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Genetic polymorphism in bladder cancer

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TABLE OF CONTENTS

1. ABSTRACT

Individual variation in the genetic constitution of humans may affect the host responses to constant assaults from exogenous and endogenous carcinogens, which will eventually impact cancer risk, disease prognosis and clinical outcome. Bladder cancer is one of the most common cancers in the world. In this review, the published research articles studying the association between genetic polymorphisms and bladder cancer risk and disease progression are summarized. Genetic polymorphisms are categorized based on their primary cellular functions: genes in carcinogen metabolism, DNA repair, cell cycle control, inflammation, apoptosis, methylation, genes functioning as G proteins, and cell adhesion molecules. Furthermore, we discuss a number of limitations of current genetic susceptibility research and suggest future directions in molecular epidemiology study. This review presents an overview of current molecular epidemiology of bladder cancer and provides a useful resource for understanding the pathogenesis of bladder cancer.

2. INTRODUCTION

Bladder cancer is the fourth most frequent cancer diagnosed in men, and the ninth most frequent cancer in women. It is estimated that 63,210 new cases of bladder cancer will be diagnosed in the United States in 2005 (1). Transitional cell carcinoma (TCC) accounts for 90% of all cases of bladder cancer, while the remainder are adenocarcinoma and squamous cell carcinoma.

Environmental exposures to tobacco and industry-related carcinogens are the primary risk factors for bladder cancer. The urinary bladder cancer incidence is two to three times higher among cigarette smokers as compared with those who have never smoked (2). Aromatic amines and polycyclic aromatic hydrocarbons are two groups of carcinogens known to initiate bladder cancer. These environmental factors can interact with genetic factors to place one individual at a greater risk of bladder cancer than another. Alcohol consumption, dietary factors and the use of hair dyes have also been suggested as risk factors for bladder cancer (3-7).

It is increasingly clear that genetic factors play a critical role in determining risk of bladder cancer. The results of large epidemiological studies suggest the existence of familial transitional cell carcinoma in which first-degree relatives appear to have an increased risk for disease by a factor of two (8). These studies indicate a genetic component to bladder cancer. Numerous studies, as summarized in this review, indicate that genetic polymorphisms in genes responsible for the metabolism of environmental carcinogens and those involved in DNA damage repair and cell cycle control may also be associated with bladder cancer risk. Epidemiologic studies investigate the role of genetic susceptibility in cancer development by focusing research from cancer risk in populations to underlying biologic processes. The establishment of molecular epidemiology has brought the most advanced discoveries in cancer research into population studies.

Genetic and epigenetic changes can induce cancer. From the initial carcinogenic exposure to cancer development, many different mechanisms (metabolism of carcinogens, DNA repair, cell cycle checkpoint control, apoptosis and other interconnected cellular processes) constitute a network that mediates the toxicologic response of the bladder micro ecosystem. These cellular processes vary from individual to individual, resulting in different susceptibilities to cancer. In the following sections, the association between genetic polymorphisms of these key cellular mechanisms, bladder cancer risk and disease progression is described in detail. We listed the chromosomal locations of all the discussed genes, common SNPs of these genes and their functional relevance in table 1.

3. GENETIC POLYMORPHISMS AND BLADDER CANCER RISK

3.1. Carcinogen Metabolism

Many chemical carcinogens require activation by drug-metabolizing enzymes to initiate the carcinogenic process. The dynamic equilibrium between carcinogen-activating enzymes and detoxifying enzymes might be fundamental to determine the cell fate after exposure to carcinogens (78). The activity of drug-metabolizing enzymes is regulated by an interplay between genetic, host, and environmental factors. Consequently, individual differences in cancer susceptibility may be explained to a certain extent by genetic differences in metabolic activation and detoxification.

In general, the metabolism of a toxicant consists of two phases, phase I and phase II. Phase I enzymes, mainly cytochromes P-450 (CYPs), are typically involved in the activation of carcinogens, whereas multiple phase II enzymes generally function to detoxify carcinogens. The balance between phase I and II enzymes often determines the accumulation of reactive intermediates, which may cause oxidative/electrophile stress and toxicity. This report summarizes current studies on the associations between bladder cancer risk and polymorphisms of genes encoding major phase I and phase II enzymes.

CYP is the key metabolic enzyme family and the terminal oxidase of the mixed-function oxygenase system capable of metabolizing drugs and chemicals (79). Detailed searches for polymorphisms in most human CYP genes have found several functionally significant CYP alleles associated with altered activity or complete absence of the enzyme. CYP1A1, CYP1A2, CYP1B1, CYP2C19, CYP2D6 and CYP2E1 are CYP genes relevant to xenobiotic metabolism. Studies have analyzed the association between polymorphisms of these genes and bladder cancer risk.

CYP1A2 activity may modulate bladder cancer risk through metabolic activation of aromatic amines, such as 4-aminobiphenyl (4-ABP), to reactive intermediates that can form DNA and hemoglobin (Hb) adducts. CYP1A2-dependent N-oxidation activity is polymorphic in humans and several CYP1A2 polymorphic alleles are linked to significantly different activities (80). CYP1A2 activity polymorphism was commonly assessed phenotypically as rapid or slow inducibility to environmental toxin and carcinogens. Rapid CYP1A2 phenotype has been implicated in the activation (N-oxidation) of aromatic amine-DNA adducts for human bladder carcinogenesis (80). However, when Gago-Dominguez et al. studied the risk between female permanent hair dye users and bladder cancer modified by CYP1A2 activity, they found that the CYP1A2 “slow” women who are permanent hair dye users had a 2.5-fold significantly increased risk of bladder cancer, while CYP1A2 “rapid” women had a 1.3-fold insignificantly increased risk for bladder cancer. The significant association between permanent hair dye usage and bladder cancer risk correlated with frequency and duration of hair dye usage in CYP1A2 “slow” individuals (81).

CYP2C19 polymorphisms are also linked to cancer risk. CYP2C19 encodes the enzyme S-mephenytoin hydroxylase, which is deficient in some individuals who are slow (poor) metabolizers of the anticonvulsant mephenytoin. Two relatively common variant alleles, together with at least five other rarer alleles and the absence of enzyme activity of CYP2C19 gene, have been identified (82). CYP2C19 poor metabolizer polymorphism is associated with low incidence of bladder cancer in a case-control study of the Chinese population (83).

CYP2D6 encodes debrisoquine hydroxylase, whose substrates include aromatic amines, tobacco nitrosamines and a wide range of commonly prescribed drugs (84). Five to ten percent of Caucasians are recessive, homozygous, and are termed poor metabolizers (in contrast to extensive metabolizers, who are wild-types) since they are unable to metabolize various substances (85). The poor metabolizer phenotype is associated with reduced bladder cancer susceptibility in several studies suggesting that the enzyme is involved in the conversion of procarcinogens to proximate carcinogens (86-88). In contrast to the consistent association of CYP2D6 phenotypes and bladder cancer risk, the role of CYP2D6 genotypes in bladder cancer is unclear. Some studies did not find an association between CYP2D6 polymorphism and bladder cancer (85, 89-92), while others found a significant increase in the proportion of poor metabolizers or heterozygotes in leukemia, bladder

Table 1. Chromosomal locations and common functional polymorphisms of discussed genes

