RESEARCH ARTICLE

XPG Asp1104His, XRCC2 Rs3218536 A/G and RAD51 135G/C Gene Polymorphisms and Colorectal Cancer Risk: A Meta-Analysis

Ebrahim Eskandari[1,2], Alireza Rezaifar[3], Mohammad Hashemi[3]*

Abstract

Background: DNA repair mechanisms are crucial for sustaining DNA integrity and preventing carcinogenesis. The xeroderma pigmentosum group G (XPG), X-ray repair cross complementing group 2 (XRCC2) and RAD51 are candidate genes for DNA repair pathways. **Methods:** We performed a meta-analysis of 26 studies that assessed the impact of XPG Asp1104His, XRCC2 rs3218536 A/G and RAD51 135G/C polymorphisms on colorectal cancer (CRC) risk. This study included 10288 CRC patients and 11885 controls, and odds ratio (OR) with its 95% confidence interval (CI) were used to calculate the strength of association. **Results:** The results of overall meta-analysis suggested an association between the XPG Asp1104His polymorphism and CRC susceptibility in allele (OR=1.06; 95% CI=1.01-1.12) and heterozygote model (OR=1.16; 95%CI=1.02-1.31). In the subgroup analysis based on ethnicity and source of control, we found significantly increased CRC cancer risk in Asians (OR=1.12, 95%CI=1.04-1.21) and in hospital-based (OR=1.22, 95%CI=1.08-1.38) populations. Moreover, the RAD51 135 G/C polymorphism increased the risk of CRC in total using allele (OR=1.21) and recessive models (OR=1.62). However, XRCC2 rs3218536 A/G was not associated with the risk of CRC in total or in subgroups. **Conclusions:** According to the results of our meta-analysis, the XPG Asp1104His and RAD51 135 G/C polymorphisms might influence colorectal cancer risk.

Keywords: XPG- XRCC2- RAD51- colorectal cancer- meta-analysis

Asian Pac J Cancer Prev, **18 (7)**, 1805-1813

Introduction

Colorectal cancer (CRC) is the third most prevalent gastrointestinal tract neoplasm and the fourth major cause of cancer mortality globally (Mao et al., 2013, Sun et al., 2015). CRC development is a multistep process, in that several factors are known to be involved including environmental and genetic alterations (Zhang et al., 2011). The polymorphisms of genes involved in different DNA repair pathways may affect repair of bulky DNA lesions and maintenance of genomic stability, and thus cancer risk (Canbay et al., 2011, Hou et al., 2014). DNA repair protects genome damages caused by oxidative DNA compounds or DNA adducts. DNA repair pathways responsible for fixing DNA damages include base excision repair (BER), nucleotide excision repair (NER) (Lefkofsky et al., 2015) and homologous recombination repair (HRR) (Kiyohara and Yoshimasu, 2007).

NER is one of the key pathways that contributes to UV light-induced DNA damage, and protects a cell against a wide spectrum of structurally unrelated DNA lesions (Sugasawa, 2016). In the inherited disorder, xeroderma pigmentosum, NER deficiency is associated with a 1,000-fold higher occurrence of skin cancer, but also a 20-fold increase in internal tumours highlighting the NER importance in the repair of endogenous DNA damage (Mort et al., 2003; Spivak, 2015). One of the key DNA repair enzymes of the NER pathway is Xeroderma Pigmentosum complementation group G (XPG), which is also known as ERCC5 (excision repair cross-complementation group 5) (Chen et al., 2016). XPG gene is mapped on chromosome 13q22-q33, and consists of 15 exons and 14 introns and is one of the seven XP complementation groups (XPA to XPG). It has reported that a defective XPG results in DNA repair malfunction which leads to genomic instability, gene malfunction and initiation of carcinogenesis (Dworaczek and Xiao, 2007; Sollier et al., 2014).

Accurate repair of double-strand breaks (DSBs) arising during DNA replication or from DNA-damaging agents is essential to conserve genomic stability. HRR is the key pathway for repairing DSBs and the maintenance of genetic stability in mammalians (Griffin, 2002). Throughout the HRR process, a sister chromatid works as a template and the homologous sequence of DNA is aligned. Several numbers of key molecules contribute

*[1]Genetic of Non-Communicable Disease Research Center, [2]Department of Clinical Biochemistry, School of Medicine, Zahedan University of Medical Sciences, Zahedan, [3]School of Medicine, Zabol University of Medical Sciences, Zabol, Iran. *For Correspondence: mhd.hashemi@gmail.com*

to the HRR process (Griffin and Thacker, 2004). Recent evidence indicated that RAD51 paralogs (RAD51B, RAD51C, RAD51D, XRCC2, XRCC3) play key roles in the HRR process (Griffin, 2002; Curtin et al., 2009). Moreover, coded by X-ray repair cross complementing group 2 (XRCC2) gene produces the XRCC2 protein that is structurally and functionally associated with RAD51; together with each other they form a fundamental complex required for chromosome segregation and apoptotic response to DSBs (Li et al., 2014). Also over 100-folds of HRR reduction in the XRCC2 deficient hamster cells compared with the parental cells has been observed which highlights the vital role of the XRCC2 protein for the HRR process (Johnson et al., 1999).

