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Short Communication

The aryl hydrocarbon receptor (AhR) 1661G>A polymorphism in human cancer: A meta-analysis

Chengzhang Luo [a], Peng Zou [a], Guixiang Ji [b,c], Aihua Gu [b], Peng Zhao [a,*], Chunsheng Zhao [a,*]

[a] Department of neurosurgery, the First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Nanjing, 210029, China
[b] School of Public Health, Nanjing Medical University, 140 Hanzhong Road, Nanjing, 210029, China
[c] Nanjing Institute of Environmental Sciences/Key Laboratory of Pesticide Environmental Assessment and Pollution Control, Ministry of Environmental Protection, Nanjing 210042, China

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ABSTRACT

The aryl hydrocarbon receptor (*AhR*) is a ligand-activated transcription factor and plays an important role in the development of cancer. Although there have been many epidemiological studies investigating the relationship between genetic polymorphisms in the aryl hydrocarbon receptor (*AhR*) gene and human cancer risk, the findings remain conflicting. To derive a more precise estimation of association between the *AhR* 1661G>A polymorphism and risk of cancer, we performed a systematic meta-analysis based on 11 case–control studies, including 8158 cancer cases and 8336 controls. We used odds ratios with 95% confidence intervals (CIs) to estimate the strength of the association. We also performed subgroup analyses, sensitivity analyses and publication bias analyses. Overall, there was not enough evidence to support the hypothesis that the *AhR* 1661G>A polymorphism was associated with human cancer risk (homozygote comparison: OR=0.974, 95% CI=0.868 to 1.092, P=0.468 for the heterogeneity test; recessive model comparison: OR=0.958, 95% CI=0.859 to 1.068, P=0.767 for the heterogeneity test). Even after stratified analysis of cancer type and source of controls, no significant association was found. This meta-analysis suggested that the *AhR* 1661G>A polymorphism does not contribute to the development of cancer in humans. We believe that future refinement of experiments and epidemiological studies will confirm this hypothesis.

1. Introduction

Cancer has become the leading cause of death in economically developed countries and the second leading cause of death in developing countries. The latest research has reported that a total of 1,596,670 new cancer cases and 571,950 deaths from cancer are projected to occur in the United States in 2011. Furthermore, one in 4 deaths is due to cancer (Siegel et al., 2011). Cancer has become one of the most significant endangerments to human health. As is widely known, the formation of a neoplasm is most likely due to both genetic mutations in the human body and the influence of the outside environment. Common environmental contaminants include polycyclic aromatic hydrocarbons (Ng et al., 2010), halogenated aromatic hydrocarbons (HAH) and heterocyclic amines (HCA). It has been reported that exposure to HAHs and PAHs results in a wide range of toxic and carcinogenic responses in animals and humans (Marlowe and Puga, 2005). Meanwhile, the risk of environmental-related carcinogenesis depends not only on the dose of the procarcinogen exposure, but also on individual susceptibility to the procarcinogen.

The aryl hydrocarbon receptor (*AhR*) is a ligand-activated transcription factor known to mediate most of the toxic and carcinogenic effects of a wide variety of environmental contaminants, such as dioxin (TCDD; 2,3,7,8-tetrachlorodibenzo-[p]-dioxin) (Barouki et al., 2007). This receptor belongs to the basic helix-loop-helix (bHLH)/PAS family of heterodimeric transcriptional regulators. bHLH/PAS proteins are involved in the control of diverse physiological processes, such as circadian rhythms, organ development, neurogenesis, metabolism and the stress response to hypoxia (Crews, 1998; Gonzalez and Fernandez-Salguero, 1998; Whitlock, 1999). The activation of the Ah receptor by high-affinity HAH or PAH ligands, such as TCDD and B[a]P, has been known for many years to result in a wide range of cell cycle perturbations, including G0/G1 and G2/M arrest, a diminished capacity for DNA replication and an inhibition of cell proliferation (Puga et al., 2002). Among the six (I227V, P517S, R554K, V570I, Q666K, and R554K/V570I) human *AhR* variants, the R554K (1661G>A) locus is the most commonly investigated polymorphism of the *AhR* gene and is located in exon 10, which is a region associated with the transactivity of other genes (Harper et al., 2002).

Over the past decades, many epidemiological studies have been done to evaluate the relationship between the *AhR* 1661G>A (Arg554Lys) polymorphism and human cancer risk. However, the results have not yet reached an agreement. In order to determine whether the *AhR* 1661G>A polymorphism is associated with human cancer risk,

Abbreviations: *AhR*, aryl hydrocarbon receptor; Arg, arginine; Lys, lysine; OR, odds ratio; CI, confidence interval.

* Corresponding authors.
E-mail addresses: zhaopeng@njmu.edu.cn (P. Zhao), zhaocs61@hotmail.com (C. Zhao).

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we conducted a systematic meta-analysis using recent case–control studies focused on the relationship between the *AhR* 1661G > A polymorphism and human cancer risk.

2. Materials and methods

2.1. Identification and eligibility of relevant references

All references of case–control studies on the association between the *AhR* 1661G > A polymorphism and human cancer risk (last search was updated on September 24, 2011) were included. To identify the qualified references, four electronic databases (MEDLINE, EMBASE, Web of Knowledge and ScienceDirect) were searched using the Medical Subject Headings (Mesh) 'Receptors, Aryl Hydrocarbon' and 'Polymorphism, Genetic' combined with 'cancer' or 'neoplasm' or 'carcinoma'. No language limitations were imposed. We evaluated potentially relevant publications by examining the titles and abstracts. All studies matching the eligible criteria were carefully retrieved. Additional studies were found by manual searches of the reference lists of relevant reviews and original retrieved articles. Studies that were not case-controlled or did not contain detailed genotyping information were excluded.

