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# Genetic Polymorphisms of DNA Repair Genes and DNA Repair Capacity Related to Aflatoxin B1 (AFB1)-Induced DNA Damages

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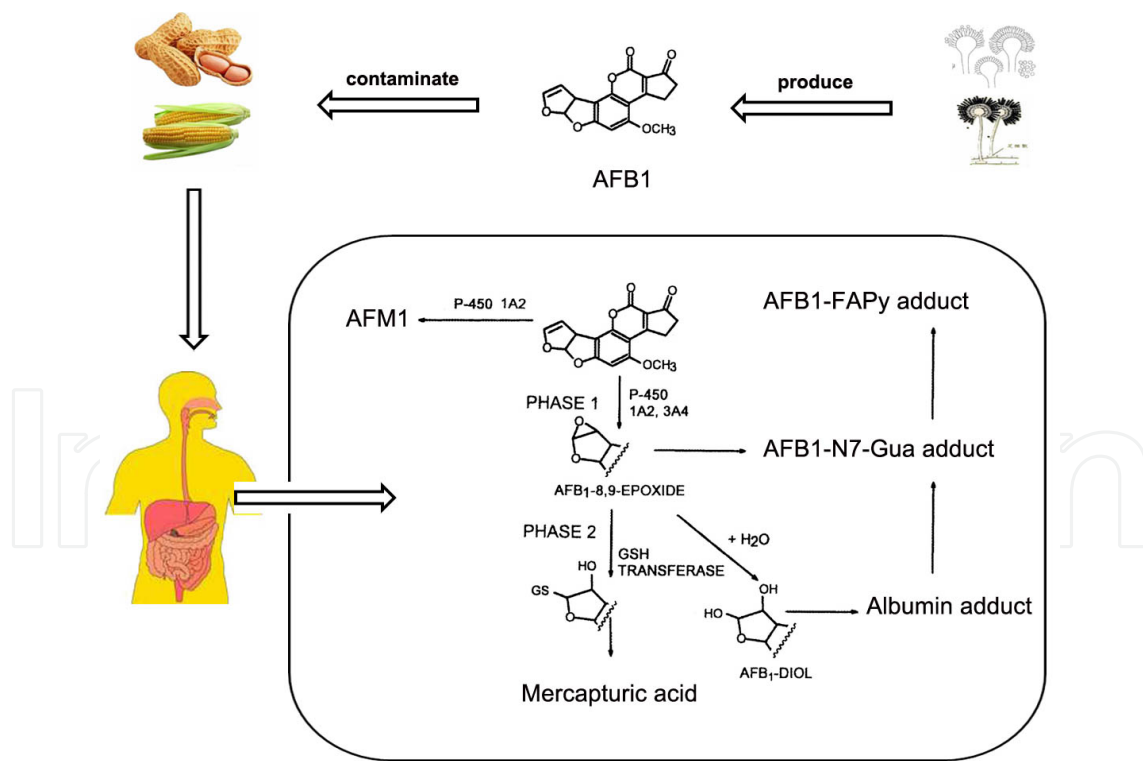
## 1. Introduction

Aflatoxin B1 (AFB1) is an important aflatoxin produced by some strains of the moulds *Aspergillus parasiticus* and *Aspergillus flavus* [1-3]. This aflatoxin was discovered as a contaminant of human and animal food, especially peanuts (ground nuts), core, soya sauce, and fermented soy beans in tropical areas such as the Southeastern China as a result of fungal contamination during growth and after harvest which under hot and humid conditions in the late 1950s and early 1960s [1-4]. Increasing evidences have shown that AFB1 exposure levels are consistent with hepatocellular carcinoma (HCC) risk values [1, 2, 4-7]. DNA damage by AFB1 plays the central role of carcinogenesis of HCC-related to this toxin in the toxic studies [2, 8-10]. Today, AFB1 has been classified as a known human carcinogen by the International Agency for Research on Cancer [1, 2, 5, 10, 11]. However, more and more epidemiological evidence has exhibited that although many people are exposed to the same levels of AFB1, only a relatively small proportion of exposure person develop HCC [6, 12-23]. This indicates individual DNA repair capacity related to AFB1-induced DNA damage might be associated with HCC carcinogenesis [4].

This study attempts to briefly review currently available data on genetic polymorphisms of DNA repair genes and DNA repair capacity related to AFB1-induced DNA Damages, with emphasis on: (1) DNA damage types, (2) DNA repair pathways, (3) the role of DNA repair genetic polymorphisms in the repair process of DNA damage by AFB1, and (4) the elucidation of corresponding DNA repair capacity. Additionally, we summarized the association between genetic polymorphisms of DNA repair genes and AFB1-related DNA repair capacity via a meta-analysis based on published data.

2. AFB1’s chemistry

In 1963, Asao *et al.* accomplished the structural elucidation of AFB1 and found AFB1 was a member of aflatoxins family (AFF) highly substituted coumarins containing a fused dihydrofurofuran moiety [24]. AFF consists of four members: AFB1, aflatoxin B2 (AFB2), aflatoxin in G1 (AFG1), and aflatoxin G2 (AFG2). Among of these members, AFB1 is the most important toxin and structurally is characterized by fusion of a cyclopentenone ring to the lactone ring of the coumarin moiety [24]. AFB1 is so named because of its strong blue fluorescence in ultraviolet light. These properties facilitated the very rapid development in the early 1960s of methods for monitoring peanuts, cores, grains, and other food commodities for the presence of the toxins (Fig. 1) [1]. This type AFF possesses an unsaturated bond at the 8,9 position on the terminal furan ring, and subsequent studies have demonstrated that AFB1 may be metabolized by cytochrome P450 (CYP) enzymes to its reactive form at this position, also called AFB1-8,9-epoxide (AFB1-epoxide) [2, 10]. AFB1-epoxide can covalently bind to DNA and induce DNA damage, thus this epoxidation at at the 8,9 position is critical for AFB1’s DNA genotoxic and carcinogenic potency [2]. Noticeably, another important chemiatic feature of AFB1 is the attraction of liver organ, possibly because the metabolic en-zymes CYPs are mainly produced by liver [2, 10, 25].



**Figure 1.** Biotransformation pathways for AFB1. AFB1, mainly produced by the moulds *Aspergillus parasiticus* (right upper figure) and *Aspergillus flavus* (right under figure), is metabolized by cytochrome P450 enzymes to its reactive form, AFB1-8,9-epoxide (AFB1-epoxide). AFB1-epoxide covalently binds to DNA strands and results in the formation of AFB1-DNA adducts (including AFB1-N7-Gua adduct and AFB1-FAPy adduct).

### 3. DNA damage by AFB1

Several previous reviews have significantly summarized the DNA toxicity of AFB1 [1, 2, 8]. Generally, the severity of DNA toxic effects in human or animals vary with exposure levels, exposure years and nutritional status [1, 2, 26]. For large doses of exposure, this agent can induce acute damage of DNA such as inhabiting DNA synthesis, decreasing DNA-dependent RNA polymerase activity, and restraining messenger RNA (mRNA) and protein synthesis, and subsequently resulting in the lethal changes of liver cells: hepatocellular severe degeneration and necrosis [1, 2].

For long-times and low-levels exposure mainly induces chronic DNA damage [1, 2]. This damage can result in neoplasia, primarily HCC, in many animals or human. Chronic DNA damages induced by AFB1 include AFB1-DNA adducts, oxidative DNA damage, DNA strand break damage, and gene mutation [1, 2, 4].

