Introduction

Bladder cancer (BC) remains the second leading malignancy of the genitourinary tract and the seventh most frequently diagnosed cancer in males, accounting for approximately 5.9% (386,300) of the new cancer cases and 3.4% (150,200) of the estimated cancer deaths annually worldwide. Bladder is the major cancer sites for males in Jordan (Ismail et al., 2013); and with an age-specific incidence rate of about 11.2/100,000, BC is also the fifth most common cancer among men in Iran (Karbakhsh et al., 2013). The etiology and carcinogenesis of BC is unclear, but smoking, especially opium abusing simultaneously (Shakhssalim et al., 2010), is thought to be a major risk factor followed by occupational exposure (Zeegers et al., 2000). Over 60 carcinogens, including polycyclic aromatic hydrocarbons (PAHs) such as benzo[a]pyrene and aromatic amines, have been identified in cigarette smoke (Luch et al., 2005). These carcinogens, which have been proven to be associated with BC in aluminum workers exposure to PAHs and coal gasification workers exposure to aromatic amines (Boffetta et al., 1997), can be converted, in vivo, into more hydrophilic and chemically active derivatives by the CYP450 enzyme superfamily (Grando et al., 2009).

CYP1A1, an important phase I xenobiotic metabolizing enzyme of the cytochrome P450 superfamily, is well known for its involvement in the metabolic activation of tobacco procarcinogens such as PAHs and aromatic amines (Vineis et al., 2007), and has been found in many epithelial tissues (Romkes et al., 1996). It is a highly polymorphic gene with more than 11 alleles thought to lead to amino acid changes (Shimada et al., 2006). One of the most common mutations described is a single-base exchange from A to G at position 2455 of exon 7, also called CYP1A1*2B or m2 (Hayashi et al., 1991). Polymorphism of this heme-binding region causes a substitution of isoleucine with valine in codon 462 (Ile462Val), resulting in an alteration of the functional protein and thus increasing enzyme activity (Kawajiri et al., 1996). Furthermore, mutation of this gene exhibits strong potential linkage disequilibrium with another mutation of CYP1A1-MspI (m1) polymorphism (Bartsch et al., 2000), a point mutation (T to C) at the MspI site in the 3’-untranslated region, and has also been proven to be associated with increased catalytic activity.

Such genetic differences in enzymes involved in the biotransformation of environmental risk factors are believed to play a pivotal role in an individual’s susceptibility to environmentally induced cancer and their relationship with various malignancies has been extensively studied (Bartsch et al., 2000). An initial study
regarding the association between CYP1A1 variations and cancer risk was conducted by Kellerman et al. in 1973 (Kellermann et al., 1973), investigating the correlation between benzo[a]pyrene hydroxylase inducibility and bronchogenic carcinoma. Since then, numerous studies on CYP1A1 polymorphisms and various cancers have been conducted, including lung cancer (Ji et al., 2012), head and neck cancer (Hiyama et al., 2008), brain cancer (Wahid et al., 2013), and breast cancer (Sergentanis et al., 2010), among others (Dai et al., 2009). However, less attention has been paid on the relationship between CYP1A1 variations and BC, with only a few studies having been conducted and their conclusions remaining controversial (Bartsch et al., 2000). As the statistical power of an individual study may be too weak to identify associations between CYP1A1 polymorphisms and BC risk, a meta-analysis combining data from all published studies may be more convincing. We thus carried out a meta-analysis to evaluate the association between CYP1A1 polymorphisms and BC risk including all eligible publications to date.

Materials and Methods

Literature Search

A comprehensive literature search was carried out by two independent investigators. The PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), and WanFang databases were searched using the following keywords: “CYP1A1”, “bladder cancer”, and “polymorphism”, in both English and Chinese. Synonyms and different search term styles were also used to obtain every relevant paper. Further, the bibliographies of all retrieved articles were manually checked for other relevant publications to find additional eligible studies. Searches were not restricted in language or publication date, although no efforts were made to obtain unpublished studies. The final search was updated on November 20, 2013.