Genes	Chromosome Location	Polymorphism location	Nucleotide Change	Amino Acid Change	Functional Relevance (Reference)
Carcinogen Metabolism Genes					
CYP1A2	15q24.1	Intron	C734A	N/A	Associated with an increased activity in smokers (9)
		5'UTR	G-2964A	N/A	Associated with a decreased activity in smokers (10)
CYP2C19	10q23.33	Coding	G681A	Premature stop codon	Associated with a poor metabolize phenotype (11)
		Coding	G636A	Premature stop codon	Associated with a poor metabolize phenotype (12)
CYP2D6	22q13.2	Entire gene	footnote 1	footnote 2	Associated with an increased enzyme activity (13)
		Intron	CYP2D6*4, G1846A	Splicing defect	Associated with an increased enzyme activity (13)
		Entire gene	CYP2D6*5, deletion	deletion	Associated with an increased enzyme activity (13)
		Coding	CYP2D6*10, C/T, T/A	Pro34Ser, Ser486Thr	Associated with an increased enzyme activity (13)
		Coding	CYP2D6*17 C/T,C/T,T/A	Thr107Ile, Arg296Cys, Ser496Thr	Associated with an increased enzyme activity (13)
CYP2E1	10q26.1	5' UTR	G-1259C	N/A	Associated with an altered enzyme activity (14-15)
		5'UTR	C-1019T	N/A	Associated with an altered enzyme activity (14-15)
CYP1A1	15q24.1	3' UTR	C/T (Msp1)	N/A	Associated with an increased lung cancer risk (16)
CYP1B1	2q22.2	Coding	C/G	Arg48Gly	Associated with a higher catalytic efficiency for the estrogen hydroxylation than the wild-type (17)
		Coding	G/T	Ala119Ser	Same as above
		Coding	G/C	Val432Leu	Same as above
		Coding	A/G	Asn453Ser	Same as above
NQO1	16q22.1	Coding	C/T	Pro187Ser	Associated with a reduced enzyme activity (18)
GSTM1	1p13.3	Entire gene	Deletion	Deletion	Associated with a null phenotype (19)
GSTT1	22q11.23	Entire gene	Deletion	Deletion	Associated with a null phenotype (20)
GSTP1	11q13.2	Coding	A/G	Ile105Val	Associated with an altered enzyme activity (21-22)
GSTA1	6p12.2	Promoter	GSTA1*A GST1A*B	N/A	Associated with a significantly decreased protein expression (23)
GSTM3	1p13.3	Intron	3-bp deletion	N/A	Associated with an altered gene expression (24)
SULT1A1	16p11.2	Coding	G/A	Arg213His	Associated with a decreased activity and lower stability (25)
UGT2B7	4q13.2	Coding	C/T	His268Tyr	Associated with an elevated bladder cancer risk in workers formerly exposed to benzidine (26)
NAT1	8p22	3' UTR	NAT1*10, T1088A C1095A	N/A	Associated with a fast acetylator phenotype (27-28)
		Coding	NAT1*14, G/A	Arg187Gln	Associated with a fast acetylator phenotype (27-28)
		Coding	NAT1*15, C/T	Arg187Stop	Associated with slow acetylator phenotype (27-28)
NAT2	8p22	Coding	G/A	Arg64Gln	Associated with slow acetylation (27, 29)
		Coding	T/C	Ile114Thr	Associated with slow acetylation (27, 29)
		Coding	G/A	Arg197Gln	Associated with slow acetylation (27, 29)
		Coding	G/A	Gly286Glu	Associated with slow acetylation (27, 29)
MPO	17q23.2	Coding	C/T	Arg569Trp	Associated with complete enzyme deficiency (30)
		Promoter	G-463A	N/A	Associated with a reduced mRNA expression (31)
COMT	22q11.21	Coding	G/A	Val108Met	Associated with lower enzyme activity (32)
MnSOD	6q25.3	Coding	T/C	Ile58Thr	Associated with reduced enzyme activity (33)
		Coding	T/C	Val16Ala	Associated with defective protein localization (34)
GPX1	3p21.31	Coding	C/T	Pro198Leu	Associated with less response to selenium (35)
ADH3	4q23	Coding	Allele gamma1 or gamma2, G/A	Arg271Gln	Associated with 2.5 times slower rate to metabolize ethanol (36)
DNA Repair Genes					
XPD	19q13.32	Coding	G/A	Asp312Asn	Associated with a reduced DNA repair capacity and an increased lung cancer risk (37)
		Coding	A/C	Lys751Gln	Same as above
XPG	13q33.1	Coding	G/C	Asp1104His	Associated with a reduced bladder cancer risk (38)
XPC	3p25.1	Coding	C/T	Ala499Val	Associated with an increased lung cancer risk (39)
		Coding	A/C	Lys939Gln	Associated with increased bladder cancer risk (38)
		Intron	Poly AT	N/A	Associated with an increased risk for SCC of the head and neck (40)
APE1	14q11.2	Coding	T/G	Asp148Glu	Associated with ionizing radiation sensitivity (41)
XRCC1	19q13.31	Coding	C/T	Arg194Trp	Associated with a protective effect on bladder cancer risk (42)
		Coding	G/A	Arg280His	Associated with impaired DNA repair ability (43)

		Coding	G/A	Arg399Gln	Associated with reduced DNA repair ability and ionizing radiation sensitivity (41, 44)
		3'UTR	$(AC)_n$ Microsatellite	N/A	Associated with the clinical radiosensivity phenotype in cancer patients (45)
NBS1	8q21.3	Coding	G/C	Glu185Gln	Associated with greater prevalence of p53 mutation in lung cancer patients (46)
XRCC3	14q32.33	Coding	C/T	Thr241Met	Associated with higher DNA adduct levels (47)
		Intron	$(AC)_n$ Microsatellite	N/A	Associated with the clinical radiosensivity phenotype in cancer patients (45)
XRCC4	5q14.2	Coding	G/T	Ser307Ser	No significant association.
		Coding	T/C	Ile134Thr	No significant association
		Splice site	A/G	N/A	No significant association
MSH3	5q14.1	Coding	G/A	Pro222Pro	No significant association
		Coding	A/G	Thr1036Ala	Associated with pathological stage in bladder cancer (48)
Cell Cycle Control Genes					
P53	17p13.1	Coding	G/C	Arg72Pro	Associated with altered abilities to bind components of the transcriptional machinery, to active transcription, to induce apoptosis, and to repress transformation of primary cells (49)
		Intron 3	A 16-bp duplication	N/A	Associated with a reduced mRNA level (50)
		Intron 6	G/A	N/A	Associated with an increased lung cancer risk (51)
P21	6p21.31	Coding	C/A	Ser31Arg	Associated with an increased risk in lung cancer (52)
CCND1	11q13.3	Splice site	G870A	Pro242Pro	Associated with alternative gene expression and protein stability (53).
CDKN2A	9p21.3	Entire gene	Deletion	Deletion	Associated with altered bladder cancer risk (54)
		3' UTR	C500G	N/A	Associated with an increased risk in familial melanoma (55), and lower tumor-specific survival of bladder cancer (56)
		3' UTR	C540T	N/A	Associated with a sub-group of low grade vertical growth phase melanomas (57), and increased risk of stage progression and lower tumor-specific survival of bladder cancer (56)
Inflammation Genes					
IL-1?	2q13	Promoter	C-511T	N/A	Associated with an increased risk of gastric cancer (58)
		Promoter	C-31T	N/A	Associated with an increased risk of gastric cancer (58)
		Coding	C3954T	Phe105Phe	No significant Association
IL-4	5q23.3	Intron 3	70bp VNTR	N/A	Associated with bladder cancer occurrence (59)
IL-6	7p15.3	Promoter	G-174C	N/A	Associated with altered gene transcription and plasma IL-6 level (60)
PPARG	3p25.2	Coding	C/G	Pro12Ala	Associated with an decreased receptor activity, lower body mass index and improved insulin sensitivity (61)
TNF-alpha	6p21.33	Promoter	C-859T	N/A	Associated with an increased risk of bladder cancer (62)
		Promoter	G-308A	N/A	Associated with higher expression of TNF-alpha in vitro and in vivo (63)
		Intron	G488A	N/A	Associated with bladder cancer risk (62)
TGFBR1	9q22.33	Coding	Deletion	Deletion of three Ala.	Associated with less efficiency of transducing TGF-beta growth inhibition signal (64)
		Intron	G/A (Int7G24A)	N/A	Associated with kidney and bladder cancer risk (65)
COX-2	1q31.1	Promoter	G-765C	N/A	Associated with altered promoter activity (66)
		Promoter	T-1186G	N/A	Associated with bladder cancer risk (67)
VEGF	6p21.1	Promoter	G-1154A	N/A	Associated with VEGF production (68)
		Promoter	C-2578A	N/A	Associated with VEGF production (68)
Apoptosis Genes					
DR4	8p21.3	Coding	C/G	Thr209Arg	Associated with a decreased bladder cancer risk (69)
G proteins					
H-ras	4p14	Coding	T/C	His27His	Associated with bladder cancer risk (38, 70)
		Intron	VNTR	N/A	Associated with altered transcriptional activity (71)
RGS2	1q31.2	3' UTR	G/C	N/A	Associated with a reduced bladder cancer risk (72)
RGS6	14q24.2	3' UTR	C/T	N/A	Associated with a reduced bladder cancer risk (72)
GNAS1	20q13.32	Coding	T/C	Ile131Ile	Associated with bladder cancer outcome (73)
Cell Adhesion Molecules					
E-cadherin	16q22.1	Promoter	C-160A	N/A	Associated with a decreased gene transcription (74)
Methylation Related Genes					
DNMT3b	20q11.21	Promoter	C-149T	N/A	Associated with an increased promoter activity (75)
MTHFR	1p36.22	Coding	C/T	Ala222Val	Associated with an altered enzyme activity (76)
		Coding	A/C	Glu429Ala	Associated with an altered enzyme activity (76) and bladder cancer risk (77)
MS	1q43	Coding	A/G	Asp919Gly	Associated with bladder cancer risk (77)