#### 3.1. AFB1-DNA adducts

AFB1-DNA adducts, including 8,9-di-hydro-8-(N7-guanyl)-9-hydroxy-AFB1 (AFB1-N7-Gua) adduct and formamidopyridine AFB1 (AFB1-FAPy) adduct (Fig. 1), is the main type of AFB1-induced DNA damage [1-4, 25-39]. Among these AFB1-DNA adducts, AFB1-N7-Gua adduct is the most common type identified and confirmed in vivo researches [2, 25]. This type adduct is formed from two pathways: (1) Binding reaction of AFB1-epoxide with DNA; and (2) enzymatic oxidation of AFP1, AFM1, and others with unsaturated in the 8,9-position [2, 25]. In the first pathway, the formations of AFB1-N7-Gua adduct proceeds by a precovalent intercalation complex between double-stranded DNA and the highly electrophilic, unstable AFB1-epoxide isomer. After that, the induction of a positive charge on the imidazole portion of the formed AFB1-N<sup>7</sup>-Gua adduct gives rise to another important a DNA adduct, a ring-opened AFB1-FAPy adduct. Accumulation of AFB1-FAPy adduct is characterized by time-dependence, non-enzyme, and may be of biological basis of genes mutation because of its apparent persistence in DNA. Another pathway only gives rise to minor AFB1-DNA adducts [1, 2, 25]. Additionally, some other DNA-adducts types, ex. covalent binding of AFB1 to adenosine or cytosine in DNA, has also been reported, however, needing more evidences to support this adducts [2].

Although AFB1-DNA adducts are mainly produced in liver cells, they are also found in the peripheral blood white cells [2]. Recent studies have shown that the levels of AFB1-DNA adduct of the peripheral blood white cells are positively and lineally correlated with that of liver cells, implying analysis of AFB1-DNA adducts in the peripheral blood white cells may substitute for the elucidation of tissular levels of adducts [40].

#### 3.2. Oxidative DNA damage

In the process of agent AFB1 metabolism, this agent can induced reactive oxygen species (ROS) [2]. Especially, the metabolic particulate phases, including I and II phase involved by detoxicate enzymes such as CYP and glutathione S-transferase (GST), is postulated to con-

tain long-lived ROS that can lead to oxidative DNA damage [2, 4]. Nowadays, ROS have also been suggested to be involved in the progression of chronic liver disease and the occurrence of HCC; whereas its' subsequent Oxidative DNA damage is generally regarded as a significant contributory cause of cancer from environmental exposures such as AFB1 exposure [41]. Of oxidative DNA damage, 8-oxodeoxyguanosine (8-oxodG), a kind of especial DNA adduct, is found as a sensitive marker of the DNA damage due to hydroxyl radical attack at the C8 of guanine [2, 4, 25, 42]. This adduct, different from the aforementioned AFB1-DNA adducts, is the most abundant endogenous DNA lesion caused by ROS, and has been classified as a biomarker of oxidative DNA damage [2, 10, 43, 44].

Previous studies have shown that in vitro treatment of hepatocytes with AFB1 resulted in a dose-dependent increase in ROS formation [45]; whereas exposure of rats to AFB1 produced a time- and dose-dependent increase in 8-oxodG in hepatic DNA [46, 47]. In 2007, Wu, *et al.* investigated the association between AFB1 exposure levels and oxidative damage levels in high AFB1 areas from Taiwan, China [48]. In this case-control study nested within a community-based cohort (74 HCC cases and 290), researchers tested the levels of urinary excretion of 8-oxodG, a biomarker of oxidative DNA damage and urinary AFB1 metabolites, a biomarker of AFB1 exposure, through enzyme-linked immunosorbent assays (ELISA). Results showed 8-oxodG levels were significantly positive correlated with AFB1 exposure, suggesting AFB1 exposure should induce oxidative DNA damage [48]. Together, these data suggest that AFB1-induced oxidative DNA damage may constitute an important pathway in AFB1 toxicity.

### 3.3. DNA strand break damage

Previous reviewed adducts are capable of forming subsequent repair-resistant adducts, depurination, or lead to error-prone DNA repair resulting in single-strand breaks (SSBs) and double-strand breaks (DSBs). SSBs and DSBs are two kinds of important DNA damage types by AFB1 exposure. For SSBs, there are three pathways to produce this type DNA damage under the AFB1 exposure conditions: direct attack by ROS, through base hydrolysis, and enzymatic consequence of the repair of spontaneous base damage and base loss (such as resulting from abasic AP sites arising spontaneously or from the action of glycosylases in the process of BER pathway) [49-51]. As the most abundant lesion occurring in cellular DNA, SSBs can play havoc with replication and transcription if not efficiently eliminated. However, they might cause other DNA damage such as genic mutations, DSBs, or carcinogenesis of cells [51, 52]. While DSBs is rare and severe DNA damage type among DNA damage induced by AFB1 exposure [25], mainly produced under the high-dose AFB1 exposure conditions. This damage can lead to chromosomal rearrangements at the first mitosis after exposure to the DNA strand-breaking agent [53].

### 3.4. Gene mutations

For genes mutations induced by AFB1 exposure, the experimental and theoretical researches are briefly on the p53 gene [54-56]. Reaction with DNA at the N<sup>7</sup> position of guanine preferentially causes a G:C > T:A mutation in codon 249 of this gene, leading to an amino acid sub-



stitution of arginine to serine [54-56]. In high AFB1-exposure areas, this mutation is present in more than 40% of HCC and can be detected in serum DNA of patients with preneoplastic lesions and HCC. While codon 249 transversion mutations are either very rare or absent in low or no AFB1-exposure areas [4]. Using the human p53 gene in an in vitro assay, codon 249 has been exhibited to be a preferential site for formation of AFB1-N<sup>7</sup>-Gua adducts evidence consistent with a role for AFB1 in the mutations observed in HCC [57-65]. Therefore, the codon 249 mutation of p53 gene has been defined as the hot-spot mutation of p53 gene (TP53M) resulting from AFB1 and has become the molecular symbol of HCC induced by AFB1 exposure. The frequency of TP53M is also regarded as the molecular biomarker of AFB1-related DNA repair capacity [4].

## 4. DNA repair pathways of AFB1-related DNA damage

A wide diversity of DNA damage induced by AFB1 exposure, if not repaired, may cause chromosomal aberrations, micronuclei, sister chromatid exchange, unscheduled DNA synthesis, and chromosomal strand breaks, and can be converted into gene mutations and genomic instability, which in turn results in cellular malignant transformation [4]. Nevertheless, human cells have evolved surveillance mechanisms that monitor the integrity of genome to minimize the consequences of detrimental mutations [9]. AFB1-induced DNA damage can be repaired through the following pathways: nucleotide excision repair (NER), base excision repair (BER), single-strand break repair (SSBR), and double-strand break repair (DSBR) [4, 25].

### 4.1. NER pathway

NER pathway, a major DNA repair pathways in human cells featuring genomic DNA damage, can remove structurally such diverse lesions as pyrimidine dimers, irradiative damage, and bulky chemical adducts, and DNA damage from carcinogens and some chemotherapeutic drugs [66]. To date, the mechanism of this pathway is well understood and has been reconstituted in vitro. It consists of several sequential steps: lesion sensing, opening of a denaturation bubble, incision of the damaged strand, displacement of the lesion-containing oligonucleotide, gap filling, and ligation [66, 67]. In the fibroblast cells with the deficiency of xeroderma pigmentosum A (XPA) gene, conversion of the initial AFB1-N<sup>7</sup>-Gua adduct to the AFB1-FAPy adduct has been found to be more extensive. This suggests that NER should be a major mechanism for enzymatic repair of AFB1 adducts. Its defects lead to severe diseases related AFB1 exposure, including liver injury and HCC [4].

### 4.2. BER

Of the oxidative DNA damage resulting from AFB1 exposure, the formation of 8-oxodG is thought to be important due to being abundant and highly mutagenic and hepatocarcinogenesis [4, 25]. The 8-oxodG lesions are repaired primarily through the BER pathway. The BER pathway facilitates DNA repair through two general pathways: a. the short-patch BER

pathway, leading to a repair tract of a single nucleotide; b. the long-patch BER pathway, producing a repair tract of at least two nucleotides [68, 69]. In these two repair sub-pathways, DNA glycosylases play a central role because they can recognize and catalyze the removal of damaged bases [68, 69]. This suggests that the defect of DNA glycosylases should be related to the decreasing capacity of the BER pathway and might increase the risk of such toxicity as AFB1 [4, 25].