Selection Criteria

All identified articles were reviewed according to the inclusion criteria before further analysis, namely any type of comparative study that i) assessed the association between CYP1A1 gene polymorphisms and BC, and ii) provided the frequencies of the CYP1A1 variants in both cases and controls, or provided sufficient data to estimate the odds ratio (OR) with their 95% confidence intervals (95% CIs). Studies were excluded from the meta-analysis if they met any of the following: i) without sufficient data; ii) a lack of control population; and/or iii) assessed the association between CYP1A1 and BC in rare alleles. In the event of overlapping data, either the study with higher quality or the most recent one was included in the analysis.

Data Extraction

For each eligible study, the following information was extracted: first author, year of publication, study region, ethnicity, BC confirmation, sample size (including number of cases and controls), source of control (together with matching criteria), polymorphisms of CYP1A1, methods used for genotyping, genotype distribution in cases and controls, and whether P value for the control population deviated from the Hardy-Weinberg equilibrium (HWE). Such extraction was performed by two authors independently. In the cases of conflict evaluation, a third author was consulted.

Quality Assessment

We evaluated the quality of included studies using the set of predetermined criteria derived by Thakkinstian et al. (Thakkinstian et al., 2005). This set of predetermined criteria was structured as a 20-item list with scores ranging from 0 to 12 by Peng et al. (Li et al., 2013) (Supplement Table S2), and has been quoted by several meta-analyses (Lu et al., 2013, Peng et al., 2013). As previously performed in other meta-analyses, we also considered articles with scores <8 as low quality studies, while the rest were high quality.

Statistical Analysis

The strength of association between CYP1A1 gene polymorphisms and BC risk was assessed by calculating crude ORs with the corresponding 95% CIs under the additive, dominant, and recessive genetic models. The stratification analysis was also conducted by ethnicity to evaluate the effect of CYP1A1 gene polymorphisms on the susceptibility to BC in different populations (categorized as Turks, Caucasians, and other, based on the main racial group of the included studies). To assess heterogeneity in each combined analysis, Cochran’s Q test and I² statistics were carried out, where $P < 0.10$ or $I^2 > 50\%$ indicated significant heterogeneity. In the situation of high heterogeneity, the random-effects model was used to pool the data; otherwise, the fixed-effects model was used. Additionally, if significant heterogeneity was detected, logistic meta-regression was performed to identify four possible sources of heterogeneity including ethnicity, BC confirmation method, genotyping method, and quality score. Moreover, Galbraith plots were also used to further explore the sources of heterogeneity among studies.

A sensitivity analysis was conducted to assess the influence of a single study on the overall result of the meta-analysis, especially for studies whose genotype frequencies in the control populations were inconsistent with the HWE, given that they may generate possible bias. Potential publication bias was evaluated using funnel plots and Egger’s regression tests to provide both graphical and statistical evidence. All data analysis was completed by using STATA software version 11.0 (Stata Corp, College Station, TX, USA). A value of $P < 0.05$ was considered as statistically significant, and all $P$ values were two-sided.

Results

Study Characteristics

The systematic literature search generated a total of 39 citations based on the search strategy mentioned above (31 in PubMed and EMBASE, and 8 in the CNKI and WanFang databases), 16 of which were excluded after screening of the titles and abstracts, for they were not relevant to our study. Therefore, 23 articles were considered of potential value and the full text was
As established above, six studies, with a total of 908 cases and 815 controls, evaluated the association of BC risk in I1e462Val A/G mutation (two in Caucasians, two in Turks, one in Asian, and one was a mixed population); three studies, with a total of 519 cases and 605 controls, evaluated MspI T/C mutation (one in Caucasians, one in Turks, and one in Asian). Of all the eligible studies, the majority of BC patients were histologically diagnosed (six studies) for their genotype. The rest were pathologically diagnosed and genotyped using PCR-RFLP assays (five studies), the rest were pathologically diagnosed and genotyped using allele-specific PCR or standard PCR methods. After testing for concordance with the HWE principle, two studies were found to deviate from HWE. The quality score of all eligible studies ranged from 5 to 9, with four studies being graded as high quality and five as low quality; the detailed characteristics are shown in Table 1.

