Analysis of the association between the XRCC2 rs3218536 polymorphism and ovarian cancer risk

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Abstract

Introduction: Results conflict on the association between the XRCC2 rs3218536 polymorphism and ovarian cancer risk, despite wide-ranging investigations. This meta-analysis examines whether the XRCC2 rs3218536 polymorphism is associated with ovarian cancer risk.

Material and methods: Eligible case-control studies were searched in PubMed. We therefore performed a meta-analysis of 5,802 ovarian cancer cases and 9,390 controls from 7 articles published. The strength of association between XRCC2 rs3218536 polymorphism and ovarian cancer susceptibility was calculated using pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

Results: No statistically significant associations between XRCC2 rs3218536 polymorphism and ovarian cancer risk were found in any genetic models. However, a significant relationship with ovarian cancer risk was discovered when the high quality studies were pooled in the meta-analysis (AA vs. GG: OR = 0.59, 95% CI: 0.37–0.94, p = 0.03; GA vs. GG: OR = 0.87, 95% CI: 0.78–0.96, p = 0.009; GA + AA vs. GG: OR = 0.85, 95% CI: 0.77–0.94, p = 0.003; AA vs. GG + GA: OR = 0.60, 95% CI: 0.38–0.95, p = 0.03).

Conclusions: This meta-analysis shows that the XRCC2 rs3218536 polymorphism was associated with ovarian cancer risk overall for high quality studies. Non-Caucasian groups and high quality studies should be further studied.

Key words: ovarian cancer, XRCC2, gene polymorphism, meta-analysis.

Introduction

Ovarian cancer is the leading cause of death from gynecologic cancer in the developed world, with over 220,000 new cases and 140,000 deaths worldwide in 2008 [1–3]. Ovarian cancer is also a multifactorial disease, as is true of most carcinomas. Genetic factors play an important role in ovarian cancer susceptibility [2, 4].

The genetic factors responsible for ovarian carcinogenesis have been investigated in many studies. MLH1, MSH2, BRCA1, BRCA2, LIN28B, CASP8, SMAD6, RAD51C, RAD51D, RB1, MTDH, and GADD45A have all been implicated in ovarian cancer [1, 5–13]. Three genome-wide association studies (GWAS) have revealed a strong association between ovari-

an cancer risk and several common susceptibility alleles in four loci [2, 14–16]. The examination of genetic polymorphisms may explain individual differences in cancer risk [17]. However, the results of the three GWAS were not unanimous. Thus, further investigation is required to identify the genes that are associated with a predisposition to ovarian cancer [1, 10].

XRCC2 (X-ray repair cross-complementing group 2), located at 7q36.1, is a functional candidate gene in neoplasia [18, 19]. XRCC2/3 interacts with and stabilizes Rad51, and takes part in the HRR (homologous recombination repair) of DNA DBSs (double-strand breaks) and in cross-link repair in mammalian cells [20–22]. XRCC2 polymorphism has been associated with the risk of many cancers, such as breast cancer, prostate cancer, gastric cancer, and thyroid carcinoma [23–27].

Although the association between XRCC2 polymorphism and ovarian cancer has been studied [28–35], the experimental results remain inconclusive. Furthermore, while meta-analyses of XRCC2 polymorphism and ovarian cancer risk have also been performed [8, 19, 25, 36, 37], the results need to be supplemented. To examine the effect of XRCC2 polymorphism on ovarian cancer risk, we performed a meta-analysis.

Material and methods

Search and selection process

We performed the meta-analysis by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [38]. We searched the PubMed database using combinations of the following keywords: "XRCC2", "X-ray repair cross-complementing group 2", "rs3218536", "Arg188His", "R188H", "ovarian cancer", and "polymorphism". Two authors, Yuan and Yan, independently examined the retrieved references to evaluate their appropriateness for inclusion in this meta-analysis. In addition, we investigated all of the references cited in the articles and the relevant reviews. If an article reported results that included a number of studies, each study was treated as a separate comparison in our meta-analysis.

Included studies required the following 3 criteria:

1) Evaluated XRCC2 polymorphism and ovarian cancer risk;
2) Provided sufficient data (i.e., a detailed number of genotypes in both the case and control groups);
3) Included case-control studies.

Data extraction

The data were independently extracted from selected articles according to the pre-specified criteria by the two authors (Yuan and Wang). All of the necessary information, if available, was extracted from each study, including the first author, publication year, country, area of the cases, ethnicity, cases' source, controls' source, sample type of the cases, the total number of cases and controls, and the genotype distributions of XRCC2 in both the cases and controls [39]. Disagreements were resolved by joint review and consensus.

Quality score assessment

Eleven studies were independently evaluated by two authors according to a previously established scale for quality assessment (Table I) [2, 40]. The quality score assessment was carried out according to the following criteria: "source of cases", "source of controls", "specimens of cases for determining genotypes", "Hardy-Weinberg equilibrium in controls" and "total sample size". The total scores ranged from 0 (worst) to 15 (best). Studies scoring ≥ 10 were defined as "high quali-

Table I. Scale for quality assessment

Criteria	Score
Source of cases:	
Population or cancer registry	3
Mixed (hospital and cancer registry)	2
Hospital	1
Other	0
Source of controls:	
Population-based	3
Volunteers or blood bank	2
Hospital-based (cancer-free patients)	1
Not described	0
Specimens of cases for determining genotypes:	
Blood or normal tissues	3
Mixed (blood and archival paraffin blocks)	1
Tumor tissues or exfoliated cells of tissue	0
Hardy-Weinberg equilibrium in controls:	
Hardy-Weinberg equilibrium	3
Hardy-Weinberg disequilibrium	0
Total sample size:	
≥ 1000	3
≥ 500 and < 1000	2
≥ 200 and < 500	1
< 200	0

