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The Journal of Biomedical Research, 2013, 27(3):170–178

JBR

Invited Review

Bladder cancer epidemiology and genetic susceptibility

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Received 04 March 2013, Accepted 16 March 2013, Epub 25 March 2013

Abstract

Bladder cancer is the most common malignancy of the urinary system. The incidence of bladder cancer of men is higher than that of women (approximately 4:1). Here, we summarize the bladder cancer-related risk factors, including environmental and genetic factors. In recent years, although the mortality rate induced by bladder cancer has been stable or decreased gradually, the public health effect may be pronounced. The well-established risk factors for bladder cancer are cigarette smoking and occupational exposure. Genetic factors also play important roles in the susceptibility to bladder cancer. A recent study demonstrated that hereditary non-polyposis colorectal cancer is associated with increased risk of bladder cancer. Since 2008, genome-wide association study (GWAS) has been used to identify the susceptibility loci for bladder cancer. Further gene-gene or gene-environment interaction studies need to be conducted to provide more information for the etiology of bladder cancer.

Keywords: bladder cancer, molecular epidemiology, risk factors, genetic susceptibility

INTRODUCTION

Bladder cancer, especially transitional cell carcinoma (TCC) of the bladder, is the 7th most common cancer in men and the 17th most common cancer in women worldwide[1]. Kakehi et al. reported that the mortality rate of bladder cancer in Japan has increased dramatically, especially in men[1]. The incidence of bladder cancer is the highest in Western countries and the lowest in Asian countries[2]. Bladder cancer is a complex disease. So far, there have been many studies to investigate the etiology of bladder cancer; however, the exact causes of bladder cancer have not been clarified. Cigarette smoking and occupational exposure to chemical carcinogens have been proven to be linked with the risk of bladder cancer[3,4]. Drug use and consumption of alcohol, coffee and tea are also factors considered to be associated with bladder cancer risk[5,6]. Even although persons are exposed to the same environment, only a small frac–

This study was partly supported by National Natural Science Foundation of China (No. 81230068, and No.81102089), the Natural Science Foundation of Jiangsu Province (No. BK2011773), the Key Program for Basic Research of Jiangsu Provincial Department of Education (No. 12KJA330002, and No. 11KJB330002), Jiangsu Provincial Graduates Innovative Project (CXZZ12_0594), the Qing Lan Project of Jiangsu Provincial Department of Education, and the Priority Academic Program Development of Jiangsu Higher Education Institution (Public Health and Preventive Medicine).

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The authors reported no conflict of interests.

doi:10.7555/JBR.27.20130026

tion of individuals eventually develop bladder cancer, which implies that genetic factors may play an important role in bladder carcinogenesis. A recent study proposed that hereditary non-polyposis colorectal cancer can increase the incidence of bladder cancer[7] and family history of bladder cancer may be a potential risk factor for offspring bladder cancer[8]. In addition, common candidate genes or pathways, such as carcinogenic metabolizing genes[9], DNA repair genes[10], apoptosis-related genes[11] and microRNA (miRNA)-related genes[12], etc. have been studied widely and can contribute to the risk of bladder cancer. It is warranted to note that evidence has indicated that both the environmental and genetic factors may jointly have an effect in the development of bladder cancer[13]. Since 2008, there has been five genome-wide association studies (GWAS) involved in bladder cancer risk[14-18]. In the future, we still have more work to do in the study of preventive, diagnostic and therapeutic approaches of bladder cancer.

