Published in final edited form as:

Per Med. 2011 May ; 8(3): 365–374. doi:10.2217/PME.11.15.

Genetic susceptibility to bladder cancer risk and outcome

Jian Gu¹ and Xifeng Wu^{†,1}

¹Department of Epidemiology, The University of Texas MD Anderson Cancer Center, 1155 Pressler Street, Houston, TX 77030, USA

Abstract

Bladder cancer is an excellent model for studying genetic susceptibility and gene–environment interaction in cancer etiology. The candidate gene approach found *NAT2* slow acetylator and *GSTM1*-null genotypes to be bladder cancer susceptibility loci and also demonstrated interactions between these two genotypes and smoking in modulating bladder cancer risk. Recent genome-wide association studies identified at least eight novel genetic susceptibility loci for bladder cancer. Genetic determinants of clinical outcomes have been inconclusive. The future directions are to identify more genetic susceptibility loci for bladder cancer risk and outcome through a genome-wide association study approach, identify the causal genes and variants, study the biological mechanisms underlying the association between the causal variants and bladder cancer risk, detect gene–environment interactions and incorporate genetic knowledge into clinically applicable risk prediction models to benefit patients and public health.

Keywords

BCG; bladder cancer; candidate gene approach; genetic susceptibility; genome-wide association study; single-nucleotide polymorphism

Bladder cancer is the fourth most common cancer in men and 11th in women in the USA with approximately 70,500 new cases (52,700 men) and 14,700 new deaths (10,400 men) in 2010 [1]. The vast majority of bladder cancer cases (90–95%) in Western countries are urothelial carcinoma (transitional cell carcinoma). Bladder cancer is an excellent model for studying genetic susceptibility and gene–environment interaction (e.g., gene–smoking and gene–occupational exposure interactions) in cancer etiology. Cigarette smoking is the predominant risk factor, accounting for approximately half of the new cases in men and a third of the new cases in women [2,3]. Occupational exposure to aromatic amines and other chemicals is responsible for as many as 20% of all cases [2,4]. Other environmental risk factors for bladder cancer include higher concentrations of arsenic, chlorinated byproducts and other pollutants in drinking water [2,5–7]. Nevertheless, only a small percentage of individuals with environmental exposure develop bladder cancer, suggesting genetic contribution to bladder cancer etiology. Epidemiological studies have shown a twofold increased risk of bladder cancer among first-degree relatives of bladder cancer patients [8,9]. A large population-based twin study estimated a genetic heritability of 31% for bladder cancer [10]. There have been extensive efforts in the past decade to identify genetic

© 2011 Future Medicine Ltd

[†]Author for correspondence: Tel.: +1 713 745 2485 Fax: +1 713 792 4657 xwu@mdanderson.org .

Financial & competing interests disclosure The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

susceptibility loci for bladder cancer. A segregation analysis involving 1193 families indicated a ‘no major gene’ model for sporadic bladder cancer [11]. Recent cancer association studies by candidate gene [12–14] and genome-wide association study (GWAS) approaches [15–19] support this notion by identifying at least ten low-penetrance genetic susceptibility loci for bladder cancer. Genetic variations may also play important roles in influencing clinical outcomes of cancer patients [2,20]. However, the results in this regard have been inconsistent and not a single variant has been validated as a predictor of bladder cancer outcome. In this special report, we will focus on the ten validated genetic loci for bladder cancer risk, including *NAT2*, *GSTM1*, 8q24.21 (*MYC*), 3q28 (*TP63*), 8q24.3 (*PSCA*), 5p15.33 (*CLPTM1L-TERT*), 4p16.3 (*TACC3-FGFR3*), 22q13.1 (*APOBEC3A-CBX6*), 19q12 (*CCNE1*) and 2q37.1 (*UGT1A*) (Table 1). In addition, we will provide a few examples of candidate gene studies of genetic susceptibility to bladder cancer outcome. We refer readers to previous excellent reviews of published studies of genetic susceptibility to bladder cancer risk and clinical outcome [2,20–23].

Genetic susceptibility to bladder cancer risk

Candidate gene studies

Since the major environmental risk factors of bladder cancer have been well established and we have a basic understanding of the biology of carcinogen action and host defense, major efforts have been made to study candidate genetic variations in pathways and genes hypothesized to be involved in the carcinogenesis processes, including metabolism of carcinogens, DNA repair, cell cycle checkpoints, apoptosis and inflammatory response, for example [2,20]. Two genotypes, *N*-acetyltransferase 2 (*NAT2*) slow acetylator and glutathione *S*-transferase $\mu 1$ (*GSTM1*)-null genotypes, have been replicated and conferred relatively strong associations with bladder cancer risk. In addition, pooled analyses and meta-analyses showed weak associations between several DNA repair gene SNPs and bladder cancer risk [14]. Other candidate SNPs were not associated with bladder cancer risk.

***NAT2* slow acetylator**—*N*-acetyltransferases (NATs) are Phase II metabolism enzymes that catalyze the acetylation of aromatic and heterocyclic amine carcinogens and therapeutic drugs. There are two major isoforms of NAT in human cells: NAT1 and NAT2, both of which are polymorphic in human cells that can categorize the human population into NAT1 (or NAT2) rapid, intermediate and slow acetylator phenotypes [24,25]. NATs may either activate or inactivate carcinogens depending on the specific type of acetylation that occurs on the substrate: *N*-acetylation is typically a detoxifying reaction, whereas *O*-acetylation usually activates [25]. For cancers in which *N*-acetylation is a prominent detoxification mechanism such as aromatic amine-related bladder cancer, NAT2 slow acetylator phenotype confers increased risk because NAT2 slow acetylators have a decreased capacity to detoxify aromatic amines by *N*-acetylation [25]. In humans, NAT2 slow acetylator phenotype can be represented by combinations of several SNPs [25]. The association of *NAT2* slow acetylator genotype with increased bladder cancer risk has been compellingly demonstrated by large case–control studies and meta-analyses [12,13]. In the meta-analysis of 22 studies (5091 cases and 6501 controls), *NAT2* slow acetylator genotype conferred a 40% increased bladder cancer risk (odds ratio [OR]: 1.4; 95% CI: 1.2–1.6) [12]. In addition, there was a significant interaction between *NAT2* genotype and smoking (p for interaction = 0.009). These observations were further confirmed in a recent publication of even larger sample size (10,519 cases and 13,218 controls) [19]. A SNP (rs1495741), located at the 3′-end of *NAT2* on chromosome 8p22, was found to tag *NAT2* acetylation phenotype. The G allele was associated with a reduced bladder cancer risk (OR: 0.87; 95% CI: 0.83–0.91; $p = 4.2 \times 10^{-11}$). The AA genotype, which tags the slow acetylator as compared with the GG and AG genotypes that tag rapid and intermediate acetylator, conferred a significantly increased

bladder cancer risk (OR: 1.15; 95% CI: 1.09–1.22; $p = 2.6 \times 10^{-7}$). Moreover, the association was only evident in ever smokers (OR: 1.24; 95% CI: 1.16–1.32; $p = 1.3 \times 10^{-10}$), but not in never smokers (OR: 0.96; 95% CI: 0.86–1.08; $p = 0.52$), confirming a significant genotype–smoking interaction (p for interaction = 2.8×10^{-4}) [19]. The association between bladder cancer risk and *NAT1* acetylator genotypes has been inconsistent, mostly with null results [12,13,26].

