Systematic Review and Meta-Analysis

Medicine®

OPEN

Association between RAD51 135 G/C polymorphism and risk of 3 common gynecological cancers

A meta-analysis

Xianling Zeng, MD[a], Yafei Zhang, MD[b], Lei Yang, MD[a], Huiqiu Xu, MD[a], Taohong Zhang, MD[a], Ruifang An, MD, PhD[a,*], Kexiu Zhu, MD, PhD[a,*]

Abstract

Aim: Available data concerning the association between RAD51 135G/C (rs1801320) polymorphism and the risk of 3 common gynecological cancers still could not reach a consensus. Thus, we conducted a meta-analysis to explore the relationship.

Methods: Several electronic databases and bibliographies of relevant articles were screened to identify the studies up to July 2017. Then a meta-analysis was performed to evaluate the connection between 3 common gynecological tumors' susceptibility and RAD51 135G/C polymorphism in different inheritance models. Simultaneously, we did subgroup analysis and sensitivity analysis if necessary.

Results: A total of 11 articles including 14 studies involving 4097 cases and 5890 controls were included in this meta-analysis. Overall, RAD51 135G/C polymorphism increased the risk of 3 common gynecological tumors. The subgroup analysis stratified by cancer types- endometrial carcinoma (EC) and ovarian cancer (OC)-showed that RAD51 135G/C polymorphism increased the risk of EC: allele model (C vs G: odds ratio [OR] = 4.32, 95% confidence interval [CI] = 2.63–7.10, $P < .00001$), dominant model (CC + GC vs GG: OR = 2.28, 95% CI = 1.44–3.60, $P = .004$), recessive model (CC vs GC + GG: OR = 10.27, 95% CI = 14.71–22.38, $P < .00001$), and homozygous model (CC vs GG: OR = 7.26, 95% CI = 3.59–14.68, $P < .00001$), but there was no significant association between RAD51 135G/C polymorphism and OC. In the subgroup analysis stratified by source of controls, a significantly increased risk was observed in hospital-based studies. Nevertheless, the data showed RAD51 135G/C polymorphism had no link in population-based studies.

Conclusions: This meta-analysis suggested that RAD51 135G/C polymorphism was a risk factor for the three common gynecological tumors, especially for EC among hospital-based populations.

Abbreviations: CBM = Chinese Biomedical Literature Database, CC = cervical cancer, CIN = cervical intraepithelial neoplasia, CNKI = China National Knowledge Infrastructure, EC = endometrial carcinoma, HB = hospital-based, HPV = human papillomavirus, HWE = Hardy-Weinberg equilibrium, OC = ovarian cancer, PB = population-based, SNP = single nucleotide polymorphism.

Keywords: gynecological cancers, meta-analysis, polymorphism, RAD51 135 G/C

1. Introduction

The single nucleotide polymorphism (SNP) is the most common form of human genetic variations. A growing number of studies reported that specific SNPs locus in DNA repair gene would affect the expression or activity of certain enzymes and the ability to repair damage. Defects in DNA repair gene may lead to genetic instability and tumorigenesis.[1,2] The human RAD51 gene, located on chromosome 15q15.1, is an essential member in the DNA repair of double-strand breaks.[3] There are 2 kinds of SNPs in RAD51 gene (rs1801320), namely, 153G/C and 172G/T.[4] Of the 2, RAD51 153G/C is more common and there have been numerous reports evaluating the association between RAD51 153G/C and non small cell lung cancer, myeloid leukemia, head and neck cancer, esophagus cancer, and breast cancer.[5–12] The potential carcinogenic mechanism of RAD51 153G/C is to affect the splitting, transcription, translation efficiency, and stability of mRNA through the combination of regulatory elements with 5'-UTR, and finally leads to changes in polypeptide product level and causes changes in protein function.[13,14]

Cervical cancer (CC) is the most common genital tract tumor worldwide. Overwhelming researches have offered evidence supporting that human papillomavirus (HPV) was closely related to cervical intraepithelial neoplasia (CIN) and CC.[15] However, not all women infected with HPV will develop into CC, which suggests that other factors including genetic susceptibility may play a role in this process.[16–18] Endometrial carcinoma (EC) is a multifactorial gynecological cancer in the world.[19,20] It has been hypothesized that genetic factors, environmental factors, and

Editor: Jianfeng Li.

The authors declare no conflicts of interest.

[a] Department of Gynecology and Obstetrics, the First Affiliated Hospital of Xi'an Jiaotong University, [b] Department of General Surgery, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China.

[*] Correspondence: Ruifang An, Department of Gynecology and Obstetrics, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China (e-mail: anruifangxj@163.com), and Kexiu Zhu (e-mail: zhukexiudoc@163.com).

Medicine (2018) 97:26(e11251)

Received: 17 November 2017 / Accepted: 1 June 2018

http://dx.doi.org/10.1097/MD.0000000000011251

habitual behaviors are the potential risk factors for EC. One study implied that RAD51 G135C polymorphism might be associated with EC incidence.[21] Another study denoted that RAD51 G135C was positively associated with the incidence of EC. In light of the limited sample size, we believed that it was necessary to conduct a further study on a larger population in order to clarity this relationship. Ovarian cancer (OC) is the most lethal gynecological tumor in developed countries.[22] Owing to its various morphological and genetic characteristics and biological behavior, the early and timely diagnosis of OC is quite difficult. Once the onset of OC, it develops rapidly, leading to a high mortality.[23] Thus, it's high time to find new biomarkers in order to detect OC early. Then the polymorphic variants of RAD51 repair genes could be a potential one. A multicenter case-control study regarding OC indicated that there was no significant difference in genotype frequencies in cases and controls for RAD51 no matter when each study was analyzed separately or when the data were combined.[24] Another study designed to investigate the role of RAD51 135G/C polymorphism in breast cancer and OC patients harboring BRCA1 mutations found that the RAD51C allele seemed to protect against OC.[25] A third study did not yield any definitive association between RAD51 135G/C polymorphism and OC.[26]

As you see, RAD51 135G/C polymorphism plays a vital role in the etiology of diverse cancers owing to its modification effect in promoter activity. However, available data concerning the association between RAD51 135G/C polymorphism and the gynecological cancer risk still could not reach a consensus. So, we conducted this meta-analysis aiming to explore the relationship between RAD51 G135C polymorphism and three common gynecological tumors (CC, EC, and OC).