Table 1. Detail Characteristics of Studies Included in This Meta-analysis

| Author, Year | Region | Ethnicity | case/control | Genotyping methods | BC confirmation | Source of control | PI | HWE | QS (Yes/No) |
|--------------|--------|-----------|--------------|-------------------|----------------|------------------|----|------|------------|
| Brockmöller J, 1996 | Germany | Caucasian | 368/359 | AS-PCR | HD HB (matched for age, gender and race) | CYP1A1*2B A/G (I1e462Val) | Yes | 6 |
| Grando JP, 2009 | Brazil | Mix | 100/100 | AS-PCR | HD HB (matched for age, gender, race, and smoking status) | CYP1A1*2B A/G (I1e462Val) | No | 7 |
| Fontana L., 2009 | French | Caucasian | 51/45 | PCR | HD HB (age and sex-matched cancer-free subjects) | CYP1A1*2B A/G (I1e462Val) | No | 6 |
| Öztürk T, 2011 | Turkish | Non-Caucasian | 176/97 | PCR-RFLP | PD HB (matched for age) | CYP1A1*2B A/G (I1e462Val) | Yes | 8 |
| Berber U, 2013 | Turkish | Non-Caucasian | 114/114 | AS-PCR | HD HB (age and sex-matched cancer-free subjects) | CYP1A1*2B A/G (I1e462Val) | Yes | 8 |
| Fu J, 2013 | China | Asian | 99/100 | PCR-RFLP | PD HB (matched for age, gender, race, and smoking status) | CYP1A1*2B A/G (I1e462Val) | Yes | 8 |
| Brockmöller J, 1996 | Germany | Caucasian | 369/360 | PCR-RFLP | HD HB (matched for age, gender and race) | CYP1A1*2A T/C (MspI) | Yes | 6 |
| Yang LX, 2007 | China | Asian | 44/85 | PCR-RFLP | PD HB (matched for CYP1A1*2A T/C (MspI) | Yes | 5 |
| Srivastava DS, 2008 | North India | Non-Caucasian | 106/160 | AS-PCR | HD HB (matched for age and race) | CYP1A1*2A T/C (MspI) | Yes | 8 |

AS-PCR, Allele specific polymerase chain reaction; PCR-RFLP, Polymerase chain reaction-restriction fragment length polymorphism; HD, Histologically diagnosed; PD, Pathologically diagnosed; HB, Hospital-based; PB, Population-based; PI, Polymorphism(s) investigated; HWE, Hardy-Weinberg equilibrium; QS, quality score

Meta-Analysis Results

CYP1A1*2B A/G (I1e462Val) and Bladder Cancer Risk: As established above, six studies, with a total of 908 cases and 815 controls, evaluated the association of BC risk in I1e462Val A/G mutation (one in Caucasians, one in Turks, one in Asian, and one was a mixed population); three studies, with a total of 519 cases and 605 controls, evaluated MspI T/C mutation (one in Caucasians, one in Turks, and one in Asian). Of all the eligible studies, the majority of BC patients were histologically diagnosed (six studies) for their genotype. The rest were pathologically diagnosed and genotyped using allele-specific PCR or standard PCR methods. After testing for concordance with the HWE principle, two studies were found to deviate from HWE. The quality score of all eligible studies ranged from 5 to 9, with four studies being graded as high quality and five as low quality; the detailed characteristics are shown in Table 1.

Figure 1. Process of Data Extraction

retrieved for a detailed evaluation. An additional 15 articles were excluded following full text review; nine were review articles or conference abstracts, three were without sufficient information to access ORs and 95\% CIs, two assessed the association between CYP1A1 polymorphisms and urothelial cancer, and one assessed the association of BC risk in I1e462Val A/G mutation (one in Caucasians, one in Turks, one in Asian, and one was a mixed population); three studies, with a total of 519 cases and 605 controls, evaluated MspI T/C mutation (one in Caucasians, one in Turks, and one in Asian). Of all the eligible studies, the majority of BC patients were histologically diagnosed (six studies) for their genotype. The rest were pathologically diagnosed and genotyped using allele-specific PCR or standard PCR methods. After testing for concordance with the HWE principle, two studies were found to deviate from HWE. The quality score of all eligible studies ranged from 5 to 9, with four studies being graded as high quality and five as low quality; the detailed characteristics are shown in Table 1.
Table 2. Meta-analysis of the CYP1A1 Gene Polymorphisms on Bladder Cancer Risk

