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Role of P53 in oral squamous cell carcinoma; a systematic review with meta-analysis

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Abstract.

Background: studies on the association between a polymorphism in the human tumour suppressor p53 (TP53) and the likelihood of developing oral squamous cell carcinoma (OSCC) have produced widely varying results. Therefore, the purpose of this review is to inquire into the function of p53 in oral squamous cell cancer.

Methods: Studies that provided complete data on the genotype frequency of TP53 polymorphism in OSCC/OL patients and healthy controls were carefully selected from a comprehensive search of the scientific literature for case-control studies relevant to the study objectives. To analyses the impact of TP53 on patients' susceptibility to OSCC, we calculated P values (P values for association testing), odds ratios (ORs), and ORs with 95% confidence intervals (CIs). Eleven studies with relevant data were included, and these were found using google scholar, pubmed, and Science direct.

Results: There were twenty case-control studies that met the criteria. All six genetic models (allele C versus G, PA = 0.741; carrier C versus G, PA = 0.853; homozygote CC versus GG, PA = 0.085; heterozygote GC versus GG, PA = 0.882; dominant GC + CC versus GG, PA = 0.969; recessive CC versus GG + GC, PA = 0.966) did not show an increased or decreased risk of OSCC. Furthermore, most meta-analyses of subgroups did not find a significant difference between cases and controls (PA > 0.05). Our meta-analysis of research on OSCC using Bag's and Egger's tests revealed no significant indication of publication bias among the included articles. The sensitivity analysis has led us to these probable outcomes.

Conclusions: There is no correlation between TP53 rs1042522 and the risk of oral squamous cell carcinoma, according to our updated meta-analysis and prior studies. Our meta-analysis also found something else that came as a surprise: patients with oral leukoplakia are not at risk due to the TP53 rs1042522 polymorphism. Additional high-quality case-control studies are required to determine whether the TP53 rs1042522 polymorphism affects the risk of oral leukoplakia and oral squamous cell carcinoma.

Keywords: TP53, OSCC, Polymorphism, Meta-analysis, cell carcinoma, oral squamous cell.

Background.

The p53 (TP53) gene that acts as a tumour suppressor in humans is found on 17p13. It plays a role in regulating cell division, triggering apoptosis (programmed cell death), and preserving genomic stability. Certain variants of the TP53 gene have been linked to cancer development in humans (Ramos-Garcia, P., et al. (2022). The TP53Arg72Pro mutation, caused by the common rs1042522 G/C polymorphism in

exon 4 of TP53, is thought to impair the protein's proper function and be linked to an increased risk of a wide variety of clinical disorders (including colorectal cancer, endometriosis, and type 2 diabetes) (Mulder, F. J., et al., 2021).

The goal of this research is to establish whether or not the TP53 mutation rs1042522 is associated with an increased risk of oral squamous cell carcinoma (OSCC). The most common form of oral cancer, known as oral squamous cell carcinoma (OSCC), begins in the thin, flat cells that line the mouth and throat. White or grey keratosis on the oral mucosa is the hallmark of oral keratosis (OL), a precancerous disease. Human papillomavirus (HPV) infection, functional abnormalities, and behavioral variables like smoking, drinking, and chewing tobacco have all been linked to the development of esophageal squamous cell carcinoma (OSCC) (Almangush, A., et al., 2017).

There are presently contradictory data about the link between the TP53 gene and risks of OSCC in various populations. An increased risk of oral potentially malignant diseases (OPMD) in Argentine patients has been linked to TP53, for instance. A possible association between TP53 and elevated OSCC risk was discovered through research on the Indian population. An independent study conducted in India found a negative genetic association between TP53 and the risk of oral squamous cell cancer. Patients in Italy who have the GC genotype of TP53 may have a lower chance of developing OSCC. Accordingly, TP53 in the patient's genetic makeup in predicting their risk for OSCC is clarified by the meta-analysis (Ramos-Garcia, P., et al. (2018).

Unfortunately, we were unable to find any meta-analyses that have been conducted on the TP53 rs1042522 variant. There have only been two meta-analyses reported to far (Liu, R., et al. (2021) that look at the connection between the TP53 rs1042522 variation and OSCC risk, despite its potential significance. Based on recent publications of case-control studies, we performed a meta-analysis, rigorously screened the papers included in our analysis, and synthesized the data quantitatively to reevaluate the potential difference of TP53 rs1042522 in OSCC patients and negative controls (Awawdeh, M. A., et al. (2023).

When it comes to head and neck cancers, oral squamous cell carcinoma (OSCC) is a major cause for concern around the world. The oral cavity is a complex anatomical region important for communication, mastication, and overall quality of life. It consists of the lips, tongue, buccal mucosa, floor of the mouth, and other connected tissues. Tobacco use, heavy alcohol consumption, use of betel nuts, and human papillomavirus (HPV) infection are only a few of the environmental risk factors that make this area more susceptible to carcinogenic insults. Due in large part to these risk factors, OSCC is extremely common, with an estimated 300,000 new cases diagnosed annually around the world (Sun, Z., Gao, W., & Cui, J. T. (2018).

The development of OSCC tumours involves multiple factors, including the accumulation of genetic and epigenetic changes. The TP53 gene, which codes for the P53 tumour suppressor protein, has received particular attention. Genomic stability relies heavily on P53's ability to regulate cell cycle arrest, apoptosis, and DNA repair in response to cellular stress. Many types of cancer are strongly linked to P53 dysregulation, which occurs frequently owing to mutations or changed expression and is commonly present at the time of cancer onset or development (Parwaiz, I., et al. (2019).

While the significance of P53 in cancer is well established, the exact role it plays in OSCC is still being investigated and debated. P53 expression, mutations, and their significance in OSCC have been the subject of a great deal of research. P53 changes have been linked to aggressive tumour behavior and poor patient outcomes, and some research suggests they occur often in OSCC. However, there are also contradicting findings, calling into doubt the precise nature and relevance of P53 dysregulation in OSCC (Dioguardi, M., et al. (2022).

The necessity for a comprehensive review and meta-analysis to integrate the available evidence on the involvement of P53 in OSCC is highlighted by this uncertainty in the literature. A more in-depth knowledge of P53's role in OSCC pathogenesis and its potential as a diagnostic biomarker and therapeutic target can be gained from such an investigation. In order to better manage OSCC, early identification, risk stratification, and treatment options, it is crucial to determine if P53 can be used to do so. More research on P53's therapeutic potential in OSCC is needed because of the rise of precision medicine and targeted medicines in cancer treatment (Hosmani, J., et al. (2021).

This study attempts to fill in the gaps in our understanding of P53's function in OSCC by doing a comprehensive literature review, synthesizing the results, and providing a more nuanced point of view. The findings of this research may help improve clinical decision-making, patient outcomes, and the effectiveness of therapies targeting oral squamous cell cancer.

Objectives.