2. Materials and methods

2.1. Literature searching strategy

Our study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[27] We conducted a comprehensive literature search through PubMed, Web of Science, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), and the Cochrane Library published up to July 2017, using the following keywords

RAD51/rs1801320/135G/C, polymorphism/variant/genotype/polymorphism/SNP, cervical/endometrial/ovarian cancer/carcinoma*/neoplasm*/tumor, and the combinations. The relevant bibliographies of identified studies were examined for additional articles. There exited no language limitations during the retrieval procedure.

2.2. Inclusion and exclusion criteria

A study was recruited in this meta-analysis on the condition that it must meet the following criteria: independent case-control study that addressed for humans; the study evaluating the association between RAD51 135G/C polymorphism and the risk of 3 common gynecological cancers (CC, EC, and OC); genotype frequencies in case and control groups were available; subjects in control groups should have no cancer history, previous radiotherapy, chemotherapy history, or family history of tumor; and the diagnosis of the cases was based on pathology. Exclusion criteria: abstracts, case reports, letters, comments, editorials, reviews, and meta-analysis; not a case-control study concerning the association between RAD51 135G/C polymorphism and the risk of targeted cancers; and studies lacking eligible data. Simultaneously, the most newly-published studies were included once the studies were duplicated or shared in more than 1 articles. What is important was that all potential studies were screened carefully by 2 investigators independently and any disagreements were resolved by discussing with a third reviewer.

2.3. Data extraction and synthesis

Characteristics of the eligible studies were extracted independently by 2 authors according to the inclusion and exclusion criteria and the data was reviewed by a third investigator. The following data were extracted from each study: first author, year of publication, country of origin, ethnicity, and source of the control group, genotyping method, cancer types, sample size, and numbers of case and control subjects. Ethnicity was categorized as "Caucasian," "Asian," and "mixed." When one study did not state which ethnic groups belonged to, then the sample was termed as "mixed population". Meanwhile, multi-center studies were divided into several separate studies according to the origin.

2.4. Quality assessment

The methodological quality assessment was performed based on the modified scoring system used for studies in genetic epidemiological issues.[28] Points were awarded on the basis of representativeness of cases, source of controls, HWE in controls, genotyping examination, and association assessment. Total score ranged from 0 (lowest quality) to 8 (highest quality). A study with a score of 6 or higher was classified as high quality and vice versa.

2.5. Statistical analysis

Statistical analysis was carried out using Review Manage version 5.2.0 (the Cochrane Collaboration, 2012) and STATA version 11.0 software (StataCorp LP, College Station, TX). Hardy-Weinberg equilibrium (HWE) of the genotype frequencies in the control group of each study was assessed by χ^2 test and $P>.05$ was considered to be consistent with HWE.[29] We calculated a summary odds ratio (OR) and 95% confidence interval (CI) for dichotomous variables, using Mantel–Haenszel and fixed/random effects mode to evaluate the strength of the association between RAD51 135G/C polymorphism and cancer risk. Heterogeneity among studies was tested using the I^2 and Q statistic. If substantial heterogeneity was found (I^2 greater than 50%), we used a random effects model. Otherwise, the fixed effects model was adopted. In addition, a subgroup analysis was conducted according to source of controls and cancer types. Sensitivity analysis was performed to assess the stability of the results. Each stud y involved in this meta-analysis was deleted each time to reflect the influence of the individual data exerted on the pooled OR. The association was estimated in the allele model (C vs G), the dominant model (CC + GC vs GG), the recessive model (CC vs GC + GG), the homozygous genetic model (CC vs GG), and the heterozygous genetic model (GC vs GG), respectively. $P<.05$ was considered statistically significant. Begg funnel plot and Egger plot were used to examine the possibly exiting publication bias and $P>.05$ was considered to have no potential publication bias.

2.6. Ethical approval

The ethical approval was not necessary for the reason that our study was a meta-analysis belonging to secondary analysis.

3. Results

3.1. Characteristics of included studies

Totally, the literature search generated 210 articles after eliminating 311 duplicated articles. Subsequently, 185 articles were excluded unquestionably after screening the abstracts. Eleven articles [21,24–26,30–36] were included in this meta-analysis because the other 14 articles couldn't offer available data. Among these articles, 1 article [26] distinguished Caucasian from other ethnic groups, so we divided it into 2 studies. As to another article,[24] the multi-center study was performed in three countries, hence we considered it as 3 studies. Eventually, the remaining articles including 14 studies involving 4097 cases and 5890 controls were reviewed carefully (Fig. 1).

All the studies were done in recent years. Seven studies were conducted in Poland, with others in Australia, China, Danish, Serbia, United Kingdom, and United States. There were 12 studies of Caucasians, one mixed and another Asian. Seven studies had population-based (PB) controls. The largest number of subjects was 1126, almost 40-fold of the smallest number and only 5 studies had the number of objectives more than 500. Hardy–Weinberg equilibrium (HWE) examination of the included studies was showed in Table 1. As to quality assessment, 13 out of the 14 studies were scored 6 to 8 points and of high quality (Table 2), And RAD51 135G/C polymorphism genotype distribution and allele frequency in cases and controls were displayed in Table 3.

3.2. Meta-analysis results

Overall, there was obvious association between RAD51 135G/C polymorphism and the risk of 3 common gynecological tumors in 4 genetic models: allele model (C vs G: OR = 2.00, 95% CI = 1.38–2.89, P = 0.0002), dominant model (CC + GC vs GG: OR = 1.47, 95% CI = 1.15–1.87, P = 0.002), recessive model (CC vs GC + GG: OR = 4.29, 95% CI = 2.55–7.21, P < 0.00001), homozygous model (CC vs GG: OR = 4.13, 95% CI = 2.54-6.71, P < 0.00001). While there was no significant difference in heterozygous model (GC *vs*. GG: OR = 0.86, 95% CI = 0.67-1.10, P = 0.22; Table 4 and Fig. 2A, B, C).