ENVIRONMENTAL FACTORS

Cigarette smoking

Cigarette smoking is the most important risk factor in the development of bladder cancer; the incidence of bladder cancer is approximately 4 times higher in smokers than that in non-smokers[3]. Zeggers et al. conducted a meta-analysis to summarize the epidemiology of urinary tract cancer (primarily bladder cancer) risk and cigarette smoking. Their findings support that current cigarette smokers have an approximate three fold higher risk of urinary tract cancer than nonsmokers[19]. However, the relationship between secondhand smoke and bladder cancer risk remains debatable. Exposure to secondhand smoke is considered to be associated with the development of bladder cancer through inducing changes in DNA methylation of several CpG loci in bladder cancer[20]. Recently, a prospective cohort study was performed to investigate the influence of both active smoking and exposure to secondhand smoke on bladder cancer risk[21]. Current smokers were found to have an increased risk of bladder cancer in both the 1963 cohort [relative risk (RR) = 2.7, 95% confidence intervals (CIs): 1.6-4.7] and the 1975 cohort (2.6, 1.7-3.9) after adjustment for age, education, and marital status. However, secondhand smoke exposure may not be associated with bladder cancer risk in the 1975 cohort (0.9, 0.4-2.3)[21]. Over the past several decades, cohort studies also have reported similar results[22-24]. In addition, the associations between active cigarette smoking and bladder cancer risk were consistent in both men and women[21]. A Korean population study also demonstrated that cigarette smoking is an independent risk factor for bladder cancer and similar results were found for incidence among men and women[25].

Occupational exposure

Occupational exposure to chemical carcinogens has been established to attribute to 20% of all bladder cancer[26,27]. It is the second most important risk factor for bladder cancer, immediately after cigarette smoking. Data from 11 European case-control studies found that the attributable risks in any high-risk occupation ranged from 4% to 7%[4]. At the end of 1970s, occupational exposures caused 10% of male bladder cancers and 5% of female bladder cancers in America[28]. Most of the occupational exposure to chemical carcinogens containing aromatic amine and polycyclic aromatic hydrocarbons (PAHs) has been proven to elevate the risk of bladder cancer, and the population attributable risk for the exposure to PAHs was estimated to be 4%[4]. Sorahan et al. investigated occupational exposure to aromatic amine. It was observed that aromatic amine, including dyestuff manufacture (RR = 2.51, 95% CI = 1.44-4.35), leather work (2.51, 1.20-5.04), and cable manufacture (2.46, 1.20-5.04), increased the risk of bladder cancer, based on a hospital case-control study in the United Kingdom and after adjusting for smoking[29]. Additionally, a number of studies also reported increased risks of bladder cancer in individuals exposed to aromatic amine[4,26,30]. It is worthwhile noting that Brown et al. recently calculated overall RR estimates for occupational exposure to PAHs and bladder cancer based on 26 previous studies (RR = 1.4, 95% CI = 1.2-1.7), suggesting PAHs as an important risk factor of bladder cancer[31]. Other occupations, such as hairdressers, are exposed to aromatic amine, aminophenols and hydrogen peroxide, etc. A follow-up study of a cohort of 38,866 female and 6,824 male hairdressers from Sweden showed that the highest risk was a standardized incidence ratio of 2.56 for bladder cancer in male hairdressers working in 1960. Follow-up studies during 1960-1969, and during the period of 1960-1998, found that the risk decreased to 1.31. However, no significant association with bladder cancer in women was found[32].

Drug use

Acetaminophen is the aromatic amine metabolite of phenacetin. Several studies have proposed that the use of phenactin can be as a risk factor in the development of bladder cancer[5,33]. In 1985, Piper and his group investigated the use of analgesics containing phenacetin or acetaminophen. In a case-control study,

which involved 173 young women with bladder cancer and 173 matched cancer-free controls, it was suggested that regular use of phenacetin was associated with a 6.5-fold higher risk for bladder cancer than the matched controls (95% CI = 1.5-59.2)[34]. However, Kaye et al. observed that heavy use of acetaminophen was not associated with the risk of bladder cancer, while its use was associated with a 2-fold increase risk of renal cancer[35]. The results of acetaminophen use in bladder cancer risk are not consistent. In recent years, small case-control studies or cohort studies have been used to estimate the relationship of acetaminophen and bladder cancer risk. Studies showed that the toxic metabolite of acetaminophen directly caused hepatotoxicity[36], and acetaminophen currently is considered to be the most common cause of acute liver failure in both the United States and United Kingdom[37,38]. Additionally, Peniston et al. conducted a review to estimate the risk of acetaminophen in athletes experiencing low back pain, which suggested that acetaminophen had the potential for misuse[39], and several guidelines confirmed that acetaminophen had little effect for osteoarthritis pain[40,41].

