REVIEW

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Survivin (*BIRC5*) Gene Polymorphism (rs9904341) Is Associated with Cancer Risk: A Meta-Analysis

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Abstract

Introduction: Survivin (BIRC5) is an anti-apoptosis protein over expressed in most cancers and associated with poor clinical outcomes. We have provided an updated meta-analysis of -31G/C (rs9904341) gene polymorphism which is highly associated with cancer risk. **Methodology:** A comprehensive literature search in PubMed and Google Scholar databases was conducted. A total of 10472 cases and 12193 controls from 51 studies were included in this meta-analysis. This study was prospectively registered in PROSPERO, and sensitivity analysis, risk of bias analysis, and statistical analysis were performed. A pooled odds ratio (OR) with 95% confidence interval (CI) was calculated to assess the strength of the association. All analyses were achieved using RevMan 5.4 software and Excel 2013 version. **Results:** The overall meta-analysis indicates that survivin gene polymorphism -31G/C (rs9904341) is highly associated with overall cancer risk in allelic (C vs. G, OR=1.25,95% CI= 1.15 to 1.37, P<0.00001), homozygous co-dominant (CC vs. GG, OR=1.53, 95% CI= 1.23 to 1.90, P=0.0001), heterozygous co-dominant (CC vs. CG, OR= 1.34, 95% CI= 1.18 to 1.52, P<0.00001), dominant model(CC+CG vs. GG, OR= 1.29, 95% CI= 1.14 to 1.46, P= <0.0001) and recessive model (CG+GG vs. CC, OR= 0.70, 95% CI= 0.61 to 0.81, P<0.00001). The stratified analysis revealed that the variant significantly increases the risk in the Asian population. **Conclusion:** -31G/C (rs9904341) polymorphism of the BIRC5 gene is associated with the risk of cancer in the Asian population. However, further large-scale clinical studies are required to re-evaluate this result in the future.

Keywords: Survivin- BIRC5- Polymorphism- Cancer- rs9904341- -31G/C

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Introduction

Head-neck cancer is a complex and multifactorial disease with a significant global health burden. It encompasses various malignancies, including the oral cavity, pharynx, larynx, and paranasal sinuses. Genetic factors have been implicated in the development and progression of head and neck cancer, with numerous studies focusing on the association between specific gene polymorphisms and disease risk [1].

One such gene of clinical interest in head-neck cancer is the Survivin gene, also known as BIRC5, located on chromosome 17q25.3. It is the smallest member of the inhibitor of the apoptosis protein family; other members are NAIP, cIAP1, cIAP2, XIAP, BRUCE, livin, and ILP2, which plays a crucial role in regulating cell apoptosis and proliferation [2, 3]. Survivin is a 16.5 kDa protein approximately 14.7 kb long and composed of four exons and three introns [4, 5]. It is structurally unique as it contains only one BIR (Baculoviral inhibitor of apoptosis repeat) domain, and the C-terminal ring finger is absent. It has been shown through various studies that overexpression of Survivin plays a vital role in the development and progression of the tumor by reducing the tumor cell apoptosis and increasing the cell proliferation rate [6, 7]. Survivin is a member of the inhibitor of apoptosis protein family and is involved in preventing programmed cell death and promoting cell survival. It prevents apoptosis by inhibiting intrinsic and extrinsic apoptosis pathways, increasing cell survival [8]. Also, the upregulation of Survivin increases therapy resistance [9, 10]. The expression of Survivin could be up-regulated due to a variety of molecular and genomic mechanisms, including gene amplification, promoter and exon demethylation, genetic variation in the regulatory region, and enhanced promoter activity leading to tumorigenesis and/or progression [11]. Survivin is polymorphic, and so far, several single nucleotide polymorphisms in the survivin gene have been characterized in the promoter, exon, intron, 3'UTR (untranslated region), and 5'UTR

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regions [12, 13].

Among them, -31G/C (rs9904341) is the most commonly studied variant. It is located at the cell cycle-dependent element and cell cycle homology regions and the repressor binding site of the survivin promoter [14]. Roodi et al. in 2019 reported that -31C is more transcriptionally efficient as compared to -31G allele, where this polymorphism, which is located within the survivin promoter region, specifically at the cell cycle-dependent element and repressor binding site, shows that the -31C allele exhibits higher transcriptional efficiency compared to the -31G allele, suggesting its potential influence on survivin expression and subsequent cancer risk. This observation was followed by several studies investigating the role of Survivin -31G/C (rs9904341) polymorphism in different cancers [15]. Most studies observed that over-expression of the survivin gene promote tumor development and progression. However, some studies show no association between survivin gene expression and cancer risk [16]. Therefore, we performed a subgroup analysis based on ethnicity and cancer types to estimate the association between survivin gene -31G/C (rs9904341) polymorphism and cancer risk.

The present study examines the association between the Survivin -31G/C (rs9904341) polymorphism and the risk of head and neck cancer in the Asian population. By conducting a systematic review and meta-analysis, we synthesized available evidence from relevant studies to better estimate the association. Further, subgroup analyses were performed based on ethnicity and cancer types to explore potential variations in the observed associations, particularly in the Asian population.

Understanding the role of survivin gene polymorphisms, particularly the -31G/C (rs9904341) variant, in developing head and neck cancer holds significant clinical implications. Elucidating the genetic factors contributing to disease risk can aid in identifying high-risk individuals, facilitate personalized treatment strategies, and provide valuable insights into the underlying molecular mechanisms involved in tumorigenesis.

Numerous studies have investigated the correlation between survivin polymorphisms and susceptibility to cancer among different populations. The findings of these investigations in case-control studies and previous meta-analyses are either contradictory or need to be sufficiently powered. To determine the probable effect of survivin rs9904341 polymorphisms on the likelihood of different cancers based on published case-control studies, we conducted comprehensive meta-analyses by including recently published articles.

Materials and Methods

Study Registration

This study was prospectively registered in PROSPERO (International Prospective Register of Systematic Reviews) for its design feasibility and vetted for its accuracy vide registration number CRD42023405571

Selection criteria

Before data selection and extraction, a predefined preselected set of criteria is defined by the first and second author and consensus by all authors. The selection criteria were based on a two-tier system of primary inclusion with broad sensitivity for potential articles and secondary exclusion criteria to filter out unnecessary pieces from the articles satisfying the inclusion criteria (Table 1).

Search strategy and study selection

A computer-based literature search was conducted on PubMed, Embase, Google Scholar, and Cochrane Library for all studies from inception till the 12th of June 2022 using Boolean operators and Medical Subject Headings

PubMed/ Medline: ((“Survivin”) OR (“BIRC5” [Supplementary Concept])) AND ((“Genetic Predisposition”[Mesh]) OR “GeneticVariation”[Mesh] OR “Polymorphism, genetic”[Mesh] OR “Polymorphism, Single Nucleotide”[Mesh]) OR“-31G/C” OR “rs9904341”) AND “Apoptosis”[Mesh]

Embase: (‘Survivin’/exp OR ‘BIRC5’) AND (‘Genetic Predisposition’/exp) OR (‘Genetic Variation’/exp OR‘-31G/C’ OR ‘rs9904341’)) AND (‘Head and Neck Neoplasms’/exp OR ‘Apoptosis’/exp)

Cochrane Library: ([Survivin] OR [BIRC5]) AND (MeSHDescriptor[Gene] OR MeSH Descriptor[Genetic Polymorphism] OR MeSH Descriptor[Genetic Variant] AND MeSH Descriptor[Head and Neck Neoplasms] OR MeSH Descriptor[Apoptosis])

Google Scholar: “Survivin BIRC5 genetic polymorphism -31G/C leading to head and neck cancer”

Additionally, a manual search from the bibliography of selected studies, textbook references on related topics, and manual additions by the corresponding author were used to add articles if they met the pre-defined selection criteria for the study.

Data extraction

Sixty-six articles were found using the above search terms and inclusion criteria (by choosing ‘filters’), and two articles were added using manual citations from the bibliography of selected articles. All collected articles were exported onto a Microsoft Excel Spreadsheet for

Table 1. Inclusion and Exclusion Criteria for the Studies Include in the Meta-Analysis

S. No.	Inclusion Criteria	Exclusion Criteria
1	Case-Control or Cohort study, Meta-analysis	Case reports,incomplete/unpublisheddata, review articles, animal Artilclesand editorial letters
2	Sufficient data forrs9904341 polymorphism is available	Irrelevant or no data included for genotype number or frequency
3	The most comprehensive and latest results were utilized where there were multiple studies from the identical study group.	Control population was not included

removal of duplicates and further analysis. Duplicates were excluded using the title-author-date criteria, which yielded 58 articles eligible for title and abstract screening. Each screening stage was performed by two individual authors (NM &AnK) and was further verified by two independent authors (AS &AsK). All ties were broken by the expert reviewer (RJK). Additionally, full-text screening and the risk of bias analysis were performed in parallel. Data extraction was performed on all selected articles using predetermined data points with the consensus of all authors; the corresponding author settled any disagreements.

