL. The intra-assay coefficient of variance (CV) was 9.8 % and the inter-assay CV was 6.7 %. The urinary concentrations of 8-OHdG were corrected using individual urinary creatinine concentrations.

Determination of urinary arsenic species

To ensure the reliability of the urinary arsenic profiles, arsenic species were detected within 6 months after collection of urine samples (Chen et al. 2002). Frozen urine samples were thawed at room temperature, dispersed by ultrasonic wave, and filtered through a Sep-Pak C18 column (Mallinckrodt Baker, Inc., Phillipsburg, NJ, USA). A 200-μL urine aliquot was applied to each Phenomenex column (Nucleosil, Torrance, CA, USA) to determine the concentrations of arsenic species by high-performance liquid chromatography (Waters Corporation, Milford, MA, USA). Next, the proportions of inorganic arsenic (iAs), including both arsenite (As^{III}) and arsenate (As^{V}), monomethylarsonic acid (MMA^{V}), and dimethylarsonic acid (DMA^{V}) were quantified using a hybrid generator and atomic absorption spectrometry (Hsueh et al. 1998). The presence of arsenic species is not influenced by dietary factors such as the ingestion of shellfish, fish, or other seafood (Hsueh et al. 2002). The recovery rates of As^{III}, As^{V}, MMA^{V}, and DMA^{V} ranged from 93.8 to 102.2 %, with detection limits of 0.02, 0.06, 0.07, and 0.10 μg/L, respectively. The standard reference material, SRM 2670, was obtained from the National Institute of Standards and Technology (Gaithersburg, MD, USA), and it contained 480 ± 100 μg/L iAs. SRM 2670 was analyzed at the same time as the test urine samples to control for the quality of the method; an average value of 507 ± 17 μg/L ($n = 4$) iAs was recorded for the reference material. The reliability of urinary arsenic measurements was assessed by the CV of duplicate samples, which was calculated to be less than 5 %. The sum of As^{V}, As^{III}, and the methylated metabolites (MMA^{V} and DMA^{V}) was defined as total urinary arsenic; this level was not affected by organic arsenic species from seafood. Arsenic methylation capacity indices were defined as the percentage of iAs (iAs%), the percentage of MMA^{V} (MMA^{V}%), and the percentage of DMA^{V} (DMA^{V}%), which were calculated by dividing the concentration of each arsenic species by the total urinary arsenic concentration and then multiplying by 100.

Genotype determination

Genomic DNA was extracted using proteinase K digestion after phenol and chloroform extraction. Genotyping for *hOGG1* (Ser326Cys) and *hOGG1* (−15C>G) was performed with the Sequenom MassARRAY platform with iPLEX Gold chemistry (Sequenom, San Diego, CA, USA). According to the manufacturer's guidelines, the specific polymerase chain reaction (PCR) primer and extension primer sequences were designed with the Assay Designer software package (v.4.0). A 1-μL sample of genomic DNA (10 ng/μL) was used for the multiplex PCR; the total reaction mixture had a volume of 5 μL and contained 0.2 units of Taq polymerase, 2.5 pmol of each PCR primer, and 25 mM of each deoxynucleotide (dNTP) (Sequenom, PCR Accessory and Enzyme Set). The thermocycler protocol was as follows: 94 °C for 4 min; 45 cycles of 94 °C for 20 s, 56 °C for 30 s, and 72 °C for 1 min; and a final step of 72 °C for 3 min. Unincorporated dNTPs were deactivated using 0.3 U of shrimp alkaline phosphatase. The single-base extension reaction was conducted with the iPLEX enzyme, terminator mix, and extension primer mix. The thermocycler protocol was as follows: 94 °C for 30 s; 40 cycles of 94 °C for 5 s, including 5 inner cycles of 56 °C for 5 s and 80 °C for 5 s; and a final step of 72 °C for 3 min (Sequenom, iPLEX Gold kit). A cation exchange resin was added to remove residual salt from the reactions, and 7 nL of the purified primer extension reaction was loaded onto a matrix pad of a SpectroCHIP (Sequenom). SpectroCHIPs were analyzed using the MassARRAY Analyzer 4, and the clustering analysis was completed with TYPER 4.0 software.

Statistical analysis

Continuous variables are shown as means ± standard error. The analysis of variance and least significant difference test were applied to compare different urinary 8-OHdG levels among combined groups of urinary total arsenic levels and *hOGG1* haplotypes. The Hardy–Weinberg equilibrium (HWE) was assessed by a goodness-of-fit Chi-square test to examine possible genotyping errors for each SNP among the controls. The frequencies of *hOGG1* (Ser326Cys) and *hOGG1* (−15C>G) were fit to HWE among the controls. Dose–response relationships for continuous variables were estimated by the cutoff points of the respective tertiles of the distribution of the controls. A trend test was performed by treating ordinal variables as continuous variables in the logistic regression model. Multivariate-adjusted ORs and 95 % confidence intervals (CIs) were estimated by multiple logistic regression models. The strength of the linkage disequilibrium (LD), shown by Lewontin *D'*, was calculated using the Haploview software package, version 4.1 (Barrett et al. 2005). *hOGG1* haplotypes were estimated based on the expectation–maximization algorithm using the SAS/Genetics module. We used the additive model (synergy index) to evaluate the joint effects of *hOGG1* haplotype and urinary 8-OHdG level, urinary total arsenic level or arsenic methylation capacity indices on UC risk (Hosmer and Lemeshow 1992). All analyses were conducted using the Statistical Analysis Software (SAS) statistical package (SAS, version 9.2, Cary, NC, USA).