GSTM1-null genotype on 1p13.3—Glutathione *S*-transferases are a major family of phase II enzymes for detoxifying environmental carcinogens. *GSTM1* detoxifies a number of carcinogens including polycyclic aromatic hydrocarbons (PAHs) such as benzopyrene. A meta-analysis of 28 studies (5072 cases and 6466 controls) showed that *GSTM1*-null genotypes conferred a 50% increased bladder cancer risk (OR: 1.5; 95% CI: 1.3–1.6) [12], which was further confirmed in a recent larger study of 7552 cases and 9688 controls (OR: 1.47; 95% CI: 1.38–1.57; $p = 5.0 \times 10^{-31}$) [19]. Interestingly, this association was strongest in never smokers (OR: 1.71; 95% CI: 1.38–2.12) and became progressively weaker in former (OR: 1.62; 95% CI: 1.39–1.89) and current smokers (OR: 1.19; 95% CI: 1.00–1.40; p for interaction = 8.1×10^{-3} for current smokers vs never smokers). This observation suggests that *GSTM1*-null genotype lowers the risk of bladder cancer through mechanisms that are not specific to the detoxification of tobacco carcinogens. In never smokers, *GSTM1* may protect cells from oxidative damage through metabolism of reactive oxygen species and loss of *GSTM1* allele would lose the protection and lead to increased bladder cancer risk. In current smokers, the heavy tobacco carcinogen exposure may overwhelm the genetic effect of *GSTM1* genotype.

DNA repair gene SNPs—Stern *et al.* performed meta-analyses and pooled analyses including 5282 cases and 5954 controls of non-Hispanic white origin [14]. Weak but consistent associations were observed for *ERCC2* D312N (rs1799793; per-allele OR: 1.10; 95% CI: 1.01–1.19; $p = 0.021$), *NBN* E185Q (rs1805794; per-allele OR: 1.09; 95% CI: 1.01–1.18; $p = 0.028$) and *XPC* A499V (rs2228000; per-allele OR: 1.10; 95% CI: 1.00–1.21; $p = 0.044$). The association with *NBN* E185Q was only evident in ever smokers (p for interaction = 0.002).

Genome-wide association studies

The hypothesis-driven candidate gene approach only achieved limited success after a decade of extensive studies [27]. The candidate gene approach is easy to perform and only requires small sample sizes. However, it is limited by current knowledge and will miss true variants due to the limited number of SNPs examined. In addition, publication bias has resulted in numerous false-positive findings [2,20,21]. In recent years, with the completion of the human genome project, the International HapMap Project, advances in genotyping technology and reduction of genotyping cost, the application of GWAS in cancer association studies has exploded [101]. GWAS use high-density SNP arrays (generally from half a million up to 5 million tagging SNPs) in a large number of cases and controls. Because of the large number of SNPs tested for their associations with diseases, stringent criteria (generally $p < 10^{-7}$ after Bonferroni correction for multiple testing) are set to report significant results to avoid false-positive findings. Compared with the candidate gene approach, GWAS are hypothesis-generating, discovery-driven and do not depend on current knowledge. They are capable of identifying completely novel genetic loci through a nonbiased global screening and validation scheme. The limitations are the requirement for large sample size typically for multiple validation stages and the high genotyping cost. Three independent bladder cancer GWAS have been conducted and each has produced exciting data [15–17,19], culminating in a recent landmark joint publication of the three

GWAS that either confirmed or identified all of the ten currently established bladder cancer susceptibility loci [19].

Rs9642880 near *MYC* oncogene on 8q24.21—The first GWAS on bladder cancer identified rs9642880 on 8q24.21 as a bladder cancer susceptibility variant [15]. This SNP is located in a ‘gene-desert’ region that harbors multiple independent susceptibility variants for several different cancers [28–36]. This region is centromeric to the *MYC* oncogene, with rs9642880 being the closest to *MYC* (~30 kb) and all the other cancer susceptibility SNPs a few hundred kilo-bases away [37]. The allelic OR is 1.22 (95% CI: 1.15–1.29; $p = 7.8 \times 10^{-12}$) [15]. Rs9642880 has also been confirmed as a bladder cancer susceptibility variant in two independent Chinese populations [38,39]. Since *MYC* is one of the most frequently activated oncogenes in human cancers, it is logical to hypothesize that these different genetic variants may affect cancer risk through the *MYC* oncogene. Indeed, several recent publications have shown that this region contains multiple tissue-specific transcriptional enhancers and several cancer-predisposing variants are located in these enhancers and are capable of modulating the expression of the *MYC* oncogene through long-range interaction with the *MYC* promoter region in a tissue-specific manner [40–43]. However, no studies have specifically evaluated the functional impact of rs9642880 on *MYC* transcription in bladder cancer.

Rs710521 near *TP63* on 3q28—Rs710521 on 3q28 was identified in the same study with a borderline genome-wide significance ($p = 1.15 \times 10^{-7}$). Since then, it has been further validated in GWAS [16,19] and candidate gene studies [44,45] with a combined allelic OR of 1.18 (95% CI: 1.12–1.24; $p = 1.8 \times 10^{-10}$) [19] in a white population. Similar borderline associations have been shown in Chinese populations [39,45]. Rs710521 is located in a linkage disequilibrium block that encompasses only one gene, *TP63*, which is a *p53* homolog and plays an important role in proliferation and apoptosis. *TP63* expression is decreased in early-stage bladder tumors [46] and loss of *TP63* expression has been associated with progression of bladder tumors [47,48]. The functional impact of rs710521 is not clear. No significant correlation between *TP63* mRNA expression and rs710521 was observed [15].

