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Research Article

RAD51 135G>C Polymorphism and Cancer Risk: An Updated Meta-Analysis Involving 54,239 Subjects

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Abstract

The *RAD51* plays a pivotal role in homologous recombination repair of DNA double-strand breaks inducing chromosomal breaks and genomic instability. Previous studies yielded conflicting results for the association between *RAD51* 135G>C polymorphism and risk of cancer. The present study aimed at investigating the pooled association using a meta-analysis on the published studies, involving 27,895 cases and 26,344 controls to assess the effect of *RAD51* 135G>C on cancer susceptibility. Across all populations, our results indicated that significant associations were found between *RAD51* 135G>C polymorphism and risk of cancer under genotypic C allele vs. G allele (OR =1.36 95% CI: 1.31-1.41), CC vs. GG (OR =2.37 95% CI: 2.12-2.65), CC vs. CG (OR =4.02 95% CI: 3.62-4.46), recessive model (OR =3.74, 95% CI: 3.40-4.11), and dominant model (OR =1.08, 95% CI: 1.03-1.13). In subgroup analyses, similar associations were found among Caucasians but not Asians. Moreover, the significant associations were found in subgroups of breast cancer, hematologic malignances, colorectal cancer, endometrial cancer, and ovarian cancer. This meta-analysis suggests that the *RAD51* 135G>C polymorphism was associated with susceptibility of cancer. The effect of the variants on the expression levels and the possible functional role of the variants in cancer should be addressed in further studies.

Key words: *RAD51,* Polymorphism, Cancer risk, Meta-analysis

Introduction

Epidemiologic studies reveal a significant environmental contribution to the pathogenesis of cancer [1,2]. Familial aggregation and twin studies indicate that the presence of genetic factors are for susceptibility to this condition [3-5]. A number of genomic screens have been performed to find genetic linkage to cancer [6-8]. The faithful repair of DNA damage such as chromosomal double-strand breaks (DSBs) is crucial for genomic integrity [9]. DSBs may cause chromosomal breaks and genomic instability, thus increasing the probability of developing cancer [10]. Homologous recombination (HR), single-strand annealing and non-homologous end-joining are considered to be the main pathways for repairing the DSBs [11]. Among them, the central HR protein is *RAD51* which ensures high fidelity DNA repair by facilitating strand exchange between damaged and undamaged homologous DNA segments [10]. Thus far, two SNPs (135G/C [rs1801320] and 172G/T [rs1801321]) were discovered in the 5 UTR of *RAD51* [12]. The effect of 135G→C variant on the *RAD51* was alternative splicing within the 5 UTR, while the latter SNP was found to have weak effect [13].

The genetic variations of *RAD51* gene may contribute to the development and progression of cancers [14]. Many original studies have reported the role of *RAD51* 135G>C polymorphism and cancer risk, but the findings are inconclusive [15,16]. Partially, it may due to the fact that the *RAD51* gene was a minor gene for risk of cancers and/or the relatively small sample-size in each published studies. Therefore, we performed this updated meta-analysis to derive a more precise estimation of the association between *RAD51* 135G>C polymorphism and cancer.

Materials and methods

Selection of published studies

Case-control studies reporting the association between the *RAD51* 135G>Cpolymorphisms and risk of cancer published in English before *February 2013* were identified by comprehensive computer-based searches of Medline, EBSCO, and BIOSIS databases. The references of reviews and retrieved articles were also searched simultaneously to find additional eligible studies. The following keywords were used for searching: "*RAD51*" AND ("genetic variant*" or "genetic variation" or "polymorphism*") AND ("cancer" or "carcinoma" or "tumor" or "leukemia" or "laukaemia"). The most complete and recent results were used when there were multiple publications from the same study group.

Two investigators reviewed all identified studies independently to determine whether an individual study was eligible for inclusion. The selection criteria for studies to be considered for this meta-analysis were as follows: 1) case-control or case-cohort study; 2) the *RAD51*135G>Cpolymorphism in cancer; 3) proper cancer diagnosis criteria; 4) original data; 5) not animal studies. The study would be excluded if the information could not be obtained.

Ethical consideration

The study has been approved by the Ethics committee of our Institutions.

Data extraction

The characteristics of selected studies were independently extracted through a standardized protocol by two authors, and the