This research aims to achieve the following:

- Review Existing Literature of the current literature to consolidate and critically analyze studies related to P53 in OSCC.
- Perform a Meta-Analysis data from selected studies to provide a comprehensive overview of P53 expression levels, mutations, and their associations with clinical outcomes in OSCC patients.
- To Determine the Role of P53 in OSCC, including its impact on tumor initiation, progression, and patient prognosis.
- Examine P53 as a Biomarker for OSCC, with a focus on its sensitivity and specificity.

- Explore Therapeutic Implications of P53 in OSCC, examining whether targeting P53 or its associated pathways could be a viable approach to improve patient outcomes.
- Offer clear insights into the role of P53 in OSCC, resolving any existing controversies and providing recommendations for its clinical and research implications.

Rationale.

Research into P53's role in oral squamous cell carcinoma (OSCC) is being conducted because of the pressing need to lessen the massive toll this cancer has on society. The worldwide prevalence and lethality of OSCC highlights its clinical significance. The complicated anatomical region it affects and the difficulties connected with its diagnosis and treatment have a significant effect on both individual quality of life and the healthcare system. It is crucial to better understand OSCC and uncover factors that play a major role in its aetiology and clinical behavior due to its high prevalence and large impact.

P53 is a well-studied tumour suppressor protein that plays a pivotal function in preserving genomic stability across a wide range of cancers. Since P53 dysregulation via mutations or changed expression is so prevalent in cancer, it is an attractive research target for ovarian squamous cell carcinoma (OSCC). Conflicting findings in the available literature further confound attempts to determine P53's role in this particular malignancy. Getting to the bottom of these disparities is crucial for advancing our knowledge of OSCC, as it may have far-reaching implications for the creation of better diagnostic and treatment approaches.

With the rise of precision medicine and targeted medicines in oncology, P53 deserves additional investigation as a therapeutic target in OSCC. The potential for vastly improved patient outcomes hinges on our ability to better understand the role of P53 in the pathogenesis of OSCC. The potential to revolutionize clinical practise through earlier intervention and improved treatment outcomes is further highlighted by the finding of P53 as a reliable biomarker for early detection of OSCC.

In view of these facts, our study was inspired by the need to settle the debate over P53's function in OSCC, evaluate its diagnostic and prognostic use, and uncover its therapeutic potential. The study's goals are to improve clinical decision-making, patient outcomes, and the creation of more effective therapies for oral squamous cell carcinoma by providing clarity and recommendations that address these issues.

Materials and methods.

- Database searching:

Our studies adhered to the PRISMA standards. The PRISMA 2009 Checklist is in the First Additional File. No restrictions on language or time period were set on the articles found during the June 2018

search of PUBMED, WOS, and EMBASE. The PICOS framework was used, which stands for population, intervention, comparison, outcomes, and study designs. Patients with OSCC were the "population," while TP53 gene polymorphism was the "intervention." The electronic database search was conducted without limiting the search to verifying the "comparator" (negative control), "outcomes" (OSCC risk), or "study designs" (case-control study) in order to prevent bias. Terms for indexing are included in File 2. All of the duplicates were removed thanks to Endnote X7's "Find Duplicates" function (Thomson Reuters, Philadelphia, PA, USA).

- Inclusion and exclusion criteria:

Using the PICOS method and our inclusion and exclusion criteria, ZS and WG independently screened and evaluated the articles for eligibility. criteria for admittance: Oral squamous cell carcinoma (OSCC) risk can be evaluated using six genetic models: (P) patients with OSCC and oral leukoplakia; (I) focusing on the TP53 rs1042522 polymorphism; (C) negative controls; and (O) the finished genotype distribution of GG, GC, and CC. (Exclusion criteria are as follows: (P) data from animals or cells; (I) data from other diseases; (C) lack of a control group; (O) lack of complete genotype frequency data in both the case and control groups; and (I) data from other genes, variants, or an unconfirmed TP53 mutation site.

- Data collection and quality assessment:

The most important parameters, such as genotype frequency, were collected with great care and are reported in Tables (method, age, gender, smoking, alcohol, location, ethnicity, disease type). Email was used to transmit the missing data. The NOS (Newcastle-Ottawa quality evaluation Scale) assigns a score between 1 and 9 to each study to determine its overall quality. You have outstanding qualities if your NOS score is above 5. We had to have a serious discussion about the quality evaluation issue because it was so divisive.

- Association and heterogeneity test:

STATA 12.0 (Stata Corporation; Texas, USA) was used for statistical testing and data collection. Six genetic models (C versus G allele, C versus G carrier, CC versus GG homozygote, GC versus GG heterozygote, GC + CC versus GG dominant, and CC versus (recessive)) were used to determine two-sided P-values of association tests, pooled odds ratios (ORs), and 95% confidence intervals (CIs). P 0.05 and OR > 1 indicate an increased risk of OSCC due to the TP53 C minor allele. The Q statistic and I2 test were used to evaluate the degree of consistency between investigations. When the Q Statistic P-value is less than 0.05 or the I2 value is larger than 50%, a DerSimonian and Laird random-effect model for large heterogeneity is used. Otherwise, fixed-effect models based on the work of Mantel-Haenszel

were used. OSCC subtype (oral cavity vs. HPV16 /+), control source (population vs. hospital), race (White vs. Asian), place of origin (India, United States of America, and China), and region were all used in the subgroup analyses.

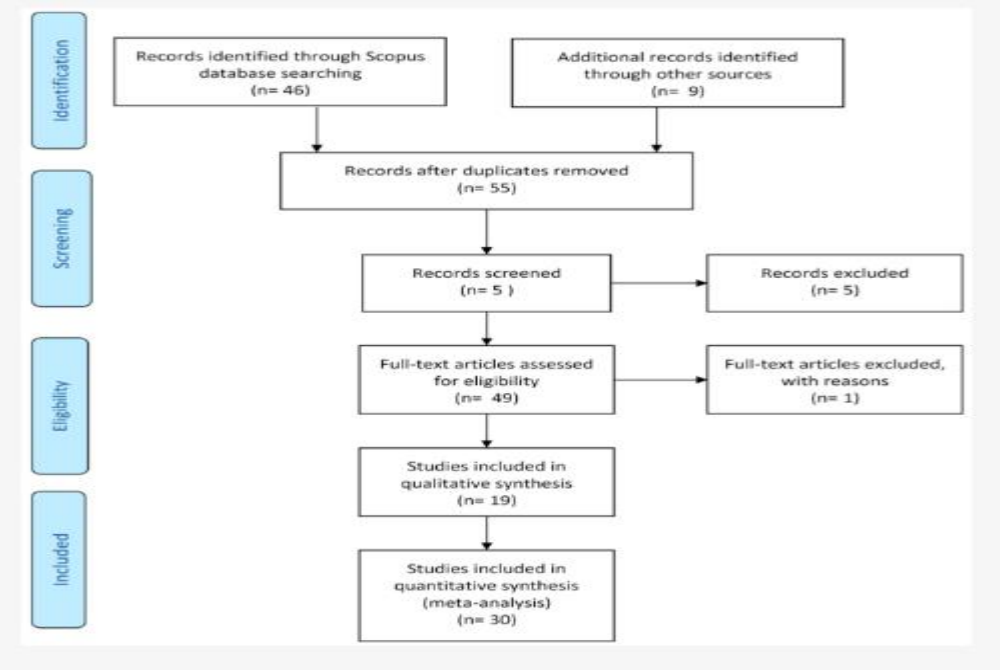

Figure 1:The PRISMA 2009 flow diagram of the study.