| Genetic model | Population | No. of studies | Test of association | Mode | Heterogeneity | Publication |
|---------------|------------|----------------|--------------------|------|---------------|-------------|
|               |            |                | OR (95% CI)        | p value | I² (%) | p value | bias |
| CYP1A1*2B A/G(I1e462Val) |            |                |                    |        |        |        |      |
| G vs. A       |            |                | 1.04 (0.74–1.47)   | 0.810 | R      | 47.2   | 0.092 | 0.451 |
| Turkish       | 2          |                | 0.89 (0.63–1.28)   | 0.539 | F      | 31.1   | 0.228 | —     |
| Caucasian     | 2          |                | 0.69 (0.37–1.27)   | 0.230 | F      | 47.9   | 0.166 | —     |
| Other         | 2          |                | 1.39 (0.98–1.98)   | 0.068 | F      | 37.4   | 0.206 | —     |
| GG vs. AA     |            |                | 1.47 (0.70–3.07)   | 0.308 | F      | 0.0    | 0.789 | 0.416 |
| Turkish       | 2          |                | 1.60 (0.41–6.20)   | 0.498 | F      | 0.0    | 0.803 | —     |
| Caucasian     | 2          |                | 0.61 (0.10–3.63)   | 0.586 | F      | 36.9   | 0.208 | —     |
| Other         | 2          |                | 1.89 (0.67–5.35)   | 0.232 | F      | 0.0    | 0.890 | —     |
| AG vs. AA     |            |                | 0.97 (0.74–1.27)   | 0.819 | F      | 40.9   | 0.132 | 0.792 |
| Turkish       | 2          |                | 0.77 (0.51–1.17)   | 0.224 | F      | 48.7   | 0.163 | —     |
| Caucasian     | 2          |                | 0.73 (0.37–1.42)   | 0.351 | F      | 0.0    | 0.918 | —     |
| Other         | 2          |                | 1.42 (0.76–2.64)   | 0.271 | R      | 50.2   | 0.157 | —     |
| GG+AG vs. AA  |            |                | 1.01 (0.68–1.48)   | 0.970 | R      | 47.2   | 0.092 | 0.709 |
| Turkish       | 2          |                | 0.82 (0.54–1.22)   | 0.326 | F      | 48.3   | 0.164 | —     |
| Caucasian     | 2          |                | 0.70 (0.37–1.33)   | 0.280 | F      | 0.0    | 0.407 | —     |
| Other         | 2          |                | 1.44 (0.95–2.19)   | 0.084 | F      | 47.0   | 0.170 | —     |
| GG vs. AG+AA  |            |                | 1.45 (0.70–3.02)   | 0.317 | F      | 0.0    | 0.809 | 0.445 |
| Turkish       | 2          |                | 1.79 (0.46–6.87)   | 0.399 | F      | 0.0    | 0.906 | —     |
| Caucasian     | 2          |                | 0.61 (0.10–3.65)   | 0.592 | F      | 37.4   | 0.206 | —     |
| Other         | 2          |                | 1.71 (0.61–4.80)   | 0.308 | F      | 0.0    | 0.992 | —     |
| CYP1A1*2A T/C(MspI) |      |                |                    |        |        |        |      |
| C vs. T       |            |                | 1.24 (0.98–1.58)   | 0.078 | F      | 1.6    | 0.362 | 0.953 |
| CC vs. TT     |            |                | 1.93 (0.95–3.93)   | 0.071 | F      | 0.0    | 0.787 | 0.310 |
| TC vs. TT     |            |                | 1.19 (0.89–1.60)   | 0.24  | F      | 0.0    | 0.398 | 0.644 |
| CC+TC vs. TT  |            |                | 1.24 (0.93–1.64)   | 0.14  | F      | 16.0   | 0.304 | 0.673 |
| CC vs. TC+TT  |            |                | 1.67 (0.84–3.34)   | 0.145 | F      | 0.0    | 0.883 | 0.430 |

R, random effects model; F, fixed effects model.