Only those studies assessing the association between the *AhR* gene polymorphisms and cancer risk in humans were included. The identified articles had to meet the criteria: (1) evaluation of *AhR* 1661G > A polymorphism and human cancer risk, (2) using a case–control design, (3) containing information about available genotype frequency. The major reasons for exclusion of studies were: (1) no usable data reported, (2) no control population, and (3) duplicates.

2.2. Data extraction

Two of the authors extracted the information independently by complying with the selection criteria and reached a consensus on each item. The following data were exacted from each study: the first author's last name, the country of origin, the ethnicity, the year of publication, the cancer type, the source of the control group (population or hospital-based control), the genotyping method and the frequencies of genotyped cases and controls, as was shown in Table 1.

2.3. Statistical analyses

For the control group in each study, the allelic frequency was calculated, and the observed genotype frequencies of the *AhR* 1661G > A polymorphism were assessed for Hardy–Weinberg equilibrium using χ^2 test. The odds ratios with 95% confidence intervals (CIs) were calculated to assess the strength of association between the *AhR* 1661G > A polymorphism and cancer risk. The statistical significance of the pooled OR was determined by the Z-test. For the *AhR* Arg554Lys polymorphism, we examined the association between the A allele and cancer risk and compared this with that for the G allele (A vs. G); homozygote AA was compared with GG (AA vs. GG), and recessive (AA vs. GG + GA) and dominant (AA + GA vs. GG) models for allele A were also used. Stratified analyses were also conducted by cancer type (if one cancer type was investigated in less than 3 studies, it was merged into the 'other type' group), the source of controls as well as for the different SNP detection methods.

We assessed the statistical heterogeneity between each group using the Q-statistic in order to determine whether to use fixed-effects or random-effects models. A P value of <0.05 was considered statistically significant, except for the Q-statistic, which was considered significant if $P<0.10$ (Berman and Parker, 2002). We used a fixed-effects model if the result of the Q-statistic was not significant. Otherwise, the random-effects model was more appropriate when heterogeneity was present. Funnel plots and the Egger's test were used to investigate publication bias (Egger et al., 1997). For these analyses, an asymmetric plot suggests possible publication bias. A sensitivity analysis was performed to determine whether the deletion of a single study in the meta-analysis could influence the pooled OR. All of the statistical analyses were done with Stata software (version 11.0).

3. Results

3.1. Characteristics of studies

There were 407 studies relevant to the search terms (Fig. 1). After screening the titles and abstracts, seven full-text articles were identified as eligible for our analysis (Cauchi et al., 2001; Chen et al., 2009; Kawajiri et al., 1995; Ng et al., 2010; Sangrajrang et al., 2009; Zhang et al., 2002; Zhang et al., 2011). We included an additional four studies (Cotterchio et al., 2008; De Roos et al., 2006; Kim et al., 2007; Le Marchand et al., 2005) that were retrieved manually from the references of the original articles. Thus, eleven studies evaluating the relationship between the *AhR* 1661G > A polymorphism and cancer risk were included in the meta-analysis. Table 1 lists the information extracted from each of the studies admitted. All studies were case–control studies, three were breast cancer studies, four were lung cancer studies, and the other four studies were merged into the 'other cancer' group. In regard to the source of the control among the eleven studies, one was a hospital-based control study, nine were population-based control studies. While, the remaining study was mixed with population-based controls (PCC) and hospital-based controls (HCC), and the respective genotyping information was not given. For these, we used 'Mixed' instead (Kim et al., 2007). The distribution of the genotyping information in the controls from the studies was consistent with Hardy–Weinberg equilibrium for all but two studies (De Roos et al., 2006; Le Marchand et al., 2005), which were used in the sensitivity analyses.

Table 1
Characteristics of literatures included in the meta-analysis.

First author	Year	Country	Ethnicity	Cancer type	Source of controls	Genotyping method	Cases			Controls		
							GG	GA	AA	GG	GA	AA
Ben	2011	China	Asian	Breast cancer	PCC	Masscode array	793	862	234	734	826	241
Carmen	2010	Britain	European	Non-Hodgkin's lymphoma	PCC	TaqMan	594	175	22	573	177	25
Sangrajrang	2009	Thailand	Asian	Breast cancer	PCC	TaqMan	238	260	59	245	189	48
Chen	2009	China	Asian	Lung cancer	PCC	TaqMan	197	205	48	222	218	49
Cotterchio	2008	Canada	European	Colorectal cancer	PCC	TaqMan	646	168	20	986	242	16
Kim	2007	China/South Korea	Asian	Lung cancer	Mixed	Single base primer extension	263	258	90	237	278	100
Roos	2006	U.S.A.	Mixed	Non-Hodgkin's lymphoma	PCC	TaqMan	863	233	32	701	202	35
Marchand	2005	U.S.A.	Mixed	Breast cancer	PCC	Allele-specific PCR	721	463	155	756	456	158
ZHANG	2002	China	Asian	Bladder cancer	PCC	Allele-specific PCR	29	23	9	81	75	27
Cauchi	2001	France	European	Lung cancer	HCC	PCR-DGGE	147	28	2	137	22	3
Kawajiri	1995	Japan	Asian	Lung cancer	PCC	PCR-SSCP	89	174	58	94	129	54

PCC, population-based control; HCC, hospital-based control; PCR, polymerase chain reaction; PCR-DGGE, polymerase chain reaction-denaturing gradient gel electrophoresis; PCR-SSCP, polymerase chain reaction with single strand conformation polymorphism.