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The influence of *RAD51* (rs1801320) on breast cancer risk: an updated meta-analysis

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Abstract

Background DNA repair mechanisms, particularly *RAD51*-mediated homologous recombination repair, play a crucial role in breast cancer development, with the rs1801320 (135G > C) polymorphism showing conflicting associations across studies. This meta-analysis aimed to assess the relationship between *RAD51* rs1801320 polymorphism and breast cancer susceptibility.

Method We systematically searched PubMed and Web of Science databases through August 15, 2024, and included 16 case–control studies comprising 4743 breast cancer cases and 4448 controls, analyzing various genetic models using R Studio.

Results Our results revealed significant associations in several genetic models: the allele contrast model (C vs. G) showed an increased risk (OR = 1.37, 95% CI: 1.04–1.80, p = 0.0249. The recessive model (CC vs. CG + GG) demonstrated a strong risk association (OR = 2.68, 95% CI: 1.55–4.61, p = 0.00038), while the dominant model (CC + CG vs. GG) showed no significant association (OR = 1.12, 95% CI: 0.98–1.28, p = 0.1037). Pairwise comparisons revealed the CC genotype as a substantial risk factor, particularly in CC vs. GG (OR = 2.31, 95% CI: 1.58–3.37, p = 0.00001) and CC vs. CG (OR = 2.97, 95% CI: 1.53–5.77, p = 0.00128) comparisons. Most models showed moderate to high heterogeneity (I^2 = 30–93%), though publication bias was detected in some analyses.

Conclusion This comprehensive meta-analysis is larger than previous studies and provides robust evidence that the *RAD51* rs1801320 CC genotype significantly increases breast cancer risk, particularly in recessive and homozygous comparison models, suggesting potential implications for cancer risk assessment and therapeutic strategies targeting DNA repair mechanisms.

Keywords Breast cancer · Genetic susceptibility · *RAD51* polymorphism · Meta-analysis · Genotype association

1 Introduction

Breast cancer is a serious public health issue across the world, with one out of every eight women suffering from it during her lifetime [1]. Some major risk factors of breast cancer in women have been determined in several evaluations directed within the past five years, nearly all of which revolve around age, family history, obesity, consumption of oral

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contraceptives, menopausal status, smoking status, alcohol intake, lifestyles, and genes [2]. High-risk cases include those women with a family history of the development of breast cancer; normally, they inherit genetic alterations that have a powerful influence on personal risk [3]. Though germline mutations in *BRCA1* and *BRCA2* genes have been greatly focused on in hereditary breast tumor studies [4], the remaining genes that have substantial penetration found to be involved include *TP53,* and *PTEN* conversely, those with a modest penetration are *CHEK2*, *ATM*, *BRIP1*, *PALB2,* and *RAD51C* [5].

It is deliberated that DNA double-strand breaks (DSBs) are among the most disastrous forms of DNA damage and are repaired by two key pathways: homologous recombination repair (HRR) and non-homologous end joining [6]. Most often, the former pathway is upregulated in breast cancer cells, indicating that DNA repair mechanisms are crucial for the development of cancer. *RAD51* is a homolog of the *E. coli* RecA protein and participates in the repair of DNA DSBs through the HRR process [7]. Defects in the HRR pathway genes, such as *ATM*, *CHEK2*, *PALB2*, *NBN* as well as *RAD51* paralogs including *RAD51C* and *RAD51D*, are all found to be in a heightened risk for breast cancer manner and, hence, part of most genetic panels [8]. Beyond the rare mutations, there are several common genetic variants, known as single nucleotide polymorphisms (SNPs), in genes involved in repairing DNA, for example, *NBN*, *RAD51*, and *XRCC3*. The variants can alter the activity of these genes and might therefore impact the risk of breast cancer [9]. The rs1801320 is also known as 135G > C. Notably, one of these is *RAD51* (rs1801320), the 135G > C substitution in the 5′ untranslated region (5′UTR) of the *RAD51* gene. SNPs are common genetic variations that can influence how proteins are produced, folded, or function, but not all SNPs result in observable changes in protein expression or activity [10].

There has been conflicting research on the relationship between rs1801320 and the risk of breast cancer. According to some research, there is no statistically significant difference in the genotype and allele frequencies of breast cancer patients and controls [11–13], while others reported conflicting results, with a strong correlation between the rs1801320 variant and breast cancer susceptibility [14, 15], and some have even suggested a protective effect [16, 17]. These discrepancies emphasize the need for further in-depth analysis towards clarification of the relationship between rs1801320 and breast cancer risk.