Growing evidence has explored the role of common single nucleotide polymorphism (SNP) located in exon 15 of XPG (Asp1104His; dbSNP ID rs17655 G/C) in the etiology of CRC in various populations (Chen et al., 2009; Luo et al., 2014; Steck et al., 2014; Zeng et al., 2015). Additionally, common variants within XRCC2 (R188H, dbSNP ID rs3218536), and RAD51 (135G/C, dbSNP ID rs1801320) have been determined as potential cancer susceptibility loci in recent studies (Curtinet et al., 2009). However, the results of some publications are contradictory (Bigleret al., 2005; Pardini et al., 2008), and some of the individual studies included small sample sizes as well as lack of power to identify a mild gene effect (Mort et al., 2003; Canbay et al., 2011; Krupa et al., 2011; Gil et al., 2012; Nissar et al., 2014; Cetinkunar et al., 2015). Hence, a comprehensive retrieval of the related literature would help obtain a more precise estimation of the association with disease susceptibility. Consequently, we performed a meta-analysis of case-control studies and investigated whether XPG Asp1104His, XRCC2 R188H A/G and RAD51 135G/C polymorphisms are associated with susceptibility to CRC using multiple genetic models.

Materials and Methods

Study assessment

Our literature search included the electronic databases such as PubMed, EMBASE, and MEDICINE. All languages were searched, and inclusive search strategies included the Mesh term and Keywords: ('XPG', 'xeroderma pigmentosum group G', 'excision repair cross-complementing group 5', 'ERCC5', 'RAD51','XRCC2' or 'NER'), ('polymorphism', 'variant' or ' 'mutation') along with (colorectal', 'rectal', 'gastrointestinal', 'colon cancer'.) through Jan 2, 2017. Eligible studies were selected and evaluated cautiously. Review articles and bibliographies of other relevant studies found were hand-searched to find further qualified studies.

Selection of eligible studies

The articles were filtered by two independent reviewers (M.H, A.R) to assess the appropriateness of the articles selected by using a standardized protocol and data collection form. The following inclusion criteria were used to determine qualified studies: (a) a human case-control study on the association between XPG, XRCC2 and RAD51 SNPs and CRC (b) adequate allele or genotype data needed for assessing an odds ratio (OR) and 95% confidence interval (CI). Exclusion criteria were (a) non-human studies, abstracts only, comments, reviews, editorials or letters, mechanism studies and cohort comprising of a case population; (b) family-based design or sibling pair studies, (c) studies with lack of enough information for data extraction and (d) unpublished data. Discrepancies about inclusion of studies and interpretation of data were solved with conversation.

We used following data information from each study: authors, year of publication, country, ethnicity, source of controls, genotype methods, sample size, allele and genotype frequency distribution and Hardy Weinberg equilibrium (HWE) (Table 1).

Statistical analyses

The risk of CRC associated with the SNPs were examined for each study by odds ratio (OR) and 95% confidence interval (95% CI). The significance of the summary OR was calculated by the Z-test, and $P<0.05$ was applied as statistically significant. Five different ORs were computed for XPG Asp1104His: the codominant homozygote (His/His vs. Asp/Asp), codominant heterozygote (Asp/His vs. Asp/Asp), dominant (Asp/His+His/His vs. Asp/Asp), recessive model (His/His vs. Asp/Asp+Asp/His), and allelic comparison (His vs Asp). As for XRCC2 rs3218536 A/G, we used codominant heterozygote (A/G vs. A/A), codominant homozygote (G/G vs. A/A), dominant (G/G + A/G vs. A/A), recessive (G/G vs. A/G+A/A) and allelic comparison (G vs A) to calculate the pooled ORs. For the RAD51 135G/C, the codominant heterozygote (G/C vs. G/G), codominant homozygote (C/C vs. G/G), dominant (C/C + G/C vs. G/G), recessive (C/C vs. G/C + G/G) and allelic comparison (C vs G) were chosen to compute the pooled ORs. A χ2-test-based Q statistic test was done to assess the between-study heterogeneity [24]. We also quantified the effect of heterogeneity by I2 test. Once a significant Q test ($P > 0.05$) or $I2 < 50\%$ indicated homogeneity across studies, the fixed effects model was utilized [25]; otherwise the random effects model was used [26]. Then, we performed stratification analyses on ethnicity (Asian, Caucasian or African) and source of control (Population-based or PB, Hospital-based or HB and family-based or FB). Analysis of sensitivity was performed to assess the stability of the results. Potential publication bias was examined using Begg's funnel plot. All analyses were performed using the Cochrane Collaboration RevMan 5.3. HWE was calculated for each study using an internet-based HWE calculator (http://ihg.gsf.de/csgi-bin/hw/hwa1.pl).

Results

Characteristics of studies

After preliminary search with duplicates discarded, a total of 412 records of publications were yielded. Following the predefined inclusion and exclusion criteria, eventually 26 case-control studies were included in this

Table 1. Main Characteristics of Studies Included for the Association between the XPG Asp1104His, XRCC2 Rs3218536 A/G and RAD51 135G/C Polymorphisms and Colorectal Cancer