Results

Participants with a higher educational level had a significantly lower risk of UC than those with a lower educational level. Former cigarette smokers had a significantly higher risk of UC than non-smokers (OR 3.42, 95 % CI 2.05–5.68) and ever-smokers had a 2.59-fold higher risk of UC than non-smokers (data not shown). The distribution of genotypes and haplotypes of *hOGG1*, urinary 8-OHdG levels, and urinary arsenic profiles of UC patients and healthy controls are shown in Table 1. The distribution of each genotype fit the HWE in the control participants. After multivariate adjustment, participants with the *hOGG1*-326 Cys/Cys genotype had a significantly higher risk of UC than those with the *hOGG1*-326 Ser/Ser + Ser/Cys genotype (OR 1.57, 95 % CI 1.04–2.35). Participants with the *hOGG1*−15 G/G genotype also had a significantly higher risk of UC than those with the *hOGG1*−15 G/C + C/C genotype.

In the present study, the Lewontin *D'* between *hOGG1* (Ser326Cys) and *hOGG1* (−15C>G) polymorphisms was 0.98, which indicated LD. The associations between *hOGG1* haplotypes (326, −15) composed of two loci at Ser326Cys and −15C>G and the risk of UC were evaluated. The *hOGG1* low-risk haplotype, C–C/G–C, was associated with a significantly lower risk of UC (OR 0.77; 95 % CI 0.57–1.02) compared with the high-risk haplotype, G–G, in a multivariate-adjusted model. We also observed significant dose–response relationships between high urinary total arsenic levels, inefficient arsenic methylation capacity indices (high inorganic arsenic percent, high MMA^{V} percent, and low DMA^{V} percent) and high urinary 8-OHdG levels and the increased risk of UC in this study.

Table 2 lists the associations between urinary arsenic profiles, urinary 8-OHdG levels, and UC risk stratified by *hOGG1* haplotype. Among patients with the *hOGG1* C–C/G–C haplotype, high urinary 8-OHdG levels, and high urinary total arsenic levels, inefficient arsenic methylation capacity indices were associated with an increased risk of UC; the ORs (95 % CI) associated with increasing 8-OHdG levels were 1.00, 2.10 (1.15–3.84), and 2.10 (1.13–3.90), and the ORs (95 % CI) associated with increasing urinary total arsenic levels, increasing iAs%, increasing MMA^{V}%, and increasing DMA^{V}% were 1.00, 2.66 (1.20–5.92), and 7.72 (3.58–16.67); 1.00, 1.53 (0.84–3.40), and 1.92 (1.08–3.40); 1.00, 0.85 (0.43–1.68), and 3.40 (1.89–6.09); and 1.00, 0.38 (0.22–0.66), and 0.31 (0.17–0.55), respectively. Among participants with the *hOGG1* G–G haplotype, we also observed similar associations between urinary 8-OHdG levels, urinary total arsenic levels, and arsenic methylation capacity indices and UC risk.

Table 3 lists the joint effects of urinary arsenic profiles and urinary 8-OHdG levels on UC risk stratified by *hOGG1* haplotype. Participants with low 8-OHdG levels and low urinary total arsenic levels, low iAs%, low MMA%, or high DMA% were used as the reference group for analysis. A trend analysis revealed progressively increasing risks through exposure to no risk factors, either one of the risk factors, or both risk factors. The risk of UC was more pronounced in participants with high urinary 8-OHdG and high urinary total arsenic or inefficient arsenic methylation indices, with the exception of MMA%, who had the *hOGG1* G–G haplotype than in participants who had the *hOGG1* C–C/G–C haplotype; the risk was evident in a dose–response manner. Although urinary 8-OHdG concentration tended to interact additively with urinary total arsenic or arsenic methylation capacity indices to modify UC risk, none of the synergy indices of the interactions were statistically significant.

We further analyzed the joint effects of *hOGG1* haplotype and urinary arsenic profiles or urinary 8-OHdG levels on UC risk after adjusting for age, sex, educational level, and cigarette smoking status (Table 4). Participants with low 8-OHdG levels and the *hOGG1* C–C/G–C haplotype were used as the reference group; the ORs (95 %

Table 1 *hOGG1* genotypes, *hOGG1* haplotypes, urinary arsenic profiles, and urinary 8-OHdG levels of urothelial carcinoma (UC) cases and healthy, non-UC controls