### 4.3. SSB

SSB is a relative severe type of DNA damage produced by AFB1 exposure. If not repaired, it can disrupt transcription and replication and can be converted into potentially clastogenic and/or lethal DSBs [51]. This DNA damage is repaired via SSB pathway. SSB pathway includes four basic steps: a. SSB detection and signaling, through poly (ADP-ribose) polymerase (PARP); b. DNA break end processing, through the role of polynucleotide kinase (PNK), AP endonuclease-1 (APE1), DNA polymerase  $\beta$  (Pol  $\beta$ ), tyrosyl phosphodiesterase 1 (TDP1), and flap endonuclease-1 (FEN-1); c. gap filling, involving in multiple DNA polymerases; d. DNA ligation, involving in multiple DNA ligases [49, 50, 52]. This pathway mainly plays an important role in the repair process of SSBs induced AFB1.

### 4.4. DSB

DSBs, although only make up a very small proportion of AFB1-induced DNA damage, are critical lesions that can result in cell death or a wide variety of genetic alterations including large- or small-scale deletions, loss of heterozygosity, translocations, and chromosome loss [70]. This type damage is repaired DSBR consisting of non-homologous end-joining (NHEJ) and homologous recombination (HR) [71, 72]. There are several decades DNA repair genes involve in DSBR pathway and the defects in these genes cause genome instability and promote tumorigenesis [71-77]. During the process of damage removed by aforementioned repair pathways, DNA repair genes play a central role, because their function determines DNA repair capacity [4]. It has been shown that reduction in DNA repair capacity related to DNA repair genes is associated with increasing frequency of genic mutation, levels of DNA adducts, and risk of cancers [8, 78]. Thus, genetic polymorphisms in DNA repair genes might be correlated with AFB1-related DNA repair capacity.

## 5. The elucidation of DNA repair capacity related to AFB1-induced DNA damage

As shown in the previous review, two main characteristics of AFB1-induced DNA damage are AFB1-DNA adducts and the hot-spot mutation of tumor suppressor gene p53 at codon 249 (TP53M) [4, 25]. Thus, DNA repair capacity related to this type DNA damage might be elucidated using the analysis of AFB1-DNA-adducts levels and TP53M frequency in the liver tissues or other tissues. For AFB1-DNA adducts, many researchers in the relative fields regard AFB1-FAPy adduct as a validated biomarker of AFB1 exposure

based on as following reasons: (1) that AFB1-FAPy adduct is the imidazole ring-opened product of AFB1-N7-Gua adduct, also the stable of form of the later adduct, and may play an important role in the development of HCC. Moreover, the accumulation of this adduct is time-dependent and non-enzymatic, and may have potential biological importance because of its apparent persistence in DNA; (2) that AFB1-N7-Gua adduct is unstable and easily lost from DNA. Increasing evidences have exhibited that AFB1-FAPy-adducts levels in the liver or placenta tissues are lineally correlated with AFB1 exposure levels and HCC risk [79, 80], suggesting this adduct should be regarded as a biomarker for DNA repair capacity related to AFB1-induced DNA damage. Remarkably, the monoclonal antibodies recognizing AFB1-FAPy adduct have been developed by several research groups. These types of antibodies are not only used to orientationally and semi-quantitatively test AFB1-DNA adduct information in the tissue specimens through immunochemistry (IHC), but to quantitatively analyze the levels of this adduct using a competitive enzyme-linked immunosorbent assay (ELISA) in human liver and placenta tissue specimens. Additionally, a quantitative indirect immunofluorescence method using monoclonal antibody 6A10 has also been developed to measure AFB1-DNA adducts in liver tissues. In 2009, Long *et al.* evaluated the validation of AFB1-FAPy adduct in DNA samples from peripheral blood leukocytes representing AFB1 exposure levels [40]. Through linear regression analysis of the adduct levels in DNA samples from peripheral blood leukocytes and from liver tissue specimens, they found peripheral blood leukocytes' adduct levels were positively and linearly related to AFB1-DNA adduct levels of the HCC cancerous tissue. These data suggested that the levels of peripheral blood leukocytes' DNA adducts were representative of the tissues' DNA-adduct levels and might be regard as a biomarker for AFB1 exposure [4, 25, 40, 78]. Together, AFB1-FAPy adduct in DNA from such tissues as liver and placenta or from such as blood leukocytes should be potential biological importance in the elucidation of DNA repair capacity related to AFB1-caused DNA damage.

As regard of the mutations of p53 gene, because AFB1 exposure results in G to T transversion in both bacteria and human cells and AFB1 preferentially binds to codon 249 of p53 gene, as previous mentioned, AFB1 mainly induces the transversion of G → T in the third position at codon 249 of TP53M. The frequent value of TP53M is more persistent biomarker and more directly represents DNA repair capacity compared with AFB1-DNA adducts. In the studies from higher AFB1 exposure areas, researchers have found TP53M frequency associates with AFB1 exposure levels and HCC risk. Thus, this mutation is the selective elucidative marker for DNA repair capacity correlated with AFB1-induced DNA damage as well as AFB1-DNA adducts.

Additionally, HCC is the most common malignant tumors caused by AFB1 exposure. More and more epidemiological studies have shown AFB1-related HCC risk is related to different DNA repair capacity [4, 8, 15, 22, 40, 78, 81-90], suggesting that tumor risk value might be regard as a selective elucidative marker for DNA repair capacity correlated with AFB1-induced DNA damage.



## 6. Genetic polymorphisms of DNA repair genes involved in NER pathway for AFB1-related DNA damage repair

Accumulating evidences have implied that genetic polymorphisms in NER genes are associated with DNA repair capacity related to AFB1-induced DNA damage. Molecular epidemiology studies in this field are mainly from high AFB1 exposure areas such as in China. To date, two genes involved in NER pathway, namely xeroderma pigmentosum C (XPC) and xeroderma pigmentosum D (XPD), have been investigated in the DNA repair capacity analysis.

### 6.1. XPC

XPC gene (Genbank accession NO. AC090645), consisting of 16 exons and 15 introns, spans 33kb on chromosome 3p25. This gene encodes a 940-amino acid protein, an important DNA damage recognition molecule which plays an important role in NER pathway. XPC protein binds tightly with another important NER protein HR23B to form a stable XPC-HR23B complex, the first protein component that recognizes and binds to the DNA damage sites [91-98]. XPC-HR23B complex can recognize a variety of DNA adducts formed by exogenous carcinogens such as AFB1 and binds to the DNA damage sites [4, 91, 99]. Therefore, it may play a role in the process of DNA repair of DNA damage related to AFB1 exposure.

Some recent studies have showed that defects in XPC have been related to many types of malignant tumors [99-114]. Transgenic mice researches have also exhibited predisposition to many kinds of neoplasms in mice model with XPC gene knockout [115]. Moreover, pathological and cellular studies have shown that increasing expression of this gene is associated with hepatocarcinogenesis [116]. Together, these studies suggest the genetic polymorphisms localizing at conserved sites of XPC gene might modify the risk of HCC induced by AFB1 exposure and decrease DNA repair capacity related to AFB1-related DNA damage. Recently, four studies from high AFB1-exposure areas have supported abovementioned hypothesis [84, 89, 101, 117].