Rs2294008 in *PSCA* on 8q24.3—Wu *et al.* published the second independent GWAS of bladder cancer and identified rs2294008 as a novel susceptibility variant for bladder cancer using a total of 6667 cases and 39,590 controls [16]. The allelic OR was 1.15 (95% CI: 1.10–1.20; $p = 2.14 \times 10^{-10}$). This SNP has been validated in additional white [19] and Chinese populations [49]. Rs2294008 is located approximately 15 Mb telomeric to the *MYC* gene and it is not believed to act through *MYC*. Rs2294008 is a missense SNP located in exon 1 of the *PSCA* gene and alters the start codon. The T allele is hypothesized to produce a protein peptide of 123 amino acids, compared with 114 amino acids for the peptide encoded by the C allele that uses a downstream alternative start codon. This 9-amino acid N-terminus signal sequence difference may affect protein folding, intracellular modifications and trafficking of *PSCA* proteins. However, attempts to characterize these two different forms of *PSCA* *in vivo* have not been successful. On the other hand, *in vitro* luciferase reporter assays in three different bladder cancer cell lines (UC1, UC3 and UC13) showed that the variant T allele reduced *PSCA* promoter activity by over 80% [16] and the T allele was also associated with lower *PSCA* mRNA expression in adjacent normal bladder tissues [49]. *PSCA* is expressed at low levels in the urothelial epithelium of normal bladder, but it is overexpressed in urothelial carcinoma [50]. The expression level of *PSCA* was shown as an independent predictor of recurrence in superficial bladder cancer [51]. Rs2294008 is also associated with the risk of diffuse-type gastric cancer in Asians [52], but the expression level of *PSCA* in gastric cancer is downregulated, in contrast to the overexpression of *PSCA* in

bladder cancer [53,54]. It is intriguing that the T allele confers increased cancer risk in both cancer types even though *PSCA* is downregulated in one and upregulated in another malignancy. Future functional studies are warranted to delineate the physiological role of *PSCA* and the biological mechanisms of *PSCA* and rs2294008 in bladder carcinogenesis.

Rs798766 near *FGFR3* on 4p16.3—Following their first GWAS of bladder cancer, Kiemeny *et al.* found that the T allele of rs798766 on 4p16.3 was associated with bladder cancer risk (OR: 1.24; 95% CI: 1.17–1.32; $p = 9.9 \times 10^{-12}$) [17]. Rs798766 is located in an intron of *TACC3*, approximately 70 kb from *FGFR3*. Activating mutations in *FGFR3* are the most common and most specific genetic aberrations in noninvasive bladder cancer [55]. Consistently, rs798766 shows stronger association with tumors of low grade and low risk of progression [17,19]. The T allele (risk allele) frequency is higher in Ta (papillary carcinoma, accounts for 70% of non-muscle-invasive bladder cancer [NMIBC]) tumors that carry an activating mutation in *FGFR3* than in Ta tumors with wild-type *FGFR3*. In addition, the T allele was associated with an increased expression of *FGFR3* in adipose tissue, which was used as a surrogate tissue due to lack of expression data from normal urothelial tissue [17]. These data suggest that *FGFR3* is the causal gene in this region. Further fine-mapping and functional studies are needed to identify the causal variant.

***TERT* & 5p15.33 region**—Genetic variations in the 5p15.33 region, which contains the *CLPTMIL* and *TERT* (encoding the catalytic subunit of telomerase) genes, have been associated with increased or decreased risk of multiple cancer types [18,56–60]. Rs401681, located in an intron of *CLPTMIL*, was associated with an increased risk of lung, bladder, prostate and cervical cancer and basal cell carcinoma, but was protective against melanoma [56]. The association reached borderline genome-wide significance ($p = 5.0 \times 10^{-7}$) with bladder cancer in a combined analysis of the original European [18] and additional US populations of European descent [19] (a total of 7673 cases and 40,105 controls) with an OR of 1.11 (95% CI: 1.07–1.16). Rs2736098, a synonymous SNP (A350A) in exon 2 of *TERT*, was associated with increased risks of lung, bladder, prostate cancer and basal cell carcinoma [56]. This SNP was not covered in Illumina's SNP arrays, but direct genotyping in 3669 cases and 9076 controls resulted in an OR of 1.16 (95% CI: 1.08–1.23; $p = 1.3 \times 10^{-4}$) [18]. Although it is generally believed that SNPs in this region act through *TERT* function and by affecting telomere length, these two SNPs have not been associated with altered telomere length [18,61]. The causal variants are still elusive and the biological mechanisms remain unknown.

Rs1014971 on 22q13.1—Rothman *et al.* recently reported a large GWAS of bladder cancer with a primary scan of 3532 cases and 5120 controls [19], followed by validation in 8382 cases and 48,275 controls from 16 studies, including populations from the aforementioned published GWAS [15–17]. Three new regions associated with bladder cancer were identified. The most significant one was rs1014971 (OR: 0.88; 95% CI: 0.85–0.91; $p = 8.4 \times 10^{-12}$) on 22q13.1. This SNP is located in an intergenic region, approximately 25 kb centromeric to *APOBEC3A* and approximately 64 kb telomeric to *CBX6*, neither of which have been implicated in carcinogenesis yet and further studies are needed to identify the causal gene and variant.

Rs8102137 in *CCNE1* on 19q12—The second hit by Rothman *et al.* was rs8102137 on 19q12, which maps to the genomic region of *CCNE1* [19]. The OR was 1.13 (95% CI: 1.09–1.17; $p = 1.7 \times 10^{-11}$). Cyclin E plays an important role in the G1 to S cell cycle control and is amplified or overexpressed in many tumor types, including bladder tumors [62]. Whether this SNP is a causal variant regulating the expression of cyclin E or tags the causal variant remains to be studied.

Rs11892031 in *UGT1A* cluster on 2q37.1—The third novel SNP identified by Rothman *et al.* was rs11892031 (OR: 0.84; 95% CI: 0.79–0.89; $p = 1.0 \times 10^{-7}$) [19]. This SNP resides in an intron of the *UGT1A* gene cluster on 2q37.1. UDP-glucuronosyltransferases (UGTs) are a major phase II metabolizing enzyme family playing critical roles in the detoxification of endo- and xeno-biotics by glucuronidation [63]. Previous candidate gene studies have evaluated a few SNPs in this family with cancer risk but none have been validated [21]. However, genetic variation in *UGT1A1* has been convincingly linked to severe toxicity of irinotecan, which resulted in an approved clinical test for the *UGT1A1**28 allele by the US FDA [64]. Reduced expression of *UGT1A* isoforms has been observed in bladder tumor tissues and chemically induced mouse bladder cancer models [65,66]. It is likely that *UGT1A* is the causal gene in this region; however, rs11892031 is an intronic SNP and is most likely a tagging SNP. Further studies are needed to identify the causal SNP that is linked to rs11893021.