The data points included

1. Genetic variation in the surviving gene in those with a documented form of cancer
2. The type of cancer documented
3. The genotypic method
4. Ancestry of participants ((categorized as Caucasian, Asian and mixed)
5. study design (categorized as population-based and hospital-based)
6. Number of cases and controls

Apart from these, information regarding the author, the study design, and the year of publication were also recorded for risk of bias assessment. Finally, the decision to include articles for the meta-analysis was decided by consensus among the authors, and the decision of the first author resolved any disagreement.

A schematic representation of the search and data extraction has been provided in the PRISMA flowchart in Figure 1.

Study outcomes

The primary objective was identifying whether individuals with cancer showed specific genetic polymorphisms of -31C/G (rs9904341) in the surviving gene. The secondary objective was to evaluate the association between the presence of a risk allele among cases with polymorphism and Controls without the polymorphism using statistical methods as specified below.

Quality assessment of studies

Two authors independently (AS and NM) assessed the methodological quality of the studies included in the review by using the New Castle Ottawa risk of a bias assessment tool for case-control studies. The NOS (Newcastle-Ottawa Scale) is a tool that was developed by the Universities of Newcastle, Australia, and Ottawa, Canada, to evaluate the quality of non-randomized studies. The primary goal of the tool is to incorporate quality assessments in the interpretation of meta-analytic results. The scale uses a 'star system' to assess a study based on three perspectives: selection of the study groups, comparability of the groups, and ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. At the end of the assessment of each study, a total score was obtained. For assessing the risk of bias in studies included in our meta-analyses, scores greater than 7 were considered low risk, above 5 to moderate risk, and below as high risk of bias. The risk of bias was schematically represented using a traffic signal plot and a Cochrane summary plot using the RobVis tool using the generic dataset. Publication bias was evaluated by Begg's and Egger's regression test and graphically represented as a funnel plot. Stratified analysis was also carried out by ethnicity and cancer type. Sensitivity analysis was performed to assess the stability of the results. Each study was removed from the total (one at a time), and the remaining were re-analyzed.

Statistical Analysis

All statistical analyses were conducted by Review Manager (RevMan) Version 5.4(Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), The Cochrane Collaboration 2020 and MS Excel 2017. The strength of the association between the survivin -31 G/C (rs9904341) promoter polymorphism and risk of cancer was measured by odds ratio (ORs) with 95% confidence interval (CIs) under different genetic models, including allelic model (C vs. G), dominant model (CC+GC vs. GG), recessive model (CC vs. GG+GC), additional model (CG vs CC+GG), homozygous model (CC vs. GG), heterozygous model (CC vs. GC) and (GG vs GC). Z test was employed to determine the significance of the pooled ORs. We also quantified the effect of heterogeneity by using the I^2 test and Cochrane Q statistic (ranges from 0 to 100%), which represents the proportion of inter-study variability that can be attributed to heterogeneity rather than by chance. When a significant I^2 is more than 50% (I^2 indicated that heterogeneity among studies existed, the random effects model (Der Simonian Laird method) was conducted or selected for meta-analysis. Otherwise, the fixed effect model (Mantel-Haenszel method) was used. We tested whether the genotype frequencies of controls were in HWE using the $\chi 2$ test.

Results

Study characteristics

In this meta-analysis, nine studies [17-24] were excluded while 51 studies were included based on the predetermined inclusion and exclusion criteria. The flow chart of the selection process of studies is schematically represented in Figure 1. 10,472 cancer patients and 12,193 genetically unrelated healthy individuals were included in the research. These case-control studies were published between 2007 and 2022. Thirty-three studies on Asian populations, 14 studies on Caucasian populations, and four studies on mixed populations made up the 51 studies that were chosen. Table 2 comprehensively summarizes the examined studies and the variables that were compared.

Quantitative synthesis

By combining genotype data from all 51 studies, our meta-analysis demonstrated a substantial correlation between the C allele and the G allele (OR= 1.25, 95% CI= 1.15 to 1.37, P<0.00001). Additionally, there was a strong correlation between the variables of CC vs CG (OR= 1.34, 95% CI= 1.18 to 1.52, P0.00001), CC vs. GG (OR= 1.53, 95% CI= 1.23 to 1.90, P=0.0001), and CC+CG vs.

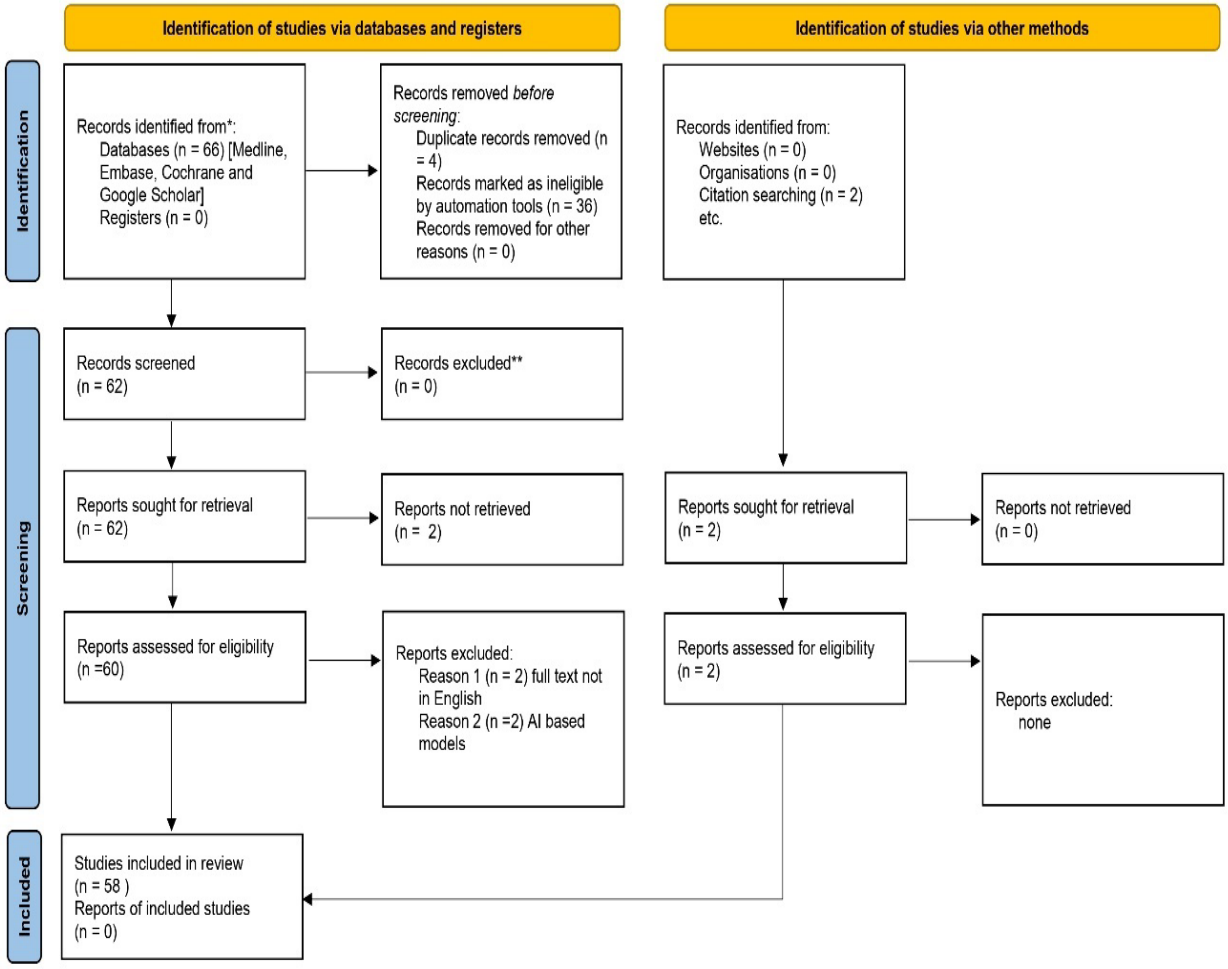


Figure 1. Schematic Representation of Included Studies through PRISMA Flowchart

GG (dominant model, OR= 1.29, 95% CI= 1.14 to 1.46, P=0.0001), GG vs. CG (OR= 0.79, 95% CI= 0.71 to 0.89, P<0.0001) and CG+GG vs. CC (OR= 0.67, 95% CI= 0.57 to 0.79, P<0.0001). There was a questionable correlation in the comparison of CC+GG and CG (OR=1.03, 95% CI=0.94 to 1.12, P=0.57). Due to the high heterogeneity, the random effect model was used for the aforementioned genetic models (Table 3).