The subgroup analysis stratified by cancer types (EC and OC) showed that there still exited obvious association between this polymorphism and EC: allele model (C vs G: OR = 4.32, 95% CI = 2.63–7.10, *P* < .00001), dominant model (CC + GC vs GG: OR = 2.28, 95% CI = 1.44–3.60, *P* = .004), recessive model (CC vs GC + GG: OR = 10.27, 95% CI = 14.71–22.38, *P* < .00001), homozygous model (CC vs GG: OR = 7.26, 95% CI = 3.59–14.68, *P* < .00001). However, there was no significant association between RAD51 135G/C polymorphism and OC (Table 4 and Fig. 2D). Given that there was only one study focusing on the association between this polymorphism and CC, it was not rigorous to do a subgroup analysis on CC.[34] So we just assess the synthetic effect of this polymorphism on 3 common gynecological cancers. Thus the relationship between the polymorphism and CC was not definite.

In the subgroup analysis by source of controls, a significantly increased risk was observed in hospital based (HB) studies in 4 genetic models in addition to the heterozygous model: allele model (C vs G: OR = 2.76, 95% CI = 1.80–4.22, *P* < .00001), dominant model (CC + GC vs GG: OR = 1.78, 95% CI = 1.22–2.61, *P* = .003), recessive model (CC vs GC + GG: OR = 7.35, 95% CI = 4.24–12.73, *P* < .00001), homozygous model (CC vs

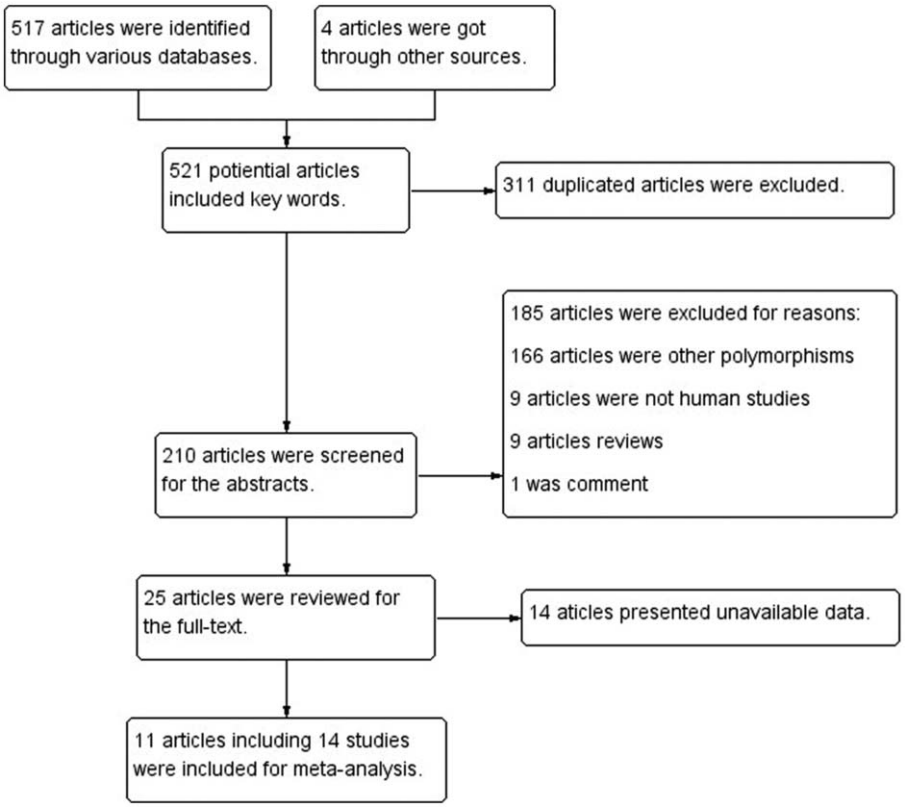

Figure 1. Search flow diagram.

Table 1

Characteristics of the studies included in the meta-analysis.

First author	Year	Country	Ethnicity	Cancer type	Source of control	Genotyping method	Number (case/control)	Age/Median (range), ys	FIGO stage	Histological grade	HWE
Zhang et al[34]	2012	China	Asian	CC	PB	PCR	80/175	43* (24–55)	–	–	0.4052
Romanowicz-Makowsa et ala[32])	2012	Poand	Caucasian	EC	HB	PCR-RFLP	230/236	66 (53–82)	I (n=58) II (n=157) III (n=15)	G1 (n=66) G2 (n=154) G3 (n=10)	0.0597
Smolarz et al(a[31])	2011	Poand	Caucasian	EC	HB	PCR-RFLP	240/240	63.80±7.1* (–)	I (n=159) II (n=71) 1II (n=10)	–	0.0102
Michalska et al[21]	2014	Poand	Caucasian	EC	HB	PCR-RFLP	630/630	69 (50–84)	I (n=174) II (n=441) III (n=15)	G1 (n=180) G2 (n=420) G3 (n=30)	0.1892
—Krupa et al[25]	2011	Poand	Caucasian	EC	HB	PCR	30/30	55 (–)	-	–	0.5245
Jakubowska et al[30]	2007	Poand	Caucasian	OC	HB	PCR-RFLP	127/127	45 (25–71)	-	–	0.1734
Smolarz et al(b[35])	2013	Poand	Caucasian	OC	HB	PCR	210/210	54 (37–80)	I (n=80) II (n=2) III (n=120) IV (n=6) No data (n=2)	G1 (n=2) G2 (n=64) G3 (n=100) No data (n=44)	0.4484
Malisic et al[36]	2015	Serbia	Caucasian	OC	PB	PCR-RFLP	50/78	59 (25–81)	I (n=11) II (n=9) III (n=27) IV (n=3)	G1 (n=18) G2 (n=19) G3 (n=5) No data (n=8)	0.0572
Web et al(a[26])	2005	Australia	Caucasian	OC	PB	PCR-RFLP	451/953	–	–	–	0.0075
Web et al(b[26])	2005	Australia	Mixed	OC	PB	PCR-RFLP	546/1126	58 (18–95)	–	–	0.0826
Romanowicz-Makowsa et al. (b[33])	2012	Poand	Caucasian	OC	HB	PCR-RFLP	120/120	54 (37–79)	I (n=35) II (n=0) III (n=77) IV (n=6) No data (n=2)	G1 (n=2) G2 (n=34) G3 (n=70) No data (n=14)	0.0653
Auranen et al(a[24])	2005	Danish	Caucasian	OC	PB	PCR	278/699	– (35–79)	–	–	0.1527
Auranen et al(b[24])	2005	UK	Caucasian	OC	PB	PCR	729//847	– (45–74)	–	–	0.4771
Auranen et al(c[24])	2005	US	Caucasian	OC	PB	PCR	326/419	– (20–64)	–	–	0.3364

CC = cervical cancer, EC = endometrial cancer, HB = hospital-based, HWE = Hardy-Weinberg equilibrium, OC = ovarian cancer, PB = population based, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism. UK = United Kingdom, US = United States.