Genetic susceptibility to clinical outcomes in bladder cancer

Bladder cancer can be classified into two groups: 75–80% of cases are NMIBC (stages Ta, T1 and TIS) and the rest are muscle-invasive or metastatic bladder cancer (MIMBC; T2–T4). NMIBCs tend to recur but rarely progress to invasive cancer. The vast majority of invasive bladder cancers occur in patients without a prior history of papillary tumors [67]. These two groups of tumors also involve distinct molecular pathways; for example, *p53* mutations were associated with high-stage, high-grade tumors, but rarely observed in Ta tumors. By contrast, *FGFR3* mutations occurred in the majority (>70%) of Ta tumors. The mutations in these two genes were almost mutually exclusive [68]. The distinct prognosis and molecular genetics of NMIBC and MIMBC dictate that NMIBC and MIMBC be analyzed separately, particularly for outcome studies. The standard treatment for NMIBC is transurethral resection (TUR) alone for low-risk patients and TUR followed by adjuvant intravesical therapy for high-risk patients. Intravesicle bacille Calmette–Guérin (BCG) therapy is the prevalent choice for high-risk NMIBC patients. Although NMIBC can generally be treated successfully with these therapies, tumor recurrence is a major clinical problem. Following TUR, recurrence rate is approximately 70% [69,70], whereas TUR plus BCG reduces recurrence by 30% [71]. The effect of BCG treatment on progression is less certain [72,73]. The response rate for BCG treatment is 60–70% and approximately a third of initial responders develop recurrence and progression [74,75]. For MIMBC, radical cystectomy, multimodal therapy (TUR, cystectomy, preoperative radiotherapy and/or neoadjuvant chemotherapy) or systemic cisplatin-containing combination chemotherapy are used. The 5-year recurrence-free survival for patients with organ-confined, lymph-node-negative tumors reaches approximately 80%, but the number falls progressively with increasing tumor stage [76]. Multimodal therapy, specifically cisplatin-based neoadjuvant chemotherapy and radical cystectomy, has been shown to improve survival among patients with high-risk, locally advanced bladder cancer compared with radical cystectomy alone [77]. However, the modest clinical benefit of neoadjuvant chemotherapy is accompanied by a substantial treatment-related mortality and toxicity [78,79]. Clearly, objective biomarkers are needed in clinics to complement conventional clinicopathological markers to predict prognosis, treatment response and survival in both NMIBC and MIMBC patients.

There have been numerous candidate gene studies reporting positive associations between SNPs and outcomes in both NMIBC and MIMBC patients. The evaluated SNPs were implicated in multiple pathways including inflammation, xenobiotic metabolism, DNA repair, cell cycle control, apoptosis, cell adhesion, angiogenesis, growth factor and stem cell biology [20,21]. Of particular interest is the assessment of inflammation-related SNPs with recurrence in NMIBC patients receiving BCG treatment, since intravesical BCG instillation creates a strong local immune response, generating a Th1 cytokine milieu at the tumor site,

which is essential for the success of the BCG treatment [80,81]. One study showed that the variant allele of a promoter SNP in the *IL-6* gene was associated with an increased risk of recurrence in NMIBC patients receiving maintenance BCG and also an increased overall progression risk in NMIBC patients [82]. The largest bladder cancer outcome study to date was recently reported by Chen *et al.*, who evaluated a panel of SNPs in the Sonic hedgehog (Shh) pathway [83], a critical pathway involved in stem cell maintenance. Two SNPs, *SHH* rs1233560 and *GLI2* rs11685068, were significantly associated with recurrence in 419 US NMIBC patients treated with TUR alone, which was replicated in 356 independent TUR-only NMIBC patients from Spain. For MIMBC, since systemic platinum-based chemotherapy and/or preoperative radiotherapy are used in some patients and these therapies induce DNA damage, SNPs in DNA repair genes may modulate DNA repair capacity and therefore affect prognosis and response of MIMBC patients following chemo- and/or radiotherapy. There were a few positive results on DNA repair gene SNPs with MIMBC prognosis and response [84]. Nevertheless, most of the candidate gene studies of bladder cancer outcomes had small sample sizes and the results were either contradictory or lacked independent validation [20]. Large, well-characterized, independent patient cohorts are needed to validate these results.

Given the high success of GWAS in identifying novel cancer susceptibility loci, it has been expected that similar success would be achieved in GWAS of clinical outcomes. However, the GWAS of clinical outcomes have been lagging behind. There were a few successful stories of GWAS of drug response and drug toxicity with small sample sizes, but none were in the treatment of common cancers [85]. The major rate-limiting factor is the requirement of a large patient population with well-annotated tumor characteristics, treatment regimens and follow-up data. There have been a few GWAS on overall survival in lung, prostate and breast cancers [86–88], but no SNPs have reached genome-wide significance. The largest GWAS of survival in cancer patients had 1145 postmenopausal women with invasive breast cancer as primary screening and 4335 women as validation and no SNPs were found to be significantly associated with survival [88]. A plausible explanation is that common variants associated with survival could be specific to tumor subtypes or treatment approaches, which highlights the challenges in performing GWAS of clinical outcomes. There are ongoing efforts in the bladder cancer research community to pool data from independent GWAS and then perform validation in multiple independent populations through international collaborations and we expect initial results will be available in the next year or two.

Future perspective

It is clear that bladder cancer is a polygenic disease and there are multiple low-penetrance susceptibility loci. Besides the ten confirmed loci as summarized in this report, it was estimated that there would be an additional two dozen bladder cancer susceptibility SNPs of similar risks and frequencies to be identified [19,89]. Pooled or meta-analysis of published GWAS followed by large-scale replication would identify most of the remaining loci. Although we have some plausible causal genes, almost all of the identified SNPs, with the exception of rs2294008 in *PSCA*, appear to be tagging SNPs. Fine-mapping and genomic resequencing are needed to identify the causal variants, which should be followed by functional genomics to characterize the causal variants and genes in the context of bladder carcinogenesis. From a practical point of view, all the identified SNPs confer modest risks with the highest OR of 1.47 for *GSTM1*-null genotype and the rest between 1.1 and 1.2. Incorporation of three GWAS identified SNPs to a basic bladder cancer risk prediction model only improved the risk prediction accuracy by 1% [37]. It is unlikely that addition of more SNPs will dramatically increase the prediction accuracy. The exploration of gene–gene and gene–environment interactions may provide better opportunities to increase the predictive power. Research in this area has a few challenges, such as the requirement of

even larger sample sizes, the collection and standardization of environmental exposure data and the development of powerful statistical tools for complex interactions. On the other hand, phenotypic assays, such as mutagen sensitivity, DNA repair capacity and telomere length, have been associated with bladder cancer risk [90–93]. These phenotypic biomarkers measure the cumulative effect of genetic variants, have strong genetic heritability and have a stronger effect on cancer risk prediction than individual SNPs [90]. There is potential to develop reproducible and high-throughput phenotypic assays as intermediate biomarkers for bladder cancer risk prediction; for example, a real-time PCR-based telomere length assay has been widely used to determine telomere length and cancer risk [92,94].

The future of studying genetic variants as predictors of clinical outcomes clearly lies in GWAS. GWAS of clinical outcomes are more challenging than GWAS of cancer risks but offer better opportunities for clinical application. Treatment heterogeneity is a major concern for outcome studies and great efforts need to be taken to address this concern. A large, well-characterized, homogeneously treated patient population is required for GWAS of outcomes, which necessitates multi-institutional, international collaboration. Electronic medical records should be encouraged to obtain detailed treatment information. Statistical analysis should account for treatment variation from person to person. Outcome variables should be uniformly defined across institutions. Biospecimens, particularly peripheral blood, should be collected in prospective clinical trials conducted by national clinical trial groups. These clinical trial samples are an invaluable resource for future validation of SNPs obtained from studies using retrospectively identified patients. The ultimate goal of identifying prognostic or predictive SNPs is to incorporate them into a comprehensive risk prediction model to improve prediction over currently applied models that are based only on host and clinicopathological variables. The incorporation of genetic markers to epidemiological and clinicopathological variable-based risk prediction models holds great promise for future personalized risk assessment, prevention and treatment of cancer.