Results.

- Study selection and characteristics:

Figure 1 is a visual depiction of the research process that went into creating the PRISMA 2009 database. Searches of PUBMED (n = 31), WOS (n = 84), and EMBASE (n = 28) yielded a total of 143 records. Only 137 records were left after we eliminated the duplicates. A total of 114 records were excluded after the initial screening of titles and abstracts due to the following reasons: animal or cell data, other disease, or unconfirmed OSCC (n = 31); other genes, other variants, or an unconfirmed TP53 mutation site (n = 35); lack of a control group, or lack of full genotype frequency data in both the case and control groups (n = 21); metanalysis, review, and meeting abstracts (n = 27). The next step was to assess the significance of 23 longer publications. In three of these papers, the genotype distributions significantly diverged from HWE. Twenty papers were included in our quantitative synthesis. Sixteen of these investigations concerned oral squamous cell carcinoma (OSCC). Additional Files 3 and 4 contain introductory data and genotype frequencies from the included studies, respectively. Data from the NOS assessment system (Additional file 5) shows that all of the recruited case-control studies are of excellent quality, with NOS quality scores above five.

- TP53 rs1042522 and OSCC risk:

The meta-analysis of TP53 rs1042522 and OSCC risk started with data from 17 case-control studies in 16 papers, including a total of 3047 patients and 3305 controls. Allele C versus G [I 2 = 55.0%, PH (P-value of heterogeneity = 0.003) and dominant GC + CC versus GG [I 2 = 47.6%, PH = 0.015] and all three genetic models show considerable heterogeneity, as shown in Table 1. (An Algorithm Based on Laird's and DerSimon's Work) For these individuals, we used a fixed-effects model (the Mantel-Haenszel method). Conclusions Six different genetic models were used to compile the data shown in Table 1: allele C versus G (PA (P-value of association test) =0.741], carrier C versus G (PA =0.853), homozygote CC versus GG (PA =0.085), heterozygote GC versus GG (PA =0.882), dominant GC + CC versus GG (PA =0.969), and recessive CC versus GG (PA =0.969)). Fig. 2 is a forest plot showing the C versus G allele model data. Also, meta-analyses were conducted on subgroups defined by race, ethnicity, and the presence or absence of the human papillomavirus type 16 in the oral cavity.

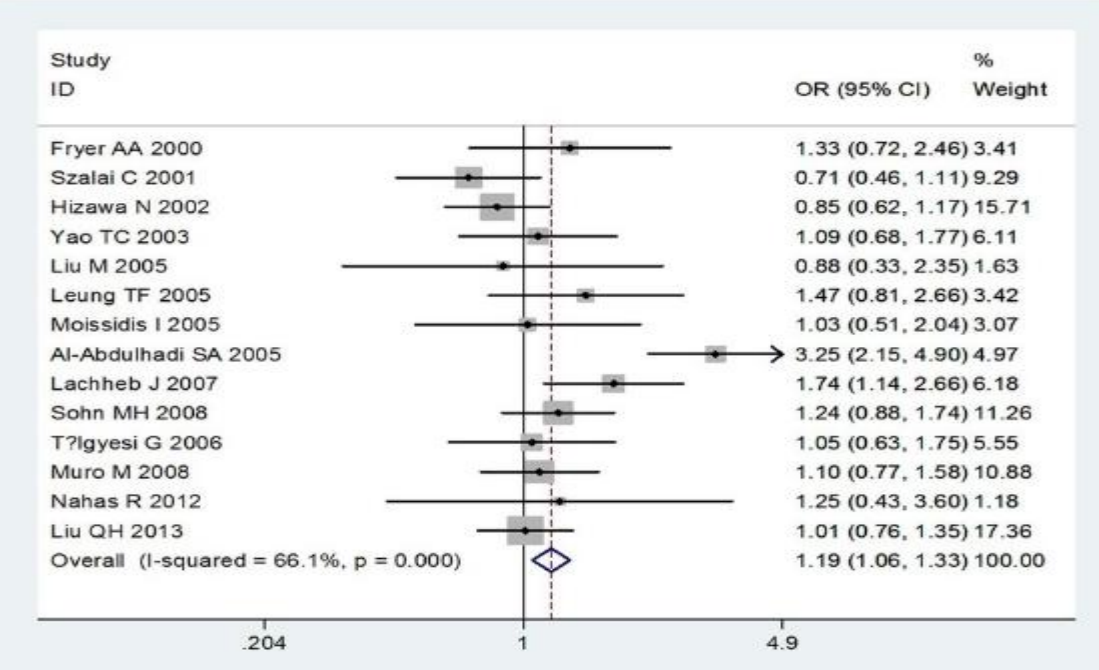

Figure 2:Meta-analysis (allele C vs. G) of TP53 rs1042522 and OSCC risk.

Data from 17 case-control studies in 16 papers, involving a total of 3047 patients and 3305 controls, were the basis for the meta-analysis of TP53 rs1042522 and OSCC risk. Table 1 shows that there is a significant amount of genetic variation between the three investigated models (allele C vs. G [I 2 = 55.0%, PH (P-value of heterogeneity = 0.003) and dominant GC + CC vs. GG [I 2 = 47.6%, PH = 0.015]). (An Algorithm Developed From Laird's and DerSimonian's Research) A fixed-effects model (the Mantel-Haenszel method) was used to analyses the data from the participants in this study. Conclusions Table 1 summarizes results from six genetic models: allele C versus G (PA (P-value of association test) =0.741], carrier C versus G (PA =0.853), homozygote CC versus GG (PA =0.085),

heterozygote GC versus GG (PA =0.882), dominant GC + CC versus GG (PA =0.969), and recessive CC versus GG (PA =0.969). Forest plot (Fig. 2) showing C allele model data compared to G allele model data. Subgroup meta-analyses for the oral cavity/HPV16 (/+), Caucasians, Asians, Indians, and Chinese were also performed.

Table 1:Meta-analysis of TP53 rs1042522 and OSCC risk (Continued),Meta-analysis of TP53 rs1042522 and OSCC risk.