* mean, a, b, c: multicenter studies were divided into 2 or 3 separate studies based on ethnic or countries and marked a, b, or c respectively.

GG: OR = 5.64, 95% CI = 3.43–9.29, $P < .00001$). Nevertheless, the data showed RAD51 135G/C polymorphism had no link to PB.

3.3. Detection for heterogeneity

For the comprehensive analysis, remarkable heterogeneity was observed among studies in all models using Q statistic: allele model (C vs G: $P < .00001$, $I^2 = 94\%$), the dominant model (CC + GC vs GG: $P < .0001$, $I^2 = 73\%$), the recessive model (CC vs GC + GG: $P < .0001$, $I^2 = 76\%$), the homozygous genetic model (CC vs GG: $P < .0001$, $I^2 = 70\%$), and the heterozygous genetic model (GC vs GG: $P < .0001$, $I^2 = 70\%$), and the random-effect model was applied. For the sake of integrity, we underwent subgroup analysis stratified by cancer types and source of controls, the heterogeneity among in certain comparisons decreased greatly (PB: C vs G, $P = .91$, $I^2 = 0\%$; CC + GC vs GG, $P = .88$, $I^2 = 0\%$; CC vs GC + GG, P = 0.47, $I^2 = 0\%$; GC vs GG, $P = .80$, $I^2 = 0\%$; OC: CC vs GG, $P = .48$, $I^2 = 0\%$; Table 4).

3.4. Sensitivity analysis and publication bias

Twelve studies were in line with the balance of HWE in control groups and the another 2 [26,31] were not ($P < .05$). However, the overall results were not substantially altered after excluding these 2 studies. Sensitivity analysis was performed by sequential deletion of individual studies. The pooled ORs did not show quantitative changes when excluding any study, suggesting that the results of this meta-analysis were stable and reliable (Fig. 3).

Table 2

Quality assessment of studies based on the modified scoring system.

Study name	Representativeness of cases	Source of controls	HWE in controls	Genotyping examination blinded	Association assessment	Total
Zhang et al	2	2	2	0	2	8
Romanowicz-Makowsa et al(a)	2	1	2	0	1	6
Smolarz et al(a)	2	1	1	0	1	5
Michalska et al	2	1	2	0	1	6
Krupa et al	2	1	2	0	1	6
Jakubowska et al	2	1	2	0	2	7
Smolarz et al(b)	2	1	2	0	1	6
Malisic et al	2	2	2	0	1	7
Web et al(a)	2	2	1	0	2	7
Web et al(b)	2	2	2	0	2	8
Romanowicz-Makowsa et al(b)	2	1	2	0	1	6
Auranen et al(a)	2	2	2	0	1	7
Auranen et al(b)	2	2	2	0	1	7
Auranen et al(c)	2	2	2	0	1	7

HWE = Hardy-Weinberg equilibrium.

a, b, c: we divided 1 study into 2 or 3 studies based on ethnic or countries and marked a, b, or c respectively.

Table 3

RAD51 135G/C polymorphisms genotype distribution and allele frequency in cases and controls.

	Genotype (N)								Allele frequency (N)			
	Case				Control				Case		Control	
First author	Total	CC	CG	GG	Total	CC	CG	GG	C	G	C	G
Zhang et al[34]	80	2	20	58	175	3	50	122	24	136	56	294
Romanowicz-Makowsa et al(a[32])	230	165	25	40	236	45	132	59	355	105	222	250
Smolarz et al(a[31])	240	185	30	25	240	37	138	65	400	80	212	268
Michalska et al[21]	630	366	135	129	630	144	297	189	867	393	585	675
Krupa et al[25]	30	16	8	6	30	2	9	19	40	20	13	47
Jakubowska et al[30]	127	0	23	104	127	1	37	89	23	231	39	215
Smolarz et al(b[35])	210	122	45	43	210	48	99	63	289	131	195	225
Malisic et al[36]	50	3	14	33	78	2	10	66	20	80	14	142
Web et al(a[26])	451	3	65	383	953	10	113	830	71	831	133	1773
Web et al(b[26])	546	4	85	457	1126	10	145	971	93	999	165	2087
Romanowicz-Makowsa et al(b[33])	120	92	15	13	120	18	69	33	199	41	105	135
Auranen et al(a[24])	278	1	36	241	699	5	78	616	38	518	88	1310
Auranen et al(b[24])	729	3	84	642	847	2	100	745	90	1368	104	1590
Auranen et al(c[24])	326	4	52	270	419	1	61	357	60	592	63	775

a, b, and c: we divided 1 study into 2 or 3 studies based on ethnic or countries and marked a, b, or c respectively.

Begg and Egger tests all suggested that there was no evidence of publication bias (Fig. 4).

4. Discussion

There is emerging evidence that the RAD51 gene involves in DNA repair and in the maintenance of genome integrity and plays a crucial role in providing protection against mutations that lead to cancers. Enlightened by this hypothesis, investigators were able to explore the association between SNPs in this gene and the likelihood of developing cancer.[37] Nowadays, accumulative studies investigated the role of 135G/C SNPs in the homologous recombination repair gene RAD51 and risk of various malignancies, such as acute myeloid leukemia, head and

Table 4

Meta-analysis results.