Acknowledgments

This work was partially supported by NIH grants U01 CA 127615 (Xifeng Wu), R01 CA 74880 (Xifeng Wu), P50 CA91846 (Xifeng Wu) and R01 CA CA131335 (Jian Gu) from the National Cancer Institute and funds from the University of Texas MD Anderson Cancer Center Research Trust (Xifeng Wu).

Bibliography

Papers of special note have been highlighted as:

▪ of interest

▪▪ of considerable interest

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J. Clin.* 2010; 60(5):277–300. [PubMed: 20610543]
2. Wu X, Ros MM, Gu J, Kiemeny L. Epidemiology and genetic susceptibility to bladder cancer. *BJU Int.* 2008; 102(9 Pt B):1207–1215. [PubMed: 19035883] ▪ Comprehensive review of the environmental risk factors and genetic susceptibility to bladder cancer.
3. Zeegers MP, Tan FE, Dorant E, van Den Brandt PA. The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta-analysis of epidemiologic studies. *Cancer.* 2000; 89(3): 630–639. [PubMed: 10931463]
4. Reulen RC, Kellen E, Buntinx F, Brinkman M, Zeegers MP. A meta-analysis on the association between bladder cancer and occupation. *Scand. J. Urol. Nephrol. Suppl.* 2008; (218):64–78. [PubMed: 18815919]
5. Villanueva CM, Cantor KP, Cordier S, et al. Disinfection byproducts and bladder cancer: a pooled analysis. *Epidemiology.* 2004; 15(3):357–367. [PubMed: 15097021]

6. Villanueva CM, Cantor KP, King WD, et al. Total and specific fluid consumption as determinants of bladder cancer risk. *Int. J. Cancer*. 2006; 118(8):2040–2047. [PubMed: 16284957]
7. Chen CJ, Chuang YC, You SL, Lin TM, Wu HY. A retrospective study on malignant neoplasms of bladder, lung and liver in blackfoot disease endemic area in Taiwan. *Br. J. Cancer*. 1986; 53(3): 399–405. [PubMed: 3964542]
8. Aben KK, Witjes JA, Schoenberg MP, et al. Familial aggregation of urothelial cell carcinoma. *Int. J. Cancer*. 2002; 98(2):274–278. [PubMed: 11857419]
9. Kramer AA, Graham S, Burnett WS, Nasca P. Familial aggregation of bladder cancer stratified by smoking status. *Epidemiology*. 1991; 2(2):145–148. [PubMed: 1932313]
10. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer – analyses of cohorts of twins from Sweden, Denmark, and Finland. *N. Engl. J. Med*. 2000; 343(2):78–85. [PubMed: 10891514]
11. Aben KK, Baglietto L, Baffoe-Bonnie A, et al. Segregation analysis of urothelial cell carcinoma. *Eur. J. Cancer*. 2006; 42(10):1428–1433. [PubMed: 16737809]
12. Garcia-Closas M, Malats N, Silverman D, et al. *NAT2* slow acetylation, *GSTM1* null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. *Lancet*. 2005; 366(9486):649–659. [PubMed: 16112301] • Large candidate gene study and meta-analyses that provided compelling evidence for the association of *NAT2* slow acetylator and *GSTM1*-null genotype with bladder cancer risk.
13. Gu J, Liang D, Wang Y, Lu C, Wu X. Effects of *N*-acetyl transferase 1 and 2 polymorphisms on bladder cancer risk in Caucasians. *Mutat. Res*. 2005; 581(1–2):97–104. [PubMed: 15725609]
14. Stern MC, Lin J, Figueroa JD, et al. Polymorphisms in DNA repair genes, smoking, and bladder cancer risk: findings from the international consortium of bladder cancer. *Cancer Res*. 2009; 69(17):6857–6864. [PubMed: 19706757]
15. Kiemeny LA, Thorlacius S, Sulem P, et al. Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. *Nat. Genet*. 2008; 40(11):1307–1312. [PubMed: 18794855] • First published genome-wide association study (GWAS) of bladder cancer that identified rs9642880 on 8q24.21 as a novel bladder cancer susceptibility variant. Rs710521 on 3q28 reached borderline genome-wide significance.
16. Wu X, Ye Y, Kiemeny LA, et al. Genetic variation in the prostate stem cell antigen gene *PSCA* confers susceptibility to urinary bladder cancer. *Nat. Genet*. 2009; 41(9):991–995. [PubMed: 19648920] • Second published GWAS of bladder cancer that identified rs2294008 in *PSCA* on 8q24.3 as a novel bladder cancer susceptibility variant. This is the only functional SNP among the eight GWAS-identified bladder cancer susceptibility SNPs.
17. Kiemeny LA, Sulem P, Besenbacher S, et al. A sequence variant at 4p16.3 confers susceptibility to urinary bladder cancer. *Nat. Genet*. 2010; 42(5):415–419. [PubMed: 20348956]
18. Rafnar T, Sulem P, Stacey SN, et al. Sequence variants at the *TERT-CLPTMIL* locus associate with many cancer types. *Nat. Genet*. 2009; 41(2):221–227. [PubMed: 19151717]
19. Rothman N, Garcia-Closas M, Chatterjee N, et al. A multi-stage genome-wide association study of bladder cancer identifies multiple susceptibility loci. *Nat. Genet*. 2010; 42(11):978–984. [PubMed: 20972438] • Largest GWAS of bladder cancer. It confirmed all the previously reported bladder cancer susceptibility loci, and identified three novel loci. The large sample size also allowed stratified analyses by smoking and tumor stage and grade.
20. Grotenhuis AJ, Vermeulen SH, Kiemeny LA. Germline genetic markers for urinary bladder cancer risk, prognosis and treatment response. *Future Oncol*. 2010; 6(9):1433–1460. [PubMed: 20919828] • Comprehensive review article of published bladder cancer association studies and positive SNPs. In particular, the literature review was exhaustive for association studies of bladder cancer outcomes.
21. Wu X, Lin X, Dinney CP, Gu J, Grossman HB. Genetic polymorphism in bladder cancer. *Front Biosci*. 2007; 12:192–213. [PubMed: 17127293]
22. Horikawa Y, Gu J, Wu X. Genetic susceptibility to bladder cancer with an emphasis on gene–gene and gene–environmental interactions. *Curr. Opin. Urol*. 2008; 18(5):493–498. [PubMed: 18670273]