Author	year	Region	study base	Event	N	Response rate	Quality score	prevalence with it is 95% CI
Animaw et al. [31]	2014	Amhara	community based	461	630	100%	9	73% (70,76)
Etana and Deressa [32]	2012	Oromia	community based	193	536	100%	9	36% (32,40)
Gualu and Dilie [33]	2017	Amhara	community based	256	288	96.80%	9	89% (85,92)
Hailu et al. [8]	2019	SNNP	community based	483	1116	82.70%	10	43% (40,46)
Girmay and Dadi [25]	2019	Tegrai	community based	480	620	99.50%	10	77% (74,81)
Kassahun et al. [34]	2915	Amhara	community based	566	751	99.20%	9	75% (72,78)
Lake et al. [35]	2016	Amhara	community based	472	724	100%	6	65% (62,69)
Legesse and Dechasa [36]	2015	Oromia	community based	393	519	98.50%	9	76% (72,79)
Mekonnen et al. [37]	2019	Amhara	community based	423	566	98.80%	10	75% (71,78)
Meleko et al. [38]	2017	SNNP	community based	295	322	100%	9	92% (88,94)
Mohammed and Atomsa [39]	2013	Oromia	community based	155	685	98.70%	8	23% (20,26)
Mohamud et al. [40]	2014	Somali	community based	213	582	100%	9	37% (33,41)
Tefera et al. [27]	2018	SNNP	community based	295	484	89.60%	7	61%(57,65)
Fite and Haili [41]	2019	SNNP	community based	130	173	100%	4	75%(68,81)
Tesfaye et al. [42]	2018	Amhara	community based	494	846	98.11%	9	58% (55,62)
Wado et al. [43]	2014	Oromia	community based	329	889	100%	7	37% (34,40)
Yismaw et al. [44]	2019	Amhara	community based	228	301	100%	9	76% (71,80)
Beyene et al. [45]	2013	Afar	community based	157	762	97.10%	7	21% (1824)
Mebrahtom and Birhane [46]	2013	Afar	community based	124	1534	98.30%	9	8% (7.0,10)
Debie and Taye [47]	2014	Amhara	community based	236	479	100%	7	49% (45,54)
Facha W [48]	2015	SNNP	community based	112	210	100%	8	53% (47,60)
Ebrahim and Beyene [49]	2015	Amhara	community based	531	639	97.60%	9	83% (80,86)
Tessema et al. [50]	2019	pastoral/semi-pastoral	community based	255	600	96.60%	9	43% (39,47)
Kidane et al. [51]	2019	pastoral/semi-pastoral	community based	256	600	97%	9	43% (39,46)
Porth et al. [52]	2019	SNNP	community based	174	232	100%	6	75% (69,80)
EDHS [53]	2011	National	Survey	470	1930	97%	10	24% (22,26)
EDHS [16]	2016	National	Survey	781	2004	98%	10	39% (37,41)
EDHS [15]	2019	National	Survey	443	1026	99%	10	43% (40,46)

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Fault system	Cont. or seg.	Length (km)	Strike	$M_0 \times 10^{20}$ (Nm)	M_W	M_w range	Slip (m)	Plate motion component (m)	Rate (mm/year)	Plate motion azimuth	Overlap	Recurrence period (year)
Livingstone[a]	C	95	135	5.6	7.8	7.4–8.0	5.7	3.7	3.8 ± 0.7	85 ± 4	N	1,000
	S1	32		0.5	7.1	6.5–7.3	1.9	1.3				300
	S2	32		0.5	7.1	6.5–7.3	1.9	1.3				300
	S3	32		0.5	7.1	6.5–7.3	1.9	1.3				300
Usisya[b]	C	145	2	13.1	8.0	7.6–8.2	8.7	7.5	3.5 ± 0.7	85 ± 4	Y	4,300
	S1	32		0.6	7.2	6.5–7.3	1.9	1.7				900
	S2	48		1.4	7.4	6.9–7.6	2.9	2.5				1,400
	S3	65		2.6	7.6	7.1–7.7	3.9	3.4				1,900
Mbamba[c]	C	116	162	8.4	7.9	7.5–8.1	7.0	5.8	3.5 ± 0.7	87 ± 4	Y	3,300
	S1	29	162	0.5	7.1	6.4–7.3	1.7	1.5				800
	S2	29	162	0.5	7.1	6.4–7.3	1.7	1.5				800
	S3	29	162	0.5	7.1	6.4–7.3	1.7	1.5				800
	S4	29	162	0.5	7.1	6.4–7.3	1.7	1.5				800
Bandwe[c]	C	90	28	5.1	7.8	7.3–7.9	5.4	3.9	3.3 ± 0.7	85 ± 4	Y	2,300
	S1	30	28	0.6	7.1	6.5–7.3	1.8	1.3				800
	S2	30	28	0.6	7.1	6.5–7.3	1.8	1.3				800
	S3	30	28	0.6	7.1	6.5–7.3	1.8	1.3				800
Metangula[c]	C	160	174	16.0	8.1	7.7–8.3	9.6	8.3	3.2 ± 0.7	87 ± 4	N	2,600
	S1	54	174	1.8	7.5	7.0–7.6	3.2	2.8				900
	S2	35	174	0.8	7.2	6.6–7.4	2.1	1.8				600
	S3	35	174	0.8	7.2	6.6–7.4	2.1	1.8				600
	S4	35	174	0.8	7.2	6.6–7.4	2.1	1.8				600

Table 2:Meta-analysis of TP53 rs1042522 and OL risk.

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Analyte	ISTD†	Retention Time (min)	Target ion *m/z*	Confirming ions *m/z* (% to target ion)	Calibration range (µg/L)	Standard curve (R^2)	Purity (%)	CAS No.	Source‡
d_5-Ethyl butanoate	(1)	7.53	93	34 (94.96), 116 (31.65)			100		Lincoln
d_3-Isoamyl acetate	(2)	11.89	46	90 (18.19), 76 (9.82)			100		Lincoln
d_5-Ethyl hexanoate	(3)	16.11	93	120 (8.90), 34 (17.56)			100		Lincoln
d_{13}-Hexan-1-ol	(4)	18.68	62	50 (35.49), 78 (31.13)			98	16416-34-5	Sigma-Aldrich
d_5-Ethyl octanoate	(5)	22.99	93	106 (36.32), 74 (29.03)			100		Lincoln
d_6-Benzaldehyde	(6)	24.02	110	54 (36.98), 82 (88.45)			98	17901-93-8	Sigma-Aldrich
d_5-Ethyl decanoate	(7)	29.27	93	106 (43.61), 148 (4.84)			97		Lincoln
d_5-1-Phenyl ethanol	(8)	29.30	112	84 (85.99), 127 (26.95)			98	90162-45-1	Isotech
Ethyl 2-methyl propanoate	1	7.53	71	88 (33.41), 116 (31.65)	0–939	0.99	99	97-62-1	Sigma-Aldrich
Ethyl butanoate	1	9.36	88	101 (16.9), 60 (32.16)	0–451	0.99	99	105-54-4	Sigma-Aldrich
Ethyl 3-methyl butanoate	1	10.43	88	85 (73.60), 57 (51.36)	0–98	0.99	98	108-64-5	Sigma-Aldrich
Isoamyl acetate	2	11.99	43	87 (18.65), 73 (11.56)	0–3,659	0.99	99	123-92-2	Sigma-Aldrich
Ethyl pentanoate	1	12.46	88	85 (94.39), 101 (30.90)	0–12	0.99	98	539-82-2	Sigma-Aldrich
3-Methyl-1-butanol	4	14.76	55	70 (62.8), 42 (54.3)	0–243 902	0.90	99	123-51-3	Sigma-Aldrich
Ethyl hexanoate	3	16.24	88	115 (10.04), 60 (31.02)	0–732	0.99	99	123-66-0	Sigma-Aldrich
Hexan-1-ol	4	19.00	56	55 (52.03), 84 (6.50)	0–6098	0.99	99	111-27-3	Sigma-Aldrich
trans-3-Hexen-1-ol	4	19.20	67	82 (64.50)	0–366	0.99	98	928-97-2	Sigma-Aldrich
Ethyl heptanoate	3	19.70	88	113 (36.28)	0–12	0.99	98	106-30-9	Sigma-Aldrich
cis-3-Hexen-1-ol	4	19.90	67	82 (48.46), 107 (15.82)	0–364	0.99	98	928-96-1	Sigma-Aldrich
Ethyl octanoate	5	23.12	88	101 (38.67), 129 (11.52)	0–910	0.99	99	106-32-1	Sigma-Aldrich
Benzaldehyde	6	24.00	106	21 (33.56), 77 (90.85)	0–42	0.99	98	100-52-7	Sigma-Aldrich
Ethyl decanoate	7	29.30	88	101 (43.47), 143 (5.48)	0–884	0.98	99	110-38-3	Sigma-Aldrich
2-Phenyl ethanol	8	34.50	91	92 (57.09), 122 (31.51)	0–48 780	0.99	99	60-12-8	Sigma-Aldrich