Study	Year	Country	Ethnicity	Source of controls	Genotype methods	Genotype (case/control)				Allele (case/control)		P_{HWE}
						Total	Asp/Asp	Asp/His	His/His	Asp	His	
Sun et al.	2015	China	Asian	HB	PCR–RFLP	890/910	216/227	476/497	198/186	908/951	872/869	0.004
Kabzinski, J., et al.	2015	Poland	Caucasian	HB	QPCR	234/238	36/43	171/175	27/20	243/261	225/215	0.001
Paszkowska-Szczur, K., et al.	2015	Poland	Caucasian	PB	MassARRAY	733/1358	429/869	272/404	32/85	1130/2142	336/576	0.001
Steck, S. E, et al.	2014	USA	African	PB	MassARRAY	224/317	65/100	120/151	39/66	250/351	198/283	0.519
Steck, S. E., et al.	2014	USA	Caucasian	PB	MassARRAY	298/532	183/335	100/170	15/27	466/840	130/224	0.372
Du, H., et al.	2014	China	Asian	HB	Taqman Assay	878/884	286/355	459/405	133/124	1031/1115	725/653	0.622
Liu, D., et al.	2012	China	Asian	PB	PCR–RFLP	1028/1085	233/329	603/537	192/219	1069/1195	987/975	0.996
Gil, J., et al.	2012	Poland	Caucasian	PB	PCR–RFLP	132/100	86/64	35/31	11-May	207/159	57/41	0.624
Canbay, E., et al.	2011	Turkey	Caucasian	HB	PCR–RFLP	79/247	43/148	34/83	Feb-16	120/379	38/115	0.351
Joshi, A. D., et al	2009	USA	Caucasian	FB	Taqman assays	308/361	183/213	114/137	11-Nov	480/563	136/159	0.046
Pardini, B., et al	2008	Czech	Caucasian	HB	PCR–RFLP	532/532	334/356	177/153	21/23	845/865	219/199	0.211
Huang, W. Y., et al.	2006	USA	Caucasian	PB	Sequencing	679/697	407/403	243/265	29/29	1057/1071	301/323	0.073
Bigler, J., et al.	2005	USA	Caucasian	PB	Taqman assays	713/616	440/353	237/226	36/37	1117/932	309/300	0.917
Mort, R., et al.	2003	UK	Caucasian	HB	PCR-RFLP	40/33	-	-	-	67/58	13/22	-
XRCC2 rs3218536 A/G	Year	Country	Ethnicity	Source	Genotype methods	Total	A/A	G/A	G/G	A	G	PHWE
Cetinkunar, S., et al.	2015	Turkey	Caucasian	HB	PCR-RFLP	71/86	09-Nov	30/21	32/54	48/43	94/129	0.001
Krupa, R., et al.	2011	Poland	Caucasian	HB	PCR-RFLP	100/100	75/84	18/14	07-Feb	168/182	32/18	0.146
Curtin, K., et al.	2009	UK & US	Caucasian	PB	Sequencing	1227/1380	1014/1167	185/204	10-Sep	2213/2538	205/222	0.979
Moreno [16]	2006	Spain	Caucasian	HB	APEX	350/316	287/265	57/45	06-Jun	631/575	69/57	0.018
Tranah, G. J., et al.	2004	USA	Caucasian	PB	TaqMan	518/522	450/441	A/G+G/G	-	-	-	-
Tranah, G. J., et al.	2004	USA	Caucasian	PB	TaqMan	354/688	302/582	A/G+G/G	-	-	-	-
RAD51 135 G/C	Year	Country	Ethnicity	Source	Genotyping	Total	G/G	G/C	C/C	G	C	PHWE
Cetinkunar, S., et al.	2015	Turkey	Caucasian	HB	PCR-RFLP	71/86	39/21	21-Nov	Nov-54	99/53	43/119	0.001
Nissar, S., et al.	2014	India	Asian	HB	PCR-RFLP	100/120	25/60	56/25	19/35	106/145	94/95	0.001
Gil, J., et al.	2012	Poland	Caucasian	HB	PCR-RFLP	133/100	100/73	29/27	4/0	229/173	37/54	0.118
Mucha, B., et al.	2012	Poland	Caucasian	PB	PCR-RFLP	200/200	161/157	34/37	05-Jun	356/351	44/49	0.048
Romanowicz-Makowska, H., et al.	2012	Poland	Caucasian	HB	PCR-RFLP	320/320	51/91	56/164	213/65	158/346	482/294	0.569
Krupa, R., et al.	2011	Poland	Caucasian	HB	PCR-RFLP	100/100	61/36	36/35	Mar-29	158/107	42/93	0.003

HWE, Hardy-Weinberg equilibrium; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism;. PB, population-based; HB: hospital-based; FB, Family-based; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; APEX, arrayed primer extension