[1] CYP2D6*2xN (N=2, 3, 4, 5 or 13), and G1661C, C2850T, G4180C [2] Duplication or multiduplication of the entire gene with point mutations Arg296Cys and Ser486Thr.

cancer and melanoma patients (93). The difference in study sample sizes may account for this discordance.

CYP2E1 catalyzes the metabolic activation of various tobacco-related N-nitrosamines, such as N-nitroso-

dimethylamine and N-nitrosonornicotine, both of which are potent bladder carcinogens in experimental animals (94). Several polymorphisms of CYP2E1 were studied in bladder cancer. Two completely linked polymorphisms in the 5' flanking region of the gene, G-1259C and C-1019T, were reportedly associated with an altered enzyme activity. However, these reports have conflicting results with regard to the way in which the enzyme activity is altered. Some found that the –1259C and –1019T variants are linked with increased activity (14), while others found these variants are associated with decreased enzyme activity or non-inducibility (15, 95). Five case-control studies did not find any statistically significant impact of these polymorphisms on bladder cancer risk (89-90, 96-98). One study found the CYP2E1 –1259 G/G and -1019 C/C combined genotype was significantly higher in bladder cancer patients than in controls in their Asian population study (99). Interethnic differences in frequency of this polymorphism might account for some of the inconsistent results (100). Three less described polymorphisms, C9930G, A7766T (in intron 6), and Arg76His (in exon 2) were also studied, but no effect on bladder cancer risk was found (90, 96-97, 101).

No significant association was found between CYP1A1 and CYP1B1 polymorphisms and bladder cancer risk in previous published studies (90, 102).

NQO1 (NADPH quinine oxidoreductase-1) plays an important role in protection against endogenous and exogenous quinines by catalyzing two- or four-electron reductions of these substrates (103). NQO1 can rapidly interconvert nucleophiles and electrophiles before conjugated by phase II enzymes. NQO1 has long been viewed as a chemoprotective enzyme involved in cellular defense against the electrophilic and oxidizing metabolites of xenobiotic quinines (104). A C→T genetic polymorphism at nucleotide 609 of NQO1 results in a proline-to-serine amino acid substitution at codon 187 and reduced enzyme activity (18). Three Caucasian studies suggested that NQO1 T/T genotype was associated with higher risks of bladder cancer (105-107). A Korean study had an opposite result, indicating that the NQO1 C/C genotypes were significantly more prevalent in bladder cancer patients than in controls (99). Four studies did not find any significant overall association between the NQO1 polymorphism and bladder cancer risk (38,108-110). The distribution of this SNP was significantly different among different ethnicities, which may partly explain the contradictory results. In addition to the Pro187Ser SNP, Sanyal et al. also studied the Arg134Trp SNP of NQO1, but no significant effect was found (38).

GST (glutathione S-transferases) comprises a major group of phase II enzymes that play the key role in the detoxification of xenobiotics, environmental substances, and carcinogenic compounds (111). At least five mammalian GST families have been identified, and polymorphisms of these genes contribute to the predisposition for several diseases, including cancer (111). Among previously published reports, GSTM1and GSTT1 are two extensively studied GST genes for their association with bladder cancer risk (89, 90, 92, 102, 108-109, 112-135).

A majority of the studies suggested that the null genotypes of GSTM1 are significantly associated with increased risk of bladder cancer (89, 90, 92, 102, 109, 112, 114-120, 122, 124, 126-130). However, a few papers indicated that no statistically significant connection was identified for GSTM1 null polymorphism and bladder cancer risk (108, 113, 121, 123, 125, 131-134). Engel et al. (130) performed meta- and pooled analyses of published and unpublished, case-control, genotype-based studies (17 studies, 2,149 cases, 3,646 controls) that examined the association between GSTM1 null genotypes and bladder cancer risk, obtaining a summary odds ratio of 1.44 (95% CI: 1.23, 1.68) for GSTM1 null status with all studies included. Results from studies with at least 100 cases and 100 controls produced a summary odds ratio of 1.42 (95% CI: 1.26, 1.60). There was a suggestion of additive interaction (additive interaction = 0.45, 95% CI: -0.03, 0.93), but no evidence of multiplicative interaction between the GSTM1 null genotype and ever smoking, in relation to bladder cancer.

The results for the GSTT1 null polymorphism are controversial. Many studies indicated that increased bladder cancer risk is associated with GSTT1 null genotypes (38, 90, 92, 102, 113, 123, 125-126), while many others did not find this association (108-109, 112, 114-116, 119, 121-122, 127, 129, 131, 135). Interestingly, Brockmoller et al. found that the significant risk associated with GSTT1 null genotype was only found in the nonsmoker subgroup (90). More surprisingly, Kim et al. found that GSTT1 positive genotype was associated with increased risk (128). A synergistic effect between GSTM1 null genotype and GSTT1 null genotype was described in some studies. A significantly higher risk was found when individuals were carrying both null genotypes (102, 113, 116, 126).

An A→G transition at nucleotide 313 of GSTP1 cDNA results in an amino acid substitution (Ile105Val) that alters the catalytic activity of the enzyme. The variant G allele was found to confer increased bladder cancer risk by three different studies (21, 98, 124); however, five other studies did not find any significant association (109, 119, 131, 136-137).

Several linked polymorphisms in the proximal promoter of GSTA1, in which the variant allele is associated with decreased expression of GSTA1, has been found to be associated with breast cancer (138). Broberg et al. studied one of the polymorphisms in bladder cancer and did not find association with bladder cancer risk (109).

GSTM3 gene is in the gene cluster of GSTM1-GSTM5. A 3-bp deletion polymorphism in intron 6 of GSTM3 generates a binding site for transcription factor yin yang 1, which could influence GSTM3 expression (24). Schnakenberg et al. reported that the variant genotypes increased the risk for bladder cancer and that homozygous

wild types of GSTM1 and GSTM3 were significantly protected against bladder cancer (118).

SULT (soluble sulfotransferases) is a phase II enzyme superfamily that plays active roles in carcinogen metabolism. SULT1A1 is a highly expressed SULT gene that has a broad substrate tolerance. SULT1A1 appears to be the principle human SULT form involved in the elimination of most phenolic xenobiotics as well as some other substrates (139). The Arg213His polymorphism in SULT1A1 has a strong influence on the activity and stability of the enzyme. Zheng et al. described a statistically significant protective role of the variant His allele (140). Hung et al. also found a similar protective role, although the effect was marginal (102).

UGT (UDP-glucuronosyltransferases) represents another major phase II drug-metabolizing enzyme family. The members of this enzyme family share roles in detoxification and elimination of endo- and xenobiotics (141). UGT2B7 is involved in benzidine metabolism (26). To evaluate the possible association of UGT2B7 polymorphism with bladder cancer risk for benzidine-exposed subjects, Lin et al. studied the genotype distribution of the His268Tyr polymorphism of UGT2B7 in a cohort of benzidine-exposed workers (26). Their data indicated that there is an association between the homozygous variant genotype of His268Tyr polymorphism and elevated bladder cancer risk for workers formerly exposed to benzidine (26).