Other factors

Other factors, such as drinking alcohol, coffee or tea also are reported to be associated with the development of bladder cancer[42-44]. It has been established that alcohol drinking can cause many kinds of cancers, including cancer of the oral cavity, pharynx, esophagus, liver, colon, and rectum, and breast cancers[45]. Donato et al. showed that a dose-response association of alcohol drinking and bladder cancer was observed in men who drank more than 5 cups per day (odds ratio = 4.5, 95% CI = 1.2-16.8); however, no significant association was found in women (2.1, 1.0-4.8)[6]. In a Los Angeles population-based case-control study, alcohol drinking was considered to decrease bladder cancer risk and individuals consuming more than 4 drinks had a 0.32 decreased risk of bladder cancer than those who never drink (0.68, 0.52-0.90)[46]. Additionally, several studies did not report a significant relationship between alcohol drinking and bladder cancer risk[47-49]. Coffee drinking has been grouped as a possible human carcinogen by the International Agency for Research on Cancer (IARC); however, inconsistent findings were observed[50-52]. It may be due to factors confounded by cigarette smoking, other carcinogens, or the genetic background of different ethnicities. Lu et al. reported that in southern Taiwan, tea drinking was associated with increased risk of bladder cancer (3.29, 1.34-8.05), after adjustment of smoking status[43]. Currently, the exact mechanism is not clear. In recent years, factors including reproductive, menopausal hormone therapy, diets high in glycaemic index or glycaemic load, carotenoids, and vitamin C are also receiving much attention and being investigated in the development of bladder cancer[53-55].

GENETIC FACTORS

Family history

Family history is a known risk factor for bladder cancer[56-58]. Based on a Spanish bladder cancer case-control study, the relationship between family history of cancer in first-degree relatives and bladder cancer risk was estimated, and the subjects with family history of bladder cancer can increase the risk of bladder cancer among NAT2-slow acetylators (odds ratio = 4.76, 95% CI = 1.25-18.09)[59]. Plna et al. identified 65 families in which parents had bladder cancer with the increased risk of bladder cancer in the son (1.35, 0.97-1.79) and in the daughter (2.29, 1.46-3.29)[8]. A study by Ilić et al. found that bladder cancer risk was linked with the existence of familial bladder cancer, especially among the < 45 patients (RR = 1.45) and patients who smoked cigarettes (RR = 10.7)[60]. However, the prevalence of bladder cancer was 10% in the second-degree and third-degree relatives, and 3% in the first-degree relatives, suggesting that bladder cancer may not be a hereditary type of cancer[61]. Combined data from the Swedish, Danish, and Finnish twin registries revealed statistically significant effects of heritable factors for colorectal, breast and prostate cancer, ranging 27%-42%, but no significant association was observed in bladder cancer[62]. The finding of the relationship between family history and bladder cancer are still not consistent. The probable reason for this difference may be due to the lack of enough power to distinguish the exact heritable genetic effects from other confounding factors, such as the environmental factors[62]. It is worthy to note that the Japanese recently reported that bladder cancer was associated with hereditary colorectal cancer[7].

Genetic susceptibility

Over the past several decades, most researches have focused on studying the selected genes by using the approach of the candidate gene or candidate pathway and these studies are easy to conduct. Based on these studies, many important bladder cancer genes were found.