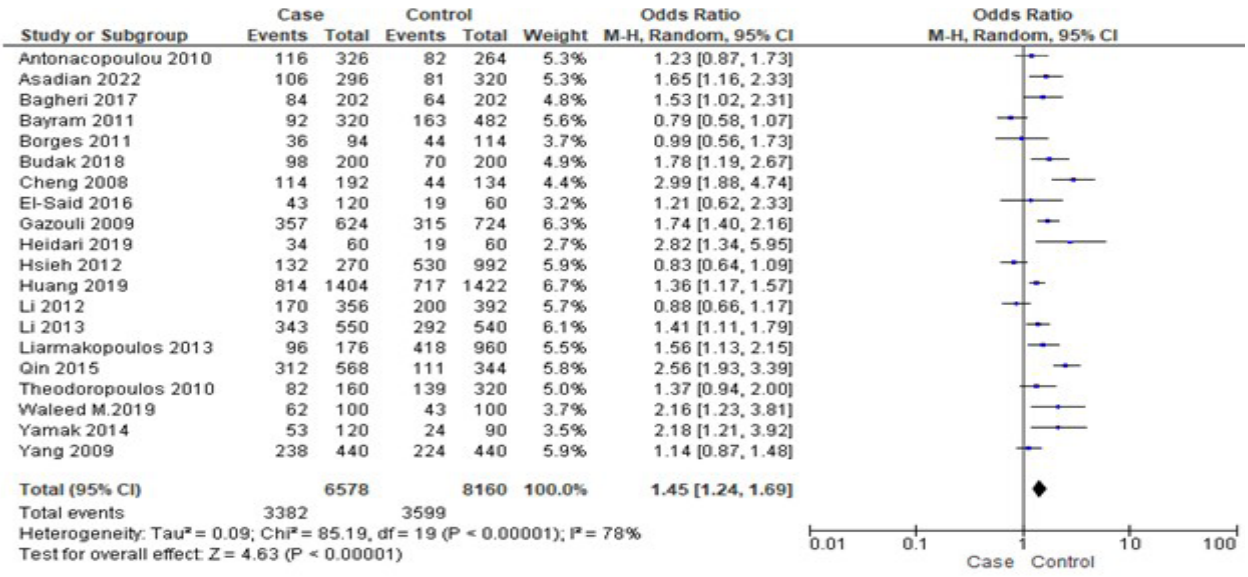
Subgroup analysis

Subgroup analysis was performed to determine the impact of cancer type and ethnicity on the possibility of acquiring the disease. While stratifying the analysis based on ethnicity, significantly higher susceptibility was seen in the Asian population under the following genetic models: C vs. G (allelic model, OR= 1.34, 95% CI= 1.21 to 1.48, P<0.00001), CC vs. CG (OR= 1.35, 95% CI= 1.16 to 1.58, P=0.0001), CC vs. GG (homozygous model, OR= 1.75, 95% CI= 1.42 to 2.14, P<0.00001), CC+CG vs. GG (dominant model, OR= 1.42, 95% CI= 1.25 to 1.61, P<0.00001), and CG+GG vs. CC (OR= 0.92, 95% CI= 0.62 to 1.36, P<0.00001) while slight association was discovered in GG vs CG (OR= 0.79, 95% CI= 0.71 to 0.89, P<0.00002) and a negligible relationship was discovered in CC+GG vs CG (OR= 1.00, 95% CI= 0.90 to 1.12, P= 0.19).

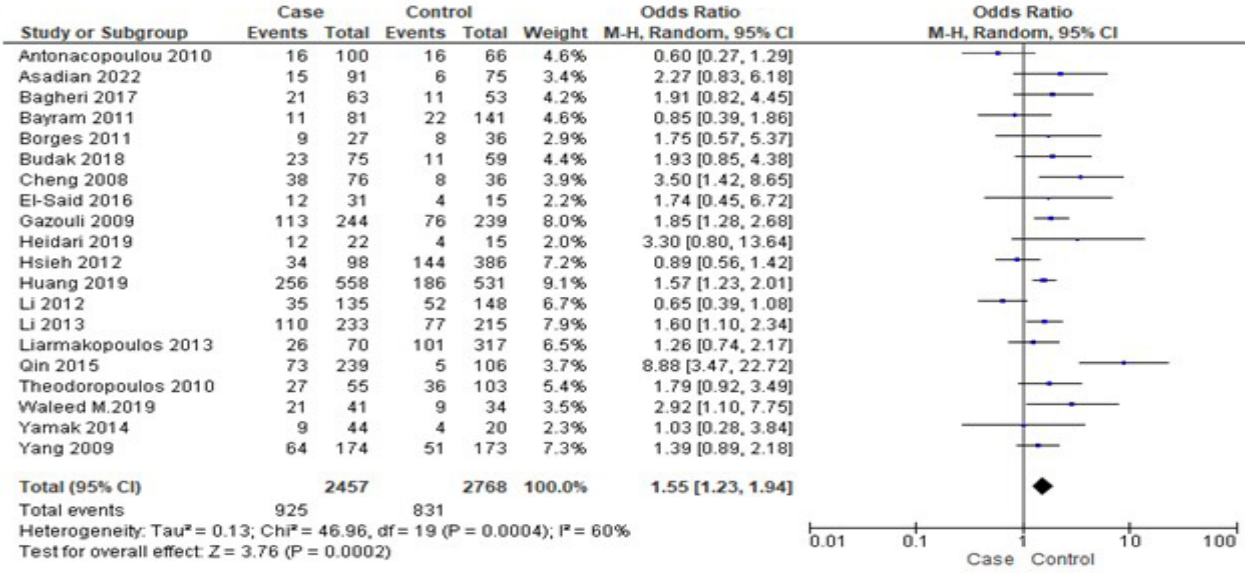
In the Caucasian population, a significant association has been found in C vs. G (allelic model, OR= 0.96, 95% CI= 0.75 to 1.23, P<0.00001) CC vs. CG models (OR= 1.35, 95% CI= 1.12 to 1.63, P=0.002), CC vs. GG (OR= 1.06, 95% CI= 0.71 to 1.58, P<0.00001), GG vs. CG (OR= 1.16, 95% CI= 0.83 to 1.62, P<0.00001) and CC+CG vs. GG (OR= 0.91, 95% CI= 0.64 to 1.28, P<0.00001) while the small association was observed in CC+GG vs CG model (OR= 1.91, 95% CI= 0.93 to 1.53, P=0.17) and CG+GG vs. CC (OR= 0.86, 95% CI= 0.65 to 1.14, P=0.010)

For mixed population, no significant association was found in C vs G (allelic model, OR= 1.37, 95% CI= 1.07 to 1.74, P= 0.27) CC vs CG models (OR= 1.59, 95% CI= 0.99 to 2.56, P=0.44), CC vs GG (OR= 1.87, 95% CI= 1.13 to 3.08, P= 0.44), GG vs CG (OR= 0.83, 95% CI= 0.57 to 1.21, P= 0.35), CC+CG vs GG (OR= 1.34, 95% CI= 0.90 to 2.00, P= 0.32), CG+GG vs CC model (OR= 0.58, 95% CI= 0.37 to 0.91, P=0.43) and CC+GG vs CG (OR= 1.04, 95% CI= 0.74 to 1.46, P=0.27).

The stratified analysis proposed that this variant is significantly associated with gastrointestinal tract and urinary cancer (Figure 2). A borderline association with reproductive system cancer was observed between -31G/C (rs9904341) polymorphism and head and neck cancer. Significant association has also been observed in Lung



(A) C vs G



(B) CC vs CG

Figure 2. Forest Plot of the Stratified Analysis of Survivin gene SNP -31G/C on the basis of Different Genotype Model in Gastrointestinal Tract Cancer (A) C vs G, (B) CC vs CG

cancer types and C allele.

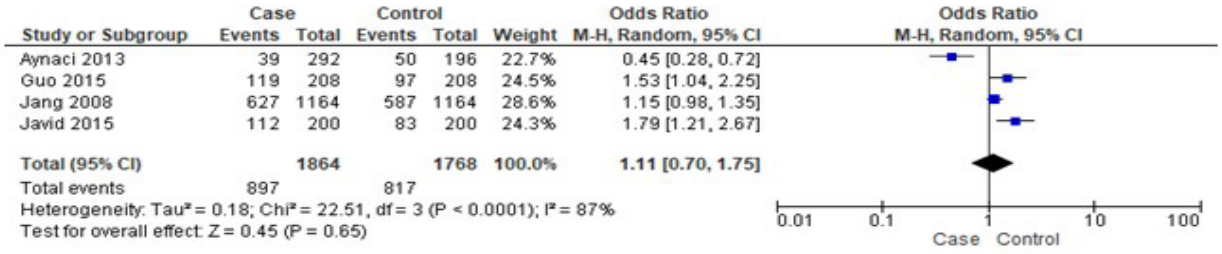
However, a strong association was observed with Lung cancer with C vs G, CC vs CG, and CC vs GG genotypic models (Figure 3).