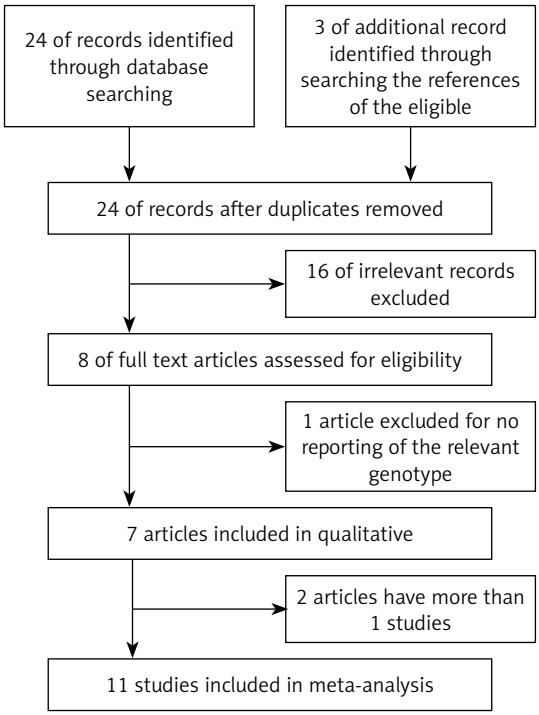

Figure 1. Study flowchart explaining the selection of the five articles included in the meta-analysis

ty", while those scoring < 10 were defined as "low quality" [2, 40, 41].

Statistical analysis

We pooled ORs with 95% CIs, according to the genotype frequencies of the case and control groups, to assess the strength of the association between the XRCC2 polymorphism and ovarian cancer susceptibility [42]. A *p*-value < 0.05 was considered statistically significant. All of the tests and CIs were two-sided. If the heterogeneity was significant, the pooled ORs were initially measured using the random effects model. Otherwise, the fixed effects model was chosen [41, 43].

XRCC2 polymorphism and ovarian cancer risk analysis was carried out for a homozygote comparison (AA vs. GG), a heterozygote comparison (GA vs. GG), a dominant genetic model (GA + AA vs. GG), and a recessive genetic model (AA vs. GG + GA). In addition, a sensitivity analysis was carried out by omitting each study. Publication bias was examined using a funnel plot. The degree of asymmetry was estimated by Egger's test ($p < 0.05$ was considered significant publication bias) [2] [44, 45]. The analysis was completed using Review Manager statistical software (RevMan version 5.0.17.0, The Nordic Cochrane Center, Rigshospitalet, Copenhagen, Denmark) and STATA software (version 11.2, Stata Corporation, College Station, TX, USA). Hardy-Weinberg equilibrium (HWE) was calculated using a web-based statistical tool (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) [2].

Results

Study characteristics

Through the article search, we found 24 articles. Of these articles, we excluded 16 because the studies were irrelevant. We also excluded one article [32] because the study did not report the relevant genotype frequencies. Although we contacted the study's authors for the genotype frequencies, we did not obtain the genotype frequencies of rs3218536 from that article. Thus, a total of 7 articles included 11 studies [28, 30, 31, 33–35, 46] of 5,802 ovarian cancer cases and 9,390 controls. The study flowchart is shown in Figure 1. The 7 articles were all published in English. The characteristics of the 11 studies from the 7 articles are summarized in Table II. The subjects in 10 of the studies [28, 30, 31, 33, 35, 46] were Caucasian. In the 1 other study, Caucasians comprised 94% of the mixed subject group [34]. Thus, most of the subjects in these 11 studies were Caucasian. The sample sizes, including cases and controls, ranged from 100 to 1,811, and the total sample sizes ranged from 200 to 3,124. The quality scores for the individual studies ranged from 5 to 12. The quality scores for 8 of the studies (72.7%) were classified as high quality (≥ 10).

The distribution of the XRCC2 rs3218536 polymorphism genotype frequencies among the ovarian cancer cases and controls from the 11 studies is shown in Table III. A Hardy-Weinberg disequilibrium of genotype frequencies among the controls was calculated in 11 studies [28, 30, 31, 33–35, 46]. In 7 studies [31, 33–35], the genotype distribution among the control groups was in agreement with HWE ($p > 0.05$). In 3 studies [28, 30, 35], the genotype distribution among the control groups was not in agreement with HWE ($p < 0.05$). In 1 study [46], the genotype distribution among the control groups was not estimable.