23. Malats N. Genetic epidemiology of bladder cancer: scaling up in the identification of low-penetrance genetic markers of bladder cancer risk and progression. *Scand. J. Urol. Nephrol. Suppl.* 2008; (218):131–140. [PubMed: 18815927]
24. Vatsis KP, Weber WW, Bell DA, et al. Nomenclature for *N*-acetyltransferases. *Pharmacogenetics.* 1995; 5(1):1–17. [PubMed: 7773298]
25. Hein DW. Molecular genetics and function of NAT1 and NAT2: role in aromatic amine metabolism and carcinogenesis. *Mutat. Res.* 2002; 506–507:65–77.
26. Agundez JA. Polymorphisms of human *N*-acetyltransferases and cancer risk. *Curr. Drug Metab.* 2008; 9(6):520–531. [PubMed: 18680472]
27. Dong LM, Potter JD, White E, Ulrich CM, Cardon LR, Peters U. Genetic susceptibility to cancer: the role of polymorphisms in candidate genes. *JAMA.* 2008; 299(20):2423–2436. [PubMed: 18505952]
28. Yeager M, Chatterjee N, Ciampa J, et al. Identification of a new prostate cancer susceptibility locus on chromosome 8q24. *Nat. Genet.* 2009; 41(10):1055–1057. [PubMed: 19767755]
29. Chung CC, Magalhaes WC, Gonzalez-Bosquet J, Chanock SJ. Genome-wide association studies in cancer – current and future directions. *Carcinogenesis.* 2010; 31(1):111–120. [PubMed: 19906782]
30. Ghoussaini M, Song H, Koessler T, et al. Multiple loci with different cancer specificities within the 8q24 gene desert. *J. Natl Cancer Inst.* 2008; 100(13):962–966. [PubMed: 18577746]
31. Eeles RA, Kote-Jarai Z, Al Olama AA, et al. Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. *Nat. Genet.* 2009; 41(10):1116–1121. [PubMed: 19767753]
32. Crowther-Swanepoel D, Broderick P, Di Bernardo MC, et al. Common variants at 2q37.3, 8q24.21, 15q21.3 and 16q24.1 influence chronic lymphocytic leukemia risk. *Nat. Genet.* 2010; 42(2):132–136. [PubMed: 20062064]
33. Tomlinson IP, Webb E, Carvajal-Carmona L, et al. A genome-wide association study identifies colorectal cancer susceptibility loci on chromosomes 10p14 and 8q23.3. *Nat. Genet.* 2008; 40(5):623–630. [PubMed: 18372905]
34. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature.* 2007; 447(7148):1087–1093. [PubMed: 17529967]
35. Zanke BW, Greenwood CM, Rangrej J, et al. Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24. *Nat. Genet.* 2007; 39(8):989–994. [PubMed: 17618283]
36. Yeager M, Orr N, Hayes RB, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Nat. Genet.* 2007; 39(5):645–649. [PubMed: 17401363]
37. Wu X, Hildebrandt MA, Chang DW. Genome-wide association studies of bladder cancer risk: a field synopsis of progress and potential applications. *Cancer Metastasis Rev.* 2009; 28(3–4):269–280. [PubMed: 20016998]
38. Cortessis VK, Yuan JM, Van Den Berg D, et al. Risk of urinary bladder cancer is associated with 8q24 variant rs9642880[T] in multiple racial/ethnic groups: results from the Los Angeles–Shanghai case–control study. *Cancer Epidemiol. Biomarkers Prev.* 2010; 19(12):3150–3156. [PubMed: 21051319]
39. Wang M, Zhang W, Yuan L, Fu G, Wei Q, Zhang Z. Common genetic variants on 8q24 contribute to susceptibility to bladder cancer in a Chinese population. *Carcinogenesis.* 2009; 30(6):991–996. [PubMed: 19369583]
40. Ahmadiyeh N, Pomerantz MM, Grisanzio C, et al. 8q24 prostate, breast, and colon cancer risk loci show tissue-specific long-range interaction with MYC. *Proc. Natl Acad. Sci. USA.* 2010; 107(21):9742–9746. [PubMed: 20453196]
41. Pomerantz MM, Ahmadiyeh N, Jia L, et al. The 8q24 cancer risk variant rs6983267 shows long-range interaction with MYC in colorectal cancer. *Nat. Genet.* 2009; 41(8):882–884. [PubMed: 19561607] ▪ First paper to show that cancer susceptibility SNPs on the 8q24.21 region reside in enhancer region and affect MYC expression through long-range interaction with MYC promoter.
42. Sotelo J, Esposito D, Duhagon MA, et al. Long-range enhancers on 8q24 regulate c-Myc. *Proc. Natl Acad. Sci. USA.* 2010; 107(7):3001–3005. [PubMed: 20133699]