Variables	UC cases *N* (%)	Controls *N* (%)	Age-gender adjusted ORs (95 % CI)	Multivariate ORs[†] (95 % CI)
hOGG1(Ser326Cys)				
Ser/Ser	26 (15.6)	55 (16.5)	1.00	1.00
Ser/Cys	67 (40.1)	161 (48.2)	0.88 (0.51–1.52)	0.94 (0.53–1.67)
Cys/Cys	74 (44.3)	118 (35.3)	1.33 (0.77–2.30)	1.49 (0.83–2.68)
Ser/Ser + Ser/Cys	93 (55.7)	216 (64.7)	1.00	1.00
Cys/Cys	74 (44.3)	118 (35.3)	1.46 (1.00–2.14)*	1.57 (1.04–2.35)*
hOGG1(C[−15]G)				
C/C	26 (15.6)	52 (15.6)	1.00	1.00
G/C	67 (40.1)	164 (49.1)	0.81 (0.47–1.41)	0.84 (0.47–1.50)
G/G	74 (44.3)	118 (35.3)	1.26 (0.72–2.18)	1.38 (0.77–2.48)
C/C + G/C	93 (55.7)	216 (64.7)	1.00	1.00
G/G	74 (44.3)	118 (35.3)	1.46 (1.00–2.14)*	1.57 (1.04–2.35)*
hOGG1 haplotypes[a]				
G–G	215 (64.4)	397 (59.4)	1.00	1.00
C–C	119 (35.6)	268 (40.1)	0.82 (0.62–1.08)	0.78 (0.58-1.04)
G–C	0	3 (0.05)	–	–
G–G	215 (64.4)	397 (59.4)	1.00	1.00
C–C/G–C	119 (35.6)	271 (40.6)	0.81 (0.62–1.06)	0.77 (0.57–1.02)$^+$
Urinary total arsenic (μg/g creatinine)	39.5 ± 3.26	20.7 ± 0.84		
≤12.24	13 (7.80)	112 (33.6)	1.00[§]	1.00[§]
12.24–21.80	35 (21.0)	111 (33.2)	3.50 (1.52–5.14)**	2.44 (1.19–5.02)*
>21.80	119 (71.2)	111 (33.2)	11.6 (5.97–22.61)**	8.44 (4.25–16.75)**
Arsenic species (%)				
Inorganic arsenic	7.74 ± 0.76	7.39 ± 0.57		
≤2.95	43 (25.8)	112 (33.6)	1.00[§]	1.00[§]
2.95–6.54	54 (32.3)	111 (33.2)	1.27 (0.79–2.05)	1.32 (0.80–2.20)
>6.54	70 (41.9)	111 (33.2)	1.68 (1.05–2.68)*	1.66 (1.01–2.73)*
MMA^V	13.1 ± 0.99	7.96 ± 0.40		
≤3.94	34 (20.4)	112 (33.6)	1.00[§]	1.00[§]
3.94–9.20	38 (22.7)	111 (33.2)	1.14 (0.67–1.94)	1.05 (0.60–1.84)
>9.20	95 (56.9)	111 (33.2)	2.87 (1.79–4.63)**	2.58 (1.56–4.25)**
DMA^V	79.3 ± 1.21	84.9 ± 0.64		
≤82.60	83 (49.7)	112 (33.6)	1.00[§]	1.00[§]
82.60–91.23	51 (30.5)	111 (33.2)	0.61 (0.40–0.95)*	0.62 (0.39–0.99)*
>91.23	33 (19.8)	111 (33.2)	0.39 (0.24–0.64)**	0.42 (0.25–0.70)**
8-OHdG (ng/mg creatinine)	8.73 ± 1.45	5.15 ± 0.17		
≤3.52	37 (22.2)	112 (33.6)	1.00[§]	1.00[§]
3.52–5.93	57 (34.1)	111 (33.2)	1.57 (0.96–2.58)$^+$	1.60 (0.95–2.69)$^+$
>5.93	73 (43.7)	111 (33.2)	2.08 (1.27–3.41)**	1.85 (1.10–3.13)*

Values expressed as number (percent) or mean ± SE unless noted otherwise

$^+$ $0.05 \leq P < 0.1$; * $P < 0.05$; ** $P < 0.01$; [§] $P < 0.05$ for trend test

[†] Adjusted for age, gender, educational level, and cigarette smoking status

[a] *hOGG1* haplotypes listed in the following order: C[−15]G and Ser326Cys, and neither case nor control with CG haplotype

CI) for the combinations of low 8-OHdG and *hOGG1* G–G haplotype, high 8-OHdG and *hOGG1* C–C/G–C haplotype, and high 8-OHdG and *hOGG1* G–G haplotype were 1.05 (0.68–1.61), 1.11 (0.70–1.78), and 1.71 (1.13–2.58), respectively. When participants with low urinary total arsenic and the *hOGG1* C–C/G–C haplotype were used as the

Table 2 Associations between 8-OHdG, urinary arsenic profiles, and urothelial carcinoma stratified by *hOGG1* haplotype

Variables	*hOGG1* haplotypes[a]			
	C–C/G–C		G–G	
	Case/control (*N*)	Multivariate ORs[†] (95 % CI)	Case/control (*N*)	Multivariate ORs[†] (95 % CI)
Urinary total arsenic (μg/g creatinine)				
≤12.24	10/91	1.00[§]	16/133	1.00[§]
12.24–21.80	31/92	2.66 (1.20–5.92)*	39/130	2.32 (1.19–4.54)*
>21.80	78/88	7.72 (3.58–16.67)**	160/134	8.82 (4.69–16.57)**
Arsenic species (%)				
Inorganic arsenic				
≤2.95	28/96	1.00[§]	58/128	1.00[§]
2.95–6.54	38/82	1.53 (0.84–3.40)	70/140	1.26 (0.80–2.00)
>6.54	53/93	1.92 (1.08–3.40)*	87/129	1.58 (1.00–2.49)*
MMA^V				
≤3.94	23/93	1.00[§]	45/131	1.00[§]
3.94–9.20	21/92	0.85 (0.43–1.68)	55/130	1.12 (0.68–1.85)
>9.20	75/86	3.40 (1.89–6.09)**	115/136	2.11 (1.34–3.33)**
DMA^V				
≤82.60	68/86	1.00[§]	98/138	1.00[§]
82.60–91.23	29/92	0.38 (0.22–0.66)**	73/130	0.80 (0.53–1.23)
>91.23	22/93	0.31 (0.17–0.55)**	44/129	0.51 (0.32–0.82)**
8-OHdG (ng/mg creatinine)				
≤3.52	26/95	1.00[§]	48/129	1.00[§]
3.52–5.93	44/85	2.10 (1.15–3.84)**	70/135	1.35 (0.84–2.17)
>5.93	49/91	2.10 (1.13–3.90)**	97/133	1.71 (1.07–2.74)*

* $P < 0.05$; ** $P < 0.01$; [§] $P < 0.05$ for trend test

[†] Adjusted for age, gender, educational level, and cigarette smoking status

[a] *hOGG1* haplotypes listed in the following order: C[−15]G and Ser326Cys

reference group, the ORs (95 % CI) for the combinations of low urinary total arsenic and *hOGG1* G–G haplotype, high urinary total arsenic and *hOGG1* C–C/G–C haplotype, and high urinary total arsenic and *hOGG1* G–G haplotype were 1.15 (0.63–2.07), 4.24 (2.49–7.22), and 5.01 (3.04–8.25), respectively. The joint effects of the *hOGG1* haplotype and inefficient arsenic methylation capacity indices had similar dose–response relationships. We noted joint effects for urinary total arsenic level or inefficient arsenic methylation capacity indices plus *hOGG1* haplotype and urinary 8-OHdG level plus *hOGG1* haplotype, with a significant dose–response relationship observed for UC risk ($p < 0.05$ for the trend test). However, these interactions were not statistically significant.