Heterogeneity and publication bias

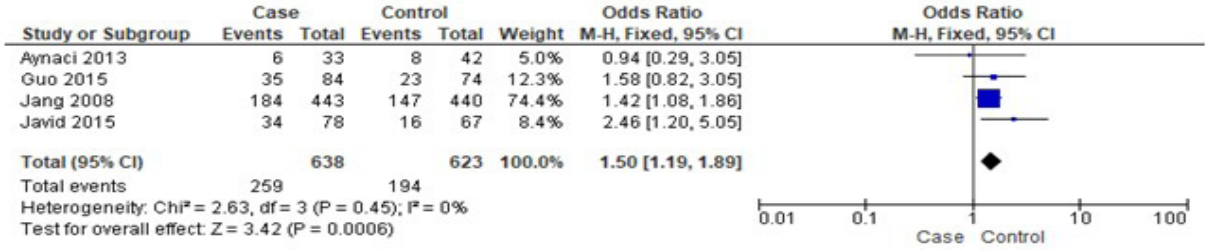
Heterogeneity among the studies was calculated using the software MedCalc. Results are in the Table 4 and Table 5 above. The results showed that in the Asian population, the heterogeneity (I^2/p-value for all genetic models was significant except for (CC+GG) vs. CG, which is 47.69% / 0.52. For the Caucasian population, the heterogeneity was not significant, as shown in Table 4. The analyzing results showed that heterogeneity existed among studies. Based on the heterogeneity results using the I^2 test, the ORs with 95% CI were estimated as a random or fixed effect model. If the I^2 of the heterogeneity test was more than or equal to 50%, then the random effect model is used as the pooling method; otherwise, the fixed effect model is used.

Some confounding factors, such as ethnicity, co-morbid conditions in the study participants, and family history of cancers in the study participants, that impact the outcome of the studies in the meta-analysis were not included. Most of the study participants included in the meta-analysis were of Asian ethnicity.

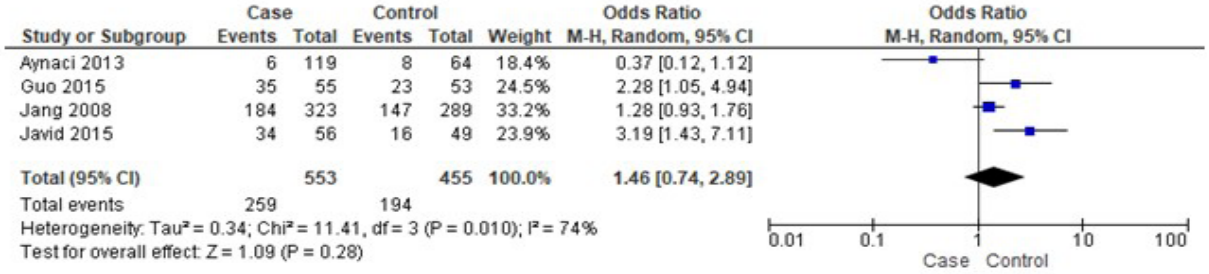
The potential publication bias was analyzed using Begg's funnel plot and Egger's linear regression test, as shown in Suoolementary Figure 2, for each of the



(A) C vs G



(B) CC vs CG



(C) CC vs GG

Figure 4. Forest Plot of the Stratified Analysis of Survivin Gene SNP -31G/C on the Basis of Different Genotype Model in Lung Cancer (A) C vs G, (B) CC vs CG, (C) CC vs GG

compared genetic models.

No significant asymmetry was noted in any of the comparisons, which leads the authors to interpret that the inclusion of studies was extensive enough to cover all types of results without preferentially neglecting any particular type singularly. The plots also depict clustering towards the apex, indicative of low standard error due to narrow confidence intervals/high sample sizes, in correlation with the forest plots in Supplementary Figure 1.

Sensitivity analysis

Sensitivity analysis was performed to assess each study's influence on the pooled ORs in which individual studies were omitted one by one. This analysis results suggested that no individual study significantly affects the pooled ORs under any genetic models of Survivin -31G/C (rs9904341).

Risk of Bias Analysis

The risk of bias of each study was analyzed based on the New Castle Ottawa scale based on parameters of selection of cases and controls, comparability of the two, and finally, measurement and expression of exposures individually. It was summated to an 'overall' bias status based on the number of 'stars' mentioned per protocol, as shown in Figure 4. A color-blind-friendly version has also been included in supplementary image 1.

An overall estimate of the risk of systematic errors has been performed by the RobVis tool to derive a summary plot, as shown in Figure 5.

The above summary plot depicts that only 25% of the total studies had a 'low' estimated risk of bias, with most of the studies having a moderate risk of bias. Compared to selection and exposure, a lower weight was given to comparability due to the increased subjectivity of that criterion in the New Castle Ottawa Scale, reflecting

Table 2. List of Relevant Studies Eligible for the Meta-Analysis

SN	Author	Year	Cancer	Ancestry	Study design	Genotypic Method	Controls				Cases				References
							GG	GC	CC	Total	GG	GC	CC	Total	
1	Borbely	2007	Cervix	Caucasian	PB	PCR-RFLP	71	85	24	180	29	45	7	81	25
2	Cheng	2008	Gastric	Asian	PB	PCR-RFLP	31	28	8	67	20	38	38	96	26
3	Jang	2008	Lung	Asian	HB	FLHP	142	293	147	582	139	259	184	582	27
4	Yang	2008	Gastric	Asian	HB	PCR-RFLP	47	122	51	220	46	110	64	220	28
5	Gazouli	2009	Colorectal	Caucasian	HB	PCR-RFLP	123	163	76	362	68	131	113	312	29
6	Wang	2009	Urothelial	Asian	HB	PCR-RFLP	80	86	44	210	33	91	66	190	30
7	Yang	2009	Oesophagus	Asian	HB	PCR-RFLP	63	124	81	268	55	108	58	221	28
8	Antonacopoulou	2010	Colorectal	Caucasian	HB	TaqMan	66	50	16	132	63	84	16	163	31
9	Theodoropoulos	2010	Pancreas	Caucasian	PB	PCR-RFLP	57	67	36	160	25	28	27	80	32
10	Upadhyay	2010	Oesophagus	Asian	HB	PCR-RFLP	105	123	22	250	96	110	44	250	33
11	Borges	2010	Gastric	Mixed	HB	PCR-SSCP	21	28	8	57	20	18	9	47	34
12	Bayram	2011	Hepatocellular	Caucasian	HB	PCR-RFLP	100	119	22	241	79	70	11	160	35
13	Ma	2011	Nasopharynx	Asian	PB	TaqMan	273	524	224	1021	205	403	236	844	36
14	Kawata	2010	Bladder	Asian	PB	PCR-RFLP	75	184	87	346	50	99	86	235	36
15	Hsieh	2012	Hepatocellular	Asian	HB	TaqMan	110	242	144	496	37	64	34	135	37
16	Weng	2012	Oral	Asian	HB	TaqMan	94	204	126	424	119	218	102	439	38
17	Yazdani	2012	Thyroid	Asian	HB	PCR-RFLP	70	54	7	131	48	56	19	123	39
18	Li	2012	Hepatocellular	Asian	PB	PCR-RFLP	48	96	52	196	43	100	35	178	40
19	Qin	2012	Renal cell	Asian	HB	TaqMan	215	385	160	760	172	345	193	710	41
20	Zahedi	2012	Endometrix	Asian	HB	PCR-RFLP	19	9	2	30	10	21	0	31	42
21	Jaiswal	2012	Bladder	Asian	HB	PCR-RFLP	98	87	15	200	83	85	32	200	43
22	Skodric	2012	Wilms tumor	Caucasian	HB	PCR-RFLP	26	45	11	82	36	19	4	59	44
23	Liarmakopoulos	2012	Gastric	Caucasian	HB	PCR-RFLP	163	216	101	480	18	44	26	88	45
24	Marques	2013	Renal	Caucasian	HB	PCR-RFLP	109	160	35	304	78	70	28	176	46
25	Aynaci	2013	Lung	Caucasian	HB	PCR-RFLP	56	34	8	98	113	27	6	146	47
26	Chen	2013	Prostate	Asian	HB	TaqMan	205	331	174	710	150	319	196	665	48
27	Li	2013	Colorectal	Asian	PB	PCR-RFLP	55	138	77	270	42	123	110	275	40
28	Kostic	2013	Oral	Caucasian	NA	PCR-RFLP	45	53	13	111	39	36	13	88	49
29	Kostic	2013	Skin	Caucasian	NA	PCR-RFLP	45	53	13	111	31	21	8	60	49
30	Huang	2013	Bladder	Asian	HB	PCR-RFLP	59	82	59	200	32	102	66	200	50