43. Wasserman NF, Aneas I, Nobrega MA. An 8q24 gene desert variant associated with prostate cancer risk confers differential *in vivo* activity to a MYC enhancer. *Genome Res.* 2010; 20(9): 1191–1197. [PubMed: 20627891]
44. Lehmann ML, Selinski S, Blaszkewicz M, et al. Rs710521[A] on chromosome 3q28 close to *TP63* is associated with increased urinary bladder cancer risk. *Arch. Toxicol.* 2010; 84(12):967–978. [PubMed: 21063684]
45. Stern MC, Van Den Berg D, Yuan JM, et al. Sequence variant on 3q28 and urinary bladder cancer risk: findings from the Los Angeles–Shanghai bladder case–control study. *Cancer Epidemiol. Biomarkers Prev.* 2009; 18(11):3057–3061. [PubMed: 19843673]
46. Comperat E, Bieche I, Dargere D, et al. *p63* gene expression study and early bladder carcinogenesis. *Urology.* 2007; 70(3):459–462. [PubMed: 17905096]
47. Urist MJ, Di Como CJ, Lu ML, et al. Loss of *p63* expression is associated with tumor progression in bladder cancer. *Am. J. Pathol.* 2002; 161(4):1199–1206. [PubMed: 12368193]
48. Zigeuner R, Tsybrovskyy O, Ratschek M, Rehak P, Lipsky K, Langner C. Prognostic impact of *p63* and *p53* expression in upper urinary tract transitional cell carcinoma. *Urology.* 2004; 63(6): 1079–1083. [PubMed: 15183954]
49. Wang S, Tang J, Wang M, Yuan L, Zhang Z. Genetic variation in *PSCA* and bladder cancer susceptibility in a Chinese population. *Carcinogenesis.* 2010; 31(4):621–624. [PubMed: 20083643]
50. Amara N, Palapattu GS, Schrage M, et al. Prostate stem cell antigen is overexpressed in human transitional cell carcinoma. *Cancer Res.* 2001; 61(12):4660–4665. [PubMed: 11406532]
51. Elsamman E, Fukumori T, Kasai T, et al. Prostate stem cell antigen predicts tumour recurrence in superficial transitional cell carcinoma of the urinary bladder. *BJU Int.* 2006; 97(6):1202–1207. [PubMed: 16686711]
52. Sakamoto H, Yoshimura K, Saeki N, et al. Genetic variation in *PSCA* is associated with susceptibility to diffuse-type gastric cancer. *Nat. Genet.* 2008; 40(6):730–740. [PubMed: 18488030]
53. Bahrenberg G, Brauers A, Joost HG, Jakse G. Reduced expression of *PSCA*, a member of the LY-6 family of cell surface antigens, in bladder, esophagus, and stomach tumors. *Biochem. Biophys. Res. Commun.* 2000; 275(3):783–788. [PubMed: 10973799]
54. Reiter RE, Gu Z, Watabe T, et al. Prostate stem cell antigen: a cell surface marker overexpressed in prostate cancer. *Proc. Natl Acad. Sci. USA.* 1998; 95(4):1735–1740. [PubMed: 9465086]
55. Pandith AA, Shah ZA, Siddiqi MA. Oncogenic role of fibroblast growth factor receptor 3 in tumorigenesis of urinary bladder cancer. *Urol. Oncol.* 2010 (Epub ahead of print).
56. Baird DM. Variation at the *TERT* locus and predisposition for cancer. *Expert Rev. Mol. Med.* 2010; 12:e16. [PubMed: 20478107]
57. Petersen GM, Amundadottir L, Fuchs CS, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. *Nat. Genet.* 2010; 42(3):224–228. [PubMed: 20101243]
58. Shete S, Hosking FJ, Robertson LB, et al. Genome-wide association study identifies five susceptibility loci for glioma. *Nat. Genet.* 2009; 41(8):899–904. [PubMed: 19578367]
59. Stacey SN, Sulem P, Masson G, et al. New common variants affecting susceptibility to basal cell carcinoma. *Nat. Genet.* 2009; 41(8):909–914. [PubMed: 19578363]
60. Wang Y, Broderick P, Webb E, et al. Common 5p15.33 and 6p21.33 variants influence lung cancer risk. *Nat. Genet.* 2008; 40(12):1407–1409. [PubMed: 18978787]
61. Pooley KA, Tyrer J, Shah M, et al. No association between *TERT–CLPTMIL* single nucleotide polymorphism rs401681 and mean telomere length or cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 2010; 19(7):1862–1865. [PubMed: 20570912]
62. Schraml P, Bucher C, Bissig H, et al. Cyclin E overexpression and amplification in human tumours. *J. Pathol.* 2003; 200(3):375–382. [PubMed: 12845634]
63. Mackenzie PI, Owens IS, Burchell B, et al. The UDP glycosyltransferase gene superfamily: recommended nomenclature update based on evolutionary divergence. *Pharmacogenetics.* 1997; 7(4):255–269. [PubMed: 9295054]

64. Perera MA, Innocenti F, Ratain MJ. Pharmacogenetic testing for uridine diphosphate glucuronosyltransferase 1A1 polymorphisms: are we there yet? *Pharmacotherapy*. 2008; 28(6): 755–768. [PubMed: 18503403]
65. Giuliani L, Gazzaniga P, Caporuscio F, Ciotti M, Frati L, Agliano AM. Can down-regulation of UDP-glucuronosyltransferases in the urinary bladder tissue impact the risk of chemical carcinogenesis? *Int. J. Cancer*. 2001; 91(1):141–143. [PubMed: 11149414]
66. Iida K, Mimura J, Itoh K, et al. Suppression of AhR signaling pathway is associated with the down-regulation of UDP-glucuronosyltransferases during BBN-induced urinary bladder carcinogenesis in mice. *J. Biochem*. 2010; 147(3):353–360. [PubMed: 19880377]
67. Dinney CP, McConkey DJ, Millikan RE, et al. Focus on bladder cancer. *Cancer Cell*. 2004; 6(2): 111–116. [PubMed: 15324694]
68. Bakkar AA, Wallerand H, Radvanyi F, et al. *FGFR3* and *TP53* gene mutations define two distinct pathways in urothelial cell carcinoma of the bladder. *Cancer Res*. 2003; 63(23):8108–8112. [PubMed: 14678961]
69. Kurth K, Denis L, Sylvester R, de Pauw M. The natural history and the prognosis of treated superficial bladder cancer. EORTC GU Group. *Prog. Clin. Biol. Res*. 1992; 378:1–7. [PubMed: 1301569]
70. Pashos CL, Botteman MF, Laskin BL, Redaelli A. Bladder cancer: epidemiology, diagnosis, and management. *Cancer Pract*. 2002; 10(6):311–322. [PubMed: 12406054]
71. Smith JA Jr, Labasky RF, Cockett AT, Fracchia JA, Montie JE, Rowland RG. Bladder cancer clinical guidelines panel summary report on the management of nonmuscle invasive bladder cancer (stages Ta, T1 and TIS). The American Urological Association. *J. Urol*. 1999; 162(5): 1697–1701. [PubMed: 10524909]
72. Gontero P, Bohle A, Malmstrom PU, et al. The role of bacillus Calmette–Guerin in the treatment of non-muscle-invasive bladder cancer. *Eur. Urol*. 2010; 57(3):410–429. [PubMed: 19969411]
73. Williams SK, Hoenig DM, Ghavamian R, Soloway M. Intravesical therapy for bladder cancer. *Expert Opin. Pharmacother*. 2010; 11(6):947–958. [PubMed: 20205607]
74. Merz VW, Marth D, Kraft R, Ackermann DK, Zingg EJ, Studer UE. Analysis of early failures after intravesical instillation therapy with bacille Calmette–Guerin for carcinoma *in situ* of the bladder. *Br. J. Urol*. 1995; 75(2):180–184. [PubMed: 7850322]
75. Schenk-Braat EA, Bangma CH. Immunotherapy for superficial bladder cancer. *Cancer Immunol. Immunother*. 2005; 54(5):414–423. [PubMed: 15565330]
76. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J. Clin. Oncol*. 2001; 19(3):666–675. [PubMed: 11157016]
77. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet*. 2003; 361(9373):1927–1934. [PubMed: 12801735]
78. Millikan R, Siefker-Radtke A, Grossman HB. Neoadjuvant chemotherapy for bladder cancer. *Urol. Oncol*. 2003; 21(6):464–467. [PubMed: 14693274]
79. Grossman HB, Dinney CP. If cystectomy is insufficient, what is an urologist to do? *Urol. Oncol*. 2003; 21(6):475–478. [PubMed: 14693276]
80. Luo Y, Chen X, O'Donnell MA. Role of Th1 and Th2 cytokines in BCG-induced IFN- γ production: cytokine promotion and simulation of BCG effect. *Cytokine*. 2003; 21(1):17–26. [PubMed: 12668155]
81. Saint F, Patard JJ, Maille P, et al. T helper 1/2 lymphocyte urinary cytokine profiles in responding and nonresponding patients after 1 and 2 courses of bacillus Calmette–Guerin for superficial bladder cancer. *J. Urol*. 2001; 166(6):2142–2147. [PubMed: 11696723]
82. Leibovici D, Grossman HB, Dinney CP, et al. Polymorphisms in inflammation genes and bladder cancer: from initiation to recurrence, progression, and survival. *J. Clin. Oncol*. 2005; 23(24):5746–5756. [PubMed: 16110031]
83. Chen M, Hildebrandt MA, Clague J, et al. Genetic variations in the sonic hedgehog pathway affect clinical outcomes in non-muscle-invasive bladder cancer. *Cancer Prev. Res*. 2010; 3(10):1235–1245.