0.97, 95% CI = 0.74–1.27, P = 0.819); iv) GG+AG vs. AA (OR = 1.01, 95% CI = 0.68–1.48, P = 0.970); v) GG vs. AG+AA (OR = 1.45, 95% CI = 0.70–3.02, P = 0.317). In the stratification analysis based on ethnicity, we also failed to find any significant association between the I1e462Val A/G polymorphism and BC risk in all comparison models (Table 2). A similar result was also found when limiting data to studies whose genotype in the control population was consistent with HWE (data not show).

As significant heterogeneity was found in the G vs. A model, the GG+AG vs. AA model in the overall population, and the AG vs. AA model in the “other” population subgroup, the random-effects model was used to pool these data. Meta-regression analyses and Galbraith plot analysis were also performed to explore the source of heterogeneity between the three comparison models. The results of meta-regression analyses revealed that sources of heterogeneity were not from any of the factors mentioned above (ethnicity, BC confirmation method, genotyping method, and quality score) in all three genetic models (data not shown). Galbraith plots identified that the study by Grando et al. (Grando et al., 2009) was the outlier and main contributor to heterogeneity in the three comparison models (Figure 2). Separate forest plots omitting the outlier study were conducted in each genetic model, the degree of heterogeneity decreased significantly (G vs. A: I² = 15.4%, P = 0.317; GG+AG vs. AA: I² = 0.0%, P = 0.437) with the insignificance result remaining the same (G vs. A: OR = 0.92, 95% CI = 0.71–1.18, P = 0.507; GG+AG vs. AA: OR = 0.86, 95% CI = 0.64–1.15, P = 0.305). However, we could not calculate the heterogeneity for the AG vs. AA model in the “other” population subgroup because only one study remained after the outlier was excluded.

**CYP1A1*2A T/C (MspI) and Bladder Cancer Risk:**

Three studies, including a total of 519 cases and 605 controls, evaluated the association between the MspI T/C variant and BC risk (Brockmoller et al., 1996; Li et al., 2007; Srivastava et al., 2008). However, though a slight trend was observed, we still failed to identify any significant association between the MspI T/C polymorphism and BC risk in all comparison models in the overall populations: i) C vs. T (OR = 1.24, 95% CI = 0.98–1.58, P = 0.078); ii) CC vs. TT (OR = 1.24, 95% CI = 0.98–1.58, P = 0.078); iii) TC vs. TT (OR = 1.19, 95% CI = 0.89–1.60, P = 0.240); iv) CC+TC vs. TT (OR = 1.24, 95% CI = 0.93–1.64, P = 0.140); v) CC vs. TC+TT (OR = 1.67, 95% CI = 0.84–3.34, P = 0.145). No subgroup analysis was conducted in this gene due to the limited number of studies. Because no significant heterogeneity was found among the studies, the fixed-effects model was used to pool the data, and meta-regression and Galbraith plot analyses were not carried out.

**Sensitivity Analysis**

Sensitivity tests for both polymorphisms showed that no single study greatly influenced the estimates of overall risk by using the leave-one-out analysis and recalculating the ORs and the 95% CIs. Although genotype frequencies
Consequently, it might affect the detoxification process and lead to the alteration of an individual’s BC susceptibility.

In this study, we analyzed the data from eight case-control studies whose results are conflicting regarding the association between CYP1A1 polymorphisms and BC susceptibility. The majority of the eligible studies included in our meta-analysis observed no significant association between CYP1A1 mutations and BC risk. On the other hand, Srivastava et al. (Srivastava et al., 2008) found a slight association with CYP1A1 (2A* T/C) for risk of BC (OR = 1.56), although it was not statistically significant \( (P = 0.093) \). In fact, there is evidence that CYP1A1 is involved in the carcinogenic progress of environmentally induced BC. A study conducted in human BC by Murai et al. (Murai et al., 1995) demonstrated an increased expression of CYP1A1 using immunohistochemistry. An in vitro investigation carried out by Wolf et al. (Wolf et al., 2005) found that cells treated with benzo[a]pyrene showed a dramatic increase in the expression of CYP1A1. Similar conclusions were also found in other experimental animals whose bladder cells were exposed to tobacco containing compounds such as benzo[a]pyrene and arylamines (Kogevinas et al., 2003; Dorrenhaus et al., 2007). However, we failed to reveal any evidence of an association between the two CYP1A1 polymorphisms and BC susceptibility overall, regardless of the additive, dominant, or recessive genetic models.