Table 2. Continued

SN	Author	Year	Cancer	Ancestry	Study design	Genotypic Method	Controls				Cases				References
							GG	GC	CC	Total	GG	GC	CC	Total	
31	Yamak	2014	Colon	Caucasian	HB	PCR-RFLP	25	16	4	45	16	35	9	60	35
32	Aminimoghaddam	2015	Endometrial	Asian	HB	PCR-RFLP	38	14	3	55	26	32	0	58	51
33	Javid	2015	Lung	Asian	HB	PCR-RFLP	33	51	16	100	22	44	34	100	52
34	Guo	2015	Lung	Asian	HB	PCR-RFLP	30	51	23	104	20	49	35	104	53
35	Qin	2015	Pancreas	Asian	HB	PCR-RFLP	66	101	5	172	45	166	73	284	54
36	El-Said	2016	Hepatocellular	African	HB	TaqMan	15	11	4	30	29	19	12	60	55
37	Bogdanovic	2017	Urothelial	Caucasian	HB	PCR-RFLP	26	45	11	82	54	31	7	92	44
38	Lin	2017	Urothelial	Asian	HB	TaqMan	48	99	41	188	43	112	30	185	56
39	Lin	2017	Bladder	Asian	HB	TaqMan	48	99	41	188	9	25	12	46	56
40	Bagheri	2017	Gastric	Asian	HB	PCR-RFLP	48	42	11	101	38	42	21	101	57
41	Rasool	2018	Breast	Asian	HB	PCR-RFLP	55	105	40	200	33	108	49	190	58
42	Karimian	2018	Prostate	Asian	HB	PCR-RFLP	69	55	21	145	53	67	37	157	59
43	Budak	2018	Colorectal	Caucasian	HB	PCR-RFLP	41	48	11	100	25	52	23	100	60
44	Waleed M	2018	Colorectal	Egypt	PB	PCR-RFLP	16	25	9	50	9	20	21	50	61
45	Li	2018	Leukemia	Asian	HB	PCR-LDR	54	93	53	200	36	76	70	182	60
46	Mehdi	2019	Oral	Asian	HB	PCR-RFLP	58	43	1	102	18	24	4	46	12
47	Wang	2019	Oesophagus	Asian	HB	PCR-LDR	140	294	163	597	153	318	126	597	9
48	Huang	2019	Colorectal	Asian	PB	PCR-RFLP	180	345	186	711	144	302	256	702	13
49	Heidari	2019	Colorectal	Asian	HB	PCR-RFLP	15	11	4	30	8	10	12	30	14
50	Mashadiyeva	2021	Breast	Mixed	HB	PCR-RFLP	54	62	18	134	37	68	21	126	62
51	Asadian	2022	Colorectal	Asian	PB	PCR-RFLP	85	69	6	160	57	76	15	148	63

Table 3. Summarized Table of the Results of the Association between Survivin Gene SNP -31G/C and Cancer Risk

Parameter	N	TESTS		GENETIC MODEL						
				C vs G	CC vs CG	CC vs GG	GG vs CG	(CC+CG) vs GG	(CG+GG) vs CC	(CC+GG) vs CG
Overall cancer	51	Association test	OR (95% CI)	1.25 [1.15, 1.37]	1.34 [1.18, 1.52]	1.58 [1.33, 1.88]	0.85 [0.76, 0.96]	1.29 [1.14, 1.46]	0.70 [0.61, 0.81]	1.03 [0.94, 1.12]
			Z	4.93	4.53	5.19	2.73	4	5.1	0.57
			p (Random effect)	<0.001	<0.001	<0.001	0.006	<0.001	<0.001	0.569
		Heterogeneity	Q	240.1701	124.503	195.6149	144.8795	191.4584	164.7358	112.6966
			I2 (%)	79.18%	59.84%	74.44%	65.49%	73.88%	69.65%	55.63%
			p value	<0.00001	<0.00001	<0.00001	0.006	< 0.0001	< 0.00001	0.57
		Egger's test	Intercept	0.8054	0.3923	0.7271	-0.874	1.0443	-0.5224	-0.5408
			95% CI	-0.6692 to 2.2800	-0.4966 to 1.2812	-0.4553 to 1.9094	-2.1429 to 0.3950	-0.4089 to 2.4976	-1.5373 to 0.4926	-1.5810 to 0.4993
			p value	0.2778	0.3795	0.2224	0.1726	0.1551	0.3061	0.3012
		Begg's test	Kendall's Tau	0.1278	0.03216	0.1012	-0.1671	0.1765	-0.06353	-0.06824
			p value	0.1855	0.7391	0.2947	0.0836	0.0676	0.5106	0.4798

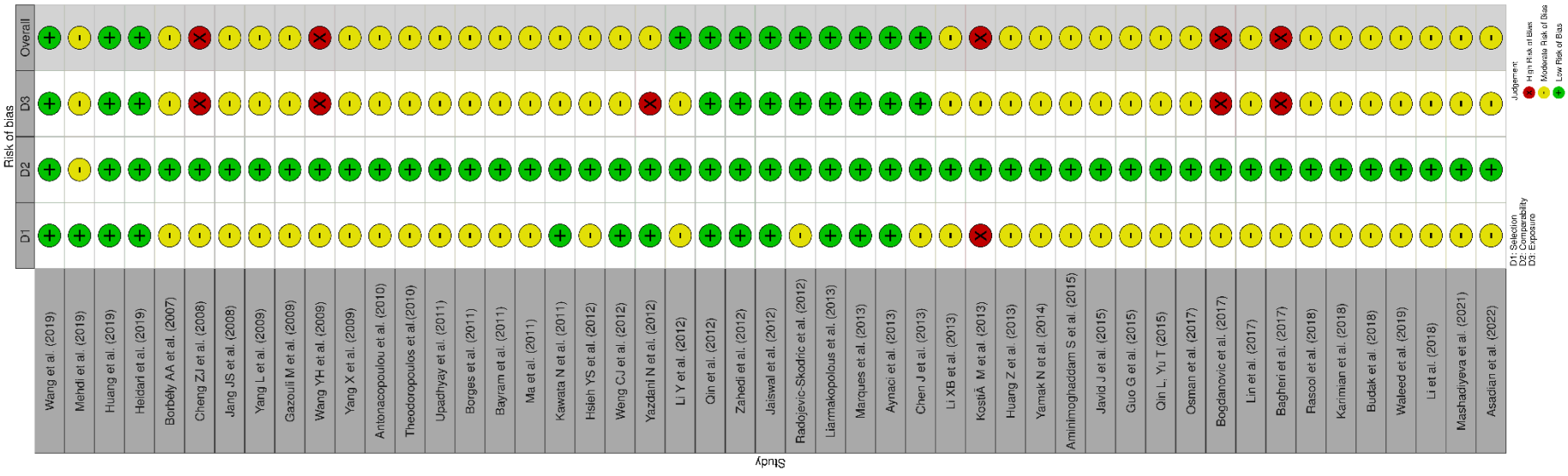


Figure 4. Traffic Plot Depicting the Risk of bias of Selected Studies.

Table 4. Summarized Table of the Results of the Association between Survivin Gene SNP -31G/C and Cancer Risk on the Basis of Ethnicity

Parameter	N			GENETIC MODEL						
				C vs G	CC vs CG	CC vs GG	GG vs CG	(CC+CG) vs GG	(CG+GG) vs CC	(CC+GG) vs CG
Asian	33	Association test	OR (95% CI)	1.34 [1.21, 1.48]	1.35 [1.16, 1.58]	1.75 [1.42, 2.14]	0.79 [0.70, 0.88]	1.42 [1.25, 1.61]	0.67 [0.57, 0.79]	1.02 [0.96, 1.08]
			p(Random Effect/Fixed Effect)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.517
			Z	5.8	3.86	5.32	4.07	5.34	4.77	0.65
		Heterogeneity	Q	148.8005	104.3648	145.4259	67.8439	96.9547	132.9545	61.1713
			I2	78.49%	69.34%	78.00%	52.83%	66.99%	75.93%	47.69%
			p	< 0.00001	0.0001	< 0.00001	< 0.0001	< 0.00001	< 0.00001	0.52
Caucasian	14	Association test	OR (95% CI)	1.00 [0.78, 1.29]	1.35 [1.12, 1.63]	1.12 [0.75, 1.68]	1.10 [0.78, 1.53]	0.97 [0.68, 1.37]	0.84 [0.63, 1.12]	1.19 [0.93, 1.53]
			p(Random Effect/Fixed Effect)	0.97	0.002	0.58	0.59	0.85	0.24	0.17
			Z	0.04	3.11	0.56	0.53	0.19	1.16	1.36
		Heterogeneity	Q	81.9059	16.2637	46.4051	65.0245	80.0757	27.8053	43.8568
			I2	84.13%	20.07%	71.99%	80.01%	83.77%	53.25%	70.36%
			p(Random Effect/Fixed Effect)	0.972	0.002	0.579	0.593	0.847	0.245	0.174
Other population	4	Association test	OR (95% CI)	1.37 [1.07, 1.74]	1.59 [0.99, 2.56]	1.87 [1.13, 3.08]	0.83 [0.57, 1.21]	1.34 [0.90, 2.00]	0.58 [0.37, 0.91]	1.04 [0.74, 1.46]
			p(Random Effect/Fixed Effect)	0.01	0.06	0.01	0.33	0.14	0.02	0.82
			Z	2.5	1.91	2.45	0.97	1.46	2.38	0.22
		Heterogeneity	Q	3.9673	2.7299	2.6814	3.3036	3.4916	2.7461	3.9376
			I2	24.38%	0.00%	0.00%	9.19%	14.08%	0.00%	23.81%
			p(Fixed Effect)	0.012	0.057	0.014	0.331	0.089	0.017	0.824

Table 5: Summarized Table of the Results of the Association between Survivin gene SNP -31G/C and Cancer Risk on the basis of Cancer Type