Meta-analysis results

The meta-analysis results of the XRCC2 rs3218536 polymorphism are shown in Tables III and IV, and Figure 2. When all 11 studies were pooled in the meta-analysis, no statistically significant associations between the XRCC2 rs3218536 polymorphism and ovarian cancer risk were found in any of the genetic models (AA vs. GG: OR = 0.96, 95% CI: 0.36–2.53, $p = 0.94$; GA vs. GG: OR = 0.80, 95% CI: 0.62–1.02, $p = 0.07$; GA + AA vs. GG: OR = 0.95, 95% CI: 0.79–1.14, $p = 0.57$; AA vs. GG + GA: OR = 0.90, 95% CI: 0.43–1.89, $p = 0.78$). However, when the high quality studies were pooled in the meta-analysis, a significant relationship with ovarian cancer risk was discovered (AA vs. GG:

Table II. Main characteristics of the 11 studies included in the meta-analysis

First author	Year	Country	Area of the cases	Ethnicity	Cases source	Controls source	Sample type of cases	Total cases/ controls	Quality score
Auranen-1	2005	UK	East Anglia and West Midlands	Caucasian	Cancer registry	Population	Blood	729/842	12
Auranen-2	2005	Denmark	Denmark	Caucasian	Population	Population	Blood	269/561	11
Auranen-3	2005	USA	Northern California	Caucasian	Cancer registry	Population	Blood	315/404	11
Auranen-4	2005	UK	United Kingdom	Caucasian	Hospital & cancer registry	Population	Blood	275/1811	11
Beesley-1	2007	Australia	New South Wales, Victoria, and Queensland	Caucasian	Cancer registry	Population	Blood	486/969	12
Beesley-2	2007	Australia	New South Wales and Victorian Cancer Registries	Caucasian	Cancer registry	Population	Blood	923/818	12
Jakubowska	2010	Poland	Poland	Caucasian	Cancer registry	Hospital	Blood	144/280	8
Michalska	2016	Poland	Institute of Polish Mother's Memorial Hospital, Lodz,	Caucasian	Hospital	Hospital	FFPE	700/700	5
Mohamed	2013	Egypt	Zagazig University Hospital at Sharkia	Caucasian	Hospital	Hospital	Blood	100/100	6
Quaye	2009	DK & UK & US	MALOVA from Denmark, SEARCH from UK, and GEOCS from USA	Caucasian	Hospital & cancer registry	Population	Blood	1337/1787	11
Webb	2005	Australia	Queensland	Mixed (Caucasian was 94%)	Hospital & cancer registry	Population	Blood	524/1118	11

OR = 0.59, 95% CI: 0.37–0.94, p = 0.03; GA vs. GG: OR = 0.87, 95% CI: 0.78–0.96, p = 0.009; GA + AA vs. GG: OR = 0.85, 95% CI: 0.77–0.94, p = 0.003; AA vs. GG + GA: OR = 0.60, 95% CI: 0.38–0.95, p = 0.03).

Sensitivity analysis and publication bias

In the sensitivity analysis, we omitted a single study from the pooled OR of the meta-analysis each time [41]. The exclusion of the low quality studies significantly modified the heterogeneity and results of the meta-analysis.

We checked the publication bias by using both Begg's funnel plot and Egger's test. The shapes of the four Begg's funnel plots for all 11 studies showed no obvious asymmetry (Figure 3). The shapes of the four Begg's funnel plots for the 8 high quality studies also showed no obvious asymmetry (Figure 4). The Egger's test of the 8 high quality studies showed no significant publication bias for any of the genetic models (data not shown).

Discussion

The XRCC2 gene plays a crucial role in homologous recombination repair and cross-link repair [20–22]. Studies have shown that the XRCC2 rs3218536 polymorphism is associated with the risk of many cancers, including prostate cancer, breast cancer, and gastric cancer [23–27]. The association between the XRCC2 rs3218536 polymorphism and the risk of ovarian cancer has been extensively studied. A 2015 meta-analysis study reported on the association between the rs3218536 polymorphism and ovarian cancer risk [36]. However, that study did not include all of the studies related to the association between the rs3218536 polymorphism and ovarian cancer risk. In 2015, another study also reported on the association between the rs3218536 polymorphism and ovarian cancer risk [28]. However, those results were inconsistent. Therefore, we performed a meta-analysis of 5,802 ovarian cancer cases and 9,390 controls from 7 published articles and 11 case-control studies.

There were no statistically significant associations between the rs3218536 polymorphism and ovarian cancer risk in any of the genetic models that included all 11 studies. However, a significant relationship with ovarian cancer risk was discovered when the 8 high quality studies were pooled. Thus, the low quality studies seriously interfered with the meta-analysis results. The quality of the study was crucial for detecting a significant relationship between ovarian cancer risk and genetic polymorphisms. Furthermore, most of the subjects were Caucasian [28, 30, 31, 33–35, 46], so further studies may be needed to explore the possible re-

Table III. Distribution of the XRCC2 rs3218536 genotype among ovarian cancer cases and controls included in the meta-analysis