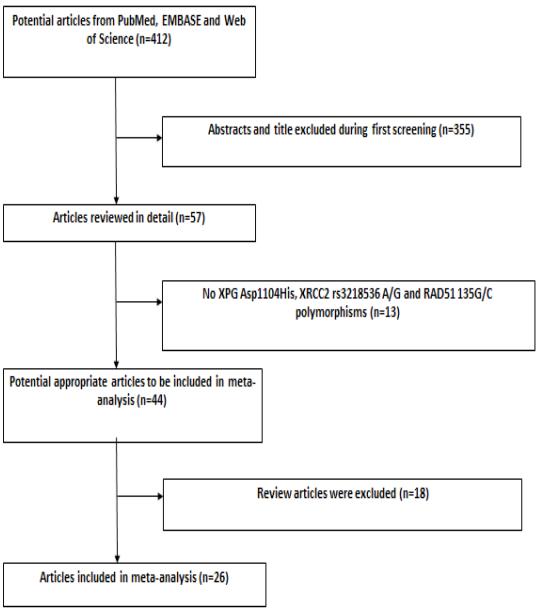

Figure 1. Flow Diagram of Included Studies for This Meta-Analysis

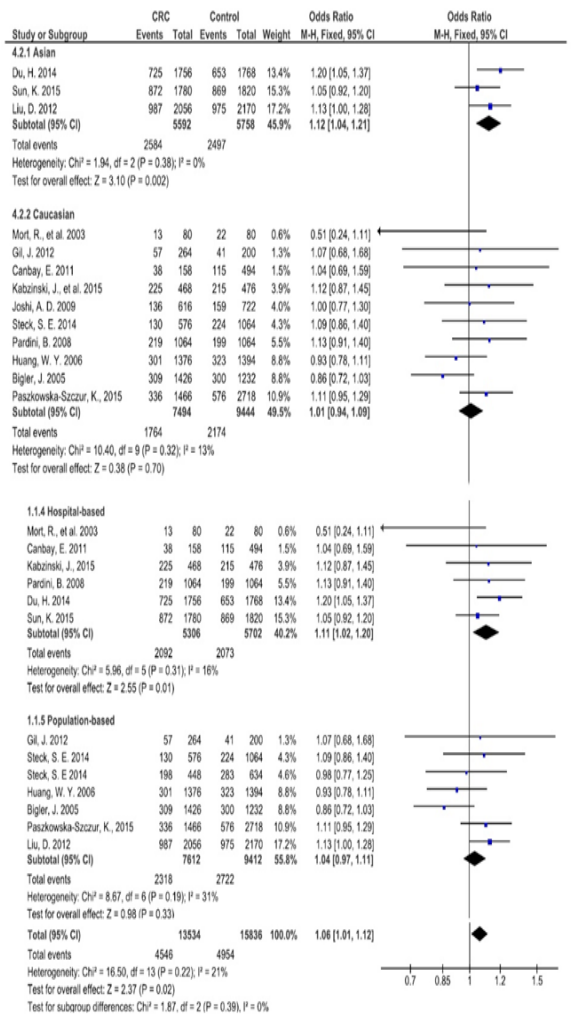

Figure 2. Forest Plot of the Risk of Colorectal Cancer Associated with XPG Asp1104His Polymorphism in Allele Comparison

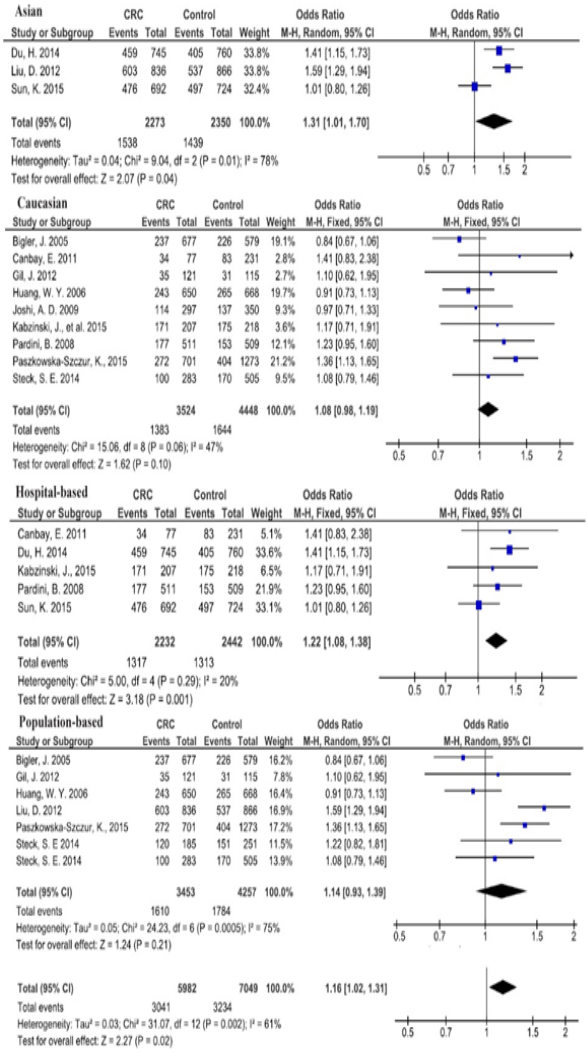

Figure 3. Forest Plot of the Risk of Colorectal Cancer Associated with XPG Asp1104His Polymorphism in Codominant (Heterozygote) Comparison

meta-analysis (details in Figure 1). These 26 studies included a total of 22173 subjects (10,288 cases and 11,885 controls), and examined the impact of XPG Asp1104His, XRCC2 rs3218536 A/G and RAD51 135G/C polymorphisms on CRC risk. Fourteen studies comprising of 6,728 cases and 7,877 controls assessed the impact of XPG Asp1104His polymorphism on CRC (Mort et al., 2003; Bigler et al., 2005; Huang et al., 2006; Pardini, Naccarati et al. 2008, Joshi, Corral et al. 2009, Canbay et al., 2011; Gil et al., 2012; Liu et al., 2012; Du et al., 2014; Li et al., 2014; Steck et al., 2014; Kabzinski et al., 2015; Paszkowska-Szczur et al., 2015; Sun et al., 2015). OF these, 10 were Caucasians, 3 were Asians and one was African. After stratification of studies according to the source of control, 7 studies were stratified as PB and 6 were HB and one was a FB study.

Six studies including 2620 cases and 3092 controls examined the association of XRCC2 rs3218536 A/G and CRC. OF these 6 studies, 3 were HB and 3 were PB studies, but as for ethnicity all were Caucasians. With respect to RAD51 135G/C polymorphism in CRC, 6

Table 2 Main Results of Pooled ORs for the XPG Asp1104His, XRCC2 Rs3218536 A/G And RAD51 135G/C Polymorphisms in Colorectal Cancer