					Heterogeneity		
Subgroup analysis		OR	95% CI	P	I^2 (%)	P	Effects model
allele model C vs G							
Overall		2.00	1.38–2.89	**.0002**	94	< .00001	R
Cancer type	EC	4.32	2.63–7.10	< **.00001**	91%	< .00001	R
	OC	1.50	1.00–2.23	.05	91	< .00001	R
Source of controls	PB	1.13	0.98–1.29	.10	0	.91	R
	HB	2.76	1.80–4.22	< **.00001**	92	< .00001	R
dominant model CC + GC vs GG							
Overall		1.47	1.15–1.87	**.002**	73	< .0001	R
Cancer type	EC	2.28	1.44–3.60	**.004**	71	.01	R
	OC	1.26	0.99–1.60	.06	64	.04	R
Source of controls	PB	1.14	0.98–1.33	.08	0	.88	R
	HB	1.78	1.22–2.61	**.003**	78	< .0001	R
recessive model CC vs GC + GG							
Overall		4.29	2.55–7.21	< **.00001**	76	< .0001	R
Cancer type	EC	10.27	4.71–22.38	< **.00001**	91	< .0001	R
	OC	1.53	0.65–3.60	.33	65	.006	R
Source of controls	PB	1.00	0.53–1.92	.99	0	.47	R
	HB	7.35	4.24–12.73	< **.00001**	85	< .00001	R
homozygous genetic model CC v GG							
Overall		4.13	2.54–6.71	< **.00001**	70	< .0001	R
Cancer type	EC	7.26	3.59–14.68	< **.00001**	83	.0005	R
	OC	2.08	0.91–4.75	.93	0	.48	R
Source of controls	PB	1.03	0.54–1.96	.07	63	.001	R
	HB	5.64	3.43–9.29	< **.00001**	73	.0003	R
heterozygous genetic model GC vs GG							
Overall		0.86	0.67–1.10	.22	70	< .0001	R
Cancer type	EC	0.61	0.33–1.12	.11	75	.007	R
	OC	1.02	0.82–1.28	.84	55	.02	R
Source of controls	PB	1.15	0.99–1.34	.07	0	.80	R
	HB	0.70	0.49–1.00	**.005**	67	.0002	R

CI = confidence interval, CC = cervical cancer, EC = endometrial cancer, F = fixed-effect model, HB = hospital-based, OC = ovarian cancer, OR = odds ratio, PB = population based, R = random-effect model. Bold value indicates $P < .05$.

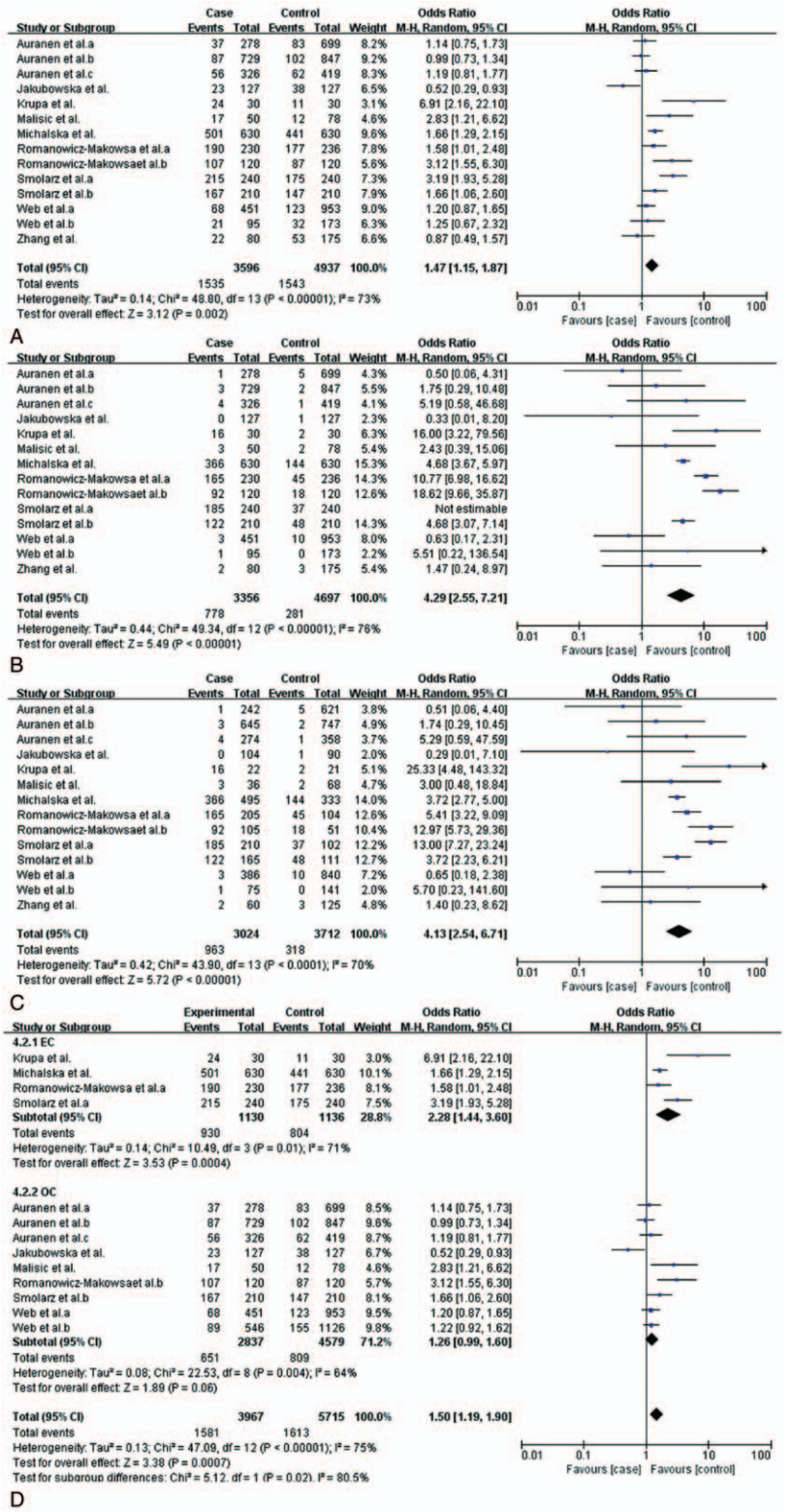

Figure 2. Meta-analysis of association between RAD51 135 G/C polymorphism and the risk of three common gynecological cancers. CI = confidence interval, OR = odds ratio. A, Dominant model, (B) recessive model, (C) homozygous model, and (D) dominant model.

neck cancer, esophagus cancer, breast cancer, and colorectal cancer.[9,38–42] However, the role in 3 common gynecological cancers was still inconclusive. So we performed this meta-analysis aiming to illuminate the association between RAD51 135G/C and CC, EC, and OC.

In this meta-analysis, the summary ORs hinted that RAD51 135G/C polymorphism increased the risk of three common gynecological malignancies with obvious statistical significance. The only drawback was the moderate to great heterogeneity. In order to rule out the effect of sample size, we excluded the large or

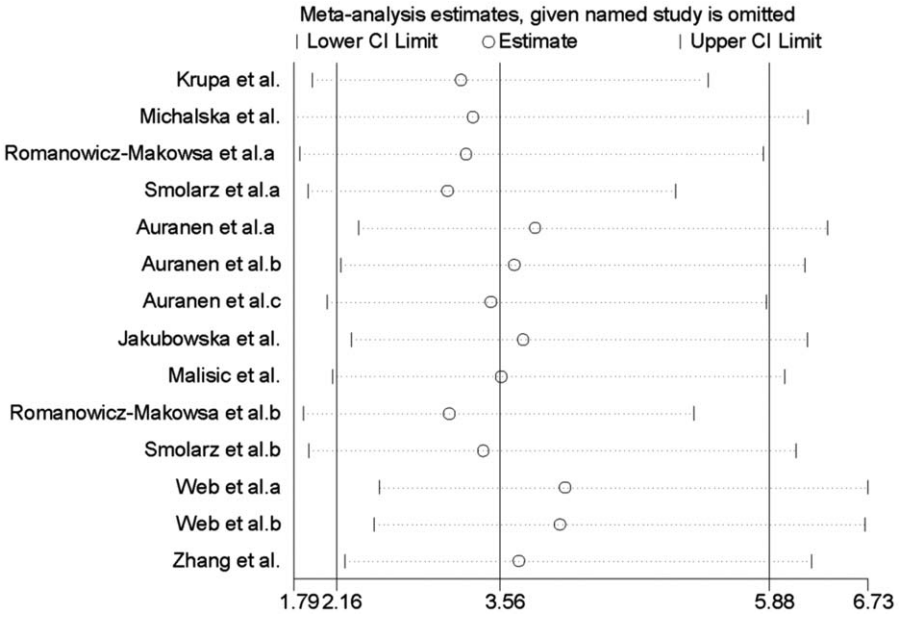

Figure 3. Sensitivity analysis of the association between RAD51 135G/C polymorphism and the risk of three types of common gynecological cancers in homozygous model.

small samples sequentially, yet the I^2 still showed a moderate to high degree variation under all comparisons. In order to figure out the influence degree exerted by the heterogeneity on the overall results, we did subgroup analysis stratified by cancer types and source of controls, the heterogeneity among certain comparisons decreased greatly.

With regard to cancer types, only 1 study was about CC,[34] 4 were EC,[21,25,31,32] and 9 were OC.[24,26,30,33,35,36] So we only performed a subgroup analysis between EC and OC. The statistic data showed RAD51 135G/C polymorphism increased EC susceptibility in allele model, dominant model, recessive model and homozygous model, which was in accordance with several case-control studies.[21,25,31,32] That is to say, this meta-analysis added much more persuasiveness to the suggestion that RAD51 135G/C polymorphism might be regarded as a neoteric biomarker of EC. Considering the role of RAD51135G/C polymorphism in increasing risk of EC, it might be used as a prognostic factor for precancerous lesions, making predicting EC possible. On the contrary, the subgroup analysis yielded no statistical significance in the relationship between RAD51 135G/C polymorphism and OC, which was in line with a previous meta-analysis.[43] Yet for another meta-analysis focusing on OC risk among Caucasians, the final result showed there was no association between RAD51135G/C polymorphism and OC susceptibility[9] and the identical result was also found in other meta-analysis.[3,38] While an individual study suggested RAD51 135G/C polymorphism seemed to reduce the incidence of OC among BRCA1/2 mutation carriers.[44] Besides, there were studies believing that there was a significant positive association between the RAD51 135G>C polymorphism and OC.[33,35,36] Confronting the controversial results, we assumed that previous studies had a limited sample size which probably led to the discrepancy. For our meta-analysis was based on more studies, involving many more objects and conducted rigorously, the result was much more convincing. The present meta-analysis showed that RAD51135G/C polymorphism increased the risk of 3 common gynecological malignancies, including OC, but there was no statistical significance. Moreover, the subgroup analysis also generated no definite effect of RAD51135G/C polymorphism on OC. As for CC, the only accessibly relevant study showed that RAD51135G/C was a risk factor for cervical intraepithelial neoplasia (CIN) for women who had the first

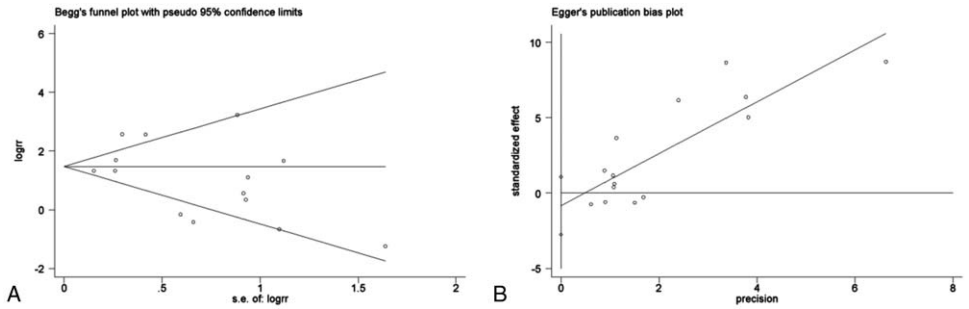

Figure 4. Publication bias was assessed by Begg funnel plot and Egger's plot ($P > .05$).

intercourse before 22 years of age, but a protective factor for squamous cell carcinoma (SCC) for women who had the first intercourse after 22 years old.[34] But the relationship between RAD51 135G/C and cervical adenocarcinoma was not mentioned. Thus the relationship between the polymorphism and CC was not definite.

Additionally, the subgroup analysis was also done according to source of controls; the summary result showed RAD51 135G/C polymorphism was a risk factor for 3 common gynecological cancers in HB studies in allele model, dominant model, recessive model, and homozygous model. Nevertheless, the data showed no linkage in PB studies.

Nevertheless, we'd better take into several study limitations when considering the generalizability of this finding. First of all, the big range in sample size from 30 to 1126 was a weakness, which may weaken the strength of the pooled result. Then the number of studies focusing on CC and EC was quite small, which may affect the comprehensive result more or less. So such problems should be paid attention to in further investigations. Despite the shortages mentioned above, the strength of this study on the whole was stronger than any single study since it recruited all studies in this kingdom. What's more, the included studies were carried out in recent years, which undoubtedly enhance the persuasiveness of this meta-analysis. Simultaneously, sensitivity analysis showed the pooled result was stable.

5. Conclusions

In conclusion, this meta-analysis suggested that RAD51 135G/C polymorphism was a risk factor for 3 common gynecological tumors, especially for EC among HB populations. Yet there was no obvious significance between RAD51 135G/C polymorphism and OC. When it comes to inconsistent results, especially in OC, the inconformity might be attributed to the different role of RAD51 gene G135/C polymorphism in different cell types or tissues. At the same time, the gene-gene and gene-environment interactions may also explain these different findings. In order to verify this finding, a series of large-scale multicenter studies are warranted.

Author contributions

Conceptualization: Xianling Zeng, Yafei Zhang, Taohong Zhang, Ruifang An, Kexiu Zhu.
Data curation: Xianling Zeng, Yafei Zhang, Huiqiu Xu, Ruifang An, Kexiu Zhu.
Formal analysis: Xianling Zeng, Yafei Zhang, Lei Yang, Huiqiu Xu, Taohong Zhang.
Funding acquisition: Ruifang An.
Investigation: Xianling Zeng, Lei Yang, Kexiu Zhu.
Methodology: Xianling Zeng, Yafei Zhang.
Project administration: Xianling Zeng, Lei Yang, Ruifang An, Kexiu Zhu.
Resources: Xianling Zeng, Huiqiu Xu.
Software: Xianling Zeng, Kexiu Zhu.
Supervision: Ruifang An, Kexiu Zhu.
Validation: Ruifang An, Kexiu Zhu.
Visualization: Ruifang An, Kexiu Zhu.
Writing – original draft: Xianling Zeng, Kexiu Zhu.
Writing – review & editing: Ruifang An, Kexiu Zhu.

References

[1] Goode EL, Ulrich CM, Potter JD. Polymorphisms in DNA repair genes and associations with cancer risk. Cancer Epidemiol Biomark Prev 2002;11:1513–30.
[2] Qiao GB, Wu YL, Yang XN, et al. High-level expression of Rad51 is an independent prognostic marker of survival in non-small-cell lung cancer patients. Br J Cancer 2005;93:137–43.
[3] Cheng D, Shi H, Zhang K, et al. RAD51 Gene 135G/C polymorphism and the risk of four types of common cancers: a meta-analysis. Diagn Pathol 2014;9:18.
[4] Rollinson S, Smith AG, Allan JM, et al. RAD51 homologous recombination repair gene haplotypes and risk of acute myeloid leukaemia. Leuk Res 2007;31:169–74.
[5] Nogueira A, Catarino R, Coelho A, et al. Influence of DNA repair RAD51 gene variants in overall survival of non-small cell lung cancer patients treated with first line chemotherapy. Cancer Chemother Pharmacol 2010;66:501–6.
[6] Liu L, Yang L, Mi YC, et al. Relationship between RAD51-g135C and XRCC3-C241T polymorphisms and prognosis of inv (16)/t(16;16) (CBFbeta-MYH11) acute myeloid leukemia. Zhonghua Xue Ye Xue Za Zhi 2011;32:433–8.
[7] Miao L, Qian XF, Yang GH, et al. Relationship between RAD51-G135C and XRCC3-C241T single nucleotide polymorphisms and onset of acute myeloid leukemia. Zhongguo Shi Yan Xue Ye Xue Za Zh 2015;23:605–11.
[8] Kayani MA, Khan S, Baig RM, et al. Association of RAD 51 135 G/C, 172 G/T and XRCC3 Thr241Met gene polymorphisms with increased risk of head and neck cancer. Asian Pac J Cancer Prev 2014;15:10457–62.
[9] Shi S, Qin L, Tian M, et al. The effect of RAD51 135 G>C and XRCC2 G>A (rs3218536) polymorphisms on ovarian cancer risk among Caucasians: a meta-analysis. Tumor Biol 2014;35:5797–804.
[10] Alshareeda AT, Negm OH, Aleskandarany MA, et al. Clinical and biological significance of RAD51 expression in breast cancer: a key DNA damage response protein. Breast Cancer Res Treat 2016;159:41–53.
[11] Krivokuca AM, Cavic MR, Malisic EJ, et al. Polymorphisms in cancer susceptibility genes XRCC1, RAD51 and TP53 and the risk of breast cancer in Serbian women. Int J Biol Markers 2016;31:e258–63.
[12] Parvin S, Islam MS, Al-Mamun MM, et al. Association of BRCA1, BRCA2, RAD51, and HER2 gene polymorphisms with the breast cancer risk in the Bangladeshi population. Breast Cancer (Tokyo, Japan) 2017;24:229–37.
[13] Poplawski T, Arabski M, Kozirowska D, et al. DNA damage and repair in gastric cancer: a correlation with the hOGG1 and RAD51 genes polymorphisms. Mutat Res 2006;601:83–91.
[14] Richardson C, Stark JM, Ommundsen M, et al. Rad51 overexpression promotes alternative double-strand break repair pathways and genome instability. Oncogene 2004;23:546–53.
[15] Silva J, Ribeiro J, Sousa H, et al. Oncogenic HPV types infection in adolescents and university women from North Portugal: from self-sampling to cancer prevention. J Oncol 2011;2011:953469.
[16] Craveiro R, Bravo I, Catarino R, et al. The role of p73 G4C14-to-A4T14 polymorphism in the susceptibility to cervical cancer. DNA Cell Biol 2012;31:224–9.
[17] Wang L, Gao R, Yu L. Combined analysis of the association between p73 G4C14-to-A4T14 polymorphisms and cancer risk. Mol Biol Rep 2012;39:1731–8.
[18] Nogueira A, Catarino R, Faustino I, et al. Role of the RAD51 G172T polymorphism in the clinical outcome of cervical cancer patients under concomitant chemoradiotherapy. Gene 2012;504:279–83.
[19] Spurdle AB, Thompson DJ, Ahmed S, et al. Genome-wide association study identifies a common variant associated with risk of endometrial cancer. Nat Genet 2011;43:451–4.
[20] Hosono S, Matsuo K, Ito H, et al. Polymorphisms in base excision repair genes are associated with endometrial cancer risk among postmenopausal Japanese women. Int J Gynecol Cancer 2013;23:1561–8.
[21] Michalska MM, Samulak D, Romanowicz H, et al. Association of polymorphisms in the 5' untranslated region of RAD51 gene with risk of endometrial cancer in the Polish population. Arch Gynecol Obstet 2014;290:985–91.
[22] Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
[23] Sudo T. Molecular-targeted therapies for ovarian cancer: prospects for the future. Int J Clin Oncol 2012;17:424–9.