Parameter	N		GENETIC MODEL						
			C vs G	CC vs CG	CC vs GG	GG vs CG	(CC+CG) vs GG	(CG+GG) vs CC	(CC+GG) vs CG
Head and Neck	6	OR (95% CI)	1.04 [0.85, 1.27]	1.08 [0.74, 1.58]	1.09 [0.70, 1.70]	1.00 [0.88, 1.15]	1.01 [0.89, 1.15]	0.92 [0.62, 1.36]	1.00 [0.90, 1.12]
		p(RE/FE)	0.7	0.68	0.69	0.95	0.87	0.68	0.94
		Z	0.38	0.41	0.4	0.06	0.17	0.42	0.05
Reproductive System	3	OR (95% CI)	1.22 [0.90, 1.65]	0.38 [0.17, 0.86]	0.59 [0.25, 1.38]	0.41 [0.19, 0.90]	2.07 [1.01, 4.24]	2.12 [0.95, 4.75]	0.38 [0.17, 0.84]
		p(RE/FE)	0.19	0.02	0.22	0.03	0.05	0.07	0.02
		Z	1.3	2.32	1.22	2.22	1.98	1.83	2.37
Gastrointestinal Tract	20	OR (95% CI)	1.45 [1.24, 1.69]	1.55 [1.23, 1.94]	2.07 [1.50, 2.86]	0.77 [0.65, 0.91]	1.51 [1.23, 1.85]	0.58 [0.45, 0.74]	1.06 [0.96, 1.16]
		p(RE/FE)	< 0.00001	0.0002	< 0.00001	0.003	< 0.0001	< 0.0001	0.26
		Z	4.63	3.76	4.45	2.99	3.98	4.37	1.13
Urinary System	12	OR (95% CI)	1.14 [0.96, 1.36]	1.28 [1.13, 1.45]	1.45 [1.09, 1.94]	0.95 [0.71, 1.27]	1.13 [0.85, 1.52]	0.74 [0.61, 0.90]	1.09 [0.89, 1.34]
		p(RE/FE)	0.14	0.0001	0.01	0.71	0.4	0.002	0.38
		Z	1.48	3.79	2.53	0.37	0.84	3.08	0.87
Respiratory System	4	OR (95% CI)	1.11 [0.70, 1.75]	1.50 [1.19, 1.89]	1.46 [0.74, 2.89]	1.13 [0.69, 1.86]	1.03 [0.57, 1.86]	0.67 [0.42, 1.08]	1.33 [1.10, 1.60]
		p(RE/FE)	0.65	0.0006	0.28	0.63	0.93	0.1	0.003
		Z	0.45	3.42	1.09	0.48	0.09	1.65	2.96
Other	5	OR (95% CI)	1.38 [1.18, 1.60]	1.44 [1.09, 1.90]	1.95 [1.43, 2.67]	0.75 [0.59, 0.96]	1.43 [1.03, 1.99]	0.63 [0.48, 0.82]	0.97 [0.79, 1.20]
		p(RE/FE)	< 0.0001	0.01	< 0.0001	0.02	0.03	0.0005	0.79
		Z	4.17	2.54	4.18	2.28	2.13	3.48	0.26

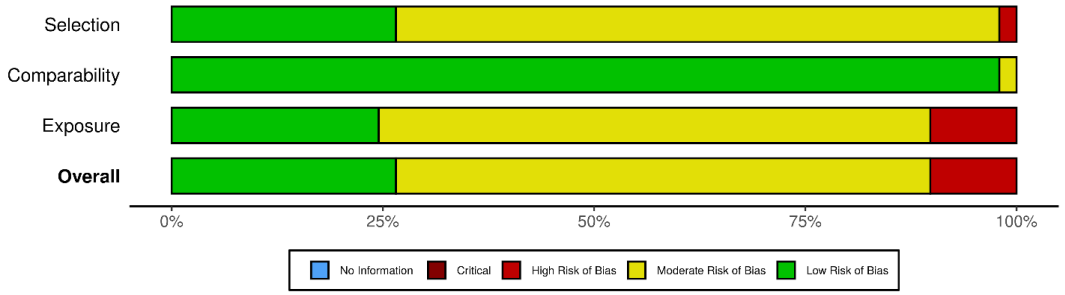


Figure 5. Summary Plot of Overall Risk of Bias of each Domain and All Selected Studies

the overall percentages being more similar to the other parameters.

Discussion

Apoptosis is involved in maintaining normal cellular processes, which is crucial in maintaining differentiated tissue homeostasis [64]. Apoptosis may be blocked in cancer cells, and this can be mediated by the members of the inhibitor of apoptosis protein family (IAPs) through directly or indirectly binding to caspase [65]. The mammalian genome encodes 8 IAP family members, including Survivin protein or BIRC5. It is the smallest member of the IAP family. Many single nucleotide polymorphisms (SNPs) have been found in different regions of the survivin gene, including promoter, exon, intron, 3'UTR, and 5'UTR region. The SNP -31G/C (rs9904341)located in the promoter region of the Survivin gene is highly associated with cancer risk. According to Ludewig et al. (2004), the C allele has a significantly higher association with cancer risk than the G allele [66].

In this meta-analysis, estimation of the association between survivin gene polymorphism -31G/C (rs9904341) and cancer risk has been done on 51 eligible case-control studies. In Roodi et al. [15], a meta-analysis was done on 43 studies. It was estimated that -31G/C (rs9904341) polymorphism is significantly associated with an increased risk of overall cancer, and our study supports their result with more studies. In subgroup analysis based on ethnicity, it was evaluated that the Asian population is significantly highly associated with cancer risk compared to cancer risk. This could be due to discrepancies caused by differences in genetic background, environmental factors, habitat, etc. However, the number of preliminary studies with the total number of cases and controls is less in Caucasian and mixed populations than in the Asian population, so this could be insufficiently powered to detect a significant association.

In this updated meta-analysis, we have performed subgroup analysis based on organ system, and results have shown a significant association between this variant and cancer of the urinary system and gastrointestinal cancer. A [17] meta-analysis conducted on 9 studies on gastrointestinal cancer estimated that the variant is significantly associated with cancer risk, and the observation from the present study supports their result. In the current meta-analysis, statistical power has been increased since we have estimated the results from 20 studies on gastrointestinal cancer. While borderline association has been reported in cancer of the reproductive system and respiratory system, and protection has been observed in head and neck cancer. There is evidence of the association between Survivin rs9904341 single nucleotide polymorphism and cancer risk [15].

There were some limitations in this meta-analysis. Firstly, the association between gene and environmental factors, age, habit, and gender was not evaluated due to a lack of relevant data across the included studies. Furthermore, different sources for controls or cases could contribute to selection bias. Most papers included in the current meta-analysis are from Asian populations; therefore, the heterogeneity existed among studies. Finally, even though all cases and controls in each research had unambiguous inclusion criteria, we overlooked other factors that could have affected our findings.

Despite the drawbacks mentioned above, our meta-analysis has the following merits. This specific goal of the study was to revise previously published meta-analysis and focus on the association between the Survivin -31G/C (rs9904341) polymorphism and the cancer risk association is statistically more powerful as compared to any individual study and the previous meta-analyses conducted on -31G/C (rs9904341) polymorphism. We implemented an efficient and effective search approach based on a computer-aided program and manual search to identify all relevant and appropriate studies. The quality of the research papers that comprised this meta-analysis met our selection criteria owing to this search approach. Moreover, before beginning the computations, precise study selection, data collection, and data evaluation techniques were adequately designed.

In summary, this meta-analysis provides strong evidence of the association between survivin gene polymorphism -31G/C (rs9904341) and cancer risk with 51 studies. However, the results for Asian and Caucasian populations were the same as in the previous analysis. At the same time, we have analyzed the association between polymorphism and cancer risk based on organ systems, which has not been done yet for all organ systems collectively. We anticipate that the -31G/C (rs9904341) polymorphism of Survivin can help screen high-risk populations for gastrointestinal cancers. However, well-designed epidemiological studies with demographic data, large sample sizes, and phenotype correlations are required

for translational application for the 31G/C polymorphism in cancer screening and diagnosis.

Author Contribution Statement

NM and AnK were responsible for study search and data extraction, data analysis, manuscript writing. AS did PROSPERO Registration and manuscript writing. AsK and RJK reviewed and approved the final manuscript.

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The study is meta-analysis and review of published literature. There was no intervention, sample collection or involvement of study participants or human ethics issue as such that required review by human ethics committee.

Availability of data (if apply to your research)

The data supporting the findings of this study are available upon reasonable request.

Was the study registered in any registering dataset (for clinical trials, guideline, meta-analysis)

This study was registered in PROSPERO, with the registration number CRD42023405571, adhering to the guidelines for clinical trials/meta-analyses.

Any conflict of interest

The authors declare that they have no conflict of interest.