Carcinogen-metabolizing genes

N-acetyl transferase2 (*NAT2*) and *glutathione S-transferase Mu 1* (*GSTM1*) are two genes which have been studied widely[63-65]. In the human popula-

tion, there are two different NAT isozymes (NAT1 and NAT2) which have different catalytic activities affecting carcinogen metabolism. The early, pooled studies showed that NAT2 slow acetylators can moderately increase the risk of bladder cancer, compared with the rapid acetylators[9,66]. Recently, a Japanese case-control study has demonstrated that *NAT2* slow genotype was significantly associated with bladder cancer risk (OR = 3.41, 95% CI = 1.68-6.87), particularly in heavy smokers (8.57, 1.82-40.25)[67]. GSTM1 is thought to detoxify the carcinogenic PAHs and its null genotype is associated with the susceptibility to bladder cancer. A Spanish bladder cancer study revealed that the deletion of one or two copies of the *GSTM1* gene increased by 1.2-fold or 1.9-fold the risk of bladder cancer, respectively. At the same time, a meta-analysis also confirmed that *GSTM1* deletion genotype contributed to bladder cancer risk after adjustment of smoking status[64]. Additional studies showed that the association between *GSTT1* genotype and bladder cancer risk remains consistent[64] and *GSTP1* Ile105Val polymorphisms might be a risk factor for the development of bladder cancer, which does not show any significant interaction with smoking status[68]. Other candidate genes, such as *myeloperoxidase* (*MPO*), *nicotinamide adenine dinucleotide phosphate quinine oxidoreductase-1* (*NQO1*) also were associated with the risk of bladder cancer, and the results were contradictory[69,70]. We also performed a meta-analysis to explore the relationship of *MPO* polymorphism and cancer risk, and found borderline association of *MPO* -463G>A polymorphism and cancer risk[71].

DNA repair genes

It has been established that endogenous and exogenous factors can affect the stability of DNA; thus, the DNA repair pathway plays an important role in DNA repair. The human DNA repair system consists of four pathways: nucleotide-excision repair (NER), base-excision repair (BER), double-strand break repair (DSBR), and mismatch repair (MMR)[72]. In the DNA repair pathway, common gene polymorphisms have been investigated regarding their effect in the development of bladder cancer. NER plays the key role in removing bulky DNA adducts[72]. Xeroderma pigmentosum group F (XPF), also known as the excision repair cross-complementing group 4 (ERCC4), is critically involved in the NER pathway[73]. In our study, we first identified that the potential functional promoter -357A>C polymorphism of *XPF* gene was associated with bladder cancer risk, and this polymorphism can reduce the survival time of bladder cancer patients[10]. XPF polymorphisms were also examined in a British melanoma study, and no significant association was observed[74]. In the *Xeroderma pigmentosum D* (*XPD*)/*ERCC2* gene, Asp312Asn and Lys751Gln have been investigated widely and Li et al. pooled data showed that Asn allele and Gln/Gln genotype have increased risk of bladder cancer[75]. Recently, Sobti et al. found that the *XPD* Gln allele showed a significantly increased risk of bladder cancer, especially in smokers (OR = 5.30, 95% CI = 2.42-11.68) and alcohol drinkers (4.33, 2.17-8.70)[76]. The *XRCC1* protein plays an important role in BER. The *XRCC1* R194W polymorphism has been investigated and studies mainly reported that the W allele can reduce the risk of bladder cancer[77], breast cancer[78], lung cancer[79], and gastric cancer[80]. In addition, a meta-analysis on the *XRCC1* R194W and R399Q polymorphisms revealed that 399QQ genotype had a reduced risk of bladder cancer, even among smokers, in the recessive (0.65, 0.49-0.86) or homozygote model (0.66, 0.49-0.86). However, compared to 194R, no statistical effect of the 194W allele on bladder cancer risk was found in all subjects and Caucasians[81].