NAT (N-acetyltransferases) catalyzes the metabolic activation of aromatic and heterocyclic amine carcinogens by acetylation. NAT1 and NAT2 are two distinct NAT isozymes existing in the human population. NAT2 gene is subject to extensive polymorphism, which segregates the populations into rapid, intermediate and slow acetylator phenotypes (142). NAT1 gene is also subject to polymorphism, but less commonly than NAT2 (143). These polymorphisms of NAT1 and NAT2 catalytic activities affect carcinogen metabolism and subsequently affect cancer risk.

NAT1*10 is a NAT1 polymorphism harboring elevated enzyme activity (27, 144), while NAT1*14A, the wild type, codes for a protein with decreased enzyme activity (27-28). Seven studies did not find a significant overall effect of NAT1*10 allele on bladder cancer risk (102, 109, 132, 145-148). A significant increased risk between bladder cancer and smokers possessing the NAT1*10 allele was reported in two studies (148-149). However, in the study by Cascorbi et al., NAT1*10 was found to have a protective role instead (150). They also showed that NAT1*14A was associated with increased bladder cancer risk (150).

NAT2 activity is highest in the liver and gastrointestinal tract. NAT2 polymorphisms and their association with bladder cancer have been extensively studied. NAT2 alleles containing the G191A, T341C, A434C, G590A, and/or G857A missense substitutions are associated with slow acetylator phenotypes (27). NAT2*4 is the wild-type allele without any mutations (27, 142). There are consistent reports on the connection of the NAT2 slow acetylator polymorphisms with higher bladder cancer risk, both independently (121, 146, 150-154) and in association with smoking or occupational exposures (especially arylamine exposure) (90, 102, 132, 145, 148, 150-151, 154-155). In several pooled analyses, NAT2 slow acetylators were associated with a modest increase (30 to 40%) in bladder cancer risk as compared with rapid acetylators (151-153, 155). Vineis et al. (151) included 6 studies for 1530 cases and 731 controls (all Caucasian) and found that there was a significant association between NAT2 polymorphisms and bladder cancer risk (OR: 1.42, 95% CI: 1.14-1.77). The risk of cancer was elevated in smokers and occupationally exposed subjects, confirming that the NAT2 slow acetylator genetypes are a risk factor for bladder cancer when paired with smoking or occupational exposures. In another meta-analysis of 21 published case-control studies, the pooled OR of bladder cancer associated with slow NAT2 acetylator genotypes was 1.31 (95% CI: 1.11-1.55) (152). Finally, Marcus et al. (153) also conducted a meta-analysis of 22 studies, 2496 cases, and 3340 controls. Slow acetylators had an approximately 40% increase in risk compared with rapid acetylators (OR=1.4, 95% CI: 1.2-1.6). This meta-analysis also suggested that the relationship between NAT2 slow acetylation and bladder cancer risk seemed to differ by geographical region. Studies conducted in Asia produced a summary OR of 2.1 (95% CI 1.2-3.8); in Europe, a summary OR of 1.4 (95% CI 1.2-1.6); and in the United States, a summary OR of 0.9 (95% CI 0.7-1.3) (153). However, a recent meta-analysis by Carreon et al (156) on Asian populations showed an OR similar to that in European populations (OR=1.4, 95% CI 1.0 – 2.0). More intriguingly, this study found a statistically significant protective association between NAT2 slow acetylator and bladder cancer risk in benzidine-exposed male workers in China, in contrast to its established link with increased bladder cancer risk in people exposed to naphthylamine, suggesting that different carcinogen exposure may modify the effect of NAT2 slow acetylation.

The combined effect of NAT1 and NAT2 genotypes were also addressed in some of the studies. Taylor et al. found that bladder cancer risk from smoking exposure is high in those who inherit NAT2 slow alleles in combination with one or two copies of the NAT1*10 allele (149). Stern et al. showed that the combined presence of the high-risk genotypes of NAT1 and NAT2 (NAT1*10/NAT2-slow) and the XPD Lys/Lys or Lys/Gln genotypes ignoring smoking had a more than 2-fold significantly increased risk for bladder cancer (157). Hung et al. observed a significant increased risk when NAT1 slow and NAT2 slow genotypes were combined (102). Cascorbi et al. described a significantly decreased risk (61%) of individuals with NAT1*10 genotypes and rapid NAT2 genotypes (150). In addition, individuals with NAT2*slow/NAT1*4 genotype combinations and a history of occupational exposure were at an approximate 6-fold significant increased risk compared to individuals without occupation exposure (150).

Myeloperoxidase (MPO), catechol-o-methyltransferase (COMT), manganese superoxide dismutase (MnSOD) and glutathione peroxidase 1(GPX1) are single genes that encode four critical phase II enzymes modulating carcinogen metabolism. MPO produces a strong oxidant, hypochlorous acid, and also activates procarcinogens in tobacco smoke (158-159). A single base transition G-463A of MPO promoter was identified at the SP1 binding site. The A allele is associated with reduced mRNA expression as a result of reduced binding of SP1 (31). COMT catalyzes the methylation of various endobiotic and xenobiotic substances, preventing quinine formation and redox cycling (160). A G-to-A allele transition, which results in a valine change to a methionine at codon 108, leads to a lower COMT enzyme activity (32). The Met/Met genotype of COMT has a quarter of the wild-type activity, and the heterozygote has the intermediate activity (32). Manganese superoxide dismutase (MnSOD) is one of the primary enzymes that directly scavenge potential harmful oxidizing species and can be induced by free radical challenge and cigarette smoke (161). The valine variant of MnSOD Val16Ala (Ala-9Val or Ala9Val) polymorphism has been associated with protein structure change leading to defective mitochondrial localization of the protein (34). Hung et al. reported the association between bladder cancer risk and genetic polymorphisms in MPO, COMT and MnSOD (105). Their data suggested that MPO G-463A homozygous variant was associated with an approximately 70% significantly reduced risk of bladder cancer. MnSOD Val/Val genotype significantly increased the risk of bladder cancer about 2-fold; and no effect was observed for COMT Val108Met polymorphism (105). GPX1 is a selenium-dependent enzyme that participates in the detoxification of hydrogen peroxide and a wide range of organic peroxides with reduced glutathione (162). The variant Leu allele of the Pro198Leu polymorphism was shown to be less responsive than the Pro allele during stimulation of the GPX1 enzyme by in vitro selenium supplementation (35). Ichimura et al. (163) analyzed the bladder cancer risk association of this GPX1 polymorphism, the MnSOD Val16Ala polymorphism, and another MnSOD SNP, Ile58Thr, which was indicated to affect stability and activity of MnSOD (33, 164). They found that the GPX1 Pro/Leu genotype might significantly increase the risk of bladder cancer and that the increased risk may be modified by the Val16Ala MnSOD polymorphism (163). The Val16Ala and Ile58Thr polymorphisms of MnSOD alone provide no significant results (163). Terry et al. also suggested that the Val16Ala SNP of MnSOD had no effect on bladder cancer risk (110).

In addition to chemical carcinogens, some studies proposed the idea of alcohol consumption as a possible risk factor for bladder cancer (3-4). Zeegers et al. (4) performed a meta-analysis of 16 epidemiological studies published up to April 1999 and calculated that the age- and smoking-adjusted summary ORs (current alcohol drinking vs. non-drinking) were 1.3 (95% CI 0.9-2.0) for six studies with men and 1.0 (95% CI 0.4-2.6) for four studies with women. They concluded that the available data suggest a slightly increased risk of bladder cancer from alcohol consumption for men. van Dijk suggested a link between polymorphisms in alcohol dehydrogenase type 3 (ADH3) and risk of bladder cancer (165). ADH3 catalyzes the oxidation of ethanol to acetaldehyde and plays a rate-limiting role in the metabolic pathway for most human ethanol oxidation (166). Genetic variants with altered kinetic properties have been identified at ADH3 locus. Gamma1 and gamma2 are two different alleles of ADH3. van Dijk et al. found that moderate drinkers with the "high-risk" (gamma1 gamma1) genotype appeared to have a 3-fold higher risk of bladder cancer compared to moderate drinkers with a "low-risk" (gamma1 gamma2 or gamma2 gamma2) genotype (165). However, there was no interaction between ADH3 genotype and alcohol intake (165).