A previous meta-analysis was conducted [18–22] that included 14, 19, 21, and 39 studies respectively, with unfiltered data to evaluate the association between rs1801320 polymorphism and breast cancer risk. The results reported that *RAD51* variation 135C homozygote is related to an increased risk of breast cancer among *BRCA2* mutation carriers. The current meta-analysis assembled data from 16 studies, including 4743 breast cancer cases and 4448 controls, to evaluate the association of the different genotypes of *RAD51* (GG, GC, and CC) with breast cancer susceptibility. However, our study analyzed studies access with HWE testing for quality of the genotype to evaluate the genetic predisposition to breast cancer posed by rs1801320 with a clearer understanding. Determining the effects of this polymorphism might provide important information about future therapeutic developments, given the critical function that *RAD51* plays in DNA repair and its possible consequences for treatment resistance and cancer prognosis.

2 Methods

2.1 Search strategy and terms

A thorough and methodical search strategy was used to track down research that looked into the possible correlation between the *RAD51* rs1801320 polymorphism and the risk of breast cancer. To ensure the most recent and relevant studies were included, we searched through several internet databases up until August 15, 2024, including PubMed and Web of Science.

To ensure that as many relevant articles as possible were found, the search approach comprised the use of selected phrases and different versions of them. The detailed search terms that were used are: 'SNP rs1801320 and breast cancer risk' OR *'RAD51* rs1801320 polymorphism and breast cancer risk' OR '135G > C SNP and breast cancer susceptibility' OR 'Impact of 135G > C variant on breast cancer'.

2.2 Inclusion and exclusion criteria

Particular inclusion and exclusion criteria that examined the connection between the *RAD51* rs1801320 polymorphism and breast cancer risk were developed to guarantee the selection of relevant research. This review includes all

case-control studies on human subjects, regardless of ethnicity or geographical location. The review excluded review articles, meta-analyses, editorials, case reports, conference abstracts, and studies involving non-human subjects.

2.3 Data extraction

To guarantee quality and consistency, data extraction was carried out separately by two reviewers utilizing a standardized form. A third reviewer was consulted or discussed with the other reviewers to settle any disagreements. The first author, the year of publication, the country, and the research design were among the variables collected (Table 1). In addition, information on the sample size, ethnicity, and demographics was reported. The distribution of GG, GC, and CC genotypes for *RAD51* rs1801320 was observed in cases and controls, and the published odds ratios (ORs) and 95% confidence intervals (CIs) for the relationship between *RAD51* rs1801320 and risk of breast cancer were also noted.

2.4 Statistical analysis

Statistical computations were performed in R Studio using the Meta package. The OR, along with the corresponding 95% CIs, was used as a principal measure to evaluate the relationship between the *RAD51* rs1801320 polymorphism and breast cancer risk. Results included pooled ORs and CIs for each genotype (GG, GC, CC) and allele comparisons. The Hardy–Weinberg equilibrium (HWE) test was applied to assess the quality of the genotype data in the control groups, ensuring the reliability of the genetic information used in the meta-analysis. A p-value threshold of 0.05 was used for HWE testing, with $p > 0.05$ indicating that the control group genotype frequencies were in equilibrium and likely representative of the general population.

3 Results

3.1 Study selection

The initial search of the Web of Science and PubMed databases identified 91 studies potentially relevant to this meta-analysis. Once duplicate studies were eliminated, the eligibility of 59 studies was evaluated. Thirty-two of these papers were determined ineligible for inclusion due to screening of the abstract and title. A full-text review was conducted on the 27 remaining papers, and 16 of them were included in the final meta-analysis based on our inclusion and exclusion criteria. These studies offer a thorough foundation for assessing the relationship between the *RAD51* rs1801320 polymorphism and breast cancer risk. They comprise a large dataset, incorporating information from 4743 breast cancer cases and 4448 healthy controls. The PRISMA flow diagram shows the study selection procedure (Fig. 1).

4 Main findings

4.1 Allele contrast (C vs. G)

The allele contrast model shows a statistically significant association between the C allele and increased risk compared to the G allele. The odds ratio (OR) is 1.37, with a 95% confidence interval (CI) of 1.04 to 1.80, and a p-value of 0.0249, indicating a significant result. There is high heterogeneity among the studies ($I2 = 90\%$) (Fig. 2a), and Egger's test for publication bias shows no significant bias ($p = 0.1424$) (Fig. 2b). This suggests a robust association between the C allele and increased risk.