The first study conducted by Cai *et al.* [117] is from Shunde area, Guangdong Province which is characterized by high AFB1 exposure and high incidence rate of HCC. Researchers analyzed the association between two common polymorphisms—Ala499Val and Lys939Gln—of XPC gene and risk of HCC via an 1-1 case-control study (including 78 HCC patients and 78 age- and sex-matching controls) method, and found these two polymorphisms modified HCC risk [adjusted odds ratios (ORs) were 3.77 with 95% confidence interval (CI) 1.34-12.89 for Ala499Val and 6.78 with 95% CI 2.03-22.69]. Although they did not directly evaluated the effects of genetic polymorphisms of XPC gene and DNA repair capacity related to AFB1-caused DNA damage, study population in their study is from high AFB1 exposure areas and.

The other three studies, from Guangxi Zhuang Autonomous Region which is the most common of high AFB1 exposure area all over the world [4, 118], directly investigated the modifying effects of genetic polymorphisms XPC on AFB1-related DNA repair capacity and HCC

risk based on hospitals via molecular epidemiological studies [84, 89, 101]. Their results showed XPC codon 939 Gln alleles increased about 2-times risk of HCC and decreased AFB1-related DNA repair capacity. Furthermore, Wu, *et al.* [89] and Long, *et al.* [84] quantitatively elucidated AFB1-exposure time and levels and their interactive effects with the genetic polymorphisms of XPC gene and found some evidence of AFB1 exposure-risk genotypes of XPC codon 939 on AFB1-related DNA repair capacity (HCC risk: XPC risk genotypes and  $18.38 > 1.11 \times 4.62$  for the interaction of AFB1-exposure levels and XPC risk genotypes;  $22.33 > 1.88 \times 8.69$  for the interaction of AFB1-exposure time).

Additionally, Long, *et al.* [84] also observed that Gln alleles at codon 939 of XPC gene was associated with the decrease of XPC expression levels in cancerous tissues ( $r = -0.369$ ,  $P < 0.001$ ) and with the poorer overall survival of HCC patients (the median survival times are 30, 25, and 19 months for patients with XPC gene codon 939 Lys/Lys, Lys/Gln, and Gln/Gln respectively). Interestingly, this decreasing 5-years survival rates would be noticeable under high AFB1 exposure conditions (the median survival times are 17 month for the joint of XPC gene codon 939 Gln/Gln and high AFB1-exposure level and 15 months for the joint of XPC gene codon 939 Gln/Gln and long-term AFB1-exposure time) [84].

As a result, these data suggest that genetic polymorphism at codon 939 of XPC gene is not only a genetic determinant in the DNA repair process of DNA damage induced by AFB1 exposure, and a risk and prognostic factor influencing HCC developing, but also is an independent genetic factor of evaluating DNA repair capacity related to AFB1-caused DNA damage. A possible reason is that this genetic polymorphism down-regulates XPC expression [84] and decrease the repair function of XPC protein [116].

However, Li *et al.* [101] reported that the proportional distribution of the Val/Val genotype at codon 499 of XPC gene did not differ between HCC cases and controls in Guangxi Zhuang Autonomous Region, China ( $P > 0.05$ ), dissimilar to the data from another high AFB1 exposure area of China, Guangdong Province, suggesting this genetic polymorphism might not modify AFB1-related DNA repair capacity. Possible explanations for these inconsistent finding may be either due to unknown confounders or due to small sample size.

## 6.2. XPD

XPD protein, a DNA-dependent ATPase/helicase encoded by DNA repair gene XPD (also called excision repair cross-complementing rodent repair deficiency complementation group 2 (ERCC2), COFS2, EM9, or TTD.) (Genbank ID. 2068) which spans about 20 kb on chromosome 19q13.3 and contains 23 exons and 22 introns is one of seven central proteins in the NER pathway [119-122]. This protein is associated with the TFIIH transcription-factor complex, and plays a role in NER pathway [66, 67, 119-121, 123-125]. During NER, XPD participates in the opening of the DNA helix to allow the excision of the DNA fragment containing the damaged base [119-122].

There are four described polymorphisms that induce amino acid changes in the protein: at codons 199 (Ile to Met), at codon 201 (His to Tyr), at codon 312 (Asp to Asn) and at codon 751 (Lys to Gln) [123]. To date, the first two polymorphisms have not investigated because

they are quite rare (~0.04%) in most population, whereas the latter two polymorphisms in conserved region of XPD have been extensively studied [123]. Several groups have done genotype-phenotype analyses with these two polymorphisms and have shown that the variant allele genotypes are associated with low DNA repair ability [126, 127]. Recent studies have showed the polymorphisms at codon 312 and 751 of XPD are correlated with DNA-adducts levels, p53 gene mutation, and cancers risk [86, 123, 128-131]. In a hospital-based case-control study conducted in a high AFB1 exposure area [40], Long, *et al.* found that the variant XPD codon 751 genotypes (namely Lys/Gln and Gln/Gln) detected by TaqMan-MGB PCR was significantly different between HCC cases (35.9% and 20.1% for Lys/Gln and Gln/Gln, respectively) and controls (26.3% for Lys/Gln and 8.6% for Gln/Gln,  $P < 0.001$ ). Individuals having variant alleles had about 1.5- to 2.5-fold risk of developing the cancer (adjusted OR 1.75 and 95% CI 1.30-2.37 for Lys/Gln; adjusted OR 2.47 and 95% CI 1.62-3.76 for Gln/Gln). Based on relative large sample size (including 618 HCC cases and 712 controls), researchers stratified genotypes of XPD codon 751 according to matching factors and observed some evidence of interaction between XPD codon 751 Gln alleles and sex. These female with Gln alleles featured increasing HCC risk compared with those without these alleles. Moreover, the multiple interactive effects of between mutant genotypes of XPD gene codon 751 environment variant AFB1 or another NER gene XPC on HCC risk were also found, with interactive value 0.85, 1.04, and 1.71 for AFB1-exposure years, AFB1-exposure levels, and XPC gene codon 939 risk genotypes ( $P_{\text{interaction}} < 0.05$ ).

Together, these results suggest the genetic polymorphisms at conserved sequence of XPD gene such as at codon 751 may have potential effect on AFB1-related HCC susceptibility. This supports different AFB1-related DNA repair capacity might be modified by genetic polymorphisms at codon 751 in DNA repair gene XPD. However, the study from AFB1-exposure areas shows that the genetic polymorphism at codon 312 in XPD polymorphism is not significantly correlated with DNA repair capacity related AFB1-induced DNA damage [4, 40].

## 7. Genetic polymorphisms of DNA repair genes involved in BER pathway for AFB1-related DNA damage repair

As previous described, DNA glycosylases play a central role in the BER pathway because they can recognize and catalyze the removal of damaged bases [68, 69]. Among having been reported genetic polymorphisms of DNA glycosylases, only human 8-oxoguanine DNA glycosylase (hOGG1) correlates with DNA repair capacity [132-143]. This gene (Genbank ID# 4968), also called HMMH, OGG1, MUTM, OGH1, 8-hydroxyguanine DNA glycosylase, AP lyase, DNA-apurinic or apyrimidinic site lyase, and N-glycosylase/DNA lyase, consisting of 7 exons and 6 introns, spans 17 kb on chromosome 3p26.2 (PubMed). This gene encodes a 546-amino acid protein, a specific DNA glycosylase that catalyzes the release of 8-<sub>oxod</sub>G and the cleavage of DNA at the AP site [142]. Genetic structure study has shown the presence of several polymorphisms within hOGG1 locus [136]. Among these polymorphisms, the polymorphism at position 1245 in exon 7 causes an amino acid substitution (namely Ser to Cys)

at codon 326, suggesting this polymorphism may glycosylase function and decrease DNA repair capacity [136].