Apoptosis-related genes

Apoptosis is a very crucial process in regulating cell homeostasis and the occurrence of imbalance for apoptosis may contribute to the development of cancer[82,83]. FAS and FAS ligand (FASL) are involved in apoptotic signal transmission and associated with cancer risk. We performed two meta-analysis studies to explore the effect of *FAS*[84] and *FASL*[85] polymorphisms, respectively. The results showed that individuals with *FAS*-1377AA genotype had an increased risk of cancer, and the *FASL*-844T allele had a lesser effect on cancer risk. CASP8 is an essential defense mechanism against over-proliferation and malignancy[86]. Wang et al. firstly confirmed that the *CASP8-652* 6N ins/del genotype can decrease the risk of bladder cancer, suggesting that it may be a marker for genetic susceptibility to bladder cancer in Chinese populations[11]. Death receptor 4 is also an important protein in apoptosis, and -397G>T polymorphism had an additive interaction in bladder cancer among the smokers[87].

MiRNA-related genes

Recently, miRNA has been a very hot issue and a number of groups have investigated the relationship between miRNA and cancer risk[88]. Single nucleotide polymorphisms (SNPs) in miRNA coding genes and seed regions are rare[89]. A case-control study also had provided evidence for the association between miRNA SNPs and cancer risk. Tian et al. found that the miR-

196a2 rs11614913 CC genotype was associated with increased risk of lung cancer, when comparing with its TT and CT (OR = 1.25; 95% CI = 1.01-1.54)[90]. We performed a meta-analysis to evaluate the association for miR-196a2 rs11614913 and cancer risk and found that this SNP can contribute to the susceptibility to bladder cancer[91]. MiR-146a also has been studied widely[92,93]. Jazdzewski et al. first reported that miR-146a rs2910164 was associated with increased the risk of papillary thyroid carcinoma[94]. In the Chinese population, we firstly found that miR-146a rs2910164 C allele was associated with a significantly decreased risk of bladder cancer (OR = 0.80, 95% CI = 0.71-0.90), and the rs2910164 GC/CC genotypes conferred a dramatically reduced risk of recurrence, compared with the GG genotype ($P = 0.016$)[12].

In addition to the above reported studies, other important genes, such as inflammation-related genes[95], cell cycle-related genes[96], folate metabolism-related genes[97], etc., were also studied for cancer risk. Most of the published studies could not be, or have not been, replicated and, thus, may bring false positives or negatives. In order to better understand the meaning of the associated results, we should expand our sample size, encourage multi-center collaboration, and reduce the candidate gene or pathway studies based on hypothesis methods[98].

GWAS

Bladder cancer is a complex disease, and candidate gene or pathway studies are lacking enough power to detect the exactly genetic loci to clarify the mechanism of bladder cancer. Therefore, GWAS is emergent, followed by the International HapMap Project (www.hapmap.org/)[99,100]. Since 2007, GWAS has been widely used to identify the genomic loci. In 2008, the first GWAS of bladder cancer was published[14]. Based on 1,803 urinary bladder cancer cases and 34,336 controls, and an additional case-control study (2,165 cases and 3,800 controls), Kiemeney et al. observed that rs9642880 T allele on chromosome 8q24 can increase the risk of bladder cancer by 0.49-fold, compared with that of non-carriers. Additionally, polymorphism rs710521 on chromosome 3q28 was also found to be associated with bladder cancer risk[14]. We replicated these two polymorphisms in our Chinese bladder cancer case-control study, and the findings suggested that individuals with rs9642880 GT or TT genotypes have an increased risk of bladder cancer (OR = 1.65, 95%,CI = 1.25-2.17). However, the rs710521 A>G polymorphism was not associated with an increased risk of bladder cancer[101]. In a German study, they observed rs710521 polymorphism to be significantly associated with increased bladder cancer risk (1.21, 1.04-1.40)[102]. It was demonstrated that genomic loci may have various effects with different ethnic backgrounds. Therefore, it is warranted to use the GWAS approach in identifying the genetic loci of Chinese bladder cancer. Subsequently, four bladder cancer GWAS found several additional common variants: rs401681 in 5p15.33[17], rs2294008 in the PSCA gene[16], rs1014971 on 22q13.1, rs8102137 on 19q12, rs11892031 on 2q37.1[18], and rs798766 on 4p16.3[15]. It is worth noting that data from GWAS is enough; however, how to deal with it in the right way is still a question. Further functional studies should be conducted to explain the etiology of bladder cancer.