We also evaluated the effect of high urinary total arsenic levels and the high-risk G–G haplotype of *hOGG1* on urinary 8-OHdG levels (Fig. 1). We found that urinary 8-OHdG levels were associated with the following haplotypes in significant dose–response relationships in the following sequence: G–G haplotype of *hOGG1* and high urinary total arsenic (mean urinary 8-OHdG 7.73 ± 0.76 ng/mg creatinine), C–C/G–C haplotype of *hOGG1* and high urinary total arsenic (mean urinary 8-OHdG 6.75 ± 0.83 ng/mg creatinine), G–G haplotype of *hOGG1* and low urinary total arsenic (mean urinary 8-OHdG 4.79 ± 0.19 ng/mg creatinine), and C–C/G–C haplotype of *hOGG1* and low urinary total arsenic (mean urinary 8-OHdG 4.64 ± 0.21 ng/mg creatinine). However, we did not observe the same effects of inefficient arsenic methylation capacity indices and the high-risk GG haplotype of *hOGG1* on urinary 8-OHdG levels (data not shown).

Discussion

This study revealed associations between genotypes and haplotypes of two *h*OGG1 genes and UC risk. Participants with the *hOGG1* (Ser326Cys) Cys/Cys and *hOGG1* (−15C>G) G/G genotypes had significantly higher risks of UC than those with the *hOGG1* (Ser326Cys) Ser/Ser + Ser/Cys genotype and the *hOGG1* (−15C>G) G/C + C/C genotype, respectively. Participants with the

Table 3 Joint effects of urinary arsenic profiles and 8-OHdG levels on urothelial carcinoma risk stratified by *hOGG1* haplotype

Variables		*hOGG1* haplotypes[a]			
		C–C/G–C		G–G	
		Case/control (*N*)	Multivariate ORs[†] (95 % CI)	Case/control (*N*)	Multivariate ORs[†] (95 % CI)
Urinary total arsenic (µg/g creatinine)	8-OHdG (ng/mg creatinine)				
≤16.47	≤4.73	15/79	1.00[§]	13/103	1.00[§]
	>4.73	9/64	1.06 (0.42–2.69)	19/88	2.31 (1.02–5.21)*
>16.47	≤4.73	40/59	4.13 (1.99–8.56)**	68/93	5.75 (2.80–11.81)**
	>4.73	55/69	4.70 (2.27–9.76)**	115/113	7.25 (3.60–14.59)**
Inorganic arsenic (%)					
≤4.23	≤4.73	20/56	1.00[§]	34/108	1.00[§]
	>4.73	21/74	0.74 (0.35–1.57)	63/96	1.88 (1.10–3.23)*
>4.23	≤4.73	35/82	1.03 (0.52–2.04)	47/88	1.60 (0.90–2.84)
	>4.73	43/59	1.91 (0.97–3.78)[+]	71/105	2.04 (1.20–3.47)**
MMA^V (%)					
≤6.54	≤4.73	9/62	1.00[§]	17/102	1.00[§]
	>4.73	22/73	2.35 (0.96–5.76)[+]	52/97	3.01 (1.55–5.82)**
>6.54	≤4.73	46/76	4.39 (1.95–9.91)**	64/94	3.28 (1.73–6.22)**
	> 4.73	42/60	4.99 (2.15–11.61)**	82/104	3.72 (1.98–6.99)**
DMA^V (%)					
>87.40	≤4.73	9/60	1.00[§]	9/110	1.00[§]
	>4.73	20/75	1.93 (0.79–4.75)	48/89	5.82 (2.60–13.01)**
≤87.40	≤4.73	46/78	4.10 (1.82–9.27)**	72/86	8.82 (4.01–19.43)**
	>4.73	44/58	4.92 (2.14–11.31)**	86/112	8.15 (3.76–17.66)**

[+] $0.05 \le P < 0.1$; * $P < 0.05$; ** $P < 0.01$; [§] $P < 0.05$ for trend test

[†] Adjusted for age, gender, educational level, and cigarette smoking status

[a] *hOGG1* haplotypes listed in the following order: C[−15]G and Ser326Cys

G–G haplotype of *hOGG1* (Ser326Cys) and the (−15C>G) polymorphism had a significantly higher risk of UC than those with the *hOGG1* C–C/G–C haplotype. There are significant dose–response relationships between high urinary total arsenic levels, inefficient arsenic methylation capacity indices and high urinary 8-OHdG levels and the increased risk of UC, which are similar to the findings of our previous studies (Chung et al. 2008; Pu et al. 2007).

To our knowledge, this is the first case–control study to simultaneously evaluate the associations among the *hOGG1* gene polymorphisms, urinary total arsenic level, inefficient arsenic methylation capacity indices, and urinary 8-OHdG levels and the risk of UC. We found that participants who had high urinary total arsenic levels and carried the high-risk G–G haplotype of *hOGG1* had high urinary 8-OHdG levels. Participants with the combination of the high-risk G–G haplotype of *hOGG1* and the high urinary 8-OHdG concentration or with the combination of the high-risk G–G haplotype of *hOGG1* and high urinary total arsenic level or inefficient arsenic methylation capacity indices had higher risks of UC than other combination groups.