References

1. Khan SA, Burke M, Zhu F, Yang DH, Dubyk C, Mehra R, et al. Survivin expression and impact on head and neck cancer outcomes. Oral Oncol. 2021;112:105049. https://doi.org/10.1016/j.oraloncology.2020.105049.
2. Jaiswal PK, Goel A, Mittal RD. Survivin: A molecular biomarker in cancer. Indian J Med Res. 2015;141(4):389-97. https://doi.org/10.4103/0971-5916.159250.
3. Garg H, Suri P, Gupta JC, Talwar GP, Dubey S. Survivin: A unique target for tumor therapy. Cancer Cell International. 2016;16(1):49. https://doi.org/10.1186/s12935-016-0326-1.
4. Fukuda S, Pelus LM. Survivin, a cancer target with an emerging role in normal adult tissues. Mol Cancer Ther. 2006;5(5):1087-98. https://doi.org/10.1158/1535-7163.Mct-05-0375.
5. Wheatley SP, Altieri DC. Survivin at a glance. J Cell Sci. 2019;132(7). https://doi.org/10.1242/jcs.223826.
6. Kanwar JR, Kamalapuram SK, Kanwar RK. Targeting survivin in cancer: The cell-signalling perspective. Drug Discov Today. 2011;16(11-12):485-94. https://doi.org/10.1016/j.drudis.2011.04.001.
7. Chen X, Duan N, Zhang C, Zhang W. Survivin and tumorigenesis: Molecular mechanisms and therapeutic strategies. J Cancer. 2016;7(3):314-23. https://doi.org/10.7150/jca.13332.
8. Lin TY, Chan HH, Chen SH, Sarvagalla S, Chen PS, Coumar MS, et al. Birc5/survivin is a novel atg12-atg5 conjugate interactor and an autophagy-induced DNA damage suppressor in human cancer and mouse embryonic fibroblast cells. Autophagy. 2020;16(7):1296-313. https://doi.org/10.1080/15548627.2019.1671643.
9. Wang Y, Li S, Li C. Perspectives of new advances in the pathogenesis of vitiligo: From oxidative stress to autoimmunity. Med Sci Monit. 2019;25:1017-23. https://doi.org/10.12659/msm.914898.
10. Miyao T, Koike H, Sekine Y, Ohtsu A, Oka D, Suzuki K. Ym155 reverses cabazitaxel resistance in castration-resistant prostate cancer by reducing survivin expression. Anticancer Res. 2020;40(9):5091-5. https://doi.org/10.21873/anticanres.14512.
11. Lyu H, Huang J, He Z, Liu B. Epigenetic mechanism of survivin dysregulation in human cancer. Sci China Life Sci. 2018;61(7):808-14. https://doi.org/10.1007/s11427-017-9230-2.
12. Mehdi RF, Sheikh F, Khan R, Fawad B, Haq AU. Survivin promoter polymorphism (-31 c/g): A genetic risk factor for oral cancer. Asian Pac J Cancer Prev. 2019;20(4):1289-93. https://doi.org/10.31557/apjcp.2019.20.4.1289.
13. Huang J, Wei Y, Zhou X, Wang L, Huang M, Wang J. The association between survivin -31g>c polymorphism and susceptibility to sporadic colorectal cancer in a southern chinese population. J Cancer Res Ther. 2019;15(1):82-6. https://doi.org/10.4103/0973-1482.202894.
14. Heidari Z, Sagheb HM, Hakimi A, Moudi B. Evaluation of immunohistochemical expression of survivin and its correlation with -31g/c gene polymorphism in colorectal cancer. Med Mol Morphol. 2019;52(2):82-9. https://doi.org/10.1007/s00795-018-0204-0.
15. Moazeni-Roodi A, Ghavami S, Hashemi M. Survivin rs9904341 polymorphism significantly increased the risk of cancer: Evidence from an updated meta-analysis of case-control studies. Int J Clin Oncol. 2019;24(4):335-49. https://doi.org/10.1007/s10147-019-01408-y.
16. Atikcan S, Unsal E, Demirag F, Köksal D, Yilmaz A. Correlation between survivin expression and prognosis in non-small cell lung cancer. Respir Med. 2006;100(12):2220-6. https://doi.org/10.1016/j.rmed.2006.02.031.
17. Liu Y, Li L, Qi H, Gao Y, Liu S, Xu C. Survivin −31g>c polymorphism and gastrointestinal tract cancer risk: A meta-analysis. PLOS ONE. 2013;8(2):e54081. https://doi.org/10.1371/journal.pone.0054081.
18. De Maria S, Lo Muzio L, Braca A, Rega P, Cassano A, Vinella A, et al. Survivin promoter -31g/c polymorphism in oral cancer cell lines. Oncol lett. 2011;2(5):935–9.
19. Chen HA, Su CM, Hsieh HY, Tung CL, Hsu CD, Wang YH, et al. Clinical significance of survivin expression in patients with urothelial carcinoma. Dis Markers. 2014;2014:574985. https://doi.org/10.1155/2014/574985.
20. Han CH, Wei Q, Lu KK, Liu Z, Mills GB, Wang LE. Polymorphisms in the survivin promoter are associated with age of onset of ovarian cancer. Int J Clin Exp Med. 2009;2(4):289-99.
21. Hmeljak J, Erčulj N, Dolžan V, Kern I, Cör A. Birc5 promoter snps do not affect nuclear survivin expression and survival of malignant pleural mesothelioma patients. J Cancer Res Clin Oncol. 2011;137(11):1641-51. https://doi.org/10.1007/s00432-011-1030-0.
22. Jamshidi M, Farnoosh G, Mohammadi Pour S, Rafiee F, Saeedi Boroujeni A, Mahmoudian-Sani Mr. Genetic variants and risk of thyroid cancer among iranian patients. Horm mol biol clin i. 2021 jul 20;42(2):223-34.
23. Li W-X, Li Y-K, Lin H-T. Correlation between survivin polymorphism and acute leukemia of children. Exp Ther Med. 2018;15(3):2941-5. https://doi.org/10.3892/etm.2018.5740.
24. Liu TC, Hsieh MJ, Wu WJ, Chou YE, Chiang WL, Yang SF, et al. Association between survivin genetic polymorphisms and epidermal growth factor receptor mutation in non-small-cell lung cancer. Int J Med Sci. 2016;13(12):929-35. https://