†ISTD, internal standard. ‡Lincoln University, Lincoln, Canterbury, New Zealand; Sigma-Aldrich, Auckland, New Zealand; Isotech, Singapore .

Table 1 and the appendices 6, 7, 8, and 9 reveal that there is no discernible pattern between the cases and controls. In the heterozygote model, only the Caucasian subgroup (PA=0.030) and the HPV16(+) subgroup (PA=0.031) stand out. After considering these findings, it seems that TP53 rs1042522 may not significantly affect the risk of oral squamous cell carcinoma.

- TP53 rs1042522 risk:

This meta-analysis of TP53 rs1042522 and OL risk combines information from six case-control studies

consisting of a total of 391 cases and 763 controls, taken from five separate papers. The carrier (I2 = 41.0%, PH = 0.132) and heterozygote (I2 = 45.2%, PH = 0.110) models were analyzed using a fixed-effects model (Mantel-Haenszel technique), whereas the remaining alleles were analyzed using a random-effects model (DerSimonian and Laird method) due to high levels of heterogeneity (I2 > 50.0%). To sum up, no meta-analysis genetic model showed a significant difference between patients and controls (Table 2, PA > 0.05). Similar negative results were found after stratifying by PB, India, and Asia (Table 2, PA > 0.05), even after excluding the homozygote (PA = 0.003) and recessive (PA = 0.004) model of PB. Fig. 3 and Additional Files 10-12 depict the forest plots. Additional evidence suggests TP53 rs1042522 is not implicated in oral leukoplakia susceptibility, and these results support that hypothesis.

- Publication bias and sensitivity analysis:

To subjectively evaluate the existence of publication bias, we used Begg's test and Egger's test. We focused our meta-analysis on investigating publication bias in OSCC studies because there were less than ten case-control studies devoted to OL. Both Begg's and Egger's tests yielded P-values larger than.05 for all of these genetic models, as shown in Table 3. Figure 4A displays the Begg's funnel plot for the allele model, and Figure 4B displays the Egger's publication bias plot. As a result, we may be confident that our findings were not skewed by a significant publication bias. Consistent OR values throughout sensitivity and full analyses (Fig. 5 for the OSCC allele model; Additional file 13 for the OL allele model; and additional data not shown) lend credence to our findings.

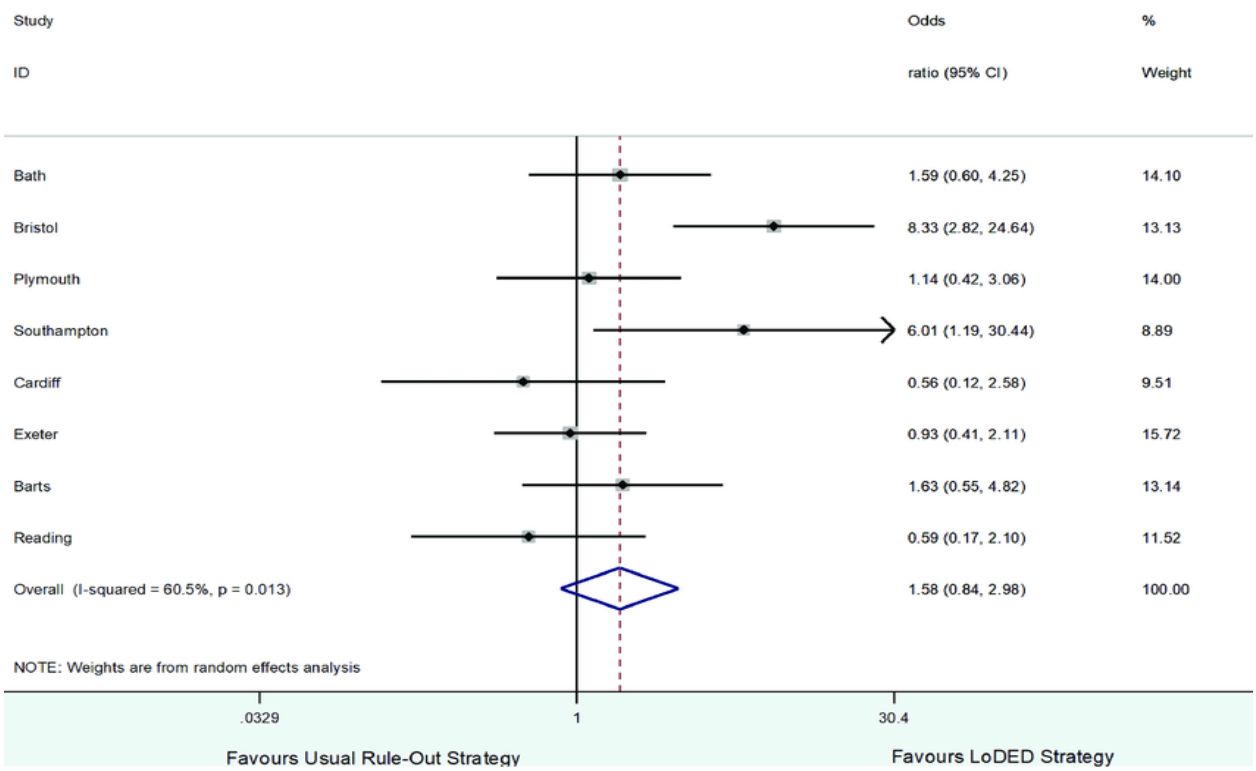

Figure 3:Meta-analysis (allele C vs. G) of TP53 rs1042522.

Table 3:Publication bias evaluation.