Arsenic induces ROS generation (Ruiz-Ramos et al. 2009) and mediates DNA damage (Nesnow et al. 2002). Urinary 8-OHdG is a marker of oxidative DNA damage (Flora 2011) and increased 8-OHdG levels have been observed in the urine of individuals with acute arsenic intoxication (Qin et al. 2008; Yamauchi et al. 2004). Our epidemiological data also show that urinary 8-OHdG levels are associated with urinary total arsenic levels and are related to an increased risk of UC and RCC, even in patients without obvious arsenic exposure (Chung et al. 2008; Huang et al. 2012). Therefore, urinary 8-OHdG levels might reflect the risk of oxidative DNA damage at varying levels of arsenic exposure. In addition, an in vitro study reported that arsenic increased oxidative DNA damage, which led to a decrease in or lack of OGG1 activity (Bach et al. 2014). A follow-up study reported that increased levels of DNA damage, measured by salivary 8-OHdG levels, and decreased DNA repair capacity, measured by levels of hOGG1 expression, may result from low arsenic exposure early in life (Hinhumpatch et al. 2013).

Table 4 Joint effects of *hOGG1* haplotype and urinary arsenic profiles or 8-OHdG on urothelial carcinoma risk

Variables		Case/control (%)	Multivariate ORs[†] (95 % CI)
Urinary total arsenic (μg/g creatinine)	*hOGG1* haplotypes[a]		
≤16.47	C–C/G–C	24/143	1.00[§]
	G–G	32/191	1.15 (0.63–2.07)
>16.47	C–C/G–C	95/128	4.24 (2.49–7.22)**
	G–G	183/206	5.01 (3.04–8.25)**
Inorganic arsenic (%)			
≤4.23	C–C/G–C	41/130	1.00[§]
	G–G	97/204	1.59 (1.12–2.50)*
>4.23	C–C/G–C	78/141	1.71 (1.06–2.74)*
	G–G	118/193	2.01 (1.29–3.15)**
MMA^V (%)			
≤6.54	C–C/G–C	31/135	1.00[§]
	G–G	69/199	1.81 (1.09–2.98)*
>6.54	C–C/G–C	88/136	2.86 (1.74–4.70)**
	G–G	146/198	3.15 (1.98–5.02)**
DMA^V (%)			
>87.40	C–C/G–C	29/135	1.00[§]
	G–G	57/199	1.57 (0.93–2.64)[+]
≤87.40	C–C/G–C	90/136	3.22 (1.94–5.36)**
	G–G	158/198	3.85 (2.37–6.20)**
8-OHdG (ng/mg creatinine)			
≤4.73	C–C/G–C	55/138	1.00[§]
	G–G	81/196	1.05 (0.68–1.61)
>4.73	C–C/G–C	64/133	1.11 (0.70–1.78)
	G–G	134/201	1.71 (1.13–2.58)**

[+] $0.05 \le P < 0.1$; * $P < 0.05$; ** $P < 0.01$; [§] $P < 0.05$ for trend test

[†] Adjusted for age, gender, educational level, and cigarette smoking status

[a] *hOGG1* haplotypes listed in the following order: C[−15]G and Ser326Cys

Cancer can develop if DNA repair systems are dysfunctional. The enzyme activity of the hOGG1 protein may be influenced by the polymorphisms of hOGG1 to decrease repair activity of 8-OHdG and DNA damage, which play critical roles in the carcinogenesis of cancers. An in vitro study showed that a cell carrying the *OGG1* (Ser326Cys) homozygous Cys allele demonstrated high genetic instability and low DNA repair capacity (Bravard et al. 2009). Other studies have also reported that the variant genotype Cys/Cys of *hOGG1* (Ser326Cys) is associated with a significant risk of bladder cancer in Japanese (Arizono et al. 2008), Turkish (Karahalil et al. 2006), and North Indian populations (Mittal et al. 2012). Another study also showed that the *hOGG1* (Ser326Cys) Cys/Cys genotype was associated with an elevated risk of urothelial bladder cancer (OR 2.10; $p = 0.028$) (Gangwar et al. 2009). These results are similar to the results of our present study, and they suggest that the *hOGG1* Cys326 allele has significantly lower hOGG1 activity, and cannot prevent mutagenesis caused by 8-OHdG in human cells compared with the *hOGG1* Ser326 allele (Simonelli et al. 2013; Yamane et al. 2004). In contrast, another study reported that the *hOGG1* (Ser326Cys) Ser/Cys + Ser/Ser genotype was associated with a significant risk of bladder cancer (Ma et al. 2012), but the *hOGG1* 326 Ser/Cys heterozygous genotype was reported to significantly reduce the risk of bladder cancer in smokers (Ramaniuk et al. 2014). These inconsistent results may suggest a role of ethnic differences, genetic background, and environmental exposure in the development of UC; the inconsistent results may also be due to small sample sizes.