It has been reported that the distribution of the Val allele of Ile462Val varies extensively between different races, with the highest rate among East Asians (25%) and rarest among Caucasians (5%); the frequency of homozygous CYP1A1 MspI has also been found to be significantly different between various ethnicities (Cascorbi et al., 1996; Ji et al., 2012). Therefore, a further meta-analysis was performed among subgroups stratified by ethnicity. However, our result still failed to identify any significant association in this subgroup analysis.

Taken together, it may be concluded that CYP1A1 polymorphisms are not associated with BC risk in the overall population. Nevertheless, these results should be taken with caution as there is increasing evidence that metabolizing enzymes do not act alone and that single polymorphisms cannot explain complex multifactorial malignancies (Manuguerra et al., 2007). BC is a multifactorial disease that develops gradually following complex interactions among many genetic, environmental factors and other disease such as Diabetes Mellitus (Pollard et al., 2010; Botelho et al., 2010; Yang et al., 2013). The analysis of various combinations of genotypes to predict the risk of BC is now urgently required, since few studies have been performed studying double or triple polymorphisms of CYP1A1 combined with other genes to explore their association with various malignancies.

Publication Bias

To evaluate the possible publication bias, the Begg’s funnel plot and Egger’s test were performed. The funnel plots were symmetrical, suggesting that there was no significant publication bias among all the compared models (Figures 3 and 4). Egger’s test, which statistically assesses the funnel plot symmetry, still did not reveal any potential publication bias, indicating that our results were relatively stable.

Discussion

Environmental carcinogens, such as air pollution and tobacco smoke, are well-established sources of DNA damage, including oxidative base damage and abasic sites as well as single- and double-strand breaks (BosettiPiraLaVecchia 2005). Through their metabolism in the organism, these risk factors can either become more carcinogenic or be detoxified. CYP1A1 is an important phase 1 enzyme involved in the biotransformation of tobacco procarcinogens (Guengerich et al., 1998), and according to Giri et al., CYP1A1 polymorphisms are modulator of genetic damage in occupational settings (Giri et al., 2012). Consequently, it might affect the detoxification process of environmental carcinogens and lead to the alteration of an individual’s BC susceptibility.
combinations, though not directly associated with risk of BC, is associated with higher grade tumors. However, due to the limited number of studies, meta-analyses on gene-gene combinations and BC risk were not conducted.

To summarize, this is the first meta-analysis assessing whether polymorphisms in CYP1A1 are associated with BC risk. A total of nine separate comparisons consisting of 1,059 BC cases and 1,061 controls were included, leading to a greater statistical power than for a single study. Our results were consistent with the majority of the eligible studies that indicated a non-significant association between CYP1A1 polymorphisms and BC risk. Nevertheless, some limitations to this meta-analysis should be considered. Firstly, there were only eight studies and therefore the limited sample size did not represent the global population. Thus, the null association between CYP1A1 mutations and BC risk may be due to the small sample size as it provides low statistical power. As is universally known, smoking is an important risk factor for BC, smokers with the CYP1A1 A/G polymorphism have been reported to have more PAH-DNA adducts than smokers without the polymorphism (Mooney et al., 1997), and some studies have found cigarette smoking to be strongly associated with tumor grade of BC (Jiang et al., 2012). However, only two studies included in our meta-analysis presented detailed frequencies of CYP1A1 polymorphisms with smoking habit. Therefore, a further analysis to clarify the effect of smoking behavior was not conducted. BC is a multifactorial disease, other risk factors such as occupational exposure and chronic irritation may modify the relationship between CYP1A1 polymorphisms and BC risk; however, these factors were not taken into consideration. Finally, a potential publication bias may exist because no effort was made to obtain unpublished studies, although the results of the Begg’s funnel plot and Egger’s test showed no evidence of publication bias among all comparison models.

In conclusion, our meta-analysis indicates that there is no relationship between CYP1A1*2B A/G, 2A* T/C polymorphisms and BC risk. Nevertheless, we have to emphasize the need for larger studies with a more rigorous design, especially studies taking the gene-gene and gene-environment interactions into consideration. In this way, the limitations mentioned above could be overcome and a more precise conclusion on the association between CYP1A1 polymorphisms and BC risk could thus be drawn.

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