Variables	No[a]	Allele	Codominant (eterozygous)	Codominant (homozygous)	Dominant	Recessive
		His vs Asp	His/Asp vs Asp/Asp	His/His vs Asp/Asp	His/Asp+His/His vs Asp/Asp	His/His vs His/Asp+Asp/Asp
XPG Asp1104His		OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Total	14	1.06(1.01-1.12)	1.16(1.02-1.31)	1.09(0.97-1.23)	1.12(0.99-1.25)	0.98(0.88-1.09)
P/P_h [b] /I^2 (%)		0.02/0.22/21	0.02/0.002/61	0.15/0.50/0	0.06/0.005/58	0.65/0.54/0
Ethnicity						
Asian	3	1.12(1.04-1.21)	1.31(1.01-1.70)	1.22(1.05-1.43)	1.29(1.05-1.60)	1.02(0.90-1.17)
P/P_h /I^2 (%)		0.002/0.38/0	0.04/0.01/78	0.01/0.69/0	0.02/0.04/69	0.73/37/0
Caucasian	10	1.01(0.94-1.09)	1.08(0.98-1.19)	0.93(0.76-1.14)	1.04(0.95-1.14)	0.91(0.75-1.12)
P/P_h /I^2 (%)		0.70/0.32/13	0.10/0.06/47	0.50/0.65/0	0.35/0.11/39	0.37/0.50/0
Source of controls						
Population-based	7	1.04(0.97-1.11)	1.14(0.93-1.39)	1.01(0.85-1.20)	1.01(0.76-1.34)	0.88(0.75-1.02)
P/P_h /I^2 (%)		0.33/0.19/31	0.21/0.001/75	0.95/0.29/18	0.95/0.001/88	0.09/0.72/0
Hospital-based	6	1.11(1.02-1.20)	1.22(1.08-1.38)	1.19(0.99-1.42)	1.21(1.08-1.37)	1.09(0.93-1.28)
P/P_h /I^2 (%)		0.01/0.31/16	0.001/0.29/20	0.06/0.46/0	0.001/0.42/0	0.28/0.55/0
XRCC2 rs3218536 A/G						
Total	6	G vs A	AG vs AA	GG vs AA	AG+GG vs AA	GG vs AA+AG
OR (95 % CI)		1.06 [0.90, 1.24]	1.10 [0.92, 1.33]	1.18 [0.69, 2.00]	1.02 [0.89, 1.18]	0.83 [0.54, 1.30]
P/P_h [b] /I^2 (%)		0.49/0.06/60	0.29/0.67/0	0.54/0.35/9	0.76/0.51/0	0.42/0.07/57
Population-based	3					
OR (95 % CI)		0.99 [0.82, 1.19]	1.07 [0.86, 1.32]	0.99 [0.51, 1.92]	1.05 [0.86, 1.29]	0.67 [0.40, 1.13]
P/P_h /I^2 (%)		0.91/0.07/69	0.55/0.34/0	0.97/0.40/0	0.63/0.93/0	0.13/0.09/65
Hospital-based	3					
OR (95 % CI)		1.28 [0.94, 1.76]	1.23 [0.85, 1.78]	1.60 [0.66, 3.89]	1.27 [0.90, 1.80]	1.54 [0.64, 3.75]
P/P_h /I^2 (%)		0.12/0.13/57	0.28/0.64/0	0.30/0.15/52	0.18/0.30/7	0.34/0.16/50
RAD51 135 G/C						
Total	6	C vs G	GC vs GG	CC vs GG	CC+GC vs GG	CC vs GC+GG
OR (95 % CI)		1.21 [1.05, 1.39]	0.98 [0.77, 1.24]	1.28 [0.98, 1.67]	1.06 [0.87, 1.31]	1.62 [1.30, 2.02]
P/P_h [b] /I^2 (%)		0.001/0.01/97	0.85/0.01/85	0.07/0.01/95	0.55/0.01/91	0.001/0.01/97

[a], Number of comparisons; [b], P value of Q test for heterogeneity test; [c], Random model was used when P value for heterogeneity test was below 0.05; otherwise, fixed model was used

studies met the inclusion criteria which included 940 cases and 926 controls. Of these, 5 studies were Caucasians and 5 were HB studies. Baseline characteristics of the included studies for XPG Asp1104His, XRCC2 rs3218536 A/G and RAD51 135G/C polymorphisms on CRC are shown in Table 1.

XPG Asp1104His polymorphism and CRC

The associations of CRC risks with XPG Asp1104His polymorphism were indicated in table 2. At allelic level, the pooled analysis showed that the His vs Asp allele was associated with increased risk of CRC in total studies with the overall OR of 1.06 (OR= 1.06; 95% CI =1.01-1.12; P=0.02) as indicated in fig 2. The subgroup analysis indicated that the variant His allele is a risk factor for CRC in Asians (OR= 1.12; 95% CI = 1.04-1.21' P=0.002). However, it was not associated with the CRC risk in either of Caucasians or Africans (P>0.05).

At genotypic level and using the codominant model, the pooled evidence suggested that His/Asp vs Asp/Asp heterozygote genotype distribution between groups was different and the association was statistically significant in total with the pooled OR of 1.16 (95%CI= 1.02-1.31; P=0.02). Similarly, this genotype was a risk factor for CRC in Asians with the OR of 1.31 (95%CI= 1.01-1.70; P=0.04) but not in Caucasians or Africans (fig 3).

In contrast, the homozygote genotype His/His vs Asp/Asp in codominant model was not associated with CRC in total (P=0.15). However, the His/His genotype was a risk factor for Asians with OR of 1.22 (95%CI= 1.05-1.43; P=0.01).

In dominant model, the His/Asp+His/His vs Asp/Asp genotype was not correlated with susceptibility to CRC in total (P=0.33) as well as in Caucasians (P=0.35). In Asians, however, His/Asp+His/His was a risk factor for CRC with the pooled OR of 1.29 (P=0.02; 95%CI= 1.05-1.60).

In recessive model, the general difference between groups for His/His vs His/Asp+Asp/Asp was not associated with the risk of CRC either in total (P=0.54) or Caucasians (P=0.50) or Asians (P=0.73).

In the subgroup analysis by source of control, the XPG Asp1104His polymorphism had statistically significant association with elevated CRC risk under allele His vs Asp (P=0.01; OR=1.11, 95% CI=1.02-1.20), codominant heterozygote His/Asp vs Asp/Asp (P=0.001; OR=1.22, 95% CI=1.08-1.38) and dominant His/Asp+His/His vs Asp/Asp (P=0.001; OR=1.21, 95% CI=1.08-1.37) in the HB subgroup.