In this study, in addition to the *hOGG1* 326 Cys/Cys genotype, we evaluated another polymorphism of the hOGG1 gene present in intron 4 of *hOGG1* −15C>G and found that the G/G genotype was associated with a significantly increased risk of UC. These polymorphisms are likely also involved in the hOGG1 mRNA; however, these two polymorphisms followed a recessive model in their effects on UC risk. Haplotype analysis revealed that

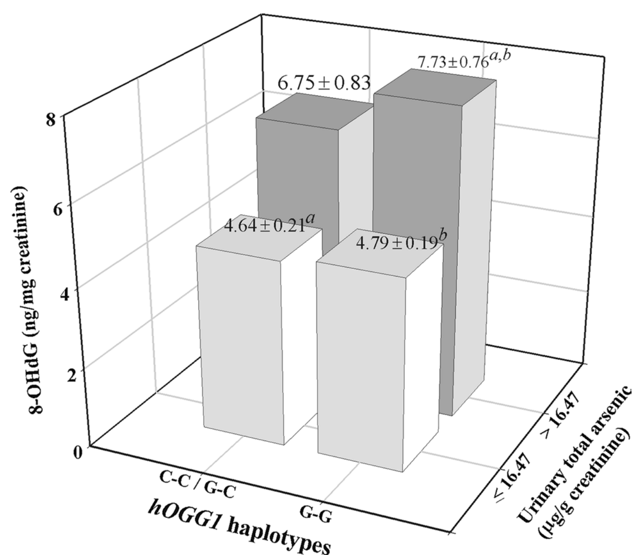

Fig. 1 Joint effects of urinary total arsenic level and *hOGG1* haplotypes on urinary 8-OHdG levels among the entire study population. [a]Urinary 8-OHdG levels of the G-G haplotype of *hOGG1* and high urinary total arsenic group compared to the C–C/G–C haplotype of *hOGG1* and low urinary total arsenic group; [b]urinary 8-OHdG levels of the G–G haplotype of *hOGG1* and high urinary total arsenic group compared to the G–G haplotype of *hOGG1* and low urinary total arsenic group

3 possible haplotypes (neither case nor control with C–G haplotype), the G–G haplotype of the *hOGG1* Ser326Cys, and the −15C>G polymorphism were significantly associated with an increased risk of UC. This finding is similar to the findings of a study that revealed that the G–G haplotype of the *hOGG1* Ser326Cys and −15C>G polymorphism were associated with a twofold increased risk of gallbladder cancer (Srivastava et al. 2010).

Participants with the combination of the G–G haplotype of the *hOGG1* Ser326Cys and the −15C>G polymorphism and high urinary total arsenic, high urinary 8-OHdG concentration, or inefficient arsenic methylation capacity indices had the highest risk of UC compared to other combination groups (Table 4); the risk was evident in a dose–response manner. This finding offers a possible explanation for increasing urinary 8-OHdG concentrations in participants with high urinary total arsenic levels (Bhattacharjee et al. 2013; Chung et al. 2008), inefficient methylation capacity indices (high urinary iAs%, MMA^{V}%, and DMA^{V}%) (Xu et al. 2008), or high urinary levels of iAs, MMA^{V}, and DMA^{V} (Chung et al. 2008; Xu et al. 2008). An in vitro study showed that acute arsenic exposure induced production of ROS and reduced hOGG1 activity in human cells (Mei et al. 2002); arsenic exposure from drinking water can cause a reduction in hOGG1 capacity in humans (Osmond et al. 2010). Additionally, arsenic can cause fragmentation of mouse OGG1, resulting in DNA repair inhibition and accumulation of 8-OHdG (Hirano et al. 2006). Another explanation is that individuals carried the *hOGG1* 326 Cys/Cys genotype had significantly higher urinary 8-OHdG than those with the 326 Ser/Cys and Ser/Ser genotypes in a population with arsenic exposure (Fujihara et al. 2011). Therefore, we conclude that participants with high urinary total arsenic level, inefficient arsenic methylation capacity, high urinary 8-OHdG level, and the high-risk G–G haplotype of *hOGG1*, have a higher risk of UC than participants with low level or efficient capacity of these risk factors.

Our recent study found that *XRCC1* 399 Gln/Gln and 194 Arg/Arg DNA repair genes play important roles in poor arsenic methylation capacity and, thereby, increase the risk of UC (Chiang et al. 2014). In this study, we only examined *hOGG1* polymorphisms involved in the BER pathway. Other polymorphisms of BER genes may actually be responsible for the observed responses. Also, untyped SNPs may be in the LD with our selected SNPs. Due to the low frequency of the allele among the Han Chinese and the limited experimental methodology, we selected *hOGG1* Ser326Cys and *hOGG1* −15C>G as representative polymorphisms in the *hOGG1* gene. In addition, we did not measure the actual hOGG1 enzyme activity to provide relevant information of the *hOGG1* gene polymorphism was the limitation. Since this was designed as a case–control study, we cannot exclude the possibility that the association between urinary 8-OHdG levels and UC is the result, and not the cause, of UC. In addition, the sample size was small, so statistical significance should be interpreted with caution.

To our knowledge, this is the first study to show a dose–response relationship of the combined effects of high urinary total arsenic levels or inefficient arsenic methylation capacity indices or high 8-OHdG level and the high-risk G–G haplotype of hOGG1 on the OR of UC. Our data provide evidence that, in humans, the combination of high urinary total arsenic and the high-risk G–G haplotype of *hOGG1* may be related to the induction of oxidative stress as indicated by increased urinary 8-OHdG levels.

Acknowledgments This study was supported by grants from the National Science Council of the Republic of China (NSC 86-2314-B-038-038, NSC 87-2314-B-038-029, NSC-88-2314-B-038-112, NSC-89-2314-B038-049, SC-89-2320-B038-013, NSC-90-2320-B-038-021, NSC-91-3112-B-038-0019, NSC-92-31 12-B-038-001, NSC-93-3112-B-038-001, NSC-94-2314-B-038-023, NSC-95-2314-B-038-007, NSC-96-2314-B038-003, NSC-97-2314-B-038-015-MY3 (1-3), NSC-97-2314-B-038-015-MY3 (2-3), NSC-97-2314-B-038-015-MY3 (3-3)), NSC 100-2314-B-038 -026, NSC 101-2314-B-038 -051-MY3 (1-3), NSC 101-2314-B-038 -051-MY3 (2-3), NSC 101-2314-B-038 -051-MY3 (3-3), MOST103-2314-B-038-021-MY2 (1-2).

Compliance withe ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

Arizono K, Osada Y, Kuroda Y (2008) DNA repair gene hOGG1 codon 326 and XRCC1 codon 399 polymorphisms and bladder cancer risk in a Japanese population. Jpn J Clin Oncol 38:186–191

Bach J, Sampayo-Reyes A, Marcos R, Hernandez A (2014) Ogg1 genetic background determines the genotoxic potential of environmentally relevant arsenic exposures. Arch Toxicol 88:585–596

Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 21:263–265

Bhattacharjee P, Banerjee M, Giri AK (2013) Role of genomic instability in arsenic-induced carcinogenicity. A review. Environ Int 53:29–40

Bravard A, Vacher M, Moritz E, Vaslin L, Hall J, Epe B, Radicella JP (2009) Oxidation status of human OGG1-S326C polymorphic variant determines cellular DNA repair capacity. Cancer Res 69:3642–3649

Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, Kassouf W, Kiemeney LA, La VC, Shariat S, Lotan Y (2013) Epidemiology and risk factors of urothelial bladder cancer. Eur Urol 63:234–241

Chen CJ, Kuo TL, Wu MM (1988) Arsenic and cancers. Lancet 1:414–415

Chen YC, Amarasiriwardena CJ, Hsueh YM, Christiani DC (2002) Stability of arsenic species and insoluble arsenic in human urine. Cancer Epidemiol Biomark Prev 11:1427–1433

Chen CJ, Wang SL, Chiou JM, Tseng CH, Chiou HY, Hsueh YM, Chen SY, Wu MM, Lai MS (2007) Arsenic and diabetes and hypertension in human populations: a review. Toxicol Appl Pharmacol 222:298–304

Chiang CI, Huang YL, Chen WJ, Shiue HS, Huang CY, Pu YS, Lin YC, Hsueh YM (2014) XRCC1 Arg194Trp and Arg399Gln polymorphisms and arsenic methylation capacity are associated with urothelial carcinoma. Toxicol Appl Pharmacol 279:373–379

Chiou HY, Huang WI, Su CL, Chang SF, Hsu YH, Chen CJ (1997) Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. Stroke 28:1717–1723

Chung CJ, Huang CJ, Pu YS, Su CT, Huang YK, Chen YT, Hsueh YM (2008) Urinary 8-hydroxydeoxyguanosine and urothelial carcinoma risk in low arsenic exposure area. Toxicol Appl Pharmacol 226:14–21

Flora SJ (2011) Arsenic-induced oxidative stress and its reversibility. Free Radic Biol Med 51:257–281

Fujihara J, Soejima M, Yasuda T, Koda Y, Kunito T, Iwata H, Tanabe S, Takeshita H (2011) Polymorphic trial in oxidative damage of arsenic exposed Vietnamese. Toxicol Appl Pharmacol 256:174–178

Gangwar R, Ahirwar D, Mandhani A, Mittal RD (2009) Do DNA repair genes OGG1, XRCC3 and XRCC7 have an impact on susceptibility to bladder cancer in the North Indian population? Mutat Res 680:56–63

Hinhumpatch P, Navasumrit P, Chaisatra K, Promvijit J, Mahidol C, Ruchirawat M (2013) Oxidative DNA damage and repair in children exposed to low levels of arsenic in utero and during early childhood: application of salivary and urinary biomarkers. Toxicol Appl Pharmacol 273:569–579

Hirano T, Kawai K, Ootsuyama Y, Kasai H (2006) Fragmentation of the DNA repair enzyme, OGG1, in mouse nonparenchymal liver cells by arsenic compounds. Genes Environ 28:62–67

Hosmer DW, Lemeshow S (1992) Confidence interval estimation of interaction. Epidemiology 3:452–456

Hsueh YM, Huang YL, Huang CC, Wu WL, Chen HM, Yang MH, Lue LC, Chen CJ (1998) Urinary levels of inorganic and organic arsenic metabolites among residents in an arseniasis-hyperendemic area in Taiwan. J Toxicol Environ Health A 54:431–444

Hsueh YM, Hsu MK, Chiou HY, Yang MH, Huang CC, Chen CJ (2002) Urinary arsenic speciation in subjects with or without restriction from seafood dietary intake. Toxicol Lett 133:83–91

Huang CY, Su CT, Chung CJ, Pu YS, Chu JS, Yang HY, Wu CC, Hsueh YM (2012) Urinary total arsenic and 8-hydroxydeoxyguanosine are associated with renal cell carcinoma in an area without obvious arsenic exposure. Toxicol Appl Pharmacol 262:349–354

Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics, 2010. CA Cancer J Clin 60:277–300

Karahalil B, Kocabas NA, Ozcelik T (2006) DNA repair gene polymorphisms and bladder cancer susceptibility in a Turkish population. Anticancer Res 26:4955–4958

Kim KY, Han W, Noh DY, Kang D, Kwack K (2013) Impact of genetic polymorphisms in base excision repair genes on the risk of breast cancer in a Korean population. Gene 532:192–196

Liang PI, Li WM, Wang YH, Wu TF, Wu WR, Liao AC, Shen KH, Wei YC, Hsing CH, Shiue YL, Huang HY, Hsu HP, Chen LT, Lin CY, Tai C, Lin CM, Li CF (2012) HuR cytoplasmic expression is associated with increased cyclin A expression and poor outcome with upper urinary tract urothelial carcinoma. BMC Cancer 12:611

Ma L, Chu H, Wang M, Shi D, Zhong D, Li P, Tong N, Yin C, Zhang Z (2012) hOGG1 Ser326Cys polymorphism is associated with risk of bladder cancer in a Chinese population: a case-control study. Cancer Sci 103:1215–1220

Mei N, Kunugita N, Hirano T, Kasai H (2002) Acute arsenite-induced 8-hydroxyguanine is associated with inhibition of repair activity in cultured human cells. Biochem. Biophys. Res. Commun. 297:924–930

Mittal RD, Mandal RK, Gangwar R (2012) Base excision repair pathway genes polymorphism in prostate and bladder cancer risk in North Indian population. Mech Ageing Dev 133:127–132

Nesnow S, Roop BC, Lambert G, Kadiiska M, Mason RP, Cullen WR, Mass MJ (2002) DNA damage induced by methylated trivalent arsenicals is mediated by reactive oxygen species. Chem Res Toxicol 15:1627–1634

Osmond MJ, Kunz BA, Snow ET (2010) Age and exposure to arsenic alter base excision repair transcript levels in mice. Mutagenesis 25:517–522

Pu YS, Yang SM, Huang YK, Chung CJ, Huang SK, Chiu AW, Yang MH, Chen CJ, Hsueh YM (2007) Urinary arsenic profile affects the risk of urothelial carcinoma even at low arsenic exposure. Toxicol Appl Pharmacol 218:99–106

Qin XJ, Hudson LG, Liu W, Ding W, Cooper KL, Liu KJ (2008) Dual actions involved in arsenite-induced oxidative DNA damage. Chem Res Toxicol 21:1806–1813

Ramaniuk VP, Nikitchenko NV, Savina NV, Kuzhir TD, Rolevich AI, Krasny SA, Sushinsky VE, Goncharova RI (2014) Polymorphism of DNA repair genes OGG1, XRCC1, XPD and ERCC6 in bladder cancer in Belarus. Biomarkers 19:509–516

Roy M, Sinha D, Mukherjee S, Biswas J (2011) Curcumin prevents DNA damage and enhances the repair potential in a chronically arsenic-exposed human population in West Bengal, India. Eur J Cancer Prev 20:123–131

Ruiz-Ramos R, Lopez-Carrillo L, Rios-Perez AD, De Vizcaya-Ruiz A, Cebrian ME (2009) Sodium arsenite induces ROS generation,

DNA oxidative damage, HO-1 and c-Myc proteins, NF-kappaB activation and cell proliferation in human breast cancer MCF-7 cells. Mutat Res 674:109–115

Saito S, Yamauchi H, Hasui Y, Kurashige J, Ochi H, Yoshida K (2000) Quantitative determination of urinary 8-hydroxydeoxyguanosine (8-OH-dg) by using ELISA. Res Commun Mol Pathol Pharmacol 107:39–44

Simonelli V, Camerini S, Mazzei F, Van LB, Allione A, D'Errico M, Barone F, Minoprio A, Ricceri F, Guarrera S, Russo A, Dalhus B, Crescenzi M, Hubscher U, Bjoras M, Matullo G, Dogliotti E (2013) Genotype-phenotype analysis of S326C OGG1 polymorphism: a risk factor for oxidative pathologies. Free Radic Biol Med 63:401–409

Srivastava K, Srivastava A, Mittal B (2010) Polymorphisms in ERCC2, MSH2, and OGG1 DNA repair genes and gallbladder cancer risk in a population of Northern India. Cancer 116:3160–3169

Srivastava K, Srivastava A, Kumar A, Mittal B (2011) Gallbladder cancer predisposition: a multigenic approach to DNA-repair, apoptotic and inflammatory pathway genes. PLoS ONE 6:e16449

Tseng CH (2008) Cardiovascular disease in arsenic-exposed subjects living in the arseniasis-hyperendemic areas in Taiwan. Atherosclerosis 199:12–18

WHO (2008) Guidelines for drinking water quality: incorporating First and second addenda to third edition. Vol 1-recommidations. WHO Press, Geneva? Ref Type: Report

Xu Y, Wang Y, Zheng Q, Li X, Li B, Jin Y, Sun X, Sun G (2008) Association of oxidative stress with arsenic methylation in chronic arsenic-exposed children and adults. Toxicol Appl Pharmacol 232:142–149

Yamane A, Kohno T, Ito K, Sunaga N, Aoki K, Yoshimura K, Murakami H, Nojima Y, Yokota J (2004) Differential ability of polymorphic OGG1 proteins to suppress mutagenesis induced by 8-hydroxyguanine in human cell in vivo. Carcinogenesis 25:1689–1694

Yamauchi H, Aminaka Y, Yoshida K, Sun G, Pi J, Waalkes MP (2004) Evaluation of DNA damage in patients with arsenic poisoning: urinary 8-hydroxydeoxyguanine. Toxicol Appl Pharmacol 198:291–296

Zhang Y, He BS, Pan YQ, Xu YQ, Wang SK (2011) Association of OGG1 Ser326Cys polymorphism with colorectal cancer risk: a meta-analysis. Int J Colorectal Dis 26:1525–1530

Zhong D, Li G, Long J, Wu J, Hu Y (2012a) The hOGG1Ser326Cys polymorphism and increased lung cancer susceptibility in Caucasians: an updated meta-analysis. Sci Rep 2:548

Zhong DY, Chu HY, Wang ML, Ma L, Shi DN, Zhang ZD (2012b) Meta-analysis demonstrates lack of association of the hOGG1 Ser326Cys polymorphism with bladder cancer risk. Genet Mol Res 11:3490–3496