Genetic models	Begg's test*		Egger's test	
	z	P_B	t	P_E
allele C vs. G	1.03	0.303	0.88	0.393
carrier C vs. G	0.78	0.434	0.52	0.609
homozygote CC vs. GG	0.78	0.434	1.51	0.152
heterozygote GC vs. GG	0.95	0.343	0.19	0.856
dominant GC + CC vs. GG	0.78	0.434	0.69	0.504
recessive CC vs. GG + GC	0.87	0.387	1.63	0.124

*continuity corrected; OSCC, oral squamous cell carcinoma;
OL, oral leukoplakia; P_B, P value of Begg's test; P_E, P value of Egger's test

Author	year	Objectives	Results	methods	Conclusion
Ramos-Garcia, P., et al.	2018	To determine if overexpression	There were 31 studies that met the criteria	To find research published before	These results suggest that CD1

		of cyclin D1 (CD1) in OSCC affects survival.	(2942). Qualitative analysis revealed a particularly significant potential for bias in the research confounding domain. The greater the T status and the N+ status, as well as the overexpression of CD1, were associated with decreased overall and disease-free survival (HR = 1.46, 95% CI = 1.13-1.87, p = 0.001; OR = 1.51, 95% CI = 1.07-2.13, p = 0.02). Except for time to disease onset and clinical stage, we found variation across all metrics. Minor studies had an effect on T and N status. CD1 overexpression was most strongly linked to worse SCC growth in the tongue. Further, a threshold of 10% cancer cells expressing nuclear CD1 preserved the majority of meaningful	August 2017, we looked via Pubmed, Embase, Web of Science, and Scopus. QUIPS was used to evaluate the quality of the studies. Effects of CD1 overexpression on overall and disease-free survival, T and N status, stage, and histological degree were analysed using a meta-analysis. We looked at issues like research diversity, study size impacts, and subgroup analysis.	overexpression can be evaluated immunohistochemically and could serve as a predictive biomarker for OSCC.

			associations.		
Liu, R., et al.	2021	Examining the role of PCNA and p53 in people who have been diagnosed with oral squamous cell carcinoma (OSCC).	There were 9 eligible studies. The percentage of OSCCs with high PCNA expression (>50%) compared to those with low PCNA expression (50%) was statistically significant (OR =3.88; 95% CI: 2.04-7.37; P0.0001; I2=0%). The odds ratio (OR) between OSCC and p53 was 1.60 (95% CI, 0.18-14.63; P=0.68; I2=86%). A decreased PCNA expression was associated with a longer overall survival time for patients with OSCC (OR =0.47; 95% CI: 0.27-0.80; P=0.005; I2=41%) during a five-year period. There was a significant difference between the 5-year survival rates of the p53-negative and p53-positive groups, with the former having a significantly better	Full-text studies on PCNA and p53 in OSCC patients were sourced from PubMed, Embase, the Cochrane library, and the China National Knowledge Database. Review Manager 5.2 was used to quantify the impact of the findings on the chosen articles. Forest plots, a network of significance table, sensitivity analysis, and bias analysis were also carried out.	Patients with OSCC may benefit from using PCNA and p53 for prognostic and survival analysis.

			prognosis. No difference in metastasis was seen between high and low PCNA (OR =0.80, 95% CI: 0.18-3.45, I2=63%, P of over effect =0.76). The odds ratio (OR) between p53 and metastasis was 0.38 (95% confidence interval [CI]: 0.13-1.10, I2=0%, P of over effect = 0.07).		
Mulder, F. J., et al.	2021	This review compiled the most up-to-date molecular data on head and neck squamous cell carcinoma (HNSCC) among never-smokers and abstainers.	In total, 902 separate studies were reviewed, with 74 contributing to the quantitative synthesis and 24 to the meta-analysis. In 38 research, HPV was reported as a molecular parameter, followed by p16 (23 studies) and TP53 (14 studies). There were a wide range of other molecular characteristics, but they only applied to isolated instances of NSND.	A comprehensive search of PubMed, Embase, and Google Scholar was conducted according to the PRISMA standards.	When compared to tumors caused by smoking and drinking, HPV and p16 overexpression are more commonly associated with HNSCC in NSND. TP53 mutations were found in one-third of virus-negative tumours, and their mutational profile was more closely linked to ageing and UV radiation exposure than to tobacco use.

Ramos-García, P., González-Moles, M. Á., & Warnakulasuriya, S.	2022	The goal of this review is to assess the available data concerning the utility of p53 overexpression as a biomarker of the risk of malignant transformation in oral potentially malignant disorders (OPMD).	In total, 24 studies were included (1,210 patients). The risk was increased by a factor of 2 when P53 was overexpressed (RR = 1.88, 95%CI = 1.39-2.56, p 0.001). Subgroup meta-analysis confirmed this significant association with LEUCOPLakia (p = 0.002). Anti-p53 DO7 antibody (p = 0.001), high concentration (dilution 1: 100, p 0.001), overnight incubation (p = 0.02), and low temperature (4 °C, p = 0.007) in immunohistochemical method yielded the best results of the subgroups analysed. Overexpression of p53 was related with an increased risk of oral cancer in a meta-regression analysis that controlled for the presence of epithelial dysplasia (p > 0.05).	We looked for cross-sectional studies on p53 overexpression by immunohistochemistry published before July 2021 in PubMed, Embase, Web of Science, and Scopus. We utilised QUIPS to evaluate the standard of the primary research. Meta-analyses, subgroup analyses, meta-regression analyses, sensitivity analyses, and evaluations of the impacts of small studies were used to assess the consistency and robustness of the results.	Our meta-analysis and systematic review confirm that p53 overexpression is useful for predicting OPMD's propensity to undergo malignant transformation.

Yang, Z. C., et al.	2016	This study seeks to answer the question, "Do patients with oral squamous cell carcinoma benefit from the presence of p53 antibodies as a prognostic indicator?" Review of existing literature using meta-analysis	Only 7 of the 150 research on p53 antibody serum levels were considered. The quality was above average (QUADAS score7) at 85.7% (6/7). PLR 2.06 [95% CI: 1.35-3.15], NLR 0.85, and DOR 2.47 were calculated as a summary estimate from a quantitative study of blood p53 antibodies for the diagnosis of squamous cell carcinoma.	Without any language constraints, we searched every article published in PubMed and Embase up until October 31, 2014. QUADAS was used to evaluate the quality of studies investigating diagnostic accuracy. DORs and SROC curves were used to compare the positive likelihood ratio (PLR) and the negative likelihood ratio (NLR) to overall accuracy assessments.	This meta-analysis suggests that s-p53-antibodies, particularly those measured in serum samples, can be helpful in the diagnosis of OSCC with a high degree of sensitivity and specificity. Low sensitivity hinders its ability to discriminate.
Rintala, M., Vahlberg, T., Salo, T., & Rautava, J.	2019	Oral proliferative verrucous leukoplakia (PVL) is a condition characterized by verrucous-like lesions that has a high risk of malignancy, and this study aimed to update information on PVL and associated	The prevalence of aneuploidy in PVL was 92% (95% CI 80%-99%) (I2 = 0%, P = 0.61). There was a 27% (95% CI 15%-40%) (I2 = 0%, P = 0.64) overlap between P53-positive cases in the two studies. Pooled HPV positive prevalence (I2 = 24%, P = 0.27) was 5% (95% CI 0%-14%) after eliminating outlier studies, while	Twenty-two biomarkers were studied in 19 separate studies after a comprehensive literature search was conducted on PVL and associated biomarkers. For HPV, aneuploidy, Ki-67, and p53, a meta-analysis was feasible.	Aneuploidy shows promise as a biomarker of PVL based on the existing literature, but it has to be further verified.