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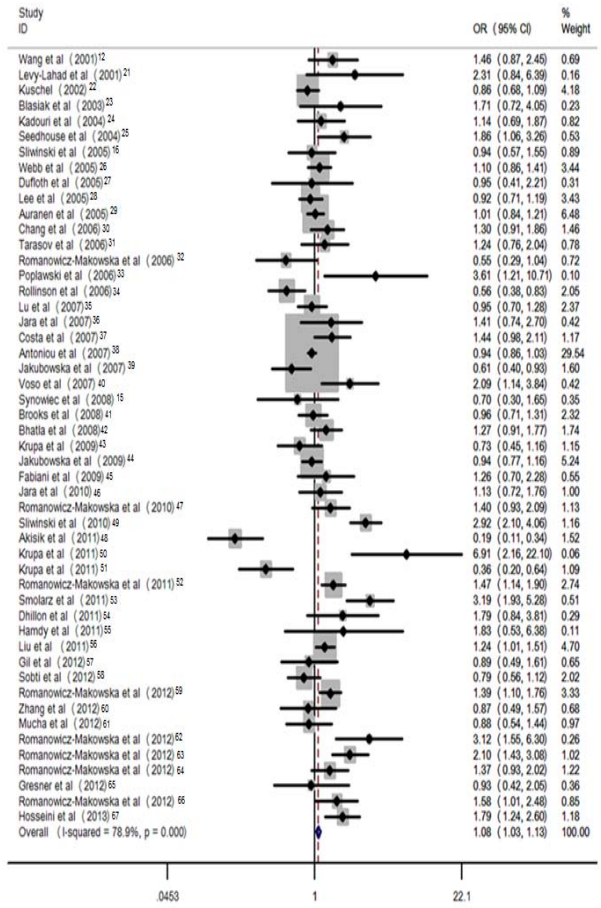

Figure 1: Pooled OR (dominant model) and 95% CI of individual studies and pooled data for the association between polymorphism of *RAD51* 135G>C and cancer risk in overall population.

result was reviewed by a third investigator. The following information was sought from each study: first author, year of publication, study population (country, ethnicity), cancer types, the number of patients and controls for a study, genotype frequency for cases and controls, allele frequency in controls, and Hardy- Weinberg equilibrium (*HWE*).

Statistical analysis

Allele frequencies (-135C) at the *RAD51* polymorphism from each respective study were determined by the allele counting method. Genotype distributions of controls were used to estimate the frequencies of the putative risk allele (-135C) using the inverse variance method [17,18]. The deviation from the Hardy-Weinberg Equilibrium (*HWE*) for distribution of the allele frequencies was analyzed by Fisher's exact test in control groups, $P < 0.05$ was considered as representative of statistically significant. We examined the contrast of the C allele vs. G allele, CC vs. GG, CC vs. CG, and also examined the recessive genetic model (CC vs. CG+GG) and the dominant genetic model (CC+CG vs. GG). The associations between *RAD51* (G135C) polymorphisms and cancer susceptibility were estimated by odds ratios (ORs) with 95% confidence intervals (CIs). The significance of the pooled OR was determined by the Z-test; $P < 0.05$ was considered statistically significant. Furthermore, to evaluate the ethnicity and cancer type-specific effects, subgroup analyses were performed.

Heterogeneity assumption was checked by a Chi-square based *Q* test, and it was considered statistically significant when $P < 0.1$ [19]. Heterogeneity was also quantified with I^2 metric ($I^2 = (Q\text{-}df)/Q \times 100\%$; $I^2 < 25\%$, no heterogeneity; $I^2 = 25\text{-}50\%$, moderate heterogeneity; $I^2 = 50\text{-}75\%$, large heterogeneity, $I^2 > 75\%$, extreme heterogeneity). When the effects were assumed to be homogenous ($P > 0.1$, $I^2 < 50\%$), the fixed-effects model was used; otherwise, the random-effects model was more appropriate. Sensitivity analysis was performed to evaluate the stability of the results. If more than seven studies were included, Begg's test was used to measure the publication bias which was shown as a funnel plot [20]. $P < 0.05$ was considered as representative of statistically significant publication bias. All analyses were performed using the software STATA software, version 12.0 (Stata Corporation, College Station, TX,USA) and R statistical software, version 2.15.2 (http://www.r-project.org).

Results

Characteristics of studies

A total of fifty studies that met the inclusion concerning the association between *RAD51*135G>C polymorphism and risk of cancer were considered in the meta-analysis [12,15,16,21-67]. These studies involved 27,895 patients and 26,344 controls, containing thirty-eight Caucasian, five Asian, and seven mixed studies. In subgroup analysis, thirty-eight Caucasian studies (14,180/12,726) and five Asian studies (1,946/2,945) were included in ethnic-specific group. Additionally, twenty-six (19,716/19,735) studies focusing on breast cancer, seven (2,169/3,629) studies focusing on hematologic malignances, four (753/720) studies focusing on colorectal cancer, three (500/506) studies focusing on endometrial cancer, three (1,085/1,160) studies focusing on head and neck cancer, and two (2,925/1,749) studies focusing on ovarian cancer were also respectively evaluated. 84% (42/50) of these studies included used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis for genotyping. Main characteristics of included studies were listed in Table 1.

Frequency of the C allele in different groups

The pooled *RAD51*-135C frequencies were 17.77 % (95 % CI: 17.29 – 18.25 %), and 32.49 % (95 % CI: 30.66 % – 34.32 %) in the controls of Caucasian, and Asian population. Genotype distributions in the controls of all studies were in agreement with *HWE*, except ten studies [10, 23-25, 27, 39, 48, 49, 58].