In the past twenty years, increasing epidemiological evidences have validated aforementioned the hypothesis [132-144]. In 2003, Peng, *et al.* [138] analyzed the correlation among 8-<sub>oxod</sub>G levels, hOGG1 expression, and hOGG1 Cys326Ser polymorphism in the high AFB1 exposure areas Guangxi Autonomous Region. They found that individuals having genotypes with hOGG1 codon 326 Cys alleles faced lower level of hOGG1 expression and higher 8-<sub>oxod</sub>G levels. Supporting their results, Cheng, *et al.* [141] reported that hOGG1 expression was significantly linear correlated with HCC. Recently, using the molecular epidemiological methods, Zhang, *et al.* [134] found that the distribution of Cys alleles at codon 326 of hOGG1 in HCC cases (43.0%) significantly differed from in controls (33.1%). Logistic regression analysis next showed that the genotypes with Cys alleles, compared to without this alleles, increased HCC risk of Chinese population, with adjusted OR-value (95% CI) 1.5 (0.79-2.93) for Cys/Ser and 1.9 (0.83-4.55) for Cys/Cys. Similar results are also observed in the study from low AFB1 exposure areas of China [144]. A functional complementation activity assay exhibited that hOGG1 protein encoded by the 326 Cys allele had substantially lower DNA repair activity than that encoded by the 326 Ser allele [140]. Similar results were observed in human cells in vivo [137, 139]. Therefore, low capacity of 8-<sub>oxod</sub>G repair resulting from hOGG1 326 Cys polymorphism might contribute to the persistence of 8-<sub>oxod</sub>G in genomic DNA in vivo, which, in turn, could be associated with increased cancer risk [4, 137, 138].

As a result, these findings suggested the genetic polymorphism at codon 326 of DNA repair gene hOGG1 should modify AFB1-related DNA repair capacity. However, another case-control study from Japan shows this genetic polymorphism is not associated with HCC risk. This might result from lower AFB1 exposure in this area and not showing the relative low DNA repair capacity related to AFB1-induced DNA damage.

## 8. Genetic polymorphisms of DNA repair genes involved in SSBR pathway for AFB1-related DNA damage repair

SSBR pathway involves in several central DNA repair genes such as XRCC1, poly (ADP-ribose) polymerase-1 (PARP-1), APE (or DNA glycosylase), DNA ligase III, Pol  $\beta$ , and so on [49-51]. Of these DNA repair genes, only XRCC1 is investigated to correlate with AFB1-related DNA repair capacity. This gene, also called RCC, spans about 32 kb on chromosome 19q13.2 and contains 17 exons and 16 introns is one of three submits of DNA repair complex in the SSBR pathway (Gene dbase from PubMed). Its' encoding protein (633 amino acids), consists of three functional domains: N-terminal domain (NTD), central breast cancer susceptibility protein-1 homology C-terminal (BRCT I), and C-terminal breast cancer susceptibility protein-1 homology C-terminal (BRCT II) [4, 51, 145-151]. This protein is directly associated with Pol  $\beta$ , DNA ligase III, and PARP, via their three functional domains and is implicated in the core processes in SSBR and BER pathway [4, 51, 145, 150-152]. Mutant hamster ovary cell lines that lack XRCC1 genes are hypersensitive to DNA damage agents



such as ionizing radiation, hydrogen peroxide, and alkylating agents [4, 51]. Furthermore, this kind of cells usually faces increasing frequency of spontaneous chromosome aberrations and deletions. Three single nucleotide polymorphisms in the coding region of XRCC1 gene that lead to amino acid substitution have been described and investigated [25]. Among these polymorphisms, the codon 399 polymorphism is of special concern, because this polymorphism resides in functionally significant regions (BRCT II) and may be related to decreasing DNA repair capacity [85, 153-179].

In 2008, Long, *et al.* [85] investigated the effects of genetic polymorphism at codon 399 in DNA repair gene XRCC1 based on the analysis of 501 AFB1-related HCC samples. They found that the HCC patients with XRCC1 genotypes with 399 Gln alleles (namely: XRCC1 codon 399 Arg/Gln or Gln/Gln) faced a significantly higher frequency of TP53M than those with the wild-type homozygote of XRCC1 [namely: XRCC1 codon 399 Arg/Arg, adjusted odds ratio (OR) = 6.13, 95% confidence interval (CI) = 3.87-9.72 for Arg/Gln; OR = 13.66, 95% CI = 4.44-42.08 for Gln/Gln, respectively]. Additionally, another study from high AFB1 areas Taiwan in China exposure showed the XRCC1 codon 399 Gln alleles were significantly associated with higher levels of AFB1-DNA adducts. Individuals with these alleles were at risk for detectable adducts (OR, 2.4; 95% CI, 1.1-5.4;  $P = 0.03$ ) [80].

As regards of risk biomarker for DNA repair capacity namely AFB1-related HCC risk, a total of fourteen molecular epidemiological studies involving genetic polymorphism at codon 399 of DNA repair gene XRCC1 were found in PubMed database, Springer database, Ovid database, Wangfang Database, and Weipu database [22, 81, 83, 162, 164, 175, 180-186], summarized in Table 1. However, associations between this genetic polymorphism and DNA repair capacity have been reported in these case-control studies with the results being contradictory [172, 187]. Possible reasons are as follows: different study population, non-scientific design, the loss of matching methods or improper match, the loss of stratified analysis based on AFB1 exposure information, repeated data, and so on. To avoid above error and achieve more scientific results, we analyzed the possible causes of contradictory using meta-analysis method (Comprehensive Meta-Analysis Version 2, <http://www.meta-analysis.com/>). Fig. 2, 3, and 4 showed the meta-analysis results of the modifying effects of genetic polymorphism at codon 399 of XRCC1 gene on AFB1-related DNA repair capacity. Based on meta-analysis of overall studies including known published literature (Fig. 2), we found contradictory results; whereas we would observe significant modifying effects of genetic polymorphism at codon 399 of XRCC1 gene on DNA repair capacity related to AFB1-caused DNA damage if these possible repeated studies from the same researchers (Fig. 3) or adding these studies from low/no AFB1 exposure areas (Fig. 4) were excluded. Actually, although Yang, *et al.* [162] and Ren, *et al.* [173] did not observed significantly modifying effects of XRCC1 gene codon 399 polymorphism in crude logistic regression, they found Gln alleles would decrease DNA repair capacity in stratified analysis with susceptible environment variants. A individually matching case-controls demonstrated that subjects having codon 399 Gln alleles might feature remarkably increasing risk of HCC under longer-term AFB1-exposure years or higher AFB1-exposure levels conditions (adjusted OR > 10) [22]. This suggests that the genotypes with codon 399 Gln alleles of XRCC1 should be a risk biomarker of low DNA repair ability related DNA damage by AFB1 exposure.