3.2. DNA repair

DNA damage, via constant attack from numerous chemical and physical agents, can initiate cancer. About 10,000 lesions are introduced in each cell every day (167). Our DNA repair mechanisms prevent the accumulation of the undesirable DNA injuries. Nucleotide-excision repair (NER), base-excision repair (BER), homologous recombination (HR), non-homologous end-joint (NHEJ) and mismatch repair (MMR) are the main DNA repair systems (168). Each of these repair systems can recognize and fix an array of damage. In the meantime, these repair systems form an intertwining network that functions cooperatively (168). Genetic polymorphisms of DNA repair proteins with a suboptimal DNA repair capacity have been linked to increased cancer risk.

NER is the most versatile DNA repair pathway. It operates primarily on bulky lesions caused by environmental mutagens, such as UV light and polycyclic aromatic hydrocarbons (168-169). XPC and ERCC6 are essential in the NER damage recognition step with different target specificity. Once the DNA damage is recognized, the XPB and XPD helicases, which are NER proteins of the multi-subunit transcription factor TFIIH, open ~30 base pairs of DNA around the damage. Here, the XPA protein confirms and binds to the damaged DNA. Subsequently, two structure-specific endonucleases, XPG and the XPF/ERCC1 complex, cleave 3' and 5' (respectively) of the borders of the opened stretch in the damaged strand. Finally, DNA polymerase and ligase complete the repair by filling the gaps. Two SNPs in the XPD gene are particularly well studied: the G→A polymorphism leading to Asp→Asn at codon 312 in exon 10 and the A→C polymorphism leading to Lys→Gln at codon 751 in exon 23. Approximately fifty papers have investigated these two polymorphisms and their association with cancer risk at ten different tumor sites. Among these publications, six described the association between Lys751Gln polymorphism and bladder cancer risk (38, 109, 157, 170-172). Although none found an overall significant association of the Lys751Gln polymorphism with bladder cancer risk, Stern et al. suggested that among ever-smokers, those with the Lys/Lys or Lys/Gln genotypes were twice more likely to have bladder cancer than those with Gln/Gln genotype (157). Conversely, Schabath et al. indicated that the variant Gln genotypes were significantly associated with an increased bladder cancer risk in women and heavy smokers, whereas no significant association between the

Asp312Asn and bladder cancer risk was observed (172). Broberg et al., however, found that the homozygous variant Asn alleles of Asp312Asn SNP were significantly associated with increased bladder cancer risk (109). A protective role for the occurrence of bladder cancer was found for the homozygous variant His allele of XPG Asp1104His by Sanyal et al. (38). Sanyal et al. also found that the variant allele frequency of Lys939Gln polymorphism of XPC was significantly higher in bladder cancer cases than in the controls (38). Broberg et al. studied two other SNPs of XPC (Ala497Val, a C→A in intron), but did not find any effect (109). Larger sample size studies and pool analysis are needed to clarify the association between XPD polymorphisms and bladder cancer risk.

BER proteins mainly work on damaged DNA bases arising from endogenous oxidative and hydrolytic decay of DNA (168, 173). APE1, a rate-limiting enzyme of BER, has endonuclease function. DNA polymerase beta performs DNA-gap filling at the lesions in BER pathway. XRCC1 functions as a scaffold protein in BER. It does this by bringing DNA polymerase beta and ligase together at the site of repair. XRCC1-ligase3 complex seals the remaining DNA nick following the action of DNA polymerase beta. Broberg et al. studied the relationship between Asp148Glu SNP of APE1 and bladder cancer risk, but did not find any significant association (109). Three common polymorphisms in XRCC1 are Arg399Gln, Arg280His and Arg194Trp. Seven epidemiological studies examined the effect of these three polymorphisms on bladder cancer risk (38, 42, 109, 170-171, 174-175). Homozygous carriers of the variant Gln alleles of the Arg399Gln polymorphism, had a 40% reduced risk when compared with those carrying one or both wild-type Arg alleles (174). Shen et al. also suggested a protective influence of Arg399Gln homozygous variant Gln alleles among heavy smokers, though no overall impact of Arg399Gln was found (171). Studies by Sanyal et al., Broberg et al. and Matullo et al. suggested Arg399Gln had no effect on bladder cancer risk (38, 109, 170). Stern et al. studied all three polymorphisms of XRCC1 (42). No statistical significant effect was found for Arg399Gln and Arg280His polymorphisms, but they reported that carrying at least one copy of the XRCC1 codon 194 variant allele has a protective impact on bladder cancer occurrence (42).

HR and NHEJ are two distinct and complementary pathways in double-strand break (DSB) repair (168, 176). DSB is considered the most detrimental DNA damage in cells, since both DNA strands are affected. DSBs arise from a number of mechanisms, such as ionizing radiation, X-ray, certain chemotherapeutic agents and replication errors (168). Previous reports studied NBS1 and XRCC3, two HR proteins, and their associations with bladder cancer (38, 109, 170-171, 175). NBS1, part of an exonuclease complex that takes part in the first event of HR, resects the DNA to yield single-strands of overhangs (168, 176). Defects in NBS1 are associated with the Nijmegen breakage syndrome (NBS), a disorder that is characterized by developmental defects, radiosensitivity and predisposition to cancer (168). No significant effect of the common NBS1 Glu185Gln polymorphism was identified in two case-control studies of bladder cancer risk (38, 109). XRCC3 has a critical role in catalyzing strand exchange reaction in HR (168, 176). XRCC3 Thr241Met polymorphism and its association with bladder cancer were described in several studies (38, 109, 170-171, 175). The variant Met allele was found associated with a 2.77-fold higher overall risk for bladder cancer by Matullo et al. (170). In the study by Shen et al., the Thr241Met variant genotype exhibited a protective effect against bladder cancer, contrasted to the finding by Matullo et al. (171). Three studies did not find a significant effect of the Thr241Met polymorphism on bladder cancer risk (38, 109, 175), but a combinatorial protective effect for bladder cancer was identified between XRCC3 and XRCC1, a BER gene, in the study by Stern et al. (175). XRCC4 stabilizes and enhances the activity of DNA ligase IV by interacting with it to form a physical complex in NHEJ (168, 176). Broberg et al. studied the association of a G→A polymorphism at the splice site of XRCC4 on bladder cancer risk, but found no effect (109).

The primary function of MMR is to eliminate base-base mismatches and insertion-deletion loops occurring as a consequence of DNA polymerase slippage during DNA replication (168). MSH3 is one of the MMR genes. Two SNPs (Pro222Pro, Thr1036Ala) were studied in MSH3, and no significant impact on bladder cancer occurrence was observed, but the Thr1036Ala SNP was significantly associated with pathological stage of bladder cancer (48).