First author	Year	Genotype distribution (case source)			Genotype distribution (controls source)			P-HWE (controls)	AA vs. GG		GA vs. GG		GA + AA vs. GG		AA vs. GG + GA	
		GG	GA	AA	GG	GA	AA		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Auranen-1	2005	629	98	2	704	129	9	0.29	0.25 (0.05–1.16)	0.054	0.85 (0.64–1.13)	0.26	0.81 (0.61–1.07)	0.14	0.25 (0.05–1.18)	0.06
Auranen-2	2005	238	31	0	484	75	2	0.6	0.41 (0.02–8.50)	0.32	0.84 (0.54–1.31)	0.45	0.82 (0.52–1.28)	0.38	0.42 (0.02–8.68)	0.33
Auranen-3	2005	260	54	1	331	68	5	0.5	0.25 (0.03–2.19)	0.18	1.01 (0.68–1.50)	0.96	0.96 (0.65–1.41)	0.83	0.25 (0.03–2.19)	0.18
Auranen-4	2005	251	23	1	1538	267	6	0.09	1.02 (0.12–8.52)	0.98	0.53 (0.34–0.82)	0.0044	0.54 (0.35–0.83)	0.005	1.10 (0.13–9.15)	0.93
Beesley-1	2007	414	67	5	819	142	8	0.52	1.24 (0.40–3.80)	0.71	0.93 (0.68–1.28)	0.67	0.95 (0.70–1.29)	0.74	1.25 (0.41–3.84)	0.7
Beesley-2	2007	799	117	7	696	115	7	0.38	0.87 (0.30–2.50)	0.8	0.89 (0.67–1.17)	0.39	0.89 (0.68–1.16)	0.38	0.89 (0.31–2.53)	0.82
Jakubowska	2010	128	16 (GA+AA)		246	34 (GA+AA)		N/E	N/E	N/E	N/E	N/E	0.89 (0.47–1.68)	0.76	N/E	N/E
Michalska	2016	120	80	500	180	400	120	< 0.0001	6.25 (4.61–8.48)	< 0.0001	0.30 (0.22–0.42)	< 0.0001	1.67 (1.29–2.17)	< 0.0001	12.08 (9.35–15.61)	< 0.0001
Mohamed	2013	6	58	36	16	60	24	0.037	4.00 (1.37–11.67)	0.0086	2.58 (0.94–7.04)	0.059	2.98 (1.12–7.98)	0.024	1.78 (0.96–3.29)	0.064
Quaye	2009	1152	182	3	1505	266	16	0.29	0.24 (0.07–0.84)	0.016	0.89 (0.73–1.10)	0.28	0.86 (0.70–1.05)	0.13	0.25 (0.07–0.86)	0.017
Webb	2005	451	68	5	952	156	10	0.23	1.06 (0.36–3.11)	0.92	0.92 (0.68–1.25)	0.59	0.93 (0.69–1.25)	0.62	1.07 (0.36–3.14)	0.91
Auranen-1	2005	629	98	2	704	129	9	0.29	0.25 (0.05–1.16)	0.054	0.85 (0.64–1.13)	0.26	0.81 (0.61–1.07)	0.14	0.25 (0.05–1.18)	0.06

N/E – not estimable.

Table IV. Results of the meta-analysis for the XRCC2 rs3218536 polymorphism and ovarian cancer risk

Study groups	Sample size (case/control)	AA vs. GG			GA vs. GG			GA + AA vs. GG			AA vs. GG + GA		
		OR (95% CI)	*P*-value[a]	*P*-value[b]	OR (95% CI)	*P*-value[a]	*P*-value[b]	OR (95% CI)	*P*-value[a]	*P*-value[b]	OR (95% CI)	*P*-value[a]	*P*-value[b]
Total	5802/9390	0.96 (0.36–2.53)	< 0.0001	0.94[c]	0.80 (0.62–1.02)	< 0.0001	0.07[c]	0.95 (0.79–1.14)	0.0003	0.57[c]	0.90 (0.43–1.89)	< 0.0001	0.78[c]
≥ 10 (Quality of studies)	4991/8642	0.59 (0.37–0.94)	0.39	0.03[d]	0.87 (0.78–0.96)	0.56	0.009[d]	0.85 (0.77–0.94)	0.59	0.003[d]	0.60 (0.38–0.95)	0.39	0.03[d]

[a]*P value of Q-test for heterogeneity test,* [b]*statistically significant results,* [c]*random-effects model was used,* [d]*fixed-effects model was used.*