XRCC2 rs3218536 A/G polymorphism and CRC

As shown in table 2, no significant association was found between XRCC2 rs3218536 A/G polymorphism and CRC using different genetic models. In allelic comparison, the distribution of G vs A allele was not different between cases and controls (P=0.49) in total or in PB (P=0.91) or HB (P=0.12) subgroups. Similar results were found for the polymorphism in total using codominant heterozygote (P=0.29), homozygote (0.54), dominant (0.76) or recessive genetic model (P=0.83). After stratification based on source of controls, no significant association was found either in PB or HB subgroups using different genetic models (P>0.05). As for ethnicity, no stratification was done because all studies belonged to the Caucasian populations.

RAD51 135 G/C polymorphism and CRC

Our pooled evidence revealed that the RAD51 135 G/C polymorphism was a risk factor for CRC in total using allele or recessive models. At allelic level, the C vs G allele was associated with increased risk of CRC with the OR of 1.21 (P=0.001; 95%CI=1.05-1.39). Using the recessive genetic model, a significant relationship between CC vs GC+GG polymorphism and CRC was observed in total (P=0.001; OR=1.62; 95%CI=1.30-2.02). For this polymorphism, no stratification based on ethnicity or sources of controls was performed due to lack of enough data for subgroups.

Heterogeneity and sensitivity analyses

We found heterogeneity in the codominant model for XPG His/Asp genotype using codominant heterozygote in overall (Ph=0.002; I^2=61%), and in Asians (Ph=0.01; I^2=78%) as well as in PB subgroup (Ph=0.001; I^2=75%). Similarly, a heterogeneity among total studies in dominant model for His/Asp+His/His genotype (Ph=0.005; I^2=58%), as well as in Asians (Ph=0.04; I^2=69%) and in PB subgroup (Ph=0.001; I^2=88%). For the RAD51 135 G/C, a significant heterogeneity was observed for all genetic models (Ph<0.05; I^2>50%); however, no heterogeneity was found for the XRCC2 rs3218536 A/G whether in total or PB/HB subgroups (Ph>0.05) as demonstrated in Table 2. Sensitivity analysis was performed according to heterogeneity. Due to significant heterogeneity across some studies, individual studies were sequentially omitted to identify the heterogeneity source by sensitivity analysis. The results showed that no individual study influenced the pooled OR values for XPG Asp1104His, XRCC2 rs3218536 A/G and RAD51 135G/C polymorphisms.

Publication bias

The funnel plots were used to evaluate the potential publication bias of included studies under each comparison model. The shape of the funnel plot did not reveal any obvious asymmetry for 3 studied polymorphisms.

Discussion

In this meta-analysis, we investigated the potential genetic association between XPG Asp1104His, XRCC2 rs3218536 A/G and RAD51 135G/C polymorphisms and CRC susceptibility. Using a meta-analytic approach, we synthesized 14 studies from 6 different countries for XPG Asp1104His variation including 6728 cases and 7877 controls. We found that XPG Asp1104His gene polymorphism was a risk factor for CRC in overall population in allele and codominant model. Besides, subgroup analysis stratified by ethnicity and source of control indicated that XPG Asp1104His polymorphism was associated with CRC susceptibility in Asians and

HB subgroups.

The association between XPG Asp1104H is polymorphism and CRC has extensively been studied but the results have been inconsistent (Kiyohara and Yoshimasu, 2007; He et al., 2014). Our pooled evidence supports the findings of Du et al., (2014), Liu et al., (2012) and Paszkowska-Szczur et al., (2015). Du et al., (2014) found a significant increased CRC risk for the His vs Asp allele (or C vs G) (OR=1.20), and genotypes under the codominant (OR=1.41) and dominant models (OR of 1.39). They also performed a meta-analysis on the association of the SNP with CRC risk on five studies with a total of 2649 CRC cases and 2848 controls included. In their meta-analysis, the association between XPG rs17655 and CRC risk was replicated under the codominant (His/His: OR=1.24) and dominant model (His/His+Asp/His: OR = 1.35). Their finding for dominant model showed lack of relationship between rs17655 and CRC which does not support our pooled results for this model. Additionally, Paszkowska-Szczur K et al., (2015) reported that XPG Asp1104His heterozygote His/Asp genotype was a CRC risk factor in a polish population, and was associated with 1.36-fold higher risk of CRC supporting our pooled findings (OR=1.16).

The XPG Asp1104His (rs17655 G/C) gene variation is the most commonly studied XPG polymorphism located in the XPG C-terminus, which is essential for its interaction with other members of the NER pathway, such as XPB, XPD and TFIIH subunits. The XPG rs17655 G/C polymorphism causes the replacement of Asp amino acid to His which may influence these protein–protein interactions; however, no functional study has been reported to date. Despite lack of functional studies for XPG rs17655 G/C, this SNP has been reported to contribute to a poorer overall survival (OS) in patients with different cancers, e.g. gastric cancer (Li et al., 2014), cutaneous melanoma (Schrama et al., 2011), squamous cell carcinoma of the oropharynx (SCCOP) (Song et al., 2013) and CRC (Liuet al., 2012; Sun et al., 2015). In CRC, Liu et al., (2012) demonstrated that XPG Asp1104His variant genotypes under dominant and codominant (heterozygote) models were associated with increased risk of CRC.

With respect to RAD51 135G/C polymorphism our pooled revealed that this genetic variation is associated with increased risk of CRC using allele and recessive models. According to our findings, individuals carrying the C vs G variant or CC genotype vs GC+GG of RAD51 135G/C were predisposed to 1.21 or 1.62-fold increased risk of CRC, respectively. In line with our findings, Romanowicz-Makowska et al., (2012) indicated that the variant 135C allele of RAD51 increased the CRC risk in a polish population with the OR of 3.59. Additionally, a recent meta-analysis (Kong et al., 2015) on six studies suggested that RAD51 G135C is associated with increased head and neck cancer (HNC) risk in allele comparison (OR=1.21) which supports our findings (OR=1.21). Another comprehensive meta-analysis (Zhao et al., 2014) indicated that the RAD51 G135C significantly increased the risk of overall cancers using homozygote, recessive and allele models. However, they found no significant association between RAD51 and CRC in all models. A meta-analysis by Cheng et al., (2014) for RAD51 G135C on four types of common cancers revealed that there was no relationship between this variation and CRC risk. Concerning XRCC2 rs3218536 A/G polymorphism, we observed no association between this variation and the risk of total cancers or CRC using all models.