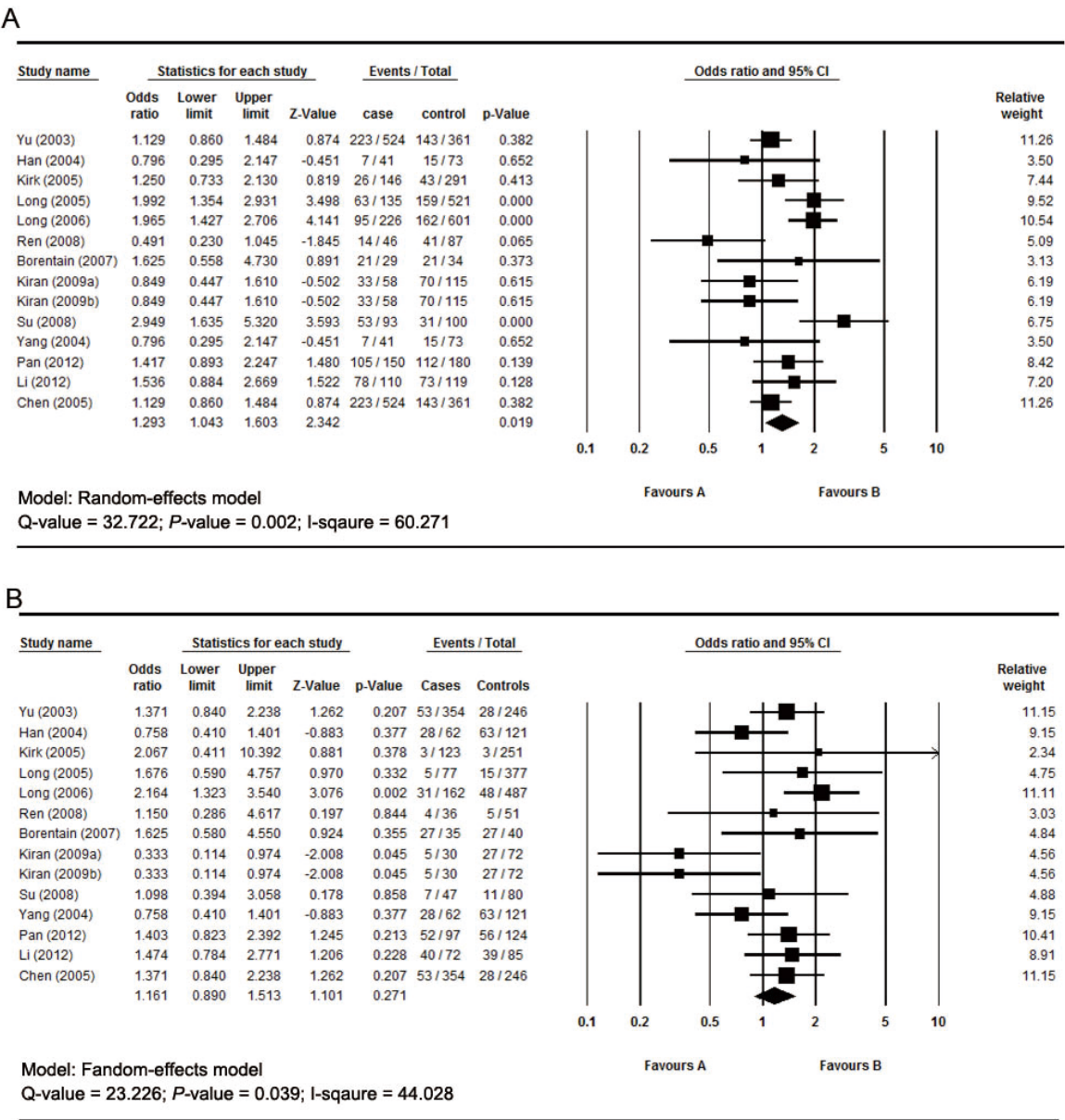


NO.	Ref.	Year	Population	AFB1 exposure <sup>a</sup>	Methods	Matching Factor	Cases (n)	Controls (n)	Risk value <sup>b</sup> (OR)
1	Yu et al. (2003)	2003	Taiwanese	high	case-control	age, sex	577	389	1.54 ( $P = 0.129$ )
2	Han et al. (2004)	2004	Qidongese	high	case-control	age, sex	69	136	about 1 ( $P > 0.05$ )
3	Kirk et al. (2005)	2005	Gimbia	high	case-control	age, sex	149	294	2.66 ( $P < 0.05$ )
4	Long et al. (2005)	2005	Guangxiense	high	case-control	age, sex, HBV, HCV, race	140	536	2.18 ( $P = 0.0001$ )
5	Long et al. (2006)	2006	Guangxiense	high	case-control	age, sex, HBV, HCV, race	257	649	2.47 ( $P = 0.0001$ )
6	Ren et al. (2008)	2008	Beijingese	low	case-control	age, sex	50	92	0.49 ( $P < 0.05$ )
7	Borentain et al. (2007)	2007	French	low	case-control	age, sex	56	61	1.84 ( $P = 0.015$ )
8	Kiran et al. (2009)	2009	Indian	low	case-control	no	63	142	0.33-0.63 ( $P < 0.05$ )
9	Kiran et al. (2009)	2009	Indian	low	case-control	no	63	142	0.33-0.63 ( $P < 0.05$ )
10	Su et al. (2008)	2008	Liaoningese	low	case-control	age, sex	100	111	2.95 ( $P < 0.001$ )
11	Yang et al. (2004)	2004	Qidongese	high	case-control	age, sex	69	136	about 1 ( $P > 0.05$ )
12	Pan et al. (2012)	2012	Shangdongese	medium	case-control	age, sex	202	236	1.35-1.55 ( $P > 0.05$ )
13	Li et al. (2012)	2012	Shangdongese	medium	case-control	age, sex	150	158	1.69-1.78 ( $P < 0.05$ )
14	Chen et al. (2005)	2005	Taiwanese	high	case-control	age, sex	577	389	1.57 ( $P > 0.05$ )

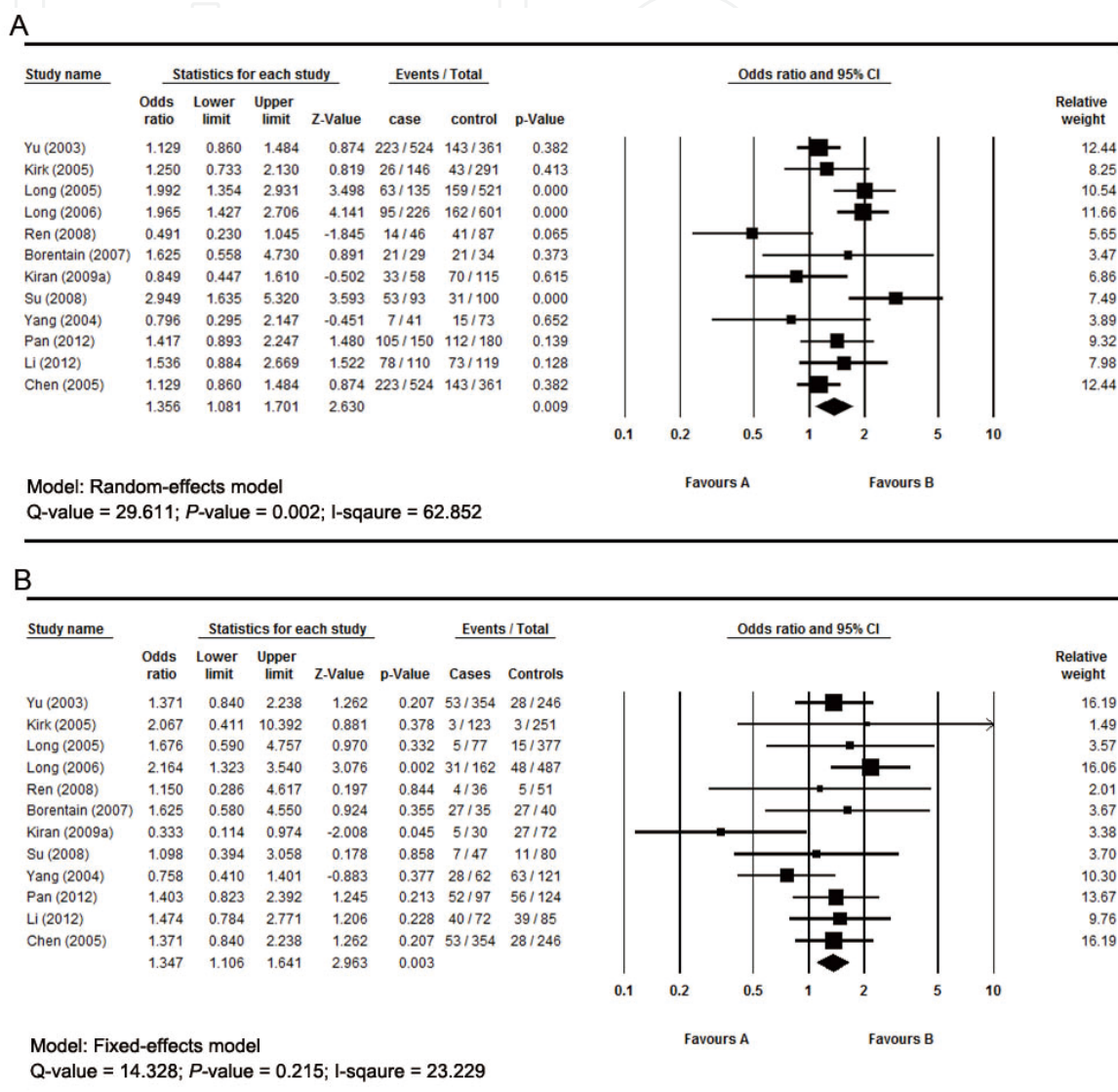
<sup>a</sup> Defined by means of Ref Henry, et al. (Science, 1999).