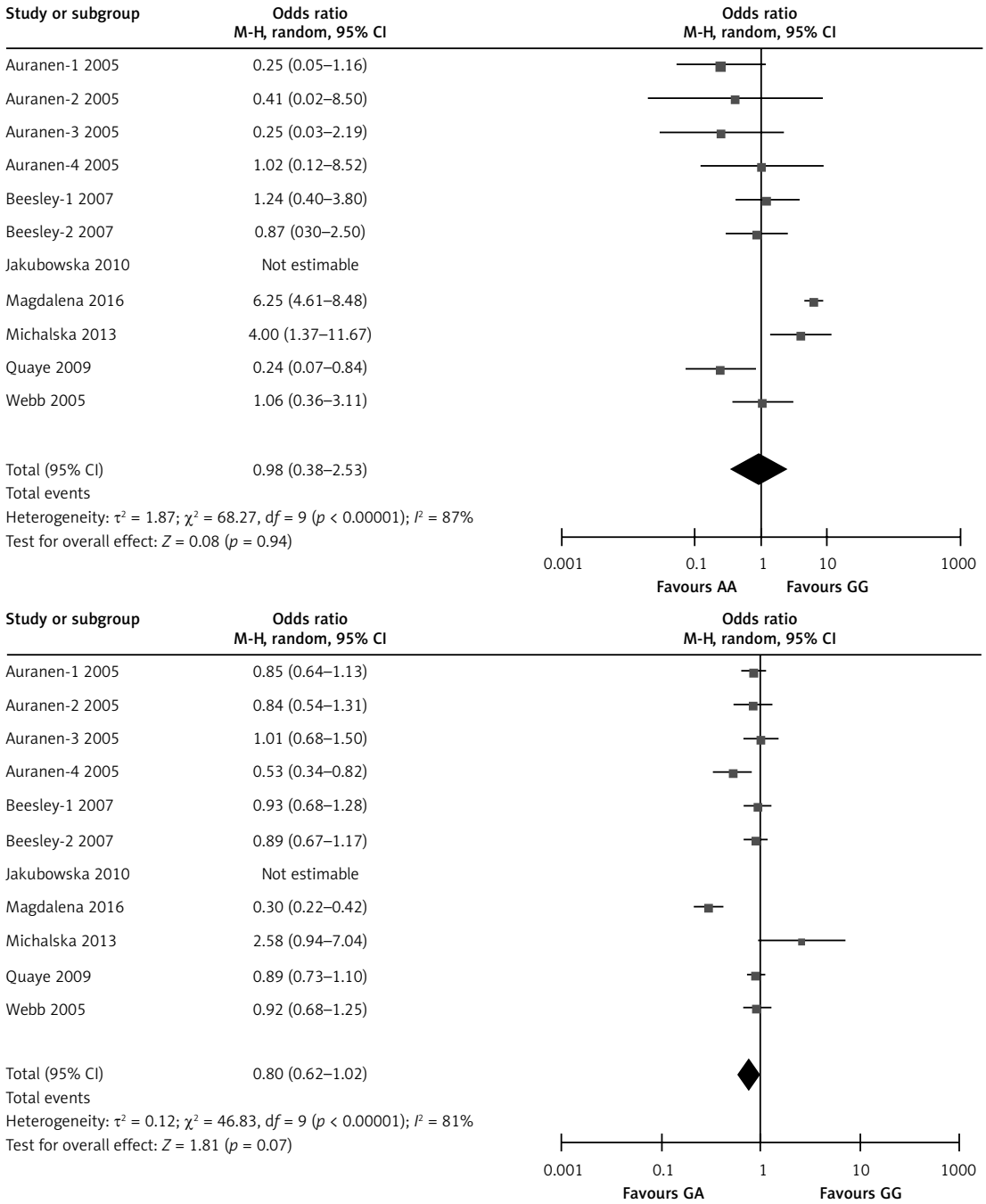

Figure 2. Forest plot summary of ORs and 95% CIs for the association between the XRCC2 rs3218536 polymorphism and ovarian cancer risk in all genetic models

lationship between the rs3218536 polymorphism and ovarian cancer risk in other ethnicities, areas, non-Caucasian groups, Africans, and Asians.

In conclusion, to our knowledge, the present meta-analysis on the association between the XRCC2 rs3218536 polymorphism and ovarian cancer risk was performed systematically and comprehensively. In conclusion, this meta-analysis shows that the XRCC2 rs3218536 polymorphism was associated with ovarian cancer risk in high quality studies overall. Non-Caucasian groups and high quality studies should be examined further.

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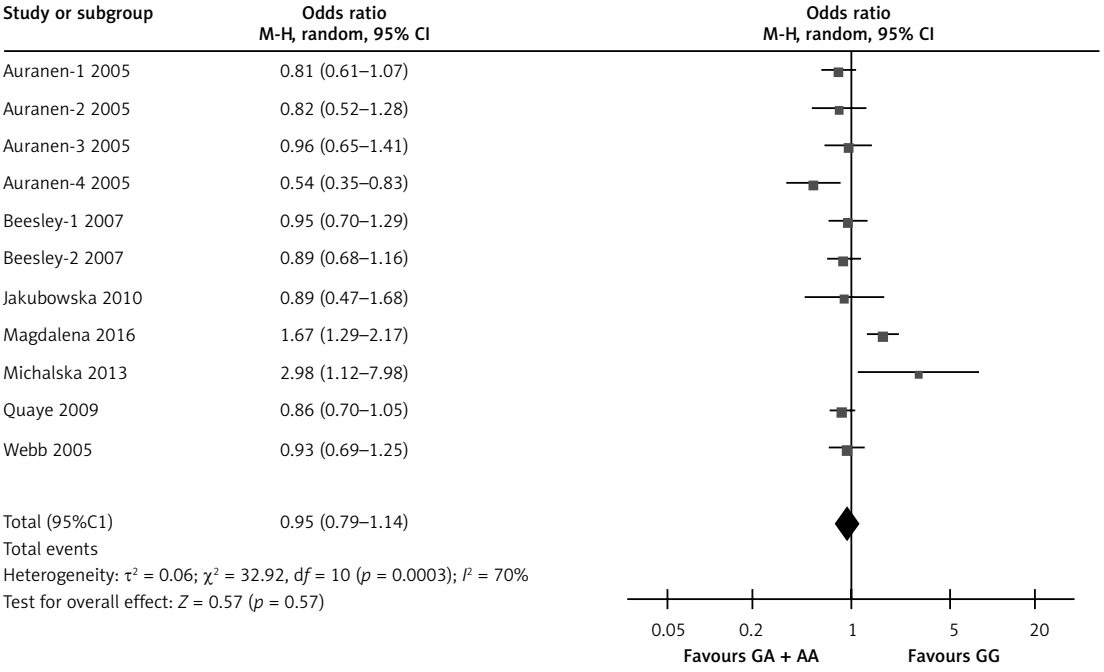