3.3. Cell cycle control

Cell cycle controls are biochemical pathways that regulate cell cycle progression in response to DNA damage. Losses of cell cycle control appear to be early steps in the development of carcinogenesis and, ultimately, cancer progression. The regulation of the cell cycle is governed by both positive and negative cell cycle regulatory factors. p53 is a transcription factor that acts as a fundamental regulator of cell cycle arrest in the cell. This is supported by the fact that p53 is the most frequently inactivated in malignantly transformed cells. p53 elicits cell cycle arrest through activation of downstream genes such as p21. Genetic variants in some of the cell cycle regulators were studied for their associations with bladder cancer risk.

p53 mutations have been described in more than 50% of human cancers. Eight case-control studies described the association between p53 polymorphism and bladder cancer risk (135, 177-183). Seven of these studies showed that there was no significant overall association between bladder cancer risk and p53 Arg72Pro, p53 intron 6, or p53 intron 7 polymorphisms (135, 177, 179-183). However, Kuroda et al. reported that even though no overall effect was found for the codon 72 SNP, smokers carrying both copies of the variant Pro alleles are at a 2.28-fold increased risk for bladder cancer and that light smokers have even higher risk (6.83-fold) (177). Soulitzis et al. indicated, on the contrary, that the wild-type Arg allele was associated with a 2.67-fold higher risk of bladder cancer (178). Chen et al. reported that the variant Arg allele of the p21 Ser31Arg polymorphism is associated with

an approximate 2-fold increased risk for bladder cancer (184). Cyclin D1 (CCND1) is a key regulator of cell cycle progression. It is over-expressed in a high proportion of human bladder tumors (185). CCND1 G870A, a common SNP in the splice donor region of exon 4, may modulate expression of the gene (53). Wang et al. suggested that the variant A/A genotype was associated with a significantly higher risk for bladder cancer when compared with the G/A+G/G genotypes (186). This effect was more pronounced in nonsmoking cases (186). The study by Cortessis et al. indicated there was no association between A/A genotype of the same CCND1 SNP and bladder cancer risk (187).

3.4. Inflammation genes

There has been compelling evidence supporting the hypothesis that chronic inflammation contributes to cancer development. A substantial number of cancers derive from sites of chronic inflammation. Among 1.2 million global cases each year, more than 15% of malignancies can be attributed to infection (188).

Chronic irritation enhances cell proliferation, which, in a microenvironment rich in inflammatory cells, growth factors, and DNA-damage-inducing agents, may strongly increase cancer risk (189). Proinflammatory cytokines, growth factors, chemokines, reactive oxygen species (ROS), and COX-2 interact in a complex manner in the development and progression of an inflammatory environment (190). Genetic variants of inflammatory mediators have emerged in recent years as important determinants of cancer susceptibility and prognosis (190). Some of these polymorphisms have been linked to bladder cancer.

Cytokine proteins have key roles in carcinogenesis. On one hand, they are involved in the activation of the immune system to limit tumor growth. On the other hand, they may be involved in malignant transformation and tumor growth. IL-1β is defined as one of the "alarm cytokines" secreted by macrophage to initiate inflammation (191). Polymorphisms of the IL-1β gene promoter and exon 5 have been screened for their role in rheumatoid arthritis and osteoporosis (192-193). Tsai et al. found that the two polymorphisms in IL-1β had no association with bladder cancer risk (59). IL-4 is a key cytokine produced by T cells and has an impact on B cell differentiation and proliferation. IL-4 inhibits macrophage activation and may be involved in cancer formation. A 70-bp sequence of variable numbers of tandem repeats (VNTR) polymorphism in the third intron of IL-4 has been studied for its disease association (194). Tsai et al. suggested that the IL-4 intron 3 VNTR is associated with bladder cancer and is a potential genetic marker in screening for possible causes of bladder cancer (59). A G→C transversion at –174 of IL6 promoter affects gene transcription and the level of IL-6 protein (60). PPARG belongs to a sub-family of the nuclear-receptor family that regulates gene expression in response to ligand binding. A PPARG polymorphism in the coding region (C34G) that results in an amino acid change (Pro12 Ala) affects its receptor activity. Wang et al. in a case-control study showed that the variant IL6 genotype was associated with 1.52-fold significant increased risk of bladder cancer (195). Furthermore, individuals with IL6 variant (C/C) and PPARG (C/G+ G/G) had an even higher bladder cancer risk (2.76-fold) (195).

TNF- alpha, a multifunctional cytokine, is key in inflammation, immunity and cellular organization (196). TNF- alpha has paradoxical roles in cancer, inducing destruction of blood vessels and cell-mediated killing of certain tumors as well as acting as a tumor promoter (197). TNF- alpha promoter region carries a large number of polymorphisms. –308G/A and –238G/A at the promoter region of TNF- alpha are well studied, but +488G/A in the first intron, as well as the promoter variants -1032T/C, -865C/A, -859C/T and –380G/A, might also have functional significance (198-199). Marsh et al. studied these seven TNF- alpha polymorphisms and their association with bladder cancer (62). In this study, a significant association between TNF polymorphisms, TNF+488A and TNF-859T, and risk of bladder cancer was detected (these two loci were in tight linkage disequilibrium) (62). No connection was discovered for the other five polymorphisms (62). Tsai et al. and Jeong et al. analyzed the link between the –308G/A polymorphism and bladder cancer risk in two different studies (200-201). Both studies did not find a significant effect of the –308G/A polymorphism (200-201) on bladder cancer occurrence.

TGF- beta is a potent inhibitor of epithelial cell proliferation and it belongs to the group of tumor-derived cytokines (202). It is a microenvironmental regulatory molecule that signals cell cycle arrest (203). TGF- beta production has been associated with the growth of a variety of cancers. Tumors frequently lose responsiveness to TGF-beta-mediated growth inhibition due to disruption in the TGF- beta signaling pathway (204). Acquisition of TGF-beta resistance has also been indicated as an important progression factor in bladder cancer (205). The TGF- beta signaling is transduced by TGF- beta type1 receptor (TGFBR1) and type 2 receptor (TGFBR2) (202). Genetic variants in these two types of receptors have been found in several cancer types (202, 206-208). A common polymorphism of TGFBR1, termed TGFBR1*6A, has a deletion of three alanines within a 9-alanine stretch in exon 1 (209). It has been reported that TGFBR1*6A transduces TGF- beta growth inhibition signal less efficiently than wild-type TGFBR1. This allele is present in 10% of the population and may act as a tumor susceptibility allele (64, 210). Kaklamani et al. performed a meta-analysis of seven case-control studies of TGFBR1*6A and cancer association (211). They concluded that there was no association between TGFBR1*6A and bladder cancer, although effects were found in other types of cancers (211). Chen et al. studied a G→A SNP 24 bp downstream of the exon/intron 7 boundary (Int7G24A) of TGFBR1 gene (65). Their data suggested that the variant genotypes (G/A and A/A) were significantly associated with bladder cancer incidences (OR=2.45, 95% CI 1.89-3.16).

COX-2 has a central role in inflammatory response. COX-2 serves as a mediator of the acute and

chronic response to inflammation, pain, and other actions involved in cellular repair and proliferation (212). Aberrant or increased expression of COX-2 has been implicated in carcinogenesis (213-214). Kang et al. reported recently that polymorphisms in the promoter region of COX-2, a NF-kappa-B binding site, were associated with an increased risk of bladder cancer (67). They identified two polymorphisms, -1166 C→G and –1186 T→ G, in the NF-kappa-B binding promoter region of COX-2 and concluded that the –1186 polymorphism is associated with bladder cancer risk (67). This may be due to the regulatory role of NF-kappa-B to COX-2 expression (67).

3.5. Apoptosis

Apoptosis plays a central role in cancer development. Two separate pathways (intrinsic and extrinsic) are able to trigger the caspase cascade of the apoptotic pathway (215-217). The extrinsic pathway is activated by the ligation of cell surface death receptors by their corresponding ligands (216-217), while the intrinsic pathway is triggered by disruption of mitochondrial membrane (215-216). Hazra et al. studied a key death receptor, DR4 (69). They found that a C→G polymorphism (C626G) at amino acid 209 (Thr209Arg), located immediately 3' to one of the main ligand interface regions, was associated with a 45% decreased risk of bladder cancer in a Caucasian population of 468 subjects (OR=0.55, 95% CI 0.36-0.84,69). This protective effect is more apparent in younger individuals, in women, and in light smokers (69).