Table 1 Studies included in the analysis and HWE values

References	Study	Country	CC_Cases	CG_Cases	GG_Cases	CC_Controls	CG_Controls	GG_Controls	HW-P.value	HW-adjusted.P.value
[17]	Gupta, 2023	India	13	76	221	10	91	171	0.621	0.828
[6]	Rajagopal, 2022	India	24	95	372	11	108	374	0.339	0.7961
[16]	Gresner, 2020	Poland	8	11	93	1	19	109	0.8641	0.9552
[12]	Korak, 2017	Turkey	6	103	439	3	60	297	0.9874	0.9874
[13]	Tulbah, 2016	Saudi Arab	10	31	59	9	31	60	0.1051	0.6091
[23]	Qureshi, 2014	Pakistan	5	49	102	2	44	104	0.2636	0.7961
[24]	Wasson, 2014	North East India	10	56	85	4	24	55	0.5184	0.7961
[25]	Krivokuca, 2013	Serbia	9	18	128	1	13	100	0.4401	0.7961
[26]	Smolarz, 2013	Poland	34	8	8	10	26	14	0.7412	0.9122
[27]	Romanowicz, 2012	Poland	526	104	160	164	426	208	0.0451	0.6091
[28]	Vral, 2011	Belgium	0	43	302	0	15	155	0.5473	0.7961
[29]	Jara, 2010	South America	2	33	232	1	58	441	0.5259	0.7961
[30]	Romanowicz, 2010	Poland	10	69	141	5	58	157	0.8955	0.9552
[31]	Krupa, 2009	Poland	11	33	91	7	63	105	0.5173	0.7961
[32]	Jara, 2007	Chile	2	16	113	0	25	222	0.4022	0.7961
[33]	Lee, 2005	Korea	28	143	611	14	123	450	0.1142	0.6091