<sup>b</sup> AFB1-related DNA repair capacity is evaluated using risk biomarker AFB1-related HCC risk (see "DNA repair capacity elucidation related to AFB1-induced DNA damage" section). Based on this thesis, AFB1-related DNA repair capacity will decrease if OR > 1 and corresponding  $P$ -value < 0.05; will increase if OR < 1 and corresponding  $P$ -value < 0.05; and will not change if OR is about 1 and/or corresponding  $P$ -value > 0.05.

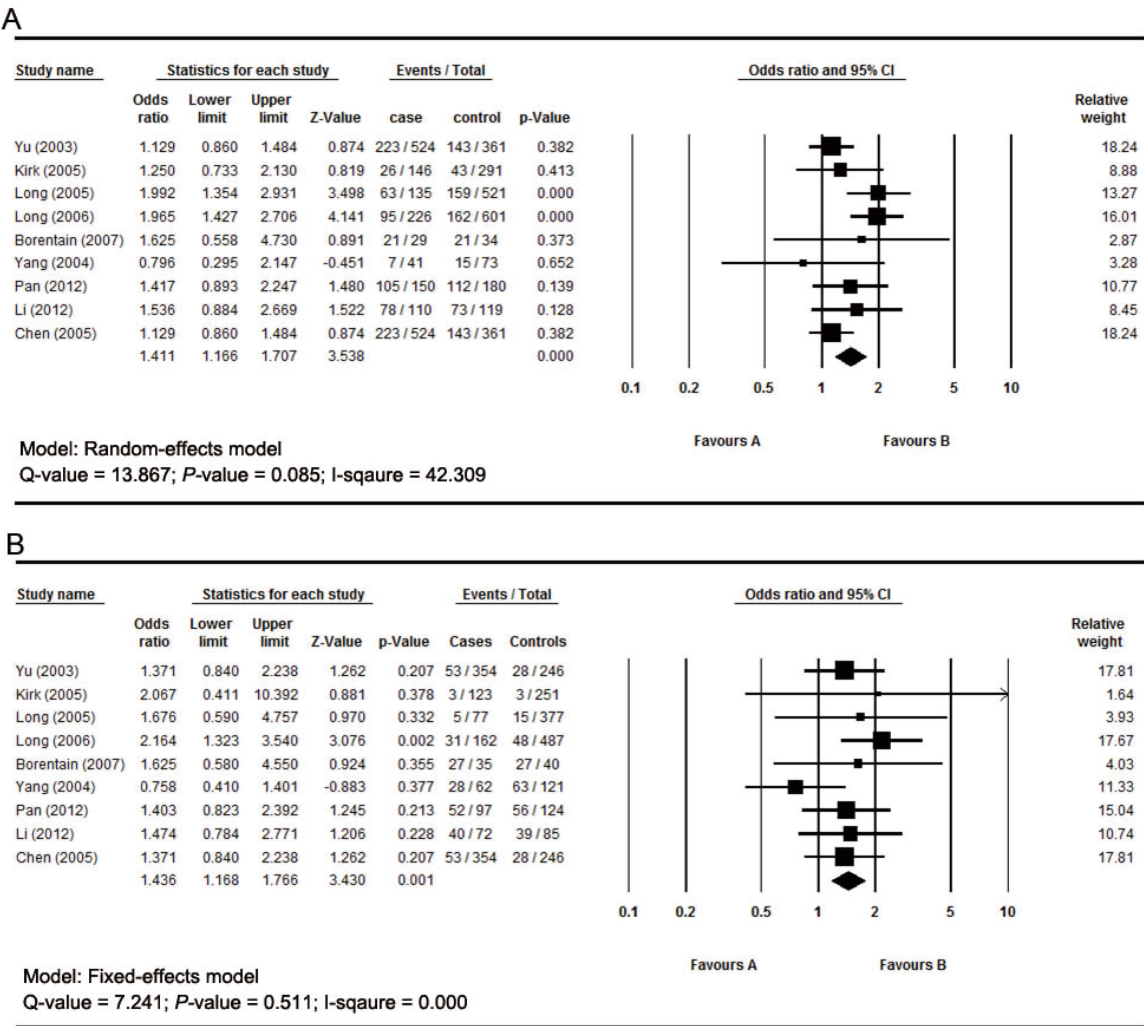
**Table 1.** Characteristics of studies about genetic polymorphism at codon 399 of DNA repair gene XRCC1 and risk biomarker for DNA repair capacity (namely HCC risk)



**Figure 2.** The meta-analysis of the relationship between genetic polymorphism at codon 399 (Arg/Gln) XRCC1 and AFB1-related HCC risk, a biomarker for DNA repair capacity correlated with AFB1-induced DNA damage, based on overall studies size. Compared with Arg/Arg genotype, Arg/Gln (A) genotype decreased AFB1-related DNA repair capacity. This effect was not observed in Gln/Gln genotype (B).



**Figure 3.** The meta-analysis of the relationship between genetic polymorphism at codon 399 (Arg/Gln) XRCC1 and AFB1-related HCC risk, a biomarker for DNA repair capacity correlated with AFB1-induced DNA damage, based on overall studies size excluded possible repeated studies. Compared with Arg/Arg genotype, Arg/Gln (A) and Gln/Gln (B) genotype decreased AFB1-related DNA repair capacity.



**Figure 4.** The meta-analysis of the relationship between genetic polymorphism at codon 399 (Arg/Gln) XRCC1 and AFB1-related HCC risk, a biomarker for DNA repair capacity correlated with AFB1-induced DNA damage, based on overall studies size excluded possible repeated studies and studies from low AFB1 exposure areas. Compared with Arg/Arg genotype, Arg/Gln (A) and Gln/Gln (B) genotype decreased AFB1-related DNA repair capacity.

These data support XRCC1 codon 399 Gln alleles decrease AFB1-related DNA repair capacity. Additionally, several studies have shown that the other two genetic polymorphisms (at codon 194 and codon 280) of XRCC1 also decrease DNA repair capacity related AFB1-induced DNA damage, with adjusted value 2.25-2.27 for codon 194 polymorphism and 4.95-6.27 for codon 280 polymorphism ( $P < 0.05$ ) [175]. Furthermore, this decreasing DNA repair ability might more noticeable under the haplotypes with both codon 194 Arg alleles and codon codon 280 His alleles conditions [183].

## 9. Genetic polymorphisms of DNA repair genes involved in DSBR pathway for AFB1-related DNA damage repair

DSBR pathway involves a series of DNA repair genes. In published molecular epidemiological studies, only XRCC3 gene codon Thr241Met polymorphism and XRCC7 rs#7003908 polymorphism affect AFB1-related DNA repair capacity [8, 15, 78].

### 9.1. XRCC3

The product of the XRCC3 gene is one of identified paralogs of the strand-exchange protein RAD51 in human beings [188-192]. This protein correlates directly with DNA breaks and facilitates the formation of the RAD51 nucleoprotein filament, which is crucial both for homologous recombination and HRR [188-192]. Previous studies have shown that a common polymorphism at codon 241 of XRCC3 gene (Thr to Met) modifies the function of this gene [193-205]. Two reports from high AFB1-exposure areas all of world supported above-mentioned conclusions [15, 90].