84. Sakano S, Wada T, Matsumoto H, et al. Single nucleotide polymorphisms in DNA repair genes might be prognostic factors in muscle-invasive bladder cancer patients treated with chemoradiotherapy. *Br. J. Cancer*. 2006; 95(5):561–570. [PubMed: 16880786]
85. Daly AK. Genome-wide association studies in pharmacogenomics. *Nat. Rev. Genet.* 2010; 11(4): 241–246. [PubMed: 20300088]
86. Penney KL, Pyne S, Schumacher FR, et al. Genome-wide association study of prostate cancer mortality. *Cancer Epidemiol. Biomarkers Prev.* 2010; 19(11):2869–2876. [PubMed: 20978177]
87. Huang YT, Heist RS, Chirieac LR, et al. Genome-wide analysis of survival in early-stage non-small-cell lung cancer. *J. Clin. Oncol.* 2009; 27(16):2660–2667. [PubMed: 19414679]
88. Azzato EM, Pharoah PD, Harrington P, et al. A genome-wide association study of prognosis in breast cancer. *Cancer Epidemiol. Biomarkers Prev.* 2010; 19(4):1140–1143. [PubMed: 20332263]
89. Park JH, Wacholder S, Gail MH, et al. Estimation of effect size distribution from genome-wide association studies and implications for future discoveries. *Nat. Genet.* 2010; 42(7):570–575. [PubMed: 20562874]
90. Wu X, Lin J, Grossman HB, et al. Projecting individualized probabilities of developing bladder cancer in white individuals. *J. Clin. Oncol.* 2007; 25(31):4974–4981. [PubMed: 17971596] ■■ Developed the first bladder cancer prediction model based on epidemiological variables and an enhanced prediction model by adding a phenotypic intermediate biomarker, mutagen sensitivity. The results showed that addition of mutagen sensitivity significantly improved risk prediction accuracy.
91. Lin J, Kadlubar FF, Spitz MR, Zhao H, Wu X. A modified host cell reactivation assay to measure DNA repair capacity for removing 4-aminobiphenyl adducts: a pilot study of bladder cancer. *Cancer Epidemiol. Biomarkers Prev.* 2005; 14(7):1832–1836. [PubMed: 16030125]
92. McGrath M, Wong JY, Michaud D, Hunter DJ, De Vivo I. Telomere length, cigarette smoking, and bladder cancer risk in men and women. *Cancer Epidemiol. Biomarkers Prev.* 2007; 16(4):815–819. [PubMed: 17416776]
93. Wu X, Amos CI, Zhu Y, et al. Telomere dysfunction: a potential cancer predisposition factor. *J. Natl Cancer Inst.* 2003; 95(16):1211–1218. [PubMed: 12928346]
94. Willeit P, Willeit J, Mayr A, et al. Telomere length and risk of incident cancer and cancer mortality. *JAMA*. 2010; 304(1):69–75. [PubMed: 20606151]

Website

101. Hindorff, LA.; Junkins, HA.; Hall, PN.; Mehta, JP.; Manolio, TA. A catalog of published genome-wide association studies. www.genome.gov/gwastudies

Executive summary

- Bladder cancer is a complex polygenic disease caused by major environmental factors and many low-penetrance predisposition genes.
- Candidate gene studies identified *NAT2* slow acetylator and *GSTM1*-null genotypes as bladder cancer susceptibility loci and there were significant genotype–smoking interactions for both genotypes.
- Genome-wide association studies have identified and validated eight novel genetic susceptibility loci for bladder cancer and an additional two dozen new SNPs are expected.
- All the identified loci confer modestly increased bladder cancer risk. With the exception of the *GSTM1*-null genotype, which has an odds ratio of 1.47, all the other loci only increase the risk by approximately 20% or less.
- Candidate gene studies have reported numerous positive associations between SNPs and bladder cancer outcomes, but none of the reported SNPs had robust association and none have been convincingly replicated.
- Genome-wide association studies of bladder cancer outcome have been hampered by small sample size and are lagging behind. There are more challenges but better opportunities for genome-wide association studies of bladder cancer outcome than candidate gene studies.
- The ultimate goal of identifying genetic susceptibility loci for cancer risk and outcome is to incorporate them into a comprehensive risk prediction model to improve prediction over currently available models based only on epidemiological and clinicopathological variables.

Table 1

Confirmed genetic variants associated with bladder cancer risk in Caucasians.

Variants	Chromosome location	SNP position	Gene	Nucleotide change	SNP function	Risk allele (frequency)	Allelic OR (95% CI)	p-value	Ref.
rs9642880	8q24.21	128,787,250	MYC	G/T	Intergene	T (0.45)	1.22 (1.15–1.29)	7.8×10^{-12}	[14]
rs710521	3q28	191,128,627	TP63	A/G	Intergene	A (0.73)	1.18 (1.12–1.24)	1.8×10^{-10}	[14,17]
rs2294008	8q24.3	143,758,933	PSCA	C/T	Start codon	T (0.46)	1.15 (1.10–1.20)	2.0×10^{-10}	[15]
rs401681	5p15.33	1,375,087	CLPTM1L, TERT	C/T	Intron	C (0.54)	1.11 (1.07–1.16)	5.0×10^{-7}	[17,18]
rs798766	4p16.3	1,704,037	TACC3, FGFR3	C/T	Intron	T (0.19)	1.24 (1.17–1.32)	9.5×10^{-12}	[16]
rs1014971	22q13.1	37,662,569	APOBEC3A, CBX6	A/G	Intergene	G (0.38) [†]	0.88 (0.85–0.91)	8.4×10^{-12}	[17]
rs8102137	19q12	34,988,693	CCNE1	T/C	5' end	C (0.33)	1.13 (1.09–1.17)	1.7×10^{-11}	[17]
rs11892031	2q37.1	234,230,022	UGT1A	A/C	Intron	C (0.08) [†]	0.84 (0.79–0.89)	1.0×10^{-7}	[17]
rs1495741	8p22	18,317,161	NAT2	A/G	3' end	G (0.20) [†]	0.87 (0.83–0.91)	4.2×10^{-11}	[17]
NAT2 slow acetylator	8p22		NAT2			Slow acetylator genotype (0.56)	1.4 (1.3–1.5)	8.0×10^{-12}	[12]
GSTM1 null	1p13.3		GSTM1			Homozygous deletion (0.51)	1.47 (1.38–1.57)	5.0×10^{-31}	[12,17]

[†]These frequencies were minor allele frequencies corresponding to the reported protective effect (OR <1) of minor alleles. OR: Odds ratio.