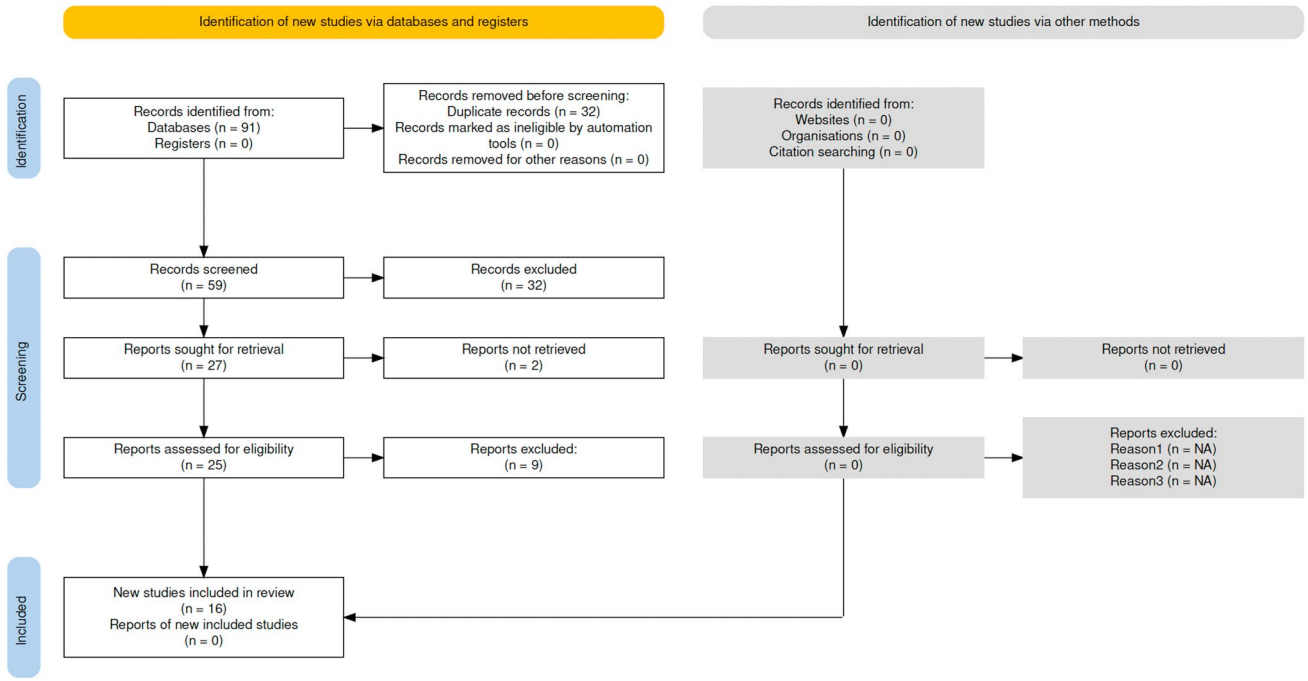

Fig. 1 PRISMA search flowchart for primary selected studies

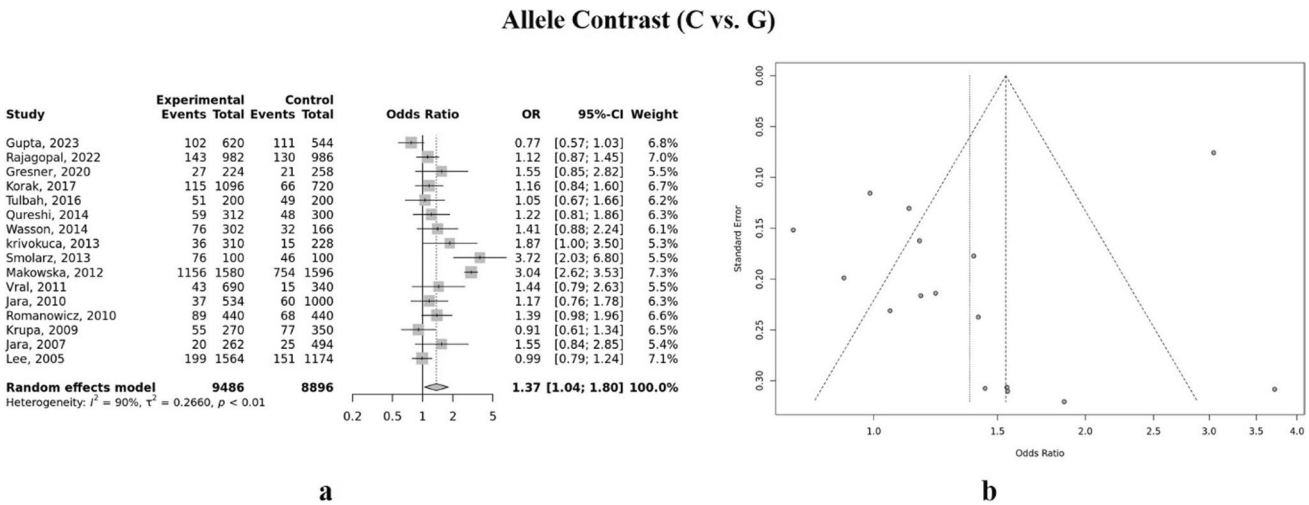

Fig. 2 Allele contrast model, **a** represents forest plot and **b** represents funnel plot

4.2 Recessive model (CC vs. CG + GG)

In the recessive model, there is a strong association between the CC genotype and increased risk compared to the combined CG + GG genotypes. The OR is 2.68 (95% CI: 1.55–4.61), and the p-value is 0.00038, which is highly significant. Heterogeneity is high (I2 = 80%), indicating variability across studies (Fig. 3a). However, there is some evidence of publication bias, as Egger's test is significant (p = 0.0176) (Fig. 3b). This model suggests the CC genotype is a strong risk factor compared to the other genotypes.

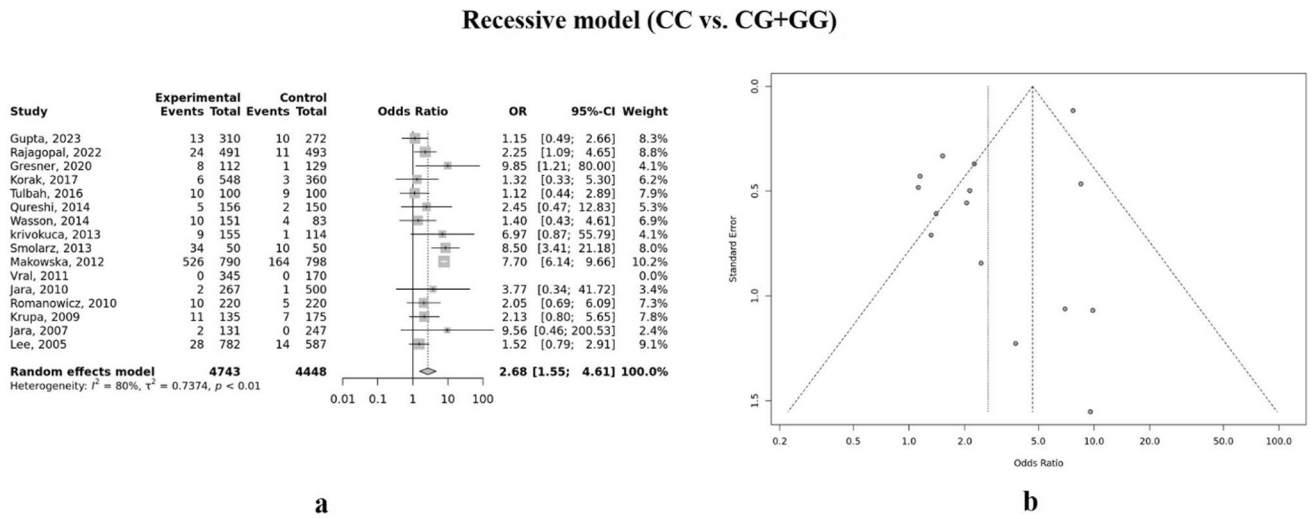

Fig. 3 Recessive model, **a** represents forest plot and **b** represents funnel plot