3.6. G proteins

G proteins are guanine-nucleotide-binding proteins that form a super-family of signal transduction proteins. The ras family of monomeric G proteins is small GTPases cycling between a GTP-bound active state and an inactive GDP-bound state (218). Three of the five human ras genes--including H-ras, K-ras, and N-ras are known to be associated with human cancer through mutation and/or over expression in tumors (219). A T→C SNP at nucleotide 81 of H-ras in exon 1 is linked to bladder cancer risk (38, 70). Individuals harboring the homozygous C/C genotype of the H-ras proto-oncogene were suggested to be at a 2-fold increased risk by Johne et al. (70); however, Sanyal et al. suggested a strong protective effect (88% reduced risk) for the same genotype in their study (38). The H-ras VNTR polymorphism, 1 kb downstream from the H-ras gene, has been reported to be associated with risk of various cancers, including bladder cancer (220-221). Krontiris et al. carried out a case-control study and meta-analysis of their study and 22 other published studies and concluded that mutant alleles of H-ras VNTR polymorphism represented a major risk factor for common types of cancers, including bladder cancer (220). However, van Gils et al. in their case-control study did not find evidence of a strong overall effect of the H-ras VNTR polymorphism on bladder cancer risk (221).

The RGS (regulators of G-protein signaling) family of proteins negatively regulate heterotrimeric G-protein signaling (222). Berman et al., in a case-control study, explored the association between 11 SNPs in five RGS genes (RGS2, 5, 6, 11 and 17) (72). Their data indicated that three noncoding SNPs in RGS2 and RGS6 were each associated with a statistically significant reduction in bladder cancer risk (72). The risk of bladder cancer was reduced by 74% in those with the variant genotype at all three SNPs (72). When the SNPs were analyzed separately, the RGS6 C→T polymorphism in the 3' UTR conferred the greatest overall reduction of bladder cancer risk (34%) (72). This result is supported by a functional assay showing that the RGS6 C→T polymorphism increased the activity of a luciferase-RGS fusion protein 2.9-fold (72).

3.7.Cell adhesion molecules

Cell adhesion is essential in all aspects of cell growth, cell migration, and cell differentiation. A growing body of evidence suggests that alterations in the adhesion properties of neoplastic cells may be pivotal in the development and progression of the malignant phenotype in a range of tumors, including bladder cancer (223).

E-cadherin, a member of the cadherin family, interacts with cytoskeletal proteins through the catenin complex. E-cadherin seems to function as a tumor-suppressor; loss of expression and/or abnormal function of E-cadherin lead to loss of cell polarity and derangement of normal tissue architecture (224). A –160 C→A polymorphism in the promoter region of E-cadherin has been shown to decrease gene transcription (74). Two case-control studies analyzed the association between this –160 SNP and bladder cancer (225-226). Significant effect of the –160 SNP was found in both studies: The A allele carriers were at more than a 4-fold higher risk for TCC risk than C-only carriers (225), and individuals carrying the A/A genotype had a 2.3-fold higher risk for urothelial cancer (226).

3.8. Methylation gene

DNA methylation is an important epigenetic mechanism of gene regulation and plays essential roles in tumor initiation and progression. Aberrant epigenetic events, such as DNA hypo- and hypermethylation of CpG-rich areas in or near the promoter region of tumor-suppressor and tumor-related genes, have been observed in various cancer types, including bladder cancer (227). Recent studies have shown that the methyltransferases DNMT1 and DNMT3b cooperatively maintain DNA methylation and gene silencing in human cancer cells (228). Given the critical roles of these methylation-related genes, genetic variants found in these genes might alter cancer susceptibility. A C→T transition at a novel promoter region of the DNMT3b is linked to significantly increased promoter activity (75). Hazra et al. studied this SNP in bladder cancer and found that the homozygous variant T/T genotype had a marginal but not significant protective effect for women when compared to C/C and C/T genotypes (229). This effect became more pronounced in women who never smoked and was exhibited by a significant 59% reduced risk (229). Methyl-binding proteins (MBD) bind to methylated DNA and recruit repression complexes containing histone deacetylaces. Zhu et al. reported that high levels of MBD2 expression were associated with a significantly reduced bladder cancer risk (230).

Genome-wide hypomethylation in human cancer might be a consequence of decreased S-adenosylmethionine (SAM) level (231). Cancer risk might be modified by polymorphisms in methyl group metabolism genes that affect intracellular concentration of SAM, such as methylene-tetrahydrofolate reductase (MTHFR) and methionine synthase (MS). Hypomethylation is particularly prevalent in TCC, making these methyl group metabolism genes good candidates for bladder cancer risk assessment (232). Four case-control studies analyzed the association between bladder cancer and two common MTHFR polymorphisms, Ala222Val (C677T) and Glu429Ala (A1298C) (38, 77, 108, 232). Two of these studies also investigated the Asp919Gly (A2756G) polymorphism of the MS gene (77, 232). Kimura et al. found that neither MTHFR Ala222Val SNP nor the MS Asp919Gly SNP had an effect on bladder cancer risk (232). Sanyal et al. did not find an effect for either MTHFR SNPs (38). Moore et al., however, showed that the MTHFR 677 C/T and T/T genotypes appeared protective against bladder cancer (108). Lin et al. investigated the joint effects of MTHFR and MS polymorphisms, dietary folate intake and cigarette smoking on bladder cancer risk (77). Compared to individuals with the MTHFR C677T wild type (C/C) and a high folate intake, those with the variant genotype (C/T or T/T) and a low folate intake were at a 3.51-fold increased risk of bladder cancer (77). When genotype was analyzed along with smoking status, it was found that current smokers with the variant genotype had a 6.56-fold increased risk compared to never smokers with MTHFR 677 wild type (77). Analyses of the MTHFR A1298C and MS A2756G revealed similar results, suggesting that polymorphisms of MTHFR and MS acted together with low folate intake and smoking to elevate bladder cancer risk (77).

4. GENETIC POLYMORPHISMS AND BLADDER CANCER PROGRESSION

Genetic differences may account for tumor progression and pathogenesis, such as tumor histopathology, cancer stage, tumor development, and tendency toward invasiveness. Several studies have demonstrated the relationship between the genotypes of enzymes in the carcinogen metabolism pathways and the aggressiveness of bladder tumors. The GSTM1-null genotype has been found to be significantly higher in invasive bladder cancer (117). GSTM1 and GSTT1 null genotypes were also found to be more prevalent in a higher grade (grade IV) of bladder cancer (92). However, Jeong et al., in their study of Korean subjects, found superficial or low-stage bladder tumors were more common among GSTM1 null genotypes (114). A different study by Kim et al. suggested that even though the GSTM1 null genotype was a statistically significant risk factor for bladder cancer, the GSTM1-positive genotype was an independent risk factor for cancer progression (128). This suggests that increased metabolism of urinary excretion by GSTM1 might promote cancer progression in bladder cancer patients (128). Ryk et al. determined that the presence of the Val allele of the GSTP1 Ile105Val SNP was significantly associated with higher stage tumors (Tis and T2+) (233). Inatomi et al. investigated NAT2 slow genotype and its connection with bladder cancer (155). They discovered that bladder cancer patients with NAT2 slow genotype were more likely to have a high-grade tumor (G3) or have an advanced stage tumor (pT2-pT4); however, no effect on survival rate of patients with invasive bladder cancer was recognized (155). Studies by Mommsen et al. also supported the finding that NAT2 slow genotypes are linked to more aggressive forms of bladder cancer (234). The GPX1 Pro198Leu SNP was analyzed for its effect on bladder cancer risk by Ichimura et al. (163). They indicated that the Pro/Leu genotype was significantly associated with advanced tumor stage compared with the Pro/Pro genotype, suggesting the GPX1 genotype may further affect the disease status of bladder cancer (163).