Results of meta-analysis

For each study, we investigated the association between the 135G>C polymorphism and risk of cancer. Overall, *RAD51* 135 C allele was associated with a statistically increased risk of cancer, compared with the G allele (OR =1.36 95% CI: 1.31-1.41) under random-effect model. Significant associations were also observed in the genetic models for CC vs. GG (OR =2.37 95% CI: 2.12-2.65), CC vs. CG (OR =4.02 95% CI: 3.62-4.46), recessive model (OR =3.74, 95% CI: 3.40-4.11), and dominant model (OR =1.08, 95% CI: 1.03-1.13, Figure 1.). Z-test indicated that the pooled ORs were statistically significant.

Table 1: Characteristics of the studies included in the meta-analysis.

Study	Year	Country	Ethnicity	Cancer types	Sample size (case/ control)	Genotyping methods	Genotype frequency						*HWE*	Allele frequency	
							Cases			Controls			*P*		
							GGGC	CC		GG	GC	CC		G	C
Wang et al. [12]	2001	America	Mixed	Breast cancer	345/263	PCR-RFLP	299	46*		238	25*		NA	NA	NA
Levy-Lahad et al. [21]	2001	Israel	Caucasian	Breast cancer	167/90	PCR-RFLP	147	20	0	85	5	0	0.79	0.97	0.03
Kuschel et al. [22]	2002	UK	Caucasian	Breast cancer	2,172/840	Taqman	1,904	255	13	722	116	2	0.23	0.93	0.07
Blasiak et al [23]	2003	Poland	Caucasian	Breast cancer	46/60	PCR-RFLP	11	28	7	21	35	4	0.04**	0.64	0.36
Kadouri et al [24]	2004	Israel	Caucasian	Breast cancer	333/260	Taqman ,PCR-RFLP	290	43*		230	30*		NA	NA	NA
Seedhouse et al [25]	2004	UK	Caucasian	AML	257/186	PCR-RFLP	210	44	3	166	18	2	0.08	0.94	0.06
Sliwinski et al [16]	2005	Poland	Caucasian	Breast cancer	150/150	PCR-RFLP	108	38	4	106	41	3	0.67	0.84	0.16
Webb et al [26]	2005	Australia	Mixed	Breast cancer	1,444/788	Taqman	1,221	212	11	676	104	8	0.08	0.92	0.08
Dufloth et al [27]	2005	Brazil	Mixed	Breast cancer	78/119	PCR-RFLP	68	9	1	103	13	3	0.01**	0.92	0.08
Lee et al [28]	2005	Korea	Asian	Breast cancer	782/587	MALDI-TOF	611	143	28	450	123	14	0.11	0.87	0.13
Auranen et al [29]	2005	Multiple	Caucasian	Ovarian cancer	2,805/1,629	Taqman	2,440	355	10	1,419	201	9	0.52	0.93	0.07
Chang et al [30]	2006	China	Asian	Breast cancer	189/421	PCR-RFLP	116	73*		284	137*		NA	NA	NA
Tarasov et al [31]	2006	Russia	Caucasian	Breast cancer	151/191	PCR-RFLP	111	36	4	148	41	2	0.65	0.88	0.12
Romanowicz-Makowska et al[32]	2006	Poland	Caucasian	Breast cancer	100/106	PCR-RFLP	31	40	29	21	48	37	0.45	0.42	0.58
Poplawski et al [33]	2006	Poland	Caucasian	Gastric cancer	28/33	PCR-RFLP	13	15	0	25	6	2	0.09	0.85	0.15
Rollinson et al [34]	2006	UK	Caucasian	AML	466/936	Taqman	431	34	1	817	115	4	0.98	0.93	0.07
Lu et al [35]	2007	USA	Caucasian	HNC	716/719	PCR-RFLP	624	91	1	622	96	1	0.17	0.93	0.07
Jara et al [36]	2007	Chile	Mixed	Breast cancer	131/247	PCR-RFLP	113	16	2	222	25	0	0.40	0.95	0.05
Costa et al [37]	2007	Portugal	Caucasian	Breast cancer	285/646	PCR-RFLP	216	45	4	558	86	2	0.49	0.93	0.07
Antoniou et al [38]	2007	UK	Mixed	Breast cancer	8,893/8,145	Taqman, PCR-RFLP .etc	7,683	1,134	76	6,977	1,130	38	0.28	0.93	0.07
Jakubowska et al [39]	2007	Poland	Caucasian	Breast cancer	258/258	PCR-RFLP	210	48*		188	70*		NA	NA	NA