4.3 Dominant model (CC + CG vs. GG)

The dominant model does not show a significant association between the combined CC + CG genotypes and the GG genotype, with an OR of 1.12 (95% CI: 0.98–1.28) and a p-value of 0.1037. Although heterogeneity is moderate (I2 = 35%) (Fig. 4a), no publication bias is detected (Egger's test p = 0.3279) (Fig. 4b). This model suggests that the dominant genetic effect does not play a significant role in increased risk.

4.4 Overdominant model (CG vs. CC + GG)

The overdominant model compares the heterozygous CG genotype to the combined CC + GG genotypes and shows no significant association with risk. The OR is 0.78 (95% CI: 0.51–1.20), and the p-value is 0.2588, indicating a non-significant result. There is high heterogeneity among the studies (I2 = 93%) (Fig. 5a), and no evidence of publication bias (Egger's test p = 0.1407) (Fig. 5b). This suggests that the CG genotype does not confer a significant difference in risk compared to the homozygous genotypes.

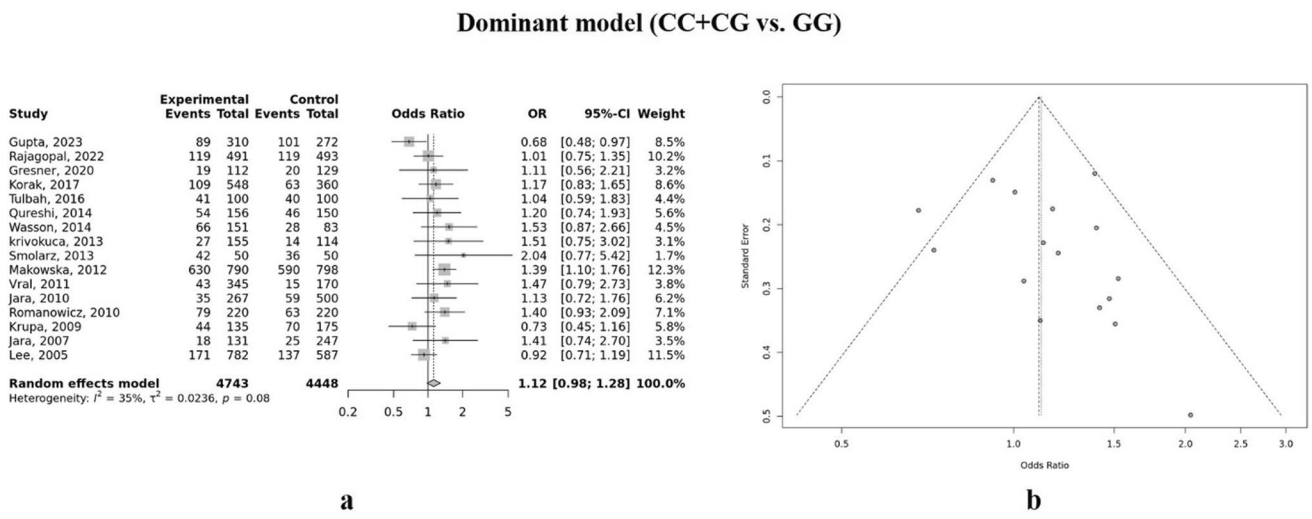

Fig. 4 Dominant model, **a** represents forest plot and **b** represents funnel plot