GENE-GENE AND GENE-ENVIRONMENT INTERACTIONS

The ultimate goal of the epidemiological study is to find harmful or beneficial factors to protect the populations´ health or reduce the development of disease. Thus, a complex disease prediction model encompassing the environmental, genetic, and personal risk factors should be established to benefit disease diagnosis, prevention, and treatment[103].

Leibovici et al. studied genetic variation in the inflammation pathway for bladder cancer risk, and the results revealed that, compared with light smokers with the variant genotype, the heavy smokers with IL-6 variant genotype had an increased risk of bladder cancer (OR = 1.65, 95% CI = 0.87-3.12)[104]. Their recent research indicated that, for esophageal adenocarcinoma, interaction between *IL1B* +3954C > T and reflux was associated with esophageal adenocarcinoma risk, and the obviously significant interaction was found among *IL1B* +3954C > T and *BAT3* S625P variant genotypes, higher body mass index, and smoking status (5.76, 2.48-13.38)[105]. Wang et al. also found an additive joint effect between *CASP8* polymorphism and bladder cancer risk among smokers[11]. In addition, gene-gene interactions also are performed to explore the etiology of bladder cancer. Chen and his colleagues showed that gene-gene interactions among *CCNH* Val270Ala, *ERCC6* Met1097Val, and *RAD23B* Ala249Val in chronic smokers was observed in bladder cancer risk, resulting in an almost 30-fold increased risk in smokers carrying the variant allele at these loci[106]. In our previous study, we found that the combination of the *IL-13* C-1055T and *IL-13* Arg130Gln in smokers can increase the risk of bladder cancer in the Chinese population. The best interactive model was the two-factor model in which smokers with the *IL-13* C-1055T genotypes were the subgroup to predict bladder cancer risk by multifactor dimen-

sionality reduction analysis[107]. In addition, one study revealed that a multiplicative interaction association between the combined *IL-4R* Ile50Val and *IL-13* C-1055T genotypes was observed to decrease the risk of renal cell carcinoma ($P = 0.036$). These data demonstrated that gene-gene or gene-environment interaction may be better to predict the risk of cancer. However, further studies should be performed to validate the results and confirm the exact causes of bladder cancer.

Although GWAS is a powerful approach to identify the genomic loci of cancer, currently during the GWAS, no study investigates the relationship of environment or other factors and cancer risk. For the next step, gene-gene or gene-environment interaction should be applied to pool all the GWAS data. Interestingly, a meta-analysis of two previously published GWAS data was pooled, and Garcia-Closas et al. found a new susceptibility locus of *SLC14A1* on chromosome 18q12.3, based on 4501 cases and 6076 controls of European populations[108].

CONCLUSION

It is warranted to note that environmental factors, such as cigarette smoking and occupational exposure, do indeed contribute to a part of the bladder cancer risk. Meanwhile, genetic factors also are very important in the development of bladder cancer. As mentioned above, gene-gene or gene-environment interaction may better predict the risk of bladder cancer. Additional risk factors, for example *G. Schistosoma* infection, irradiation, and drinking water quality, can also be considered to be associated with bladder cancer risk. At present, many GWAS are published, and this new approach has identified many new susceptibility loci, based on several thousand cancer cases and several cancer-free controls. However, data from GWAS is very large, and the results from GWAS should be interpreted carefully. In the future, epidemiological research should pay more attention to follow-up health population cohorts to reveal the etiology of bladder cancer risk through retrospective and prospective studies.

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