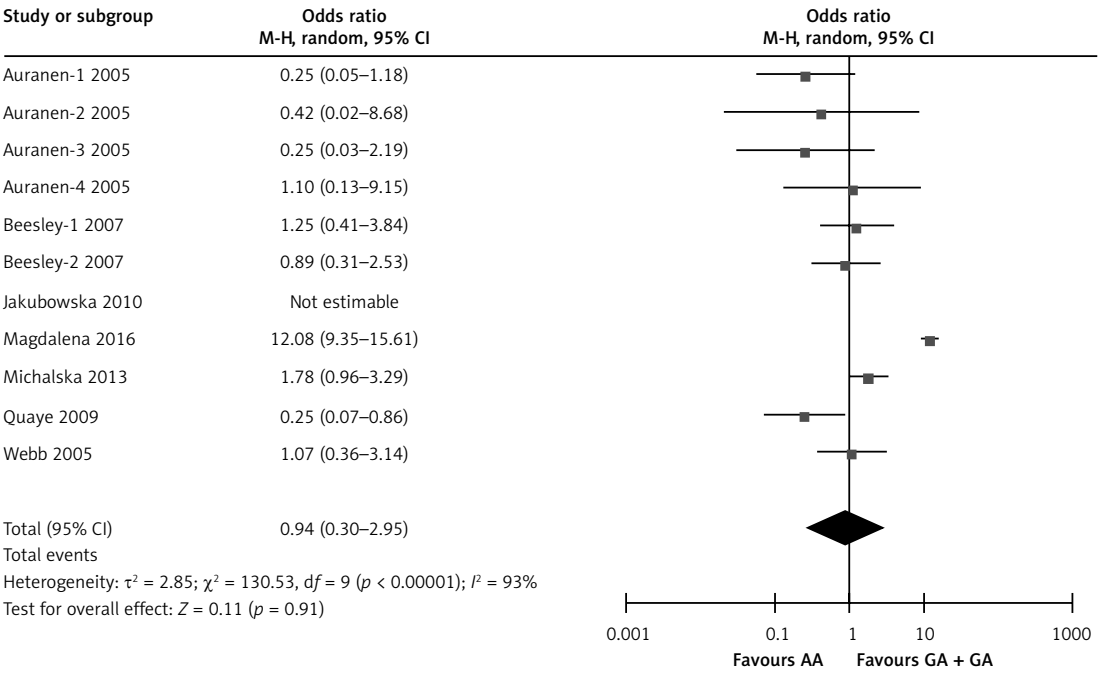

Figure 2. Cont.

decision to publish, or preparation of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

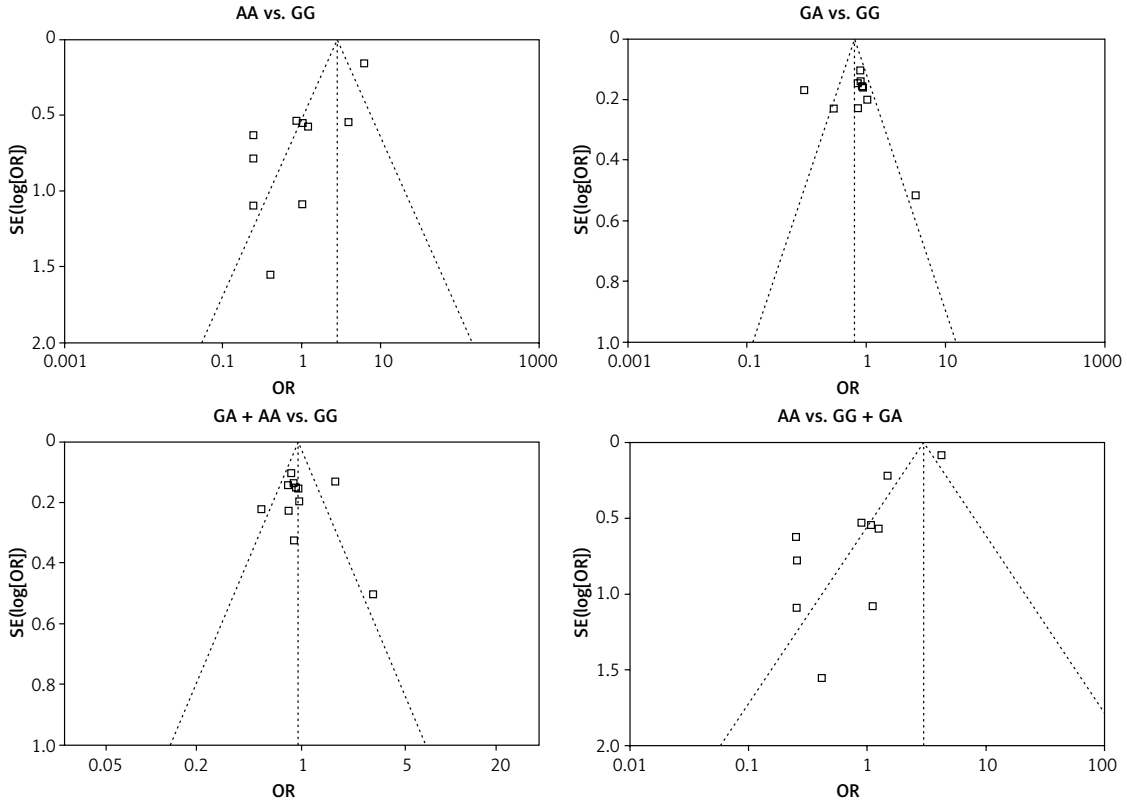

Figure 3. Begg's funnel plot of the XRCC2 rs3218536 polymorphism and ovarian cancer risk in all genetic models for all 11 studies. Each hollow circle represents a separate study for the indicated association, and its size is proportional to the sample size of each study