		biomarkers.	Ki-67 positive prevalence (I2 = 9%, P = 0.33) was 14% (95% CI 6%-26%).		
Smitha, T., Mohan, C. V., & Hemavathy, S.	2017	The following meta-analysis looked at the connection between p16INK4a and HPV DNA and oral squamous cell carcinoma (OSCC). HPV-related oral squamous cell carcinoma incidence rates have also been updated and are included in the study.	Thirty-three papers were chosen for further analysis out of a total of 145. HPV DNA was found in tissues by 13 articles, p16INK4a overexpression was found in 11 articles, and 9 articles found both. The meta-analysis revealed substantial heterogeneity (P 0.0001) between studies. Twenty-one percent (CI: 13.9-27.1, P 0.0001) of 3339 patients with OSCC had HPV16 DNA. Overexpression of p16INK4a protein was found in 25.4% of 709 patients (95% CI: 14.3-38.3, P 0.0001).	The terms "HPV infection," "oral squamous cell carcinoma," "p16INK4a," "HPV DNA," "E6," "E7," "L1," "L2," and "LCR" were used to search for relevant articles in databases like PubMed. Using MedCalc statistical software, version 16.4.3, the forest plot was generated using the proportion approach.	The identification of HPV infection in many cancer cases has been linked to the examination of HPV DNA and the expression of p16INK4a. The detection of HPV DNA and p16INK4a expression reveals a significantly greater prevalence of HPV infection in patients with OSCC. While the link between HPV infection and head and neck cancer has been established, this review has the potential to solidify that connection at the molecular level in patients with oral cancer.
Troiano, G., et al.	2018	The purpose of this study was	This meta-analysis found that the levels	Studies were graded for quality using the	This study aims to shed light on the

		to systematically review and meta-analyze the data about miRNA expression and overall survival of patients diagnosed with OSCC.	of expression for certain miRNAs are highly predictive of OSCC patient outcomes.	Newcastle-Ottawa Scale. Cohort studies were used to collect information contrasting the health outcomes of patients with high miRNA expression with those with low expression.	predictive and prognostic relevance of miRNA expression in oral squamous cell carcinoma through analysis of tissue samples. The purpose of this review is to give a holistic understanding of miRNAs and their possible clinical application in the context of OSCC prognosis by synthesizing and analyzing available research. In the long run, this research could help doctors and patients make better treatment choices for OSCC.
Jamali, Z., et al.	2015	The goal of this study was to conduct a systematic literature evaluation of	Conclusions MicroRNAs, and miR-21 in particular, show promise as prognostic indicators in head and neck	We conducted a comprehensive and sensitive search of online databases to identify the studies that investigated links	In conclusion, this paper adds to the growing body of knowledge regarding the predictive

		studies that have looked into the predictive usefulness of miRs in human HNSCC.	squamous cell carcinoma.	between the expression of various miRs and outcomes for patients with head and neck squamous cell carcinoma (HNSCC), following the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group.	usefulness of miRNAs in HNSCC by conducting a systematic review and meta-analysis. This study provides promise for improved methods in the fight against this aggressive disease by showing the potential of miRNAs as prognostic molecular signatures.
López-Ansio, M., Ramos-García, P., & González-Moles, M. Á.	2023	The purpose of this meta-analysis is to assess the available research on the prognostic and clinic pathological importance of retinoblastoma protein (pRb) changes in oral cancer.	Overall survival was significantly improved in our study when pRb expression was reduced (HR = 0.79, 95%CI = 0.64-0.98, p = 0.03) but not when other clinico-pathological parameters were analysed (T/N status, clinical stage, histological grade).	We searched PubMed, Embase, the Web of Science, and Scopus for articles published before February 2022 without regard to language or date of publication restrictions. The Quality in Prognosis Studies instrument evaluates the quality of research. Methods such as meta-analysis, heterogeneity testing, subgroup analysis, meta-regression, and effects size meta-	Our data show that a decrease in pRb function is correlated with better survival in OSCC patients. Possible future directions for research are outlined.

				analysis helped achieve the goals. Twenty studies matched the criteria, and their data was pooled to represent 2451 patients in the meta-analysis.	

Discussion.

This meta-analysis examined the association between TP53 rs1042522 and the risk of oral squamous cell carcinoma in a total of sixteen case-control studies. No significant association between TP53 rs1042522 and OSCC risk was found in the present meta-analysis among Asians or Caucasians (P value > 0.05). The current meta-analysis used all of the literature to explore the potential role of TP53 rs1042522 in oral leukoplakia risk. The TP53 rs1042522 variation may not play a role in oral leukoplakia. Results from a meta-analysis of OSCC data are consistent with those found in the aforementioned studies. A meta-analysis of nine studies published in 2009 found no association between TP53 rs1042522 and OSCC. A meta-analysis performed in 2014 by Zeng et al. found no association between TP53 rs1042522 and OSCC risk among Asians. In this meta-analysis (Ramos-Garcia, P., et al. 2018), researchers compared how the TP53 rs1042522 mutation affected the risk of developing OSCC in Asians and Caucasians.

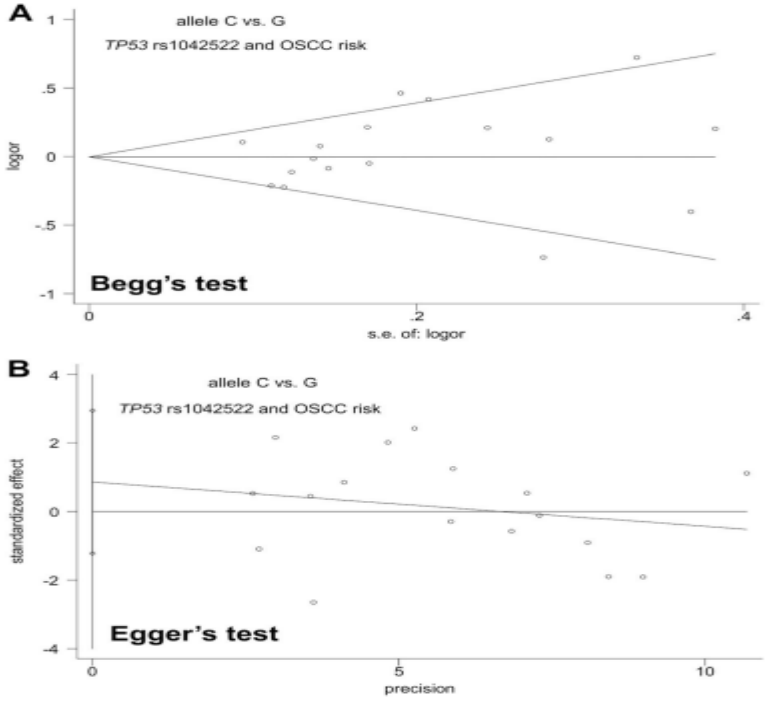

Figure 4:Publication bias evaluation (allele C vs. G) of TP53 rs1042522 and OSCC risk. (a) Begg's test; (b) Egger's test.