doi.org/10.7150/ijms.16875.
25. Borbély AA, Murvai M, Szarka K, Kónya J, Gergely L, Hernádi Z, et al. Survivin promoter polymorphism and cervical carcinogenesis. J Clin Pathol. 2007;60(3):303-6. https://doi.org/10.1136/jcp.2006.037804.
26. Cheng ZJ, Hu LH, Huang SJ. Correlation of -31g/c polymorphisms of survivin promoter to tumorigenesis of gastric carcinoma. Ai Zheng. 2008;27(3):258-63.
27. Jang JS, Kim KM, Kang KH, Choi JE, Lee WK, Kim CH, et al. Polymorphisms in the survivin gene and the risk of lung cancer. Lung cancer (Amsterdam, Netherlands). 2008;60(1):31-9. https://doi.org/10.1016/j.lungcan.2007.09.008.
28. Yang L, Zhu H, Zhou B, Gu H, Yan H, Tang N, et al. The association between the survivin c-31g polymorphism and gastric cancer risk in a chinese population. Dig Dis Sci. 2009;54(5):1021-8. https://doi.org/10.1007/s10620-008-0441-5.
29. Gazouli M, Tzanakis N, Rallis G, Theodoropoulos G, Papaconstantinou I, Kostakis A, et al. Survivin -31g/c promoter polymorphism and sporadic colorectal cancer. Int J Colorectal Dis. 2009;24(2):145-50. https://doi.org/10.1007/s00384-008-0601-2.
30. Wang YH, Chiou HY, Lin CT, Hsieh HY, Wu CC, Hsu CD, et al. Association between survivin gene promoter -31 c/g polymorphism and urothelial carcinoma risk in taiwanese population. Urology. 2009;73(3):670-4. https://doi.org/10.1016/j.urology.2008.09.048.
31. Antonacopoulou AG, Floratou K, Bravou V, Kottorou A, Dimitrakopoulos FI, Marousi S, et al. The survivin -31 snp in human colorectal cancer correlates with survivin splice variant expression and improved overall survival. Anal Cell Pathol (Amst). 2010;33(5):177-89. https://doi.org/10.3233/acp-clo-2010-0537.
32. Theodoropoulos GE, Michalopoulos NV, Panoussopoulos SG, Taka S, Gazouli M. Effects of caspase-9 and survivin gene polymorphisms in pancreatic cancer risk and tumor characteristics. Pancreas. 2010;39(7):976-80. https://doi.org/10.1097/MPA.0b013e3181d705d4.
33. Upadhyay R, Khurana R, Kumar S, Ghoshal UC, Mittal B. Role of survivin gene promoter polymorphism (-31g>c) in susceptibility and survival of esophageal cancer in northern india. Ann Surg Oncol. 2011;18(3):880-7. https://doi.org/10.1245/s10434-010-1371-y.
34. Borges Bdo N, Burbano RR, Harada ML. Survivin -31c/g polymorphism and gastric cancer risk in a brazilian population. Clin Exp Med. 2011;11(3):189-93. https://doi.org/10.1007/s10238-010-0122-5.
35. Yamak n, yaykasli ko, yilmaz u, eroz r, uzunlar ak, ankarali h, sahiner c, baltaci d. Association between survivin gene polymorphisms and the susceptibility to colon cancer development in the turkish population. Asian Pac J Cancer Prev. 2014;15(20):8963-7.
36. Kawata N, Tsuchiya N, Horikawa Y, Inoue T, Tsuruta H, Maita S, et al. Two survivin polymorphisms are cooperatively associated with bladder cancer susceptibility. Int J Cancer. 2011;129(8):1872-80. https://doi.org/10.1002/ijc.25850.
37. Hsieh YS, Tsai CM, Yeh CB, Yang SF, Hsieh YH, Weng CJ. Survivin t9809c, an snp located in 3'-utr, displays a correlation with the risk and clinicopathological development of hepatocellular carcinoma. Ann Surg Oncol. 2012;19 Suppl 3:S625-33. https://doi.org/10.1245/s10434-011-2123-3.
38. Weng CJ, Hsieh YH, Chen MK, Tsai CM, Lin CW, Yang SF. Survivin snp-carcinogen interactions in oral cancer. J Dent Res. 2012;91(4):358-63. https://doi.org/10.1177/0022034512438402.
39. Yazdani N, Sayahpour FA, Haghpanah V, Amiri P, Shahrabi-Farahani M, Moradi M, et al. Survivin gene polymorphism association with papillary thyroid carcinoma. Pathol Res Pract. 2012;208(2):100-3. https://doi.org/10.1016/j.prp.2011.12.009.
40. Li xb, li sn, yang zh, cao l, duan fl, sun xw. Polymorphisms of survivin and its protein expression are associated with colorectal cancer susceptibility in chinese population. DNA and cell biology. 2013 may 7;32(5).
41. Qin C, Cao Q, Li P, Ju X, Wang M, Chen J, et al. Functional promoter -31g>c variant in survivin gene is associated with risk and progression of renal cell cancer in a chinese population. PLoS One. 2012;7(1):e28829. https://doi.org/10.1371/journal.pone.0028829.
42. Zahedi P, Aminimoghaddam S, Sayahpour FA, Haghpanah V, Amiri P, Fereidoni F, et al. Association of survivin gene polymorphism with endometrial cancer. Int J Gynecol Cancer. 2012;22(1):35-7. https://doi.org/10.1097/IGC.0b013e318229902c.
43. Jaiswal PK, Goel A, Mandhani A, Mittal RD. Functional polymorphisms in promoter survivin gene and its association with susceptibility to bladder cancer in north indian cohort. Mol Biol Rep. 2012;39(5):5615-21. https://doi.org/10.1007/s11033-011-1366-1.
44. Bogdanovic L, Lazic M, Bogdanovic J, Soldatovic I, Nikolic N, Radunovic M, et al. Polymorphisms of survivin -31 g/c gene are associated with risk of urothelial carcinoma in serbian population. J buon. 2017;22(1):270-7.
45. Liarmakopoulos E, Theodoropoulos G, Vaiopoulou A, Rizos S, Aravantinos G, Kouraklis G, et al. Effects of stromal cell-derived factor-1 and survivin gene polymorphisms on gastric cancer risk. Mol Med Rep. 2013;7(3):887-92. https://doi.org/10.3892/mmr.2012.1247.
46. Marques I, Teixeira AL, Ferreira M, Assis J, Lobo F, Maurício J, et al. Influence of survivin (birc5) and caspase-9 (casp9) functional polymorphisms in renal cell carcinoma development: A study in a southern european population. Mol Biol Rep. 2013;40(8):4819-26. https://doi.org/10.1007/s11033-013-2578-3.
47. Aynaci E, Coskunpinar E, Eren A, Kum O, Oltulu YM, Akkaya N, et al. Association between survivin gene promoter -31g/c and -644c/t polymorphisms and non-small cell lung cancer. Genet Mol Res. 2013;12(3):3975-82. https://doi.org/10.4238/2013.February.28.9.
48. Chen J, Cui X, Zhou H, Qin C, Cao Q, Ju X, et al. Functional promoter -31g/c variant of survivin gene predict prostate cancer susceptibility among chinese: A case control study. BMC Cancer. 2013;13:356. https://doi.org/10.1186/1471-2407-13-356.
49. Kostić M, Nikolić N, Ilić B, Carkić J, Milenković S, Vukadinović M. Analysis of polymorphism in the survivin gene promoter as a potential risk factor for head and neck cancers development. Srp Arh Celok Lek. 2013;141(5-6):304-7. https://doi.org/10.2298/sarh1306304k.
50. Huang zm, chiang yt, tung mc, wu cc, chen kc, huang mt, et al. Survivin promoter rs9904341 polymorphism is associated with tumor stage and grade in patients with bladder cancer. Available from: Https://www.Scirp.Org/journal/paperinformation?Paperid=26861.
51. Aminimoghaddam S, Shahrabi-Farahani M, Mohajeri-Tehrani M, Amiri P, Fereidooni F, Larijani B, et al. Epistatic interaction between adiponectin and survivin gene polymorphisms in endometrial carcinoma. Pathol Res Pract. 2015;211(4):293-7. https://doi.org/10.1016/j.prp.2014.11.012.
52. Javid J, Mir R, Julka PK, Ray PC, Saxena A. Role of survivin re-expression in the development and progression of non-small cell lung cancer. Tumour Biol. 2015;36(7):5543-50.

https://doi.org/10.1007/s13277-015-3224-6.
53. Guo G, Zhang Q, Yu Z, Li J, Ding Z, Li J, et al. Correlation between survivin genetic polymorphisms and lung cancer susceptibility. Int J Clin Exp Pathol. 2015;8(6):7426-30.
54. Qin L, Yu T. Association between rs9904341 g<c gene polymorphism and susceptibility to pancreatic cancer in a chinese population. Genet Mol Res. 2015;14(2):5197-202. https://doi.org/10.4238/2015.May.18.10.
55. Osman D, Ali O, Obada M, El-Mezayen H, El-Said H. Chromatographic determination of some biomarkers of liver cirrhosis and hepatocellular carcinoma in egyptian patients. Biomed Chromatogr. 2017;31(6). https://doi.org/10.1002/bmc.3893.
56. Lin YC, Hour TC, Tsai YC, Huang SP, Wu WJ, Chen CH, et al. Preliminary evidence of polymorphisms of cell cycle regulatory genes and their roles in urinary tract urothelial cancer susceptibility and prognosis in a taiwan population. Urol Oncol. 2017;35(9):543.e7-.e16. https://doi.org/10.1016/j.urolonc.2016.08.001.
57. Bagheri Z, Mohamadynejad P, Moghanibashi M. Increased risk of gastric cancer in the cc genotype -31c/g polymorphism in survivin gene promoter. J gorgan univ med sci. 2017;19(3):32–7. .
58. Rasool i, wani ka, yousuf a, bhat ia, rah b, nazir su,et al. Role of the functional polymorphism of survivin gene (-31g/c) and risk of breast cancer in a north indian population. Clin breast cancer. 2018 aug 1;18(4):E671-6.
59. Karimian M, Aftabi Y, Mazoochi T, Babaei F, Khamechian T, Boojari H, et al. Survivin polymorphisms and susceptibility to prostate cancer: A genetic association study and an in silico analysis. Excli j. 2018;17:479-91. https://doi.org/10.17179/excli2018-1234.
60. Budak M, Bozkurt C, Cetin SE, Tuncel H. The -31 g/c promoter gene polymorphism of surviving in turkish colorectal cancers patients. Ceylon Med J. 2018;63(3):119-23. https://doi.org/10.4038/cmj.v63i3.8714.
61. Montaser b, amar m, ahmed m, fathy w. Association between survivin gene polymorphism and colorectal cancer. Menoufia Med J. 2019;32(1):296–300.
62. Mashadiyeva R, Cacına C, Arikan S, Turan Sürmen S, Demirkol Ş, Aksakal N, et al. The effect of survivin gene in breast cancer risk and prognosis. Turk J Biochem. 2021;48:000010151520210051. https://doi.org/10.1515/tjb-2021-0051.
63. Asadian F, Ghadyani M, Antikchi MH, Dastgheib SA, Neamatzadeh H, Sheikhpour E, et al. Association of epidermal growth factor 61a>g, survivin -31g>c, and efna1 -1732g>a polymorphisms with susceptibility to colorectal cancer. Journal of Gastrointestinal Cancer. 2022;53(1):78-83. https://doi.org/10.1007/s12029-020-00551-4.
64. Hengartner MO. The biochemistry of apoptosis. Nature. 2000;407(6805):770-6. https://doi.org/10.1038/35037710.
65. Shojaei F, Yazdani-Nafchi F, Banitalebi-Dehkordi M, Chehelgerdi M, Khorramian-Ghahfarokhi M. Trace of survivin in cancer. Eur J Cancer Prev. 2019;28(4):365-72. https://doi.org/10.1097/cej.0000000000000453.
66. Xu Y, Fang F, Ludewig G, Jones G, Jones D. A mutation found in the promoter region of the human survivin gene is correlated to overexpression of survivin in cancer cells. DNA Cell Biol. 2004;23(7):419-29. https://doi.org/10.1089/1044549041474788.

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