In the first frequent case-control study in Guangxiese [90], we observed that the genotypes with XRCC3 codon 241 Met alleles (namely Thr/Met and Met/Met) was significantly different between controls (33.01%) and HCC cases (61.48%,  $P < 0.001$ ). Met alleles increases about 2- to 10-fold risk of HCC and this running-up risk is modulated by the number of Met alleles (adjusted OR 2.48 and 10.06 for one and two this alleles). Considering small sample size in this study, we recruited, in another independent frequent case-control study [15], a relatively larger sample size to compare the results. Subjects included in this study, 491 HCC cases and 862 age-, sex, race, hepatitis virus infection information-matching controls, were permanent residents of Guangxi areas. Similar to the results of the first report, the distribution of XRCC3 codon 241 Met allele frequencies was found to be significantly different between cases (59.7%) and controls (32.1%). Individuals having the Thr/Met or Met/Met were at a 2.22-fold or 7.19 fold increased risk of developing HCC cancer. Above two studies showed this allele multiplicatively interacted with AFB1 exposure in the process of hepato-tumorigenesis. These results exhibits that the polymorphism at codon 241 of XRCC3 gene is a genetic determinant in AFB1-related DNA repair ability for DSBR pathway.

### 9.2. XRCC7

DNA repair gene XRCC7, called DNA-dependent protein kinase catalytic subunit (DNA-PKcs), DNAPK, DNP1, HYRC, HYRC1, or p350 (Genbank ID. 5591), spans about 197 kb on chromosome 8q11 and contains 85 exons and 86 introns (Gene dBase in PubMed). This gene encodes DNA-PKcs that constitutes the large catalytic subunit of the DNA-PK complex. When DNA-PKcs is recruited to the site of DSBs by the Ku70/Ku80 heterodimer, DNA-PK complex changes into its active form and subsequently initiates the non-homologous end joining (NHEJ) repair, an important DSBR pathway [206-213]. Murine mutants defective in the XRCC7 have non-detectable DNA-PK activity, suggesting that XRCC7 is required for NHEJ pathway protein. More than 20 polymorphisms have been



reported in the XRCC7 gene, some of which are correlated with malignant tumors such as bladder cancer (dbSNP in NCBI Database). Of these genetic polymorphisms in XRCC7 gene, only two loci (rs7003908 and rs10109984) are investigated their modifying effects on AFB1-related DNA repair capacity [8].

In this hospital-based case-control study conducted by Long, *et al.* [8], they found that these individuals with XRCC7 rs7003908 G alleles increased HCC risk compared the homozygote of XRCC7 rs7003908 T alleles (XRCC7-TT), with OR value 3.45 (2.40–4.94) for XRCC7-TG and 5.04 (3.28–7.76) for XRCC7-GG, respectively. Additionally, they also found this genetic polymorphism was correlated with higher the levels of AFB1-DNA adducts ( $r = 0.142$ ,  $P < 0.001$ ). However, another polymorphism rs10109984 did not modify AFB1-related HCC risk ( $P > 0.05$ ). As a result, these data explore that genetic polymorphism of XRCC7 rs7003908 but not rs10109984 might decrease AFB1-related DSB capacity, inquiring more studies to support this conclusion.

## 10. Future directions

Recently, great progress has been made in understanding the molecular mechanisms of the genetic susceptibility to DNA repair capacity related to AFB1-induced DNA damages. However, we are still far from a comprehensive view of the issue. The molecular mechanism about genetic polymorphisms in the DNA repair genes modifying DNA repair capacity related AFB1-induced DNA damages remains largely unknown. Although several reports have shown the spot mutation resulting from genetic polymorphisms may decrease DNA repair capacity via changing the structure of DNA repair proteins, downregulating expression of DNA repair genes or decreasing the function of DNA repair genes, more direct evidence is lost. Disclosing the roles of different genetic types of DNA repair genes in the different toxicity of AFB1 will greatly benefit our understanding of pathological mechanisms of the genetic polymorphisms in the DNA repair genes affecting DNA repair capacity related to AFB1-induced DNA damage, and will shed important light on the clinical therapy for these patients with risk types.

## 11. Summary

AFB1 is an important environment variation of DNA damage. This toxic variation is characterized by: (1) the attraction of specific organs, especially liver; (2) genotoxicity, mainly inducing the formation of AFB1-DNA adducts and the hot-spot mutation of p53 gene; and (3) carcinogenicity, primarily causing HCC. Among these chronic DNA damage characteristics, AFB1-DNA adducts play a central role because of their genotoxicity and interactions with genetic susceptible factors. In human, there are several repair pathways, including NER, BER, SSBR, and DSB, is able to repair this type damage. Genetic polymorphisms in DNA repair genes might modify the expression and the functions of

DNA repair proteins encoded by the relative genes and decrease the AFB1-correlated DNA repair capacity. Based on this knowledge, DNA repair capacity related to AFB1-induced DNA damage can be elucidated via the following three methods: testing the levels of AFB1-DNA adducts (mainly AFB1-FAPy adduct), analyzing the frequency of TP53M, and evaluating the risk of HCC by AFB1 exposure.

Numerous studies reviewed in this paper have demonstrated that the hereditary variations in DNA repair genes are associated with DNA repair capacity of DNA damage induced by AFB1. These molecular epidemiological studies have significantly contributed to our knowledge of the importance of genetic polymorphisms in DNA repair genes in the individual's susceptibility to AFB1 exposure. It would be expected that genetic susceptibility factors involved in DNA repair genes for AFB1-induced DNA damage repair could serve as useful biomarkers for identifying at-low-DNA-repair-capacity individuals by AFB1 exposure and, therefore, targeting prevention of this toxicity-related malignant tumor.

However, there are several issues to be noted. The conclusions should first be drawn carefully, because of conflicting data existing in the same ethnic population in view of between some genotypes of DNA repair genes and the AFB1-related DNA damage repair capacity. Second, because of the fact that AFB1-related DNA repair is polygenic, no single genetic marker may sufficiently predict DNA repair capacity. Therefore, a panel of susceptible biomarkers is warranted to define individuals at low DNA repair capacity. Last, the corresponding molecular mechanisms of risk types modifying DNA repair capacity correlated with AFB1-induced DNA damages should be paid close attention.

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## Abbreviations

AFB1, Aflatoxin B1; AFB1-epoxide, AFB1-8,9-epoxide; AFB1-N<sup>7</sup>-Gua, 8,9-di-hydro-8-(N<sup>7</sup>-guanyl)-9-hydroxy-AFB1; AFB1-FAPy, ring-opened formamidopyridine AFB1; AFF, aflatoxins family; APE1, AP endonuclease-1; BER, base excision repair; CI, confidence interval; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; DSB, double-strand break; DSBR, double-strand break repair; HBV, hepatitis virus B; HCV, hepatitis virus C; HCC, hepatocellular carcinoma; hOGG1, Human oxoguanine glycosylase 1; NER, nucleotide excision repair; OR, odds ratio; 8-<sub>oxod</sub>G, 8-oxodeoxyguanosine; PARP, poly (ADP-ribose) polymerase; PLC, Primary liver cancer; PNK, polynucleotide kinase; Pol β, DNA polymerase β; ROS, reactive oxygen species; SSB, single-strand break; SSBR, single-strand break repair;

XPA, xeroderma pigmentosum A; XPC, xeroderma pigmentosum C; XPD, xeroderma pigmentosum D; XRCC1, x-ray repair cross complementary 1; XRCC3, x-ray repair cross complementary 3; XRCC4, x-ray repair cross complementary 4; XRCC7, x-ray repair cross complementary 7.

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