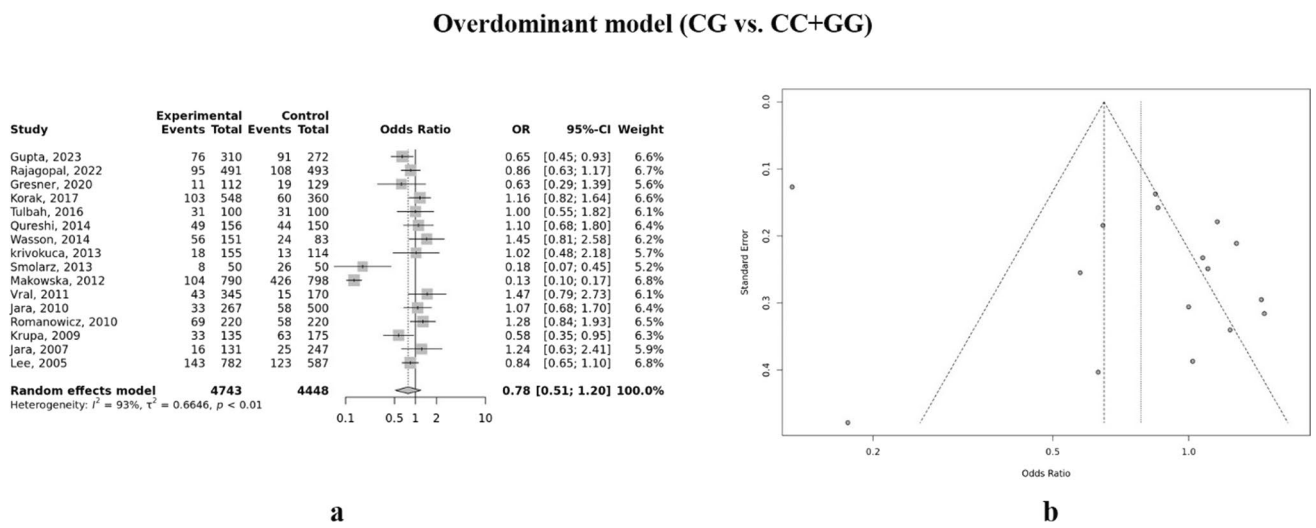

Fig. 5 Overdominant model, **a** represents forest plot and **b** represents funnel plot

4.5 Pairwise comparison 1 (CC vs. GG)

This pairwise comparison reveals a significant increase in risk for the CC genotype compared to the GG genotype, with an OR of 2.31 (95% CI: 1.58–3.37) and a highly significant p-value of 1.33e-05. Heterogeneity is moderate (I2 = 51%), suggesting some variability among studies (Fig. 6a), but no significant publication bias is observed (Egger's test p = 0.1891) (Fig. 6b). This result emphasizes the CC genotype as a strong risk factor when compared directly to GG.

4.6 Pairwise comparison 2 (CC vs. CG)

The CC genotype is also significantly associated with increased risk compared to the CG genotype, with an OR of 2.97 (95% CI: 1.53–5.77) and a p-value of 0.00128, which is highly significant. Heterogeneity is high (I2 = 84%) (Fig. 7a). However, there is potential publication bias in this comparison, as Egger's test is significant (p = 0.0099) (Fig. 7b). This comparison further supports the CC genotype as a risk factor relative to CG.

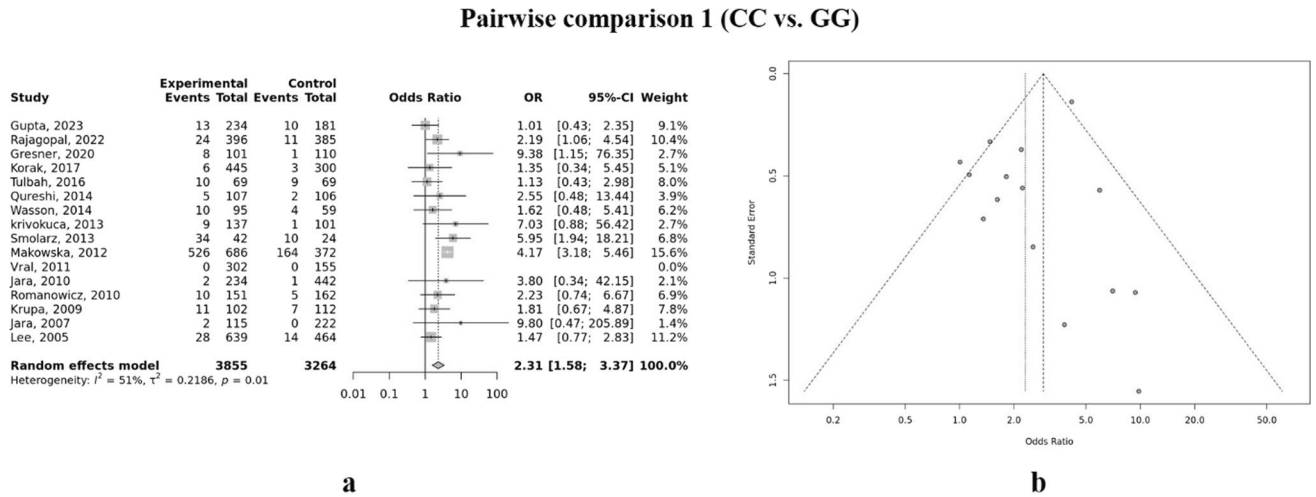

Fig. 6 Pairwise comparison (CC vs. GG) model, **a** represents forest plot and **b** represents funnel plot