Some limitations of this meta-analysis should be acknowledged. First, a common limitation of meta-analysis was heterogeneity. In our study, there was a considerable heterogeneity of studies for the dominant and codominant models of the XPG rs17655 G/C polymorphism in the overall population. However, after performing the analyses by ethnicity and source of control, the heterogeneity disappeared in Caucasian and hospital-based groups. These results propose that the heterogeneity may somewhat result from ethnicity or lacking of adequate data, hence large studies with subgroup analysis are required. Moreover, considerable inherent heterogeneity existed among different studies for RAD51 135G/C, which was confirmed by significant statistical heterogeneity we obtained. However, we detected no significant heterogeneity when three case-control studies Romanowicz-Makowska et al., (2012), Cetinkunar et al., (2015) and Krupa et al., (2011) in Table 1) were excluded, which implied the likelihood of the removed studies being the origins of heterogeneity. Second, the small sample size in some subgroups reduced the statistical power to examine the association between XRCC2 rs3218536 A/G and RAD51 135G/C and CRC with great confidence, especially in the Asians or PB subgroups. Third, our meta-analysis synthesized only published literatures, considering the fact that some pertinent important but unpublished studies were missed. Thus despite of its limitation, our meta-analysis is valuable to be interpreted with caution.

In conclusion, our meta-analysis suggested that the XPG Asp1104His and RAD51 135 G/C polymorphisms were risk factors for the pathogenesis of CRC in overall population. Besides, subgroup analysis stratified by ethnicity and source of control indicated that XPG Asp1104His polymorphism was associated with CRC susceptibility both in Asians or HB population. Further well designed studies with larger sample size on different ethnic groups are needed to confirm the risk identified in our meta-analysis.

Declaration of interest

The authors declare that there is no conflict of interests.

Funding

This study received no funding from any organization.

Acknowledgments

A.R and EEN extracted the data, MH contributed to data analysis; EEN wrote the paper.

References

Bigler J, Ulrich CM, Kawashima T, Whitton J, Potter JD (2005). DNA repair polymorphisms and risk of colorectal adenomatous or hyperplastic polyps. *Cancer Epidemiol Biomarkers Prev*, **14**, 2501-8.

Canbay E, Cakmakoglu B, Zeybek U, et al (2011). Association of APE1 and hOGG1 polymorphisms with colorectal cancer risk in a Turkish population. *Curr Med Res Opin*, **27**, 1295-1302.

Cetinkunar S, Gok I, Celep RB, et al (2015). The effect of polymorphism in DNA repair genes RAD51 and XRCC2 in colorectal cancer in Turkish population. *Int J Clin Exp Med*, **8**, 2649-55.

Chen J, Xie F, Chen K, et al(2009). ERCC5 promoter polymorphisms at -763 and +25 predict the response to oxaliplatin-based chemotherapy in patients with advanced colorectal cancer. *Cancer Biol Ther*, **8**, 1424-30.

Chen YZ, Guo F, Sun HW, et al (2016). Association between XPG polymorphisms and stomach cancer susceptibility in a Chinese population. *J Cell Mol Med*, **20**, 903-8.

Cheng D, Shi H, Zhang K, Yi L, Zhen G (2014). RAD51 Gene 135G/C polymorphism and the risk of four types of common cancers: a meta-analysis. *Diagn Pathol*, **9**, 18.

Curtin K, Lin WY, George R, et al (2009). Genetic variants in XRCC2: new insights into colorectal cancer tumorigenesis. *Cancer Epidemiol Biomarkers Prev*, **18**, 2476-84.

Du H, Zhang X, Duet M, et al (2014). Association study between XPG Asp1104His polymorphism and colorectal cancer risk in a Chinese population. *Sci Rep*, **4**, 6700.

Dworaczek H, Xiao W (2007). Xeroderma pigmentosum: a glimpse into nucleotide excision repair, genetic instability, and cancer. *Crit Rev Oncog*, **13**, 159-77.

Gil J, Ramsey D, StembalskaA, et al (2012). The C/A polymorphism in intron 11 of the XPC gene plays a crucial role in the modulation of an individual's susceptibility to sporadic colorectal cancer. Mol Biol Rep, 39, 527-34.

Griffin CS (2002). Aneuploidy, centrosome activity and chromosome instability in cells deficient in homologous recombination repair. *Mutat Res*, **504**, 149-55.

Griffin CS, Thacker J (2004). The role of homologous recombination repair in the formation of chromosome aberrations. *Cytogenet Genome Res*, **104**, 21-7.

He XF, Liu LR,Wei W, et al(2014). Association between the XPG Asp1104His and XPF Arg415Gln polymorphisms and risk of cancer: a meta-analysis. *PLoS One*, **9**, e88490.

Hou R, Liu Y, Feng Y, et al (2014). Association of single nucleotide polymorphisms of ERCC1 and XPF with colorectal cancer risk and interaction with tobacco use. *Gene*, **548**, 1-5.

Huang WY, Berndt SI, Kang D, et al (2006). Nucleotide excision repair gene polymorphisms and risk of advanced colorectal adenoma: XPC polymorphisms modify smoking-related risk. *Cancer Epidemiol Biomarkers Prev*, **15**, 306-311.

Johnson RD, Liu N, Jasin M (1999). Mammalian XRCC2 promotes the repair of DNA double-strand breaks by homologous recombination. *Nature*, **401**, 397-99.