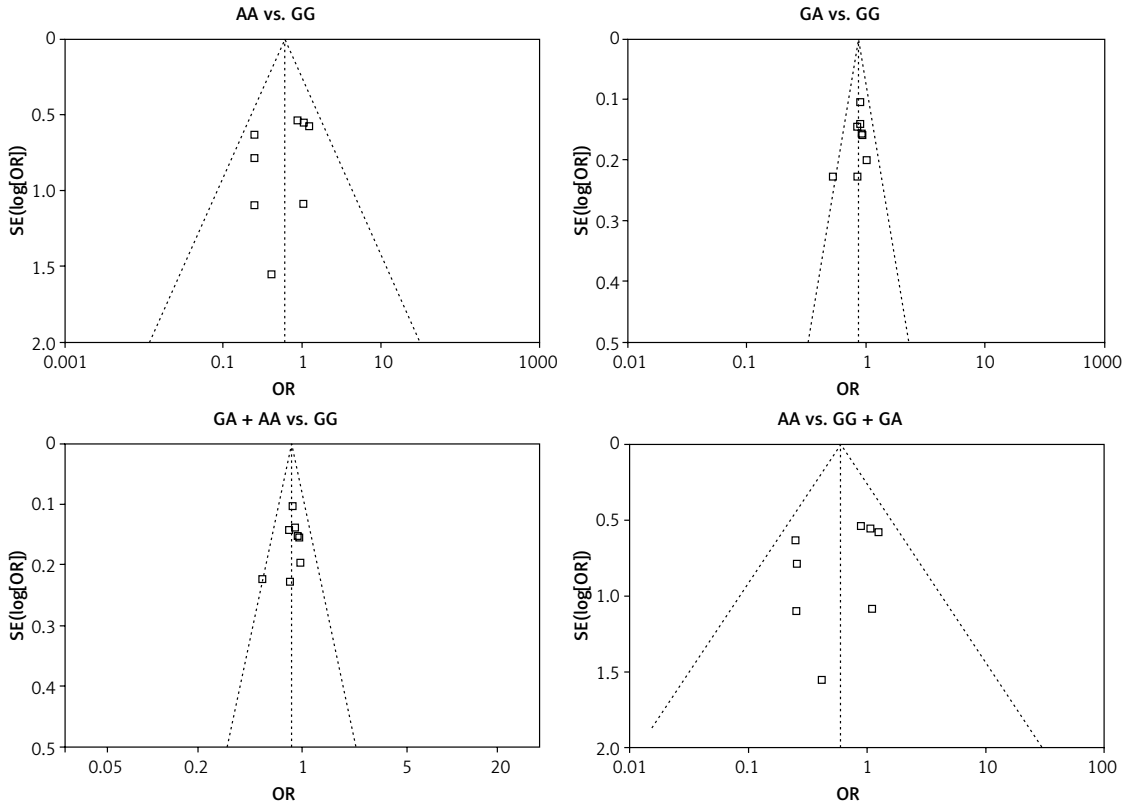

Figure 4. Begg's funnel plot of the XRCC2 rs3218536 polymorphism and ovarian cancer risk in all genetic models for the 8 high quality studies. Each hollow circle represents a separate study for the indicated association, and its size is proportional to the sample size of each study