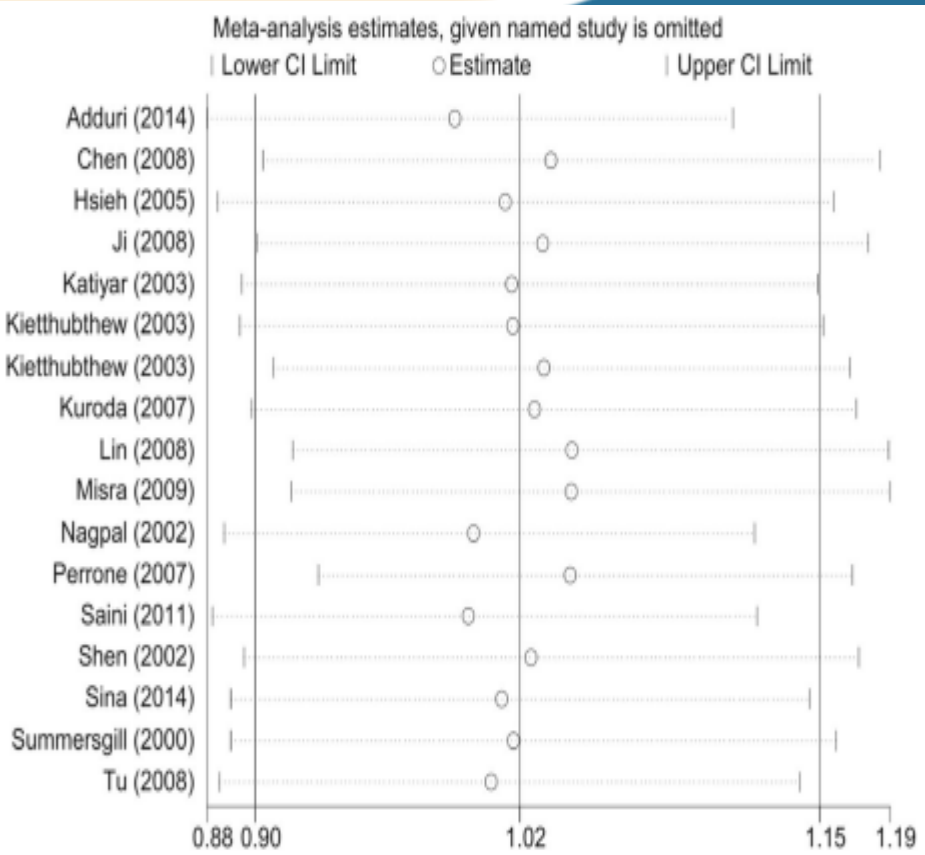

Figure 5:Sensitivity analysis (allele C vs. G) of TP53 rs1042522 and OSCC risk.

population. Two studies were excluded because of problems with the Hardy-Weinberg equilibrium, and another study was not included because the oral cancer had not been confirmed by histopathology. Our updated meta-analysis includes information from eight additional case-control studies. Meta-analyses have found different genetic associations between TP53 rs1042522 and oral cancer risk, despite the negative link. Based on a meta-analysis of 17 case-control studies, (Jiang et al. (2013) showed no connection between TP53 rs1042522 and the development of oral cancer. (Ramos-Garcia, P.; González-Moles, M. a.; and Warnakulasuriya, S. (2021); (Mulder, F. J., et al. (2021); (Warnakulasuriya, S. (2022). Another meta-analysis looked examined data from 13 studies to find a possible link between TP53 rs1042522 and oral cancer's aetiology. OSCC is the leading cause of oral cancer, but pathological type data is lacking in many case-control studies. Two studies independently found that the distribution of genotypes in the control group did not adhere to Hardy-Weinberg equilibrium (Yang, Z. C., et al. (2016).

In our revised meta-analysis, we included all studies that were relevant to our topic. Case-control studies were included if they met the inclusion and exclusion criteria. Our sensitivity analysis shows that our findings are trustworthy. Nonetheless, there are a number of significant caveats to our study. There are a few issues that need fixing. Our statistical conclusion needs to be confirmed by larger case-control studies (1). The oral leukoplakia meta-analysis contained just 5 articles, while the HPV 16 +/ subgroup

of the oral squamous cell carcinoma meta-analysis included only 4 CCS. No other types of HPV were found to be associated with the results we saw (Rintala, M., et al. (2019), (Smitha, T., et al. (2017).
In addition, for the "non-Asian, Caucasian" subgroup analysis of TP53 rs1042522 and OSCC risk, we included only four case-control studies. There was not a case-control study population available for the "Caucasian" subgroup analysis of TP53 rs1042522 risk. Second, a variety of meta-analyses demonstrated that the research did not vary widely from one another. Hospital-based, United States, and HPV16(+) subgroups have less heterogeneity than the total meta-analysis of TP53 rs1042522 and OSCC risk under allele and dominant genetic models (Ramos-Garcia, P., & González-Moles, M. (2022). There are likely other factors, including but not limited to the patient's ethnicity, that contribute to the development of OSCC. Finally, no Caucasian-specific case-control studies were included in the TP53 rs1042522 risk meta-analysis (López-Ansio, M., Ramos-Garca, P., & González-Moles, M. (2023), and we did not conduct the meta-analysis to evaluate the importance of TP53 variant combinations with other genes or other TP53 locations. There were not enough studies included in the meta-analysis (less than ten case-control studies) for the Begg or Egger tests to be run to determine whether or not there was publication bias. Even if the results of Begg's test and Egger's test demonstrate that there is no sign of publication bias in the meta-analysis of OSCC, we cannot overlook the impact of language, time, and regional variation on the presence of selection bias. The crucial stratification analysis by adjusted factors could not be performed due to a lack of original genotype frequency data in both the case and control groups, despite the acquisition of the fundamental data of gender, age, smoking, and alcohol intake (Jamali, Z., et al. (2015).

Conclusions.

In summary, this study's systematic review and meta-analysis shed new light on P53's function in oral squamous cell cancer (OSCC). The study's findings have shown the intricate relationship between P53 dysregulation and the development, diagnosis, and therapy of OSCC. While P53 changes are common in OSCC, the results show that the effect they have on clinical outcomes is complex, reflecting the multifaceted nature of the disease. The potential of P53 as a diagnostic and therapeutic target in OSCC has been highlighted in this review, highlighting the need for a more in-depth study of P53's role in OSCC.
Investigating P53's function in OSCC could guide future treatments and studies. This study has the potential to aid in the development of targeted therapeