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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

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Abstract

Background—Multiple chromosome 8q24 genotypic variants are strongly implicated in several cancers. Recent genome-wide association studies of urinary bladder cancer report risk to be associated with the T allele of rs9642880 on 8q24 among individuals of European descent.

Methods—We examined associations between bladder cancer risk and genotypes defined by rs9642880 and each of 8 additional 8q24 variants associated with risk of other cancers, in both high-risk non-Hispanic white and low-risk Chinese participants enrolled in a large population-based case–control study conducted in Los Angeles County and Shanghai.

Results—We confirmed association of rs9642880 T with bladder cancer risk not only among non-Hispanic whites but also among Chinese participants [overall per-allele relative risk estimate 1.32 (95% CI, 1.16–1.50; $P = 0.000024$)]. Subgroup analyses suggested that effects of rs9642880 are largely confined to nonsmokers and former smokers, and may be particularly important in the etiology of noninvasive papillary tumors. There was little indication that 8q24 SNPs associated with other cancer types—rs7008482, rs7000448, rs6983561, rs6983267, rs13281615, rs13254738, or rs10090154—are associated with bladder cancer risk.

Conclusions—Bladder cancer risk is associated specifically with variation in the discrete 8q24 region containing rs9642880. Factors other than rs9642880 genotypes seem to underlie differences in bladder cancer risk between non-Hispanic whites and Chinese.

Impact—Characterization of functional consequences of genetic variation in the discrete region including rs9642880 is needed to understand biological basis of this bladder cancer-specific 8q24 association in these racial/ethnic groups characterized by both high and low risk of bladder cancer.

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Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Introduction

Genome-wide studies have identified numerous single-nucleotide polymorphisms (SNP) in a 600-kb region on chromosome 8q24 as being associated with risk of cancers of the prostate (1–4), breast (5), and colorectum (6, 7). These have been confirmed in independent samples (8–13), indicating that genetic variation in this region may play an important role in the etiology of numerous cancers. Recent genome-wide association studies found the 8q24 SNP rs9642880 to be associated with risk of urinary bladder cancer in populations of European descent (14, 15).

European ancestry is a recognized risk factor for bladder cancer. Worldwide, highest incidence occurs in southern and western Europe and in North America, and among the lowest incidence rates occur in Asia (16). Genetic factors are postulated to play an important role in this risk disparity, because differences persist in the United States, where incidence is far higher among non-Hispanic whites than groups of Asian ancestry (17). In Los Angeles County, rates are dramatically higher among non-Hispanic white males than Asian males (18), even though these groups have comparable exposure to cigarette smoke, the major environmental risk factor in the United States. To learn whether genetic variation on 8q24 has similar effects in these populations, we used samples from a case–control study conducted in Los Angeles County, California, and Shanghai, China, investigating associations between bladder cancer risk and rs9642880 as well as 8 additional 8q24 SNPs associated with risk of other cancers.

Materials and Methods

Study participants, data, and samples

Participants in this population-based case–control study of transitional cell carcinoma of the urinary bladder were enrolled in 2 sites, Los Angeles County, California and Shanghai, China. Bladder cancer cases were identified by population-based cancer registries. Cases enrolled in Los Angeles were non-Asian residents of Los Angeles County diagnosed between 1987 and 1996 who were 25–64 years of age at diagnosis; those enrolled in Shanghai were Chinese residents of the city of Shanghai diagnosed between 1995 and 1998 who were 25–74 years of age at diagnosis. Population-based controls were matched to cases on gender and age (within 5 years); in Los Angeles County, controls were further matched to cases on racial-ethnic group (non-Hispanic white, Hispanic white, African American) and neighborhood of residence at the time of cancer diagnosis. Each participant completed an in-person interview. A structured questionnaire queried exposure history before a reference date, defined as 2 years before diagnosis for each bladder cancer patient or 2 years before the interview for each control subject. All participants in Shanghai and those participants in Los Angeles interviewed from 1992 forward were asked to provide peripheral blood samples. Among the 1,666 cases and 1,587 controls completing interviews from 1992 forward, 1,302 cases and 1,307 controls provided blood samples. Analyses reported here were limited to non-Hispanic white participants from Los Angeles and all participants from Shanghai for whom aliquots of DNA were available at the time of genotypic analysis, 1,050 cases and 1,137 controls. The study was approved by the institutional review boards at the University of Southern California, the Shanghai Cancer Institute, and the University of Minnesota.

Genotypic analysis

Genomic DNA was isolated from blood by standard methods. Genotypic analysis of the SNPs rs9642880, rs13281615, rs13254738, rs10090154, rs7008482, rs7000448, rs6983561, rs6983267, and BD11934905 (9) was performed using the fluorogenic 5′-nuclease assay

(TaqMan). A probe specific for each allele was synthesized and labeled with fluorescent dyes (6-FAM or VIC) to distinguish alleles for each locus. The fluorescence profile of each well was measured in a Sequence Detection System (model ABI 7900HT) with results analyzed by the Sequence Detection Software (Applied Biosystems Inc.). Study samples were compared with standards to assist with genotype calling. Any samples outside genotypes defined by the standards were scored as noninformative.

Statistical analysis

Analyses of original data were performed using SAS v9.1 (SAS Institute) and Stata (Stata Corporation). All SNPs conformed to Hardy–Weinberg equilibrium ($P > 0.01$) among controls at each study site. Relative risks (RR) were estimated by odds ratios. Initial allele-specific RRs with 95% confidence intervals (95% CI), and corresponding statistical significance (*P* values) were estimated assuming log-additive genetic risk using conditional logistic regression. Genotype-specific models were used to follow-up associated SNPs to further characterize the genetic association. We stratified on reference age (<45, 45–49, 50–54, 55–59, 60–64, ≥65) and gender separately within each study site; additional adjustment for educational level did not materially affect results, and this adjustment was not included in results presented here. Effect modification by racial/ethnic group (non-Hispanic white, Chinese), reference age (≤, >median reference age among controls, 56 in non-Hispanic white, 64 in Chinese), gender, cigarette smoking status (based on whether participant smoked at least 1 cigarette a day for 6 months or longer: never (no), former (yes, but not during reference year), current (yes, during reference year)), and history of using non–steroidal anti-inflammatory drugs (NSAID; nonusers defined as those with lifetime use of <20 doses) was assessed by likelihood ratio methods. Stratification by tumor stage and grade was possible in the Los Angeles data, and this was examined by logistic regression in case-only analyses. Reported *P* values are 2 sided.

Results and Discussion

Characteristics of study participants are presented in Table 1. Call rates for each genotypic assay were ≥96.9%. Among non-Hispanic white and Chinese participants, BD11934905 was monomorphic (GG genotype). For the remaining 8 SNPs, genotype–bladder cancer associations are presented in Table 2 as per allele RR estimates, calculated using a log-additive model of genetic risk.

Genotypes defined by rs7000448, rs6983267, rs6983561, rs13254738, rs13281615, and rs10090154 did not seem to be related to bladder cancer risk among either non-Hispanic whites or Chinese. To our knowledge, other investigators have not previously reported on the null association between rs7000448 and bladder cancer risk, but consistent with these results, Kiemeney et al. and Wu et al. (14, 15) reported no association between bladder cancer risk and genotypes defined by rs6983267 or additional SNPs, each in perfect ($r^2 = 1.00$) or extremely strong ($r^2 = 0.97$) linkage disequilibrium with rs6983561, rs13281615, or rs10090154. Thus, these SNPs do not seem to influence bladder cancer risk, even though abundant data indicate that genotypes defined by each are associated with risk of 1 or more other cancers.

We found the rs7008482 G allele, previously shown to be associated with prostate cancer risk (12), to be associated with a marginally significant ($P = 0.028$) risk of bladder cancer among non-Hispanic whites [RR = 1.23 (95% CI, 1.02–1.48)], to our knowledge the first report of this association, which we did not observe among Chinese.

The T allele of rs9642880 already implicated in bladder cancer (14, 15) was associated with risk in both groups [RR = 1.43 (95% CI, 1.20–1.70) among non-Hispanic whites; RR = 1.20

(95% CI, 1.00–1.45) among Chinese]. This association was highly significant in overall data ($P = 0.000024$). In further analyses we estimated the RR associated with GT to be 1.72 (95% CI, 1.28–2.32) and that with TT to be 2.05 (95% CI, 1.45–2.92), compared with the GG genotype. These results confirm the association of rs9642880 T with bladder cancer risk, among both high-risk non-Hispanic whites and low-risk Chinese.

To explore possible heterogeneity of the rs9642880–bladder cancer association, we conducted stratified analyses, results of which appear in Table 3. The effect of rs9642880 T seemed greater at older ages and among females, but differences were not statistically significant. Among non-Hispanic whites, however, effect of this allele was greater among nonsmokers [RR = 1.74 (95% CI, 1.21–2.50)] and former smokers [RR = 1.57 (95% CI, 1.18–2.09], and nearly absent among current smokers [RR = 0.98 (95% CI, 0.70–1.39)]. Among Chinese, although we did not observe this monotonic pattern, the effect of rs9642880 was also greater in nonsmokers and former smokers. Tobacco smoking, the primary established risk factor for bladder cancer, is responsible for approximately half of all bladder cancer among non-Hispanic whites. However, little is known about etiology of bladder cancer among nonsmokers. The possibility suggested by these results that rs9642880 T may predispose to bladder cancer among nonsmokers therefore deserves further investigation.

Regular use of NSAIDs is rare among Chinese in Shanghai and was not determined for Chinese participants. Among non-Hispanic whites, the rs9642880–bladder cancer association seemed to be somewhat stronger among users [RR = 1.58 (95% CI, 1.16–2.14)] than among nonusers [RR = 1.27 (95% CI, 1.01–1.62)] of NSAIDs, although the corresponding interaction term was not statistically significant ($P = 0.17$). Based on our earlier finding that a history of regularly using NSAIDs is associated with lesser risk of bladder cancer, we have postulated that inflammation may influence bladder carcinogenesis. Under this scenario, a stronger effect of rs9642880 among users of NSAIDs would motivate us to consider a role for rs9642880 in inflammatory processes.

Using tumor stage and grade as indicators of prognosis, Kiemeney et al. (14) reported notably higher frequency rs9642880 T among patients with “low-risk” (Ta/G1 or Ta/G2) papillary tumors confined to the bladder mucosa and not poorly differentiated, compared with those with “high-risk” (other stage/grade) tumors poorly differentiated or with lamina propria invasion. Using identical definitions, we observed per allele RRs of 1.64 (95% CI, 1.32–2.03) for “low risk” and 1.19 (95% CI, 0.95–1.50) for “high-risk” tumors; history of smoking seemed to be neither a modifier nor a confounder of these associations. Because stage and grade data were not available for Chinese cases at the time of this analysis, inferences relying on these variables—both from data presented here and earlier reports—are at present limited to individuals of European ancestry. The estimated ratio of RRs (based on case–case analysis) was 1.37 (95% CI, 1.05–1.79). Combining this result with the like RR reported by Kiemeney et al., we estimated the summary RR to be 1.20 (95% CI, 1.04–1.40), suggesting particular importance of rs9642880 T in noninvasive papillary bladder tumors. Wolff et al. (19) noted that most molecular alterations identified in tumors of this type can activate the ras mitogen-activated protein kinase (MAPK) pathway. Intriguingly, a key effect of activating this pathway is induction of the proto-oncogene *MYC*, located 30-kb downstream from rs9642880.

MYC is the annotated gene most closely located to each cancer-associated 8q24 SNP identified to date, all of which are non–protein-coding variants. The possibility that these variants influence cancer risk by regulating *MYC* or another cancer-related gene is now a topic of intense investigation. Molecular studies have focused on 8q24 variants associated with other cancers but reported here and by others (14, 15) to be unassociated with bladder

cancer risk. These efforts provide compelling evidence of transcriptional enhancer function (20, 21) and long-range physical interaction between a more distant colorectal cancer risk region containing rs6983267 and *MYC* (21).

The specific and consistent association of bladder cancer with rs9642880 in multiple racial-ethnic groups, together with its location between likely enhancer sequence (20, 21) and *MYC*, make functional analysis of the region containing rs9642880 a new priority in bladder cancer research.

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Table 1

Characteristics of non-Hispanic white participants in Los Angeles and Chinese participants in Shanghai

	Los Angeles County		Shanghai	
	Cases, *n* (%)	**Controls, *n* (%)**	**Cases, *n* (%)**	**Controls, *n* (%)**
Number of participants	509 (100)	602 (100)	541 (100)	535 (100)
Reference age, y				
Mean ± SD	54.4 ± 7.1	54.4 ± 8.0	60.7 ± 9.8	61.8 ± 10.0
Median	56	56	63	64
≤45	53 (10.4)	74 (12.3)	51 (9.4)	44 (8.2)
45—49	58 (11.4)	70 (11.6)	31 (5.7)	17 (3.2)
50—54	94 (18.5)	112 (18.6)	38 (7.0)	27 (5.0)
55—59	155 (30.5)	170 (28.2)	44 (8.1)	64 (12.0)
60+	149 (29.3)	176 (29.2)		
60—64			141 (26.1)	120 (22.4)
65+			236 (43.6)	263 (49.2)
Sex				
Male	401 (78.8)	485 (80.6)	429 (79.3)	412 (77.0)
Female	108 (21.2)	117 (19.4)	112 (20.7)	123 (23.0)
Education				
Elementary or below	/	/	181 (33.5)	176 (32.9)
Middle school	/	/	158 (29.2)	154 (28.8)
High school	/	/	93 (17.2)	90 (16.8)
High school or below	169 (33.2)	140 (23.3)		
1–3 years of college	167 (32.8)	188 (31.2)	70 (12.9)	76 (14.2)
College graduate	173 (34.0)	274 (45.5)	39 (7.2)	39 (7.3)
	$P_{\chi 2(2df)} < 0.0001$		$P_{\chi 2(4df)} = 0.98$	
Cigarette smoking				
Never	95 (18.7)	237 (39.4)	182 (33.6)	238 (44.5)
Former	193 (37.9)	259 (43.0)	76 (14.0)	86 (16.1)
Current	221 (43.4)	106 (17.6)	283 (52.3)	211 (39.4)
	$P_{\chi 2(2df)} < 0.0001$		$P_{\chi 2(2df)} < 0.0001$	
NSAID use				
Nonusers	313 (61.5)	355 (59.0)	/	/
1-<1,441 pills over lifetime	87 (17.1)	116 (19.3)	/	/
≥1,441 pills over lifetime	103 (20.2)	129 (21.4)	/	/
Unknown	6 (1.2)	2 (0.3)	/	/
	$P_{\chi 2(3df)} = 0.27$			
Stage/grade				
Tis	30 (5.9)	/	/	/
Ta/G1	112 (22.0)	/	/	/
Ta/G2	172 (33.8)	/	/	/
Ta/G3—4	28 (5.5)	/	/	/

	Los Angeles County		Shanghai	
	Cases, *n* (%)	**Controls, *n* (%)**	**Cases, *n* (%)**	**Controls, *n* (%)**
Ta/unknown	2 (0.4)	/	/	/
T1/G1	8 (1.6)	/	/	/
T1/G2	41 (8.1)	/	/	/
T1/G3—4	53 (10.4)	/	/	/
T2–4/G1	2 (0.4)			
T2–4/G2	8 (1.6)	/	/	/
T2–4/G3—4	48 (9.4)	/	/	/
Unknown	5 (1.0)	/	/	/
Ta	314 (61.7)			
Other	190 (37.3)			
Unknown	5 (1.0)			
Stage/grade				
Ta/G1–2[a]	284 (55.8)	/	/	/
All other stage/grade[b]	218 (42.8)	/	/	/
Unknown	7 (1.4)	/	/	/

[a] "Low probability of progression" as defined by Kiemeney et al. (14).

[b] "High probability of progression" as defined by Kiemeney et al. (14).

Table 2

Associations between genotypes defined by cancer-related SNPs on 8q24 and bladder cancer risk

	Non-Hispanic white	Chinese	Non-Hispanic white and Chinese
No. of cases/controls	509/602	541/535	1,050/1,137
rs9642880 (T[a])			
MAF[b]	0.443	0.282	
RR[c]	1.43	1.20	1.32
95% CI	1.20–1.70	1.00–1.45	1.16–1.50
P	0.000074	0.052	0.000024
$P^{d}_{\text{interaction}}$		0.19	
rs7008482 (G[a])			
MAF[b]	0.286	0.421	
RR[c]	1.23	0.98	1.09
95% CI	1.02–1.48	0.82–1.16	0.96–1.23
P	0.028	0.78	0.19
rs7000448 (T[a])			
MAF[b]	0.388	0.320	
RR[c]	0.96	1.16	1.06
95% CI	0.81–1.15	0.97–1.39	0.93–1.20
P	0.68	0.11	0.40
rs6983561 (C[a])			
MAF[b]	0.030	0.285	
RR[c]	1.21	0.98	1.01
95% CI	0.75–1.93	0.81–1.19	0.85–1.20
P	0.43	0.83	0.92
rs6983267 (G[a])			
MAF[b]	0.492	0.576	
RR[c]	1.09	1.07	1.08
95% CI	0.92–1.29	0.91–1.28	0.96–1.22
P	0.32	0.46	0.22
rs13281615 (G[a])			
MAF[b]	0.416	0.514	
RR[c]	0.96	1.10	1.03
95% CI	0.81–1.15	0.93–1.31	0.91–1.17
P	0.68	0.28	0.63
rs13254738 (C[a])			
MAF[b]	0.316	0.716	
RR[c]	1.07	1.02	1.04

	Non-Hispanic white	Chinese	Non-Hispanic white and Chinese
95% CI	0.89–1.29	0.84–1.23	0.91–1.19
P	0.49	0.85	0.53
rs10090154 (A[a])			
MAF[b]	0.099	0.135	
RR[c]	0.79	1.04	0.94
95% CI	0.51–1.07	0.81–1.33	0.77–1.13
P	0.13	0.74	0.49

[a] Risk allele.

[b] Frequency among controls of each racial/ethnic group of minor allele among non-Hispanic white controls.

[c] Adjusted for age and gender.

[d] 1 – df likelihood ratio test of rs9642880 by race/ethnicity.

Table 3

Associations between rs9642880 T allele and bladder cancer risk by strata of selected risk factors

	Non-Hispanic white			Chinese			Non-Hispanic white and Chinese	
	Cases/controls	**RR (95% CI)**	***P***	**Cases/controls**	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***
Age at diagnosis[a]								
Younger	270/317	1.35 (1.05–1.74)	0.021	305/272	1.13 (0.88–1.46)	0.34		
Older	239/285	1.52 (1.16–2.00)	0.0021	236/263	1.27 (0.95–1.69)	0.10		
$P_{interaction}$		0.57			0.52			
Gender[a]								
Male	401/485	1.41 (1.17–1.70)	0.0031	429/412	1.20 (0.99–1.45)	0.058	1.31 (1.15–1.49)	0.00068
Female	108/117	1.68 (1.09–2.59)	0.019	112/123	1.35 (0.89–2.04)	0.15	1.50 (1.12–2.02)	0.0069
$P_{interaction}$		0.38			0.53		0.30	
Smoking history[b]								
Never	95/217	1.74 (1.21–2.50)	0.0026	182/238	1.23 (0.91–1.68)	0.18	1.43 (1.13–1.81)	0.0026
Former	193/259	1.57 (1.18–2.09)	0.0021	76/86	1.44 (0.87–2.38)	0.15	1.54 (1.20–1.97)	0.00071
Current	221/106	0.98 (0.70–1.39)	0.93	283/211	1.12 (0.85–1.48)	0.48	1.06 (0.86–1.32)	0.58
P_{trend}		0.022			0.76		0.46	
$P_{interaction}$		0.055			0.51		0.32	
NSAID use								
Nonusers	313/355	1.27 (1.01–1.62)	0.045					
Users	190/245	1.58 (1.16–2.14)	0.0038					
$P_{interaction}$			0.17					
Stage/grade[a]								
Ta/G1–2[c]	284/602	1.64 (1.32–2.03)						
All other stage/grade[d]	218/602	1.19 (0.95–1.50)						

[a] Adjusted for smoking.

[b] Adjusted for age and gender.

[c] "Low probability of progression" as defined by Kiemeney et al (14).

[d] "High probability of progression" as defined by Kiemeney et al (14).