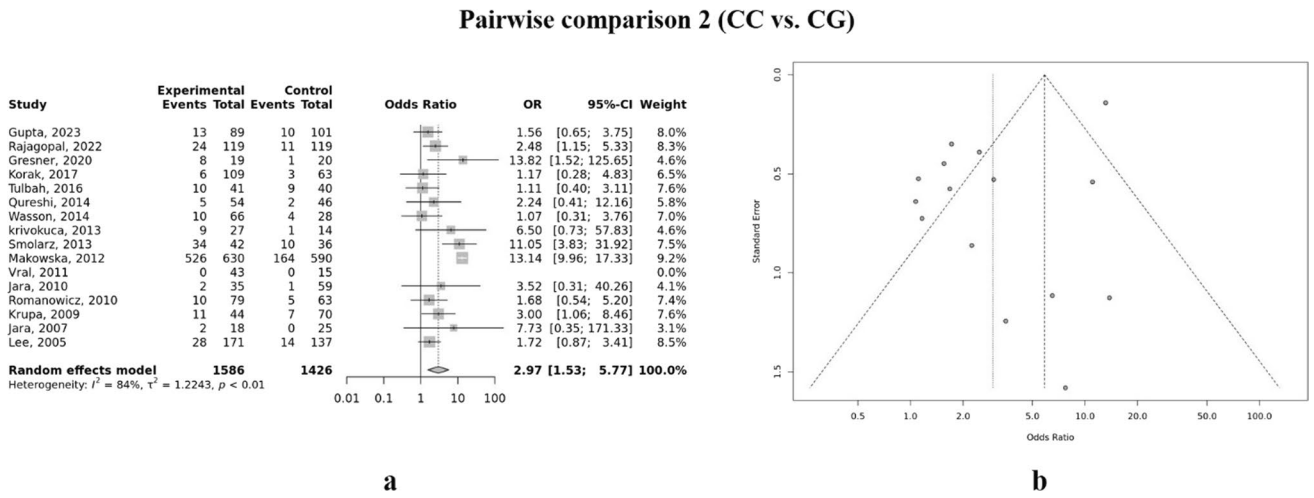

Fig. 7 Pairwise comparison (CC vs. CG) model, a represents forest plot and b represents funnel plot

4.7 Pairwise comparison 3 (CG vs. GG)

The comparison between the CG and GG genotypes shows no significant difference in risk, with an OR of 0.90 (95% CI: 0.71–1.15) and a p-value of 0.3966. Heterogeneity is high (I2 = 77%) (Fig. 8a), and there is no evidence of publication bias (Egger's test p = 0.2261) (Fig. 8b). This suggests that there is no significant difference in risk between the heterozygous CG genotype and the homozygous GG genotype.

5 Discussion

This comprehensive meta-analysis of 16 case-control studies, encompassing 4743 cases and 4448 controls, provides compelling evidence for the association between *RAD51* rs1801320 polymorphism and breast cancer risk. Our findings reveal a powerful association with the CC genotype, demonstrating its significant role in breast cancer susceptibility. The most striking observation emerged from the recessive model (CC vs. CG + GG), which showed a substantially increased risk (OR = 2.68). This finding was further reinforced by pairwise comparisons, where both CC