It has been estimated that p53 mutation accounts for up to 61% of human bladder cancers (235). The frequency of p53 mutations has repeatedly been shown to be higher in bladder tumors of high stage and grade, and more specifically with advanced bladder cancer of grades 2 and 3 (236-240). However, controversial results were reported on the possible use of p53 as a surrogate marker of bladder cancer progression or survival (241-243). The well-studied p53 Arg72Pro polymorphism was found associated with invasive bladder cancer: the Pro/Pro homozygotes were more prominent in invasive tumor (181). CCND1 G870A was related to bladder cancer progression in two studies (186, 244). Wang et al. reported that the presence of the A allele was associated with higher-grade (grade 3) tumors with a gene dosage effect (186). In tumor stage, although not significant, the AA+AG genotypes tended to be more frequently observed in cases with high-stage (T1-4) tumors than those with low-stage (Ta) tumors (186). Ito et al. found that the A/A genotype may recessively increase the risk of carcinoma in situ incidence in patients with superficial bladder cancer (244). The p21 Ser31Arg polymorphism that influenced bladder cancer risk also had an effect on disease status (184). It was shown that even though the Arg form was more prominent in cancer patients, Ser homozygotes were more prominent in the invasive group when compared to the non-invasive group (25 to 3.0%, respectively) (184). The CDKN2A gene that encodes $p16^{INK4a}$ and $p14^{ARF}$ proteins is inactivated frequently by homozygous deletion, hypermethylation of the CpG island, or point mutations (54, 245-246). A 500 C→G SNP and a 540 C→T SNP of CDKN2A in the 3' UTR region of the gene were analyzed by Sakano et al. in the clinical course of bladder cancer (56). This study found a statistically significant difference in genotype (C/C vs. C/T+T/T) for the C540T between cases with progressive disease as compared to those without evidence of progressive disease during follow-up (56). For Ta and T1-tumors, the C/T+T/T genotype had a 2.5-fold higher risk for stage progression (56). Furthermore, the probability of tumor-specific survival was significantly lower in patients with either the variant genotypes of C500G or the C540T SNP than in those with wild-type CDKN2A (56).

A polymorphism (C→A) at the position of –2578 of the promoter of vascular endothelial growth factor (VEGF) was associated with VEFG production, and was

shown to have a correlation with bladder cancer grade (68, 128). High-grade cancers were more frequently observed in patients with the C/C genotype compared with the C/A and A/A genotypes (128).

TNF alpha -308 G→A polymorphism in the promoter was analyzed for its association with bladder cancer stage and grade in three studies (62, 128, 201). Kim et al. observed that stage was significantly associated with the TNF- alpha genotype, with the G/G genotype being more frequent in patients with superficial disease compared with the G/A and A/A genotype (128). Jeong et al. found the G/A genotype was statistically more significant in patients with high-grade tumors than G/G genotype; however, tumor stage, recurrence and progression were not associated with this SNP (201). Marsh et al. did not find an effect of the –308 SNP, but they found significance of two other SNPs of TNF: TNF+488 G→A and –859 C→T (62). They also found that patients with TNF +488A or TNF –859T were more likely to present with a moderately differentiated tumor (G2) than those with the common allele (62).

The 81 T→C H-ras SNP not only increased bladder cancer risk, but also impacted disease status (70). The homozygous 81 C/C genotypes were overrepresented, particularly in the patient groups with poorly differentiated tumors (≥G3), muscle-invasive tumors (≥T2), and flat transitional cell carcinoma (advanced types of bladder cancer) (70). The $G_{alpha}s$ subunit of G protein is encoded by GNAS1 gene, which is suggested for a role in cancer initiation and/or progression (247-248). Frey et al. genotyped the synonymous T393C polymorphism in 254 TCC patients to examine an association between genotype and cancer disease progression (73). Using Kaplan-Meier estimates to evaluate 5-year probabilities of follow-up, they showed that progression-free survival, metastasis-free survival, and cancer-specific survival were significantly increased in T/T genotypes compared with C/C genotypes (73). In multivariate Cox proportional hazard analysis, the T393C polymorphism was an independent prognosis factor for clinical outcome (73). Homozygous C/C patients were at highest risk for progression, metastasis, and tumor-related death compared with T/T genotypes (73). Heterozygous patients had an intermediate risk suggesting a gene-dose effect (73). These genotypic effects were correlated with the highest $G_{alpha}s$ mRNA expression in T/T genotype, indicating a proapoptotic effect and a functional role of $G_{alpha}s$ in bladder cancer progression (73).

A growing body of evidence indicates the alterations in the adhesion properties of tumor cells play a pivotal role in development and progression of cancer. Loss of E-cadherin-mediated adhesion is an important step in the progression of many carcinomas (223, 249-250). Zhang et al. found that a C→A SNP at position –160 of the E-cadherin gene promoter was associated with TCC of bladder; the A allele was a risk allele (225). They also observed that the A allele frequencies were significantly higher in invasive TCC than in superficial carcinoma (225).

5. PERSPECTIVE

The etiology of bladder cancer is still not fully understood. Traditional epidemiology has successfully identified a number of environmental and lifestyle factors contributing to higher or lower bladder cancer risk. Over the last decade, molecular epidemiology has evolved to prominence and evidence is compelling that genetic variations play important roles in the initiation of many types of cancer. As summarized above, we have seen an explosion of literature reporting an association between genetic variation and bladder cancer risk, as well as between genetic variation and clinical outcome. With the completion of the human genome project and with several millions of SNPs identified, the number of possible genetic associations that can be tested is unlimited. However, there are clearly some major challenges that confront the molecular epidemiologists.

When summarizing previous research, we found the sheer number of contradictory results astonishing. With so many genes and SNPs reported, the only fairly consistent results were that GSTM1 null genotype and NAT2 slow acetylator genotypes conferred modestly increased bladder cancer risk. There are multiple reasons for these inconsistencies, such as small sample size, ethnic heterogeneity, poor matching between case and control populations, multiple testing, and publication bias. The application of large, well-designed association studies of common polymorphisms will help avoid spurious findings. We should also realize that the candidate gene approach is hypothesis-driven and uses *a priori* knowledge of SNP and gene functions. The selection of candidate polymorphisms and genes for costly large population studies should be functionally rational and based on biological plausibility. Previously published SNPs with functional impact are the obvious targets. A plethora of experimental assays and computational algorithms are available for testing the functional significance of novel SNPs and prioritizing those SNPs (251).

A more serious challenge to current association studies is to bypass the inherent limitation of the predominantly used candidate gene approach. Cancer is a complex multigenic and multistage disease involving the interplay of many genetic and environmental factors. It is unlikely that any single genetic polymorphism would have a dramatic effect on cancer risk. In fact, the reported significant odds ratios for individual variants are typically less than 2 (e.g., the GSTM1 and NAT2 genotypes and bladder cancer risk). The modest effect of each individual polymorphism, although providing valuable information, would have very limited value in predicting risk in the general population. Therefore, the future of risk assessment for multigenic complex diseases needs to move beyond the candidate gene approach. A pathway-based genotyping approach, which assesses the combined effects of a panel of polymorphisms that act in the same pathway, may amplify the effects of individual polymorphisms and should be more advantageous to association study than the candidate gene approach. A few recent pathway studies, including the aforementioned NER polymorphism study,

demonstrated the promising potential of applying a pathway-based approach in association studies (252-254). In all these studies, only a handful of SNPs have presented moderately significant individual effect, but when a group of SNPs in the same pathway are analyzed for their cooperative effect on cancer risk or disease progression, they find a much more pronounced trend of significance, and this combined effect becomes more evident as the SNP number increases.

The ultimate goals of molecular epidemiology studies are to provide a practical risk-assessment model that predicts if an individual is at a higher risk for cancer or to tailor cancer therapy (preventive or treatment) based on each individual's genetic profile. Unfortunately, we still have a long way to go. Hypothesis-driven genetic association studies, using either candidate gene approach or pathway-based approach, have given and will continue to provide us with very valuable information. However, our expectations should not exceed what these studies can provide. The magnitude of associations by these studies will have limited value in public health and clinical care. SNPs with potential functional significance in the most important genes have been extensively studied. Continued efforts to exhaustively search and genotype all identified SNPs with potential functional significance in so many genes are costly and unpractical. With the rapid progress of the Hapmap project, haplotyping will become more feasible. This may then be the primary research strategy in the coming years and may facilitate disease association studies. Finally, genome-wide scanning is entering the field in full stride. This technology is constantly advancing and we will see more and more genome-wide scanning followed by fine mapping used in the field. The future of genetic association studies lies in the combination of global approaches using genome-wide scanning and regional fine mapping using haplotyping and genotyping.

6. ACKNOWLEDGEMENT

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