Joshi AD, Corral R, Siegmund KD,et al (2009). Red meat and poultry intake, polymorphisms in the nucleotide excision repair and mismatch repair pathways and colorectal cancer risk. Carcinogenesis, **30**, 472-9.

Kabzinski J, Przybylowska K, Dziki L, Dziki A, Majsterek I (2015). An association of selected ERCC2 and ERCC5 genes polymorphisms, the level of oxidative DNA damage and its repair efficiency with a risk of colorectal cancer in Polish population. *Cancer Biomark*, **15**, 413-23.

Kiyohara C, Yoshimasu K (2007). Genetic polymorphisms in the nucleotide excision repair pathway and lung cancer risk: a meta-analysis. *Int J Med Sc*, **4**, 59-71.

Kong F, Wu J, Hu L, Du Y, Pan Y (2015). Association between RAD51 polymorphisms and susceptibility of head and neck cancer: a meta-analysis. *Int J Clin Exp Med*, **8**, 6412-19.

Krupa R, Sliwinski T, Wisniewska-Jarosinska M, et al (2011). Polymorphisms in RAD51, XRCC2 and XRCC3 genes of the homologous recombination repair in colorectal cancer-a case control study. *Mol Biol Rep*, **38**, 2849-54.

Lefkofsky HB, Veloso A, Ljungman M (2015). Transcriptional and post-transcriptional regulation of nucleotide excision repair genes in human cells. *Mutat Res*, **776**, 9-15.

Li XB, Luo H, Huang J, et al (2014). XRCC2 gene polymorphisms and its protein are associated with colorectal cancer susceptibility in Chinese Han population. *Med Oncol*, **31**, 245.

Li Y, Liu Z, Liu H, et al (2014). Potentially functional variants in the core nucleotide excision repair genes predict survival in Japanese gastric cancer patients. *Carcinogenesis*, **35**, 2031-8.

Liu D, Wu HZ, Zhang YN, et al (2012). DNA repair genes XPC, XPG polymorphisms: relation to the risk of colorectal carcinoma and therapeutic outcome with Oxaliplatin-based adjuvant chemotherapy. *Mol Carcinog*, **51**, 83-93.

Luo JF, Yan RC, Zou L (2014). XPG Asp1104His polymorphism and gastrointestinal cancers risk: a meta-analysis. *Int J Clin Exp Med*, **7**, 4174-82.

Mao D, Zhang Y, Lu H, Fu X (2013). Association between X-ray repair cross-complementing group 1 Arg194Trp polymorphism and colorectal cancer risk. *Tumour Biol*, **34**, 2529-38.

Mort R, Mo L, McEwan C, Melton DW (2003). Lack of involvement of nucleotide excision repair gene polymorphisms in colorectal cancer. *Br J Cancer*, **89**, 333-7.

Nissar S, Baba SM, Akhtar T, et al (2014). RAD51 G135C gene polymorphism and risk of colorectal cancer in Kashmir. *Eur J Cancer Prev*, **23**, 264-68.

Pardini B, Naccarati A, Novotny B, et al (2008). DNA repair genetic polymorphisms and risk of colorectal cancer in the Czech Republic. *Mutat Res*, **638**, 146-53.

Paszkowska-Szczur K,Scott RJ, Gorski B, et al(2015). "Polymorphisms in nucleotide excision repair genes and susceptibility to colorectal cancer in the Polish population. *Mol Biol Rep*, **42**, 755-64.

Romanowicz-Makowska H, Samulak D, Michalska M, et al (2012). RAD51 gene polymorphisms and sporadic colorectal cancer risk in Poland. *Pol J Pathol*, **63**, 193-8.

Schrama D, Scherer D, Schneider M, et al (2011). ERCC5 p.Asp1104His and ERCC2 p.Lys751Gln polymorphisms are independent prognostic factors for the clinical course of melanoma. *J Invest Dermatol*, **131**, 1280-90.

Sollier J, Stork CT, Garcia-Rubio ML, et al (2014). Transcription-coupled nucleotide excision repair factors promote R-loop-induced genome instability. *Mol Cell*, **56**, 777-85.

Song X, Sturgis EM, Jin L, et al (2013). Variants in nucleotide excision repair core genes and susceptibility to recurrence of squamous cell carcinoma of the oropharynx. *Int J Cancer* **133**, 695-704.

Spivak G (2015). Nucleotide excision repair in humans. *DNA Repair (Amst)*, **36**, 13-8.

Steck SE, Butler LM, Keku T, et al (2014). Nucleotide excision repair gene polymorphisms, meat intake and colon cancer risk. *Mutat Res*, **762**, 24-31.

Sugasawa K (2016). Molecular mechanisms of DNA damage recognition for mammalian nucleotide excision repair. *DNA Repair (Amst)*, **44**, 110-7.

Sun K, Gong A, Liang P (2015). Predictive impact of genetic polymorphisms in DNA repair genes on susceptibility and

therapeutic outcomes to colorectal cancer patients. *Tumour Biol*, **36**, 1549-59.

Zeng Y, Wei L, Wang YJ, Liu C (2015). Genetic association between ERCC5 rs17655 polymorphism and colorectal cancer risk: Evidencebased on a meta-analysis. *Asian Pac J Cancer Prev*, **16**, 5565-71.

Zhang Y B, He S, Pan YQ, et al (2011). Association of OGG1 Ser326Cys polymorphism with colorectal cancer risk: a meta-analysis. *Int J Colorectal Dis*, **26**, 1525-30.

Zhao M, Chen P, Dong Y, Zhu X, Zhang X (2014). Relationship between Rad51 G135C and G172T variants and the susceptibility to cancer: a meta-analysis involving 54 case-control studies. *PLoS One*, **9**, e87259.