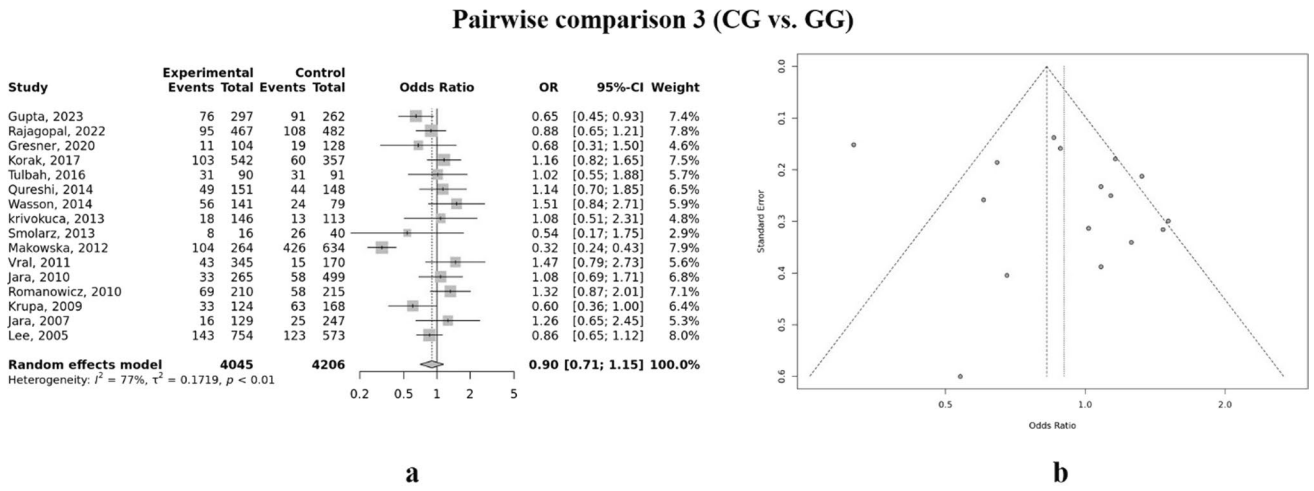

Fig. 8 Pairwise comparison (CG vs. GG) model, a represents forest plot and b represents funnel plot

vs. GG (OR = 2.31) and CC vs. CG (OR = 2.97) models demonstrated significant risk associations. The consistency of these results across multiple genetic models strengthens the evidence for the CC genotype's role in breast cancer development.

The biological plausibility of these findings aligns well with our understanding of *RAD51's* crucial function in DNA repair mechanisms [34]. Located in the 5' untranslated region of the *RAD51* gene, the rs1801320 polymorphism may influence gene expression or protein function, potentially affecting the efficiency of homologous recombination repair. This altered DNA repair capacity could explain the increased breast cancer risk associated with the CC genotype, as compromised DNA repair mechanisms are known to contribute to genomic instability and subsequent cancer development [35]. The allele contrast model (C vs. G) further supports this hypothesis, showing an increased risk for the C allele (OR = 1.37), suggesting a dose-dependent effect of the variant allele on breast cancer susceptibility.

Our analysis expands upon previous meta-analyses [18–22], including an earlier study of 14, 19, 21, and 39 studies with unfiltered data, by providing a more comprehensive evaluation of different genetic models and incorporating more recent research. An average moderate heterogeneity observed across most models (I2 = 30–93%) suggests moderate to high variability in the observed associations. However, the presence of publication bias in some models, particularly in the recessive model and CC vs. CG comparison, warrants careful interpretation and highlights the need for additional large-scale studies to confirm these associations.

Several important considerations emerge from our analysis that deserve attention in future research. The interaction between *RAD51* rs1801320 and environmental factors remains largely unexplored, and understanding these interactions could provide valuable insights into breast cancer risk modulation. Additionally, the potential impact of this polymorphism on treatment response and prognosis represents an important avenue for investigation, particularly given *RAD51's* role in DNA repair and its potential influence on therapeutic effectiveness. Functional studies are needed to elucidate the mechanical basis of how the CC genotype influences *RAD51* activity and DNA repair efficiency, which could reveal new therapeutic targets or strategies.

The clinical implications of our findings are potentially significant. The strong association between the CC genotype and breast cancer risk suggests that *RAD51* rs1801320 genotyping might have utility in risk assessment protocols. However, the translation of these findings into clinical practice requires careful consideration and validation through prospective studies. The interaction of *RAD51* rs1801320 with other genetic variants, particularly in other DNA repair genes, also warrants investigation to develop more comprehensive risk assessment models.

6 Conclusion

Our meta-analysis provides robust evidence that the *RAD51* rs1801320 CC genotype significantly increases breast cancer risk, particularly in recessive and homozygous comparison models. The consistency of these findings across multiple genetic models, coupled with low heterogeneity, underscores the potential importance of *RAD51* rs1801320 in breast cancer susceptibility. These results contribute meaningfully to our understanding of breast cancer genetics and may inform the development of more personalized prevention strategies. Moving forward, prospective studies focusing on gene-environment interactions, functional mechanisms, and clinical applications will be crucial in fully realizing the potential of these findings in breast cancer prevention and treatment. As we continue to unravel the complex landscape of breast cancer genetics, the role of *RAD51* rs1801320 polymorphism stands out as an important piece in the broader puzzle of breast cancer susceptibility and therapeutic development.

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Author contributions NUK, WK, and IS did the literature search, extracted the data, did the analysis, and wrote the manuscript. SSA, AY, TC, and WG oversaw the data extraction and review of the final manuscript. All authors revised it for important intellectual content.

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Data availability The manuscript includes all the necessary data; related data may be provided on request from the corresponding author/s.

Declarations

Consent for publication All the authors have read and approved the article for publication.

Competing interests The authors declare no competing interests.

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