[24] Auranen A, Song H, Waterfall C, et al. Polymorphisms in DNA repair genes and epithelial ovarian cancer risk. Int J Cancer 2005;117:611–8.
[25] Krupa R, Sobczuk A, Poplawski T, et al. DNA damage and repair in endometrial cancer in correlation with the hOGG1 and RAD51 genes polymorphism. Mol Biol Rep 2011;38:1163–70.
[26] Webb PM, Hopper JL, Newman B, et al. Double-strand break repair gene polymorphisms and risk of breast or ovarian cancer. Cancer Epidemiol Biomarkers Prev 2005;14:319–23.
[27] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J SurgV 8 2010;336–41.
[28] Niu YM, Du XY, Cai HX, et al. Increased risks between Interleukin-10 gene polymorphisms and haplotype and head and neck cancer: a meta-analysis. Sci Rep 2015;5:17149.
[29] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–48.
[30] Jakubowska A, Gronwald J, Menkiszak J, et al. The RAD51 135 G>C polymorphism modifies breast cancer and ovarian cancer risk in Polish BRCA1 mutation carriers. Cancer Epidemiol Biomarkers Prev 2007; 16:270–5.
[31] Smolarz B, Samulak D, Michalska M, et al. 135G>C and 172G>T polymorphism in the 5' untranslated region of RAD51 and sporadic endometrial cancer risk in Polish women. Pol J Pathol 2011;62: 157–62.
[32] Romanowicz-Makowska H, Smolarz B, Polac I, et al. Single nucleotide polymorphisms of RAD51 G135C, XRCC2 Arg188His and XRCC3 Thr241Met homologous recombination repair genes and the risk of sporadic endometrial cancer in Polish women. J Obstet Gynaecol Res 2012;38:918–24.
[33] Romanowicz-Makowska H, Smolarz B, Samulak D, et al. A single nucleotide polymorphism in the 5' untranslated region of RAD51 and ovarian cancer risk in Polish women. Eur J Gynaecol Oncol 2012; 33:406–10.
[34] Zhang L, Ruan Z, Hong Q, et al. Single nucleotide polymorphisms in DNA repair genes and risk of cervical cancer: a case-control study. Oncol Lett 2012;3:351–62.
[35] Smolarz B, Makowska M, Samulak D, et al. Association between polymorphisms of the DNA repair gene RAD51 and ovarian cancer. Pol J Patho 2013;64:290–5.
[36] Malisic EJ, Krivokuca AM, Boljevic IZ, et al. Impact of RAD51 G135C and XRCC1 Arg399Gln polymorphisms on ovarian carcinoma risk in Serbian women. Cancer Biomark 2015;15:685–91.
[37] Manuguerra M, Saletta F, Karagas MR, et al. XRCC3 and XPD/ERCC2 single nucleotide polymorphisms and the risk of cancer: a HuGE review. Am J Epidemiol 2006;164:297–302.
[38] Wang W, Li JL, He XF, et al. Association between the RAD51 135 G>C polymorphism and risk of cancer: a meta-analysis of 19,068 cases and 22,630 controls. PloS One 2013;8:e75153.
[39] Wu L, Long ZG, Dai ZS. 135G/C polymorphism in the RAD51 gene and acute myeloid leukemia risk: a meta-analysis. Genetics and molecular research: GMR 2016;15:1–9.
[40] Kong F, Wu J, Hu L, et al. Association between RAD51 polymorphisms and susceptibility of head and neck cancer: a meta-analysis. Int J Clin Exp Med 2015;8:6412–9.
[41] Zhang BB, Wang DG, Xuan C, et al. Genetic 135G/C polymorphism of RAD51 gene and risk of cancer: a meta-analysis of 28,956 cases and 28,372 controls. Fam Cancer 2014;13:515–26.
[42] Nissar S, Baba SM, Akhtar T, et al. RAD51 G135C gene polymorphism and risk of colorectal cancer in Kashmir. Eur J Cancer Prev 2014; 23:264–8.
[43] Hu X, Sun S. RAD51 Gene 135G/C polymorphism and ovarian cancer risk: a meta-analysis. Int J Clin Exp Med 2015;8:22365–70.
[44] Wang WW, Spurdle AB, Kolachana P, et al. A single nucleotide polymorphism in the 5' untranslated region of RAD51 and risk of cancer among BRCA1/2 mutation carriers. Cancer Epidemiol Biomarkers Prev 2001;10:955–60.