Voso et al [40]	2007	Italy	Caucasian	AML	160/161	PCR-RFLP	125	33	2	142	18	1	0.61	0.94	0.06
Synowiec et al [15]	2008	Poland	Caucasian	Breast cancer	41/48	PCR-RFLP	18	10	13	17	27	4	0.14	0.64	0.36
Brooks et al [41]	2008	America	Mixed	Breast cancer	611/611	PCR-RFLP	516	88	7	513	88	10	0.01**	0.91	0.09
Bhatla et al [42]	2008	America	Caucasian	AML	452/646	Taqman	374	73	5	555	85	6	0.18	0.92	0.08
Krupaet al [43]	2009	Poland	Caucasian	Breast cancer	135/175	PCR-RFLP	91	33	11	105	63	7	0.52	0.78	0.22
Jakubowska et al [44]	2009	Poland	Caucasian	Breast cancer	1,007/1,069	Simple probe	785	207	15	822	232	15	0.76	0.88	0.12
Fabiani et al [45]	2009	Italy	Caucasian	MDS	159/160	PCR-RFLP	130	28	1	136	21	3	0.06	0.92	0.08
Jara et al [46]	2010	Chile	Mixed	Breast cancer	267/500	PCR-RFLP	232	33	2	441	58	1	0.53	0.94	0.06
Romanowicz-Makowska et al[47]	2010	Poland	Caucasian	Breast cancer	220/220	PCR-RFLP	141	69	10	157	58	5	0.90	0.85	0.15
Sliwinski et al [49]	2010	Poland	Caucasian	HNC	288/354	PCR-RFLP	138	145	5	258	64	32	0.00**	0.82	0.18
Akisik et al [48]	2011	Turkey	Caucasian	Breast cancer	147/120	PCR-RFLP	125	20	2	62	57	1	0.00**	0.75	0.25
Krupa et al [50]	2011	Poland	Caucasian	Endometrial cancer	30/30	PCR-RFLP	6	8	16	19	9	2	0.52	0.78	0.22
Krupa et al [51]	2011	Poland	Caucasian	Colorectal cancer	100/100	PCR-RFLP	61	36	3	36	35	29	0.00**	0.53	0.47
Romanowicz-Makowska et al[52]	2011	Poland	Caucasian	Breast cancer	700/708	PCR-RFLP	130	74	496	178	396	134	0.00**	0.53	0.47
Smolarz et al [53]	2011	Poland	Caucasian	Endometrial cancer	240/240	PCR-RFLP	25	30	185	65	138	37	0.01**	0.56	0.44
Dhillon et al [54]	2011	Australia	Caucasian	Prostate cancer	116/132	PCR-RFLP	97	18	1	119	13	0	0.55	0.95	0.05
Hamdy et al [55]	2011	Egypt	Caucasian	AML	50/130	PCR-RFLP	39	9	2	26	3	1	0.06	0.92	0.08
Liu et al [56]	2011	China	Asian	AML	625/1,510	PCR-RFLP	421	187	17	1085	393	32	0.61	0.85	0.15
Gil et al [57]	2012	Poland	Caucasian	Colorectal cancer	133/100	PCR-RFLP	100	29	4	73	27	0	0.12	0.86	0.14
Sobti et al [58]	2012	India	Asian	Bladder cancer	270/252	PCR-RFLP	159	82	29	134	81	37	0.00**	0.69	0.31
Romanowicz-Makowska et al[59]	2012	Poland	Caucasian	Breast cancer	790/798	Taqman	160	104	526	208	426	164	0.05	0.53	0.47
Zhang et al [60]	2012	China	Asian	Cervical cancer	80/175	PCR-RFLP	58	20	2	122	50	3	0.41	0.84	0.16
Mucha et al [61]	2012	Poland	Caucasian	Colorectal cancer	200/200	PCR-RFLP	161	34	5	157	37	6	0.05	0.88	0.12
Romanowicz-Makowska et al[62]	2012	Poland	Caucasian	Ovarian cancer	120/120	PCR-RFLP	13	15	92	33	69	18	0.07	0.56	0.44
Romanowicz-Makowska et al[63]	2012	Poland	Caucasian	Colorectal cancer	320/320	PCR-RFLP	51	56	213	91	164	65	0.57	0.54	0.46
Romanowicz-Makowska et al[64]	2012	Poland	Caucasian	Larynx cancer	253/253	PCR-RFLP	174	69	10	190	58	5	0.82	0.87	0.13
Gresner et al [65]	2012	Poland	Caucasian	HNC	81/87	PCR-RFLP	67	13	1	71	14	2	0.22	0.90	0.10
Romanowicz-Makowska et al[66]	2012	Poland	Caucasian	Endometrial cancer	230/236	PCR-RFLP	40	25	165	59	132	45	0.06	0.53	0.47
Hosseini et al [67]	2013	Iran	Caucasian	Breast cancer	294/315	PCR-RFLP	203	77	14	252	42	21	0.00**	0.87	0.13

MALDI-TOF: matrix-assisted laser desorption/ionization time-of-flight; AML: acute myelogenous laukaemia; MDS: myelodyplastic syndrome; HNC: head and neck cancer; *HWE*: Hardy-Weinberg equilibrium; NA: not available.

* Number of GC+CC;

**Deviated from *HWE*.

Table 2: Summary odds ratios (ORs) of the *RAD51* 135G/C polymorphism and cancer risk.

Subgroup	Genetic model	Sample size		Test of heterogeneity			Test of association				Test of publication bias	
		Patients	Controls	Q	*P*	I^2 (%)	OR	95 % CI	Z	*P*	z	*P*
Overall	C vs. G	27,895	26,344	819.75	0.000	94.5	1.358	1.306-1.413	15.26	1.41e-52	1.73	0.083
	CC vs. GG			272.50	0.000	83.9	2.368	2.124-2.646	15.51	2.97e-54	0.92	0.358
	CC vs. CG			602.93	0.000	92.7	4.019	3.621-4.461	26.15	9.86e-151	1.26	0.207
	Recessive model			503.67	0.000	91.3	3.735	3.398-4.106	27.33	1.87e-164	1.41	0.159
	Dominant model			231.83	0.000	78.9	1.081	1.033-1.131	3.34	0.001	1.26	0.207
Ethnicities												
Caucasian	C vs. G	14,180	12,726	658.71	0.000	94.7	1.672	1.588-1.760	19.61	1.27e-85	0.87	0.383
	CC vs. GG			211.46	0.000	83.9	2.867	2.531-3.247	16.55	1.6-e-61	-0.33	0.744
	CC vs. CG			467.55	0.000	92.7	5.280	4.682-5.955	27.13	4.36e-162	-0.26	0.798
	Recessive model			367.60	0.000	90.8	4.741	4.264-5.272	28.76	6.79e-182	-0.10	0.921
	Dominant model			206.26	0.000	82.1	1.163	1.092-1.240	4.69	2.73e-06	0.79	0.428
Asian	C vs. G	1,946	2,945	7.11	0.069	57.8	1.030	0.913-1.163	0.49	0.626	—	—
	CC vs. GG			4.74	0.192	36.7	1.050	0.752-1.465	0.29	0.775	—	—
	CC vs. CG			3.26	0.353	8.0	1.111	0.785-1.573	0.59	0.553	—	—
	Recessive model			4.19	0.242	28.4	1.056	0.761-1.465	0.33	0.743	—	—
	Dominant model			7.87	0.096	49.2	1.063	0.934-1.211	0.92	0.355	—	—
Mixed	C vs. G	11,769	10,673	3.47	0.628	0.0	0.992	0.923-1.066	0.22	0.826	—	—
	CC vs. GG			8.31	0.140	39.9	1.485	1.077-2.048	2.41	0.016	—	—
	CC vs. CG			9.29	0.098	46.2	1.565	1.127-2.173	2.67	0.008	—	—
	Recessive model			8.52	0.130	41.3	1.494	1.084-2.060	2.45	0.014	—	—
	Dominant model			5.69	0.459	0.0	0.977	0.905-1.054	0.61	0.544	—	—
Cancer types												
Breast cancer	C vs. G	19,716	17,735	384.67	0.000	94.5	1.322	1.260-1.388	11.29	1.47e-29	1.55	0.121
	CC vs. GG			110.31	0.000	81.9	2.357	2.051-2.708	12.09	1.19e-33	1.57	0.116
	CC vs. CG			355.80	0.000	94.4	4.087	3.578-4.668	20.74	1.51e-95	1.81	0.070
	Recessive model			257.41	0.000	92.2	3.733	3.308-4.211	21.39	1.66e-101	2.11	0.035
	Dominant model			95.07	0.000	73.7	1.063	1.006-1.123	2.18	0.029	0.37	0.708
Hematologic malignances	C vs. G	2,169	3,629	19.67	0.003	69.5	1.157	1.020-1.313	2.27	0.023	—	—
	CC vs. GG			2.29	0.891	0.0	1.193	0.750-1.896	0.74	0.457	—	—
	CC vs. CG			1.82	0.935	0.0	0.945	0.583-1.530	0.23	0.817	—	—
	Recessive model			2.08	0.913	0.0	1.133	0.713-1.799	0.53	0.598	—	—
	Dominant model			20.73	0.002	71.1	1.181	1.027-1.357	2.34	0.020	—	—
Colorectal cancer	C vs. G	753	720	108.62	0.000	97.2	1.615	1.366-1.910	5.60	2.14e-08		
	CC vs. GG			54.38	0.000	94.5	2.063	1.484-2.869	4.31	1.63e-05	—	—
	CC vs. CG			56.03	0.000	94.6	3.739	2.716-5.146	8.09	5.97e-16	—	—
	Recessive model			64.64	0.000	95.4	3.209	2.426-4.246	8.16	3.36e-16	—	—
	Dominant model			26.55	0.000	88.7	1.064	0.840-1.348	0.51	0.608	—	—
Endometrial cancer	C vs. G	500	506	6.68	0.035	70.1	4.963	4.068-6.054	15.79	3.65e-56	—	—
	CC vs. GG			6.49	0.039	69.2	8.503	5.859-12.342	11.26	2.07e-29	—	—
	CC vs. CG			1.07	0.585	0.0	20.243	13.984-29.303	15.94	3.34e-57	—	—
	Recessive model			2.80	0.246	28.6	13.961	10.246-19.022	16.70	1.31e-62	—	—
	Dominant model			7.69	0.021	74.0	2.392	1.741-3.287	5.38	7.45e-08	—	—
HNC	C vs. G	1,085	1,160	17.64	0.000	88.7	0.701	0.554-0.887	2.96	0.003	—	—
	CC vs. GG			0.17	0.921	0.0	0.785	0.188-3.280	0.33	0.740	—	—
	CC vs. CG			1.83	0.400	0.0	1.501	0.375-6.019	0.57	0.566	—	—
	Recessive model			0.42	0.810	0.0	0.952	0.234-3.880	0.07	0.945	—	—
	Dominant model			24.08	0.000	91.7	0.672	0.524-0.862	3.12	0.002	—	—
Ovarian cancer	C vs. G	2,925	1,749	62.53	0.000	98.4	1.334	1.140-1.562	3.60	3.18e-04	—	—
	CC vs. GG			23.34	0.000	95.7	3.228	1.840-5.662	4.09	4.31e-05	—	—
	CC vs. CG			35.80	0.000	97.2	5.212	3.086-8.804	6.17	6.83e-10	—	—
	Recessive model			34.97	0.000	97.1	5.500	3.370-8.977	6.82	9.10e-12	—	—
	Dominant model			9.31	0.002	89.3	1.094	0.917-1.303	1.00	0.318	—	—
Others	C vs. G	747	845	11.31	0.023	64.6	1.044	0.869-1.255	0.46	0.645	—	—
	CC vs. GG			5.05	0.282	20.8	0.885	0.567-1.381	0.54	0.591	—	—
	CC vs. CG			4.30	0.367	6.9	0.896	0.560-1.435	0.46	0.648	—	—
	Recessive model			4.83	0.306	17.1	0.884	0.573-1.364	0.56	0.577	—	—
	Dominant model			11.42	0.022	65.0	1.098	0.882-1.367	0.84	0.402	—	—

Note: Hematologic malignances: laukaemia and myelodyplastic syndrome; HNC: head and neck cancer.

In stratified analyses of ethnicity, a significantly increased risk was observed in Caucasians for C vs. G (OR =1.67 95% CI: 1.59-1.76), and in the genetic models for CC vs. GG (OR =2.87 95% CI: 2.53-3.25), CC vs. CG (OR =5.28 95% CI: 4.68-5.96), recessive model (OR=4.74, 95% CI: 4.26-5.27) and dominant model (OR=1.16, 95% CI 1.09-1.24, Figure 2.). Significant associations were not found in Asian population (C vs. G OR =1.03 95% CI: 0.91-1.16; CC vs. GG OR=1.05, 95% CI 0.75-1.47; CC vs. CG OR=1.11, 95% CI 0.79-1.57; recessive model OR=1.06, 95% CI 0.76-1.47 and dominant model OR=1.06, 95% CI 0.93-1.21).

Additionally, the significant associations were found in the cancer subtypes including the breast cancer (C vs. G OR =1.32 95% CI: 1.26-1.39; CC vs. GG OR=2.36, 95% CI 2.05-2.71; CC vs. CG OR=4.09, 95% CI 3.58-4.67; recessive model OR=3.73, 95% CI 3.31-4.21; and dominant model OR=1.06, 95% CI 1.01-1.12, Figure 3.), hematologic malignances (C vs. G OR =1.16 95% CI: 1.02-1.31; dominant model OR=1.18, 95% CI 1.03-1.36), colorectal cancer (C vs. G OR =1.62 95% CI: 1.37-1.91; CC vs. GG OR=2.06, 95% CI 1.48-2.87; CC vs. CG OR=3.74, 95% CI 2.72-5.15; recessive model OR=3.21, 95% CI 2.43-4.25), endometrial cancer (C vs. G OR =4.96 95% CI: 4.07-6.05; CC vs. GG OR=8.50, 95% CI 5.86-12.34; CC vs. CG OR=20.24, 95% CI 13.98-29.30; recessive model OR=13.96, 95% CI 10.25-19.02, and dominant model OR=2.39, 95% CI 1.74-3.29), and ovarian cancer (C vs. G OR =1.33 95% CI: 1.14-1.56; CC vs. GG OR=3.23, 95% CI 1.84-5.66; CC vs. CG OR=5.21, 95% CI 3.09-8.80; recessive model OR=5.50, 95% CI 3.37-8.98). The detailed results of meta-analysis were shown in Table 2.

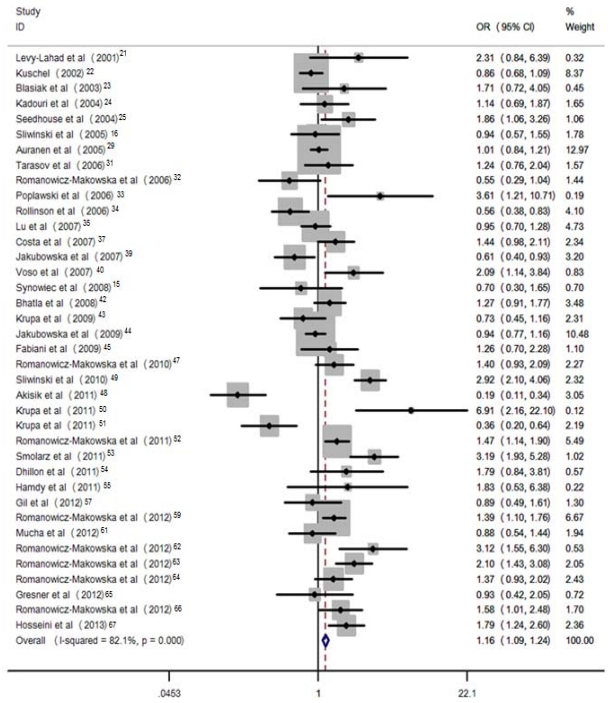

Figure 2: Pooled OR (dominant model) and 95% CI of individual studies and pooled data for the association between polymorphism of *RAD51* 135G>C and cancer risk in Caucasian population.

Sensitivity analysis

We conducted sensitivity analysis to evaluate the stability of the crude results which pooled with random-effects model. When any single study was deleted, the corresponding pooled ORs were not substantially altered (data not shown), suggesting that the results of this meta-analysis are stable.

Publication bias

Begg's test and a funnel plot were performed to assess the publication bias of the literature. The results indicated that no evidence of publication bias was detected in all the genetic models except for the recessive model in the breast cancer subgroup (Table 2, Figure 4A-C.).

Discussion

In the present study, we explored the association between the *RAD51* 135G>C polymorphism and cancer risk, involving fifty eligible case-control studies. In this meta-analysis, we collected a larger sample volume and examined the contrast of the C vs. G, CC vs. GG, CC vs. CG and also examined the recessive genetic model and the dominant genetic model. Furthermore, to evaluate the ethnicity and the disease based subtype-specific effects, subgroup analyses were performed. Our results indicated that the prevalence of the C allele varied from 17.77 % to 32.49 % in different ethnic groups and individuals with the C allele have an increased risk of cancer in Caucasian population, but not in Asian population. In stratified analysis by cancer types, the significantly elevated risks with CC genotype were also found among breast cancer, hematologic

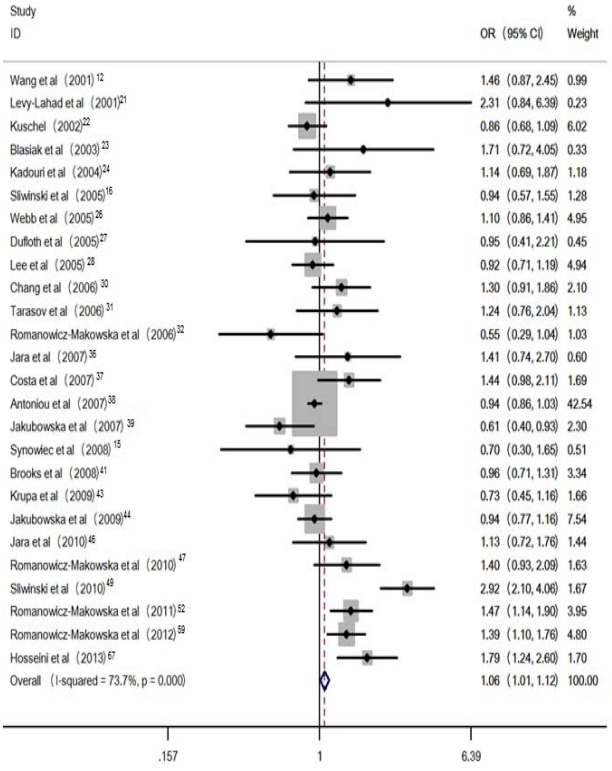

Figure 3: Pooled OR (dominant model) and 95% CI of individual studies and pooled data for the association between polymorphism of *RAD51* 135G>C and breast cancer risk in cancer subgroup analysis.

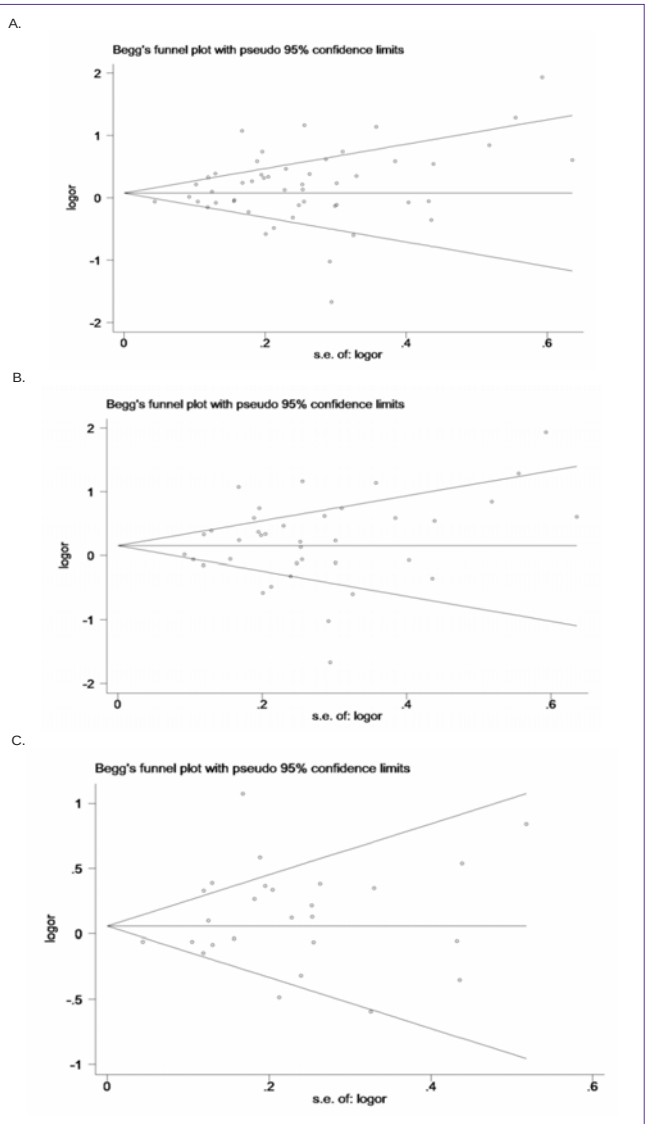

Figure 4: Funnel plot of the *RAD51* 135G>C polymorphism and cancer risk in (A) overall population in dominant model (z = 1.26, *P* = 0.207), (B) Caucasian population in dominant model (z = 0.79, *P* = 0.428), (C) breast cancer (z = 0.37, *P* = 0.708) in dominant model.

malignances, colorectal cancer, endometrial cancer, and ovarian cancer.

RAD51 is a homologue of Escherichia coli recA protein, which is responsible for the central activity of the HR repair pathway. It catalyzes the invasion of the broken ends of the DSBs into the intact sister chromatid [68,69] The *RAD51* gene containing 10 exons has been mapped to chromosome 15q15.1 [70]. The G>C polymorphism of 135-loci in *RAD51* gene locating in the 5'UTR could affect mRNA stability, translation efficiency, protein level and finally influence the risk of cancer [71].

To date, a number of studies were performed to detect the association between *RAD51* 135G>C polymorphism and cancer risk. In order to evaluate the association in a larger population, some meta-analyses were performed to evaluate the association [72-75]. However, these previous meta-analyses have limitations in relatively small sample sizes and/or limited cancer type-specific analysis using the limited genetic models. Therefore, it is essential for us to perform a new updated meta-analysis to evaluate this association. Comparing with them, our study has some improvements. First, we enlarged the sample-size including all the cancer types. Second, we performed a more comprehensive data analysis including four different genetic models. Third, we made the subgroup analysis of ethnicity, cancer types. This is the first time to evaluate the relationships between RAD51 135G>C polymorphism and so many cancer types. Previous meta-analyses were carried out to assess the effect of RAD51 135G>C polymorphism on either the risk of breast cancer, or several limited cancer types only.

Though the results of this meta-analysis were powerful, some limitations still exist. First, it is clear that environmental factors play an important role in the etiology of cancer. However, the percentage of cancer caused by environmental factors is difficult to determine. The existence of gene-environment and gene-gene interactions may affect the accuracy of our results. Second, in the subgroup analyses, the involving number of population in Asians and other cancer types except for breast cancer were relatively small which may affect to explore the real associations. Third, this meta-analysis only focused on papers published in the English language and those which were reported in other languages might bias the present results. Fourth, the significance of heterogeneity among studies was observed. We pooled ORs with random-effects model in this condition. Sensitivity analysis suggested that the results of this meta-analysis are stable. Fifth, in our study, the studies including the number of GC+CC and GG only were also included, while they were deleted in some other meta-analysis. Finally, in our meta-analyses, we found the distribution of genotypes among controls was not agreement with *HWE* in some studies, which were included in this study. This may be due to chance, because studies with small sample size and selection bias may also contribute to the disaccord of *HWE* which may influence the risk effects. Other factors like differences in gene-gene and gene-environment interactions from different genetic backgrounds and different matching criteria may also play a role in the discrepancy. In spite of these, when studies not in *HWE* were corrected to account for departures from *HWE*, then the pattern of results remained the same. And the result was also consistent with the most recently published meta-analysis [75], which excluded the studies in which genotype frequencies in controls were not in accordance with HWE. Besides, our publication bias tests indicated there was no publication bias in *RAD51* 135G>C polymorphism, and it is likely to be reliable.

In conclusion, our result revealed that the C allele in 135-loci of *RAD51* gene was associated with a significantly increased risk of cancers including breast cancer, hematologic malignances, colorectal cancer, endometrial cancer and ovarian cancer. The increased cancer risk was detected among Caucasian population, but not among Asian population. The effect of the variants on the expression levels and the possible functional role of the variants in cancer should be addressed in further studies.

Conflicts of Interest: We declare that there are no competing interests regarding the contents of this article.

Contributions

C.X. designed the study. C.X and B.B.Z. performed the literature search, data collection and data analysis. K.F.D, G.G. and L.M.L performed data gathering and quality assessment. All authors wrote and approved the manuscript.

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