References

1. Yuan C, Liu X, Yang N, et al. The GADD45A (1506T>C) polymorphism is associated with ovarian cancer susceptibility and prognosis. PLoS One 2015; 10: e0138692.
2. Yuan C, Liu X, Yan S, et al. Analyzing association of the XRCC3 gene polymorphism with ovarian cancer risk. Biomed Res Int 2014; 2014: 648137.
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012; 62: 10-29.
4. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. J Natl Cancer Inst 1998; 90: 1774-86.
5. Meindl A, Hellebrand H, Wiek C, et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. Nat Genet 2010; 42: 410-4.
6. Loveday C, Turnbull C, Ramsay E, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat Genet 2011; 43: 879-82.
7. Yin J, Lu K, Lin J, et al. Genetic variants in TGF-beta pathway are associated with ovarian cancer risk. PLoS One 2011; 6: e25559.
8. Garcia-Quispes WA, Perez-Machado G, Akdi A, et al. Association studies of OGG1, XRCC1, XRCC2 and XRCC3 polymorphisms with differentiated thyroid cancer. Mutat Res 2011; 709-710: 67-72.
9. Permuth-Wey J, Kim D, Tsai YY, et al. LIN28B polymorphisms influence susceptibility to epithelial ovarian cancer. Cancer Res 2011; 71: 3896-903.
10. Braem MG, Schouten LJ, Peeters PH, et al. Genetic susceptibility to sporadic ovarian cancer: a systematic review. Biochim Biophys Acta 2011; 1816: 132-46.
11. Pelttari LM, Heikkinen T, Thompson D, et al. RAD51C is a susceptibility gene for ovarian cancer. Hum Mol Genet 2011; 20: 3278-88.
12. Ramus SJ, Antoniou AC, Kuchenbaecker KB, et al. Ovarian cancer susceptibility alleles and risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers. Hum Mutat 2012; 33: 690-702.
13. Yuan C, Li X, Yan S, et al. The MTDH (-470G>A) polymorphism is associated with ovarian cancer susceptibility. PLoS One 2012; 7: e51561.
14. Bolton KL, Tyrer J, Song H, et al. Common variants at 19p13 are associated with susceptibility to ovarian cancer. Nat Genet 2010; 42: 880-4.
15. Goode EL, Chenevix-Trench G, Song H, et al. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. Nat Genet 2010; 42: 874-9.
16. Song H, Ramus SJ, Tyrer J, et al. A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22.2. Nat Genet 2009; 41: 996-1000.
17. Li Y, Zhao H, Sun L, et al. MDM2 SNP309 is associated with endometrial cancer susceptibility: a meta-analysis. Hum Cell 2011; 24: 57-64.
18. Thacker J, Zdzienicka MZ. The XRCC genes: expanding roles in DNA double-strand break repair. DNA Repair (Amst) 2004; 3: 1081-90.
19. 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. Tumour Biol 2014; 35: 5797-804.
20. Zhan P, Wang Q, Qian Q, Yu LK. XRCC3 Thr241Met gene polymorphisms and lung cancer risk: a meta-analysis. J Exp Clin Cancer Res 2013; 32: 1.
21. Zhao B, Ye J, Li B, et al. DNA repair gene XRCC3 Thr241Met polymorphism and glioma risk: a meta-analysis. Int J Clin Exp Med 2013; 6: 438-43.
22. Matullo G, Palli D, Peluso M, et al. XRCC1, XRCC3, XPD gene polymorphisms, smoking and (32)P-DNA adducts in a sample of healthy subjects. Carcinogenesis 2001; 22: 1437-45.
23. Yan L, Li Q, Li X, et al. Association studies between XRCC1, XRCC2, XRCC3 polymorphisms and differentiated thyroid carcinoma. Cell Physiol Biochem 2016; 38: 1075-84.
24. Gong H, Li H, Zou J, et al. The relationship between five non-synonymous polymorphisms within three XRCC genes and gastric cancer risk in a Han Chinese population. Tumour Biol 2016; 37: 5905-10.
25. He Y, Zhang Y, Jin C, et al. Impact of XRCC2 Arg188His polymorphism on cancer susceptibility: a meta-analysis. PLoS One 2014; 9: e91202.
26. Nowacka-Zawisza M, Wisnik E, Wasilewski A, et al. Polymorphisms of homologous recombination RAD51, RAD51B, XRCC2, and XRCC3 genes and the risk of prostate cancer. Anal Cell Pathol (Amst) 2015; 2015: 828646.
27. Qureshi Z, Mahjabeen I, Baig R, Kayani M. Correlation between selected XRCC2, XRCC3 and RAD51 gene polymorphisms and primary breast cancer in women in Pakistan. Asian Pac J Cancer Prev 2014; 15: 10225-9.
28. Michalska MM, Samulak D, Romanowicz H, et al. Association between single nucleotide polymorphisms (SNPs) of XRCC2 and XRCC3 homologous recombination repair genes and ovarian cancer in Polish women. Exp Mol Pathol 2016; 100: 243-7.
29. Michalska MM, Samulak D, Smolarz B. An association between the -41657 C/T polymorphism of X-ray repair cross-complementing 2 (XRCC2) gene and ovarian cancer. Med Oncol 2014; 31: 300.
30. Mohamed FZ, Hussien YM, AlBakry MM, et al. Role of DNA repair and cell cycle control genes in ovarian cancer susceptibility. Mol Biol Rep 2013; 40: 3757-68.
31. Quaye L, Tyrer J, Ramus SJ, et al. Association between common germline genetic variation in 94 candidate genes or regions and risks of invasive epithelial ovarian cancer. PLoS One 2009; 4: e5983.
32. Pearce CL, Near AM, Van Den Berg DJ, et al. Validating genetic risk associations for ovarian cancer through the international Ovarian Cancer Association Consortium. Br J Cancer 2009; 100: 412-20.
33. Beesley J, Jordan SJ, Spurdle AB, et al. Association between single-nucleotide polymorphisms in hormone metabolism and DNA repair genes and epithelial ovarian cancer: results from two Australian studies and an additional validation set. Cancer Epidemiol Biomarkers Prev 2007; 16: 2557-65.
34. 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.
35. 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.
36. Zhai M, Wang Y, Jiang MF. Arg188His polymorphism in the XRCC2 gene and the risk of ovarian cancer: a meta-analysis. Genet Mol Res 2015; 14: 10808-15.
37. Zhang Y, Wang H, Peng Y, et al. The Arg188His polymorphism in the XRCC2 gene and the risk of cancer. Tumour Biol 2014; 35: 3541-9.
38. Ma L, Chu WM, Zhu J, et al. Interleukin-1beta (3953/4) C-->T polymorphism increases the risk of chronic periodontitis in Asians: evidence from a meta-analysis of 20 case-control studies. Arch Med Sci 2015; 11: 267-73.

39. Cao Y, Wang X, Cao Z, Cheng X. Vitamin D receptor gene FokI polymorphisms and tuberculosis susceptibility: a meta-analysis. Arch Med Sci 2016; 12: 1118-34.
40. Wang C, Yuan C. Analyze association of BRCA2 Arg372His polymorphism with ovarian cancer risk. Int J Gynecol Cancer 2015; 25: 1338-44.
41. Yuan C, Wang C, Liu X, Kong B. Analyze association of the progesterone receptor gene polymorphism PROGINS with ovarian cancer risk. Mol Biol Rep 2013; 40: 6001-10.
42. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-48.
43. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-88.
44. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.
45. Sheng WY, Yong Z, Yun Z, et al. Toll-like receptor 4 gene polymorphisms and susceptibility to colorectal cancer: a meta-analysis and review. Arch Med Sci 2015; 11: 699-707.
46. Jakubowska A, Gronwald J, Menkiszak J, et al. BRCA1-associated breast and ovarian cancer risks in Poland: no association with commonly studied polymorphisms. Breast Cancer Res Treat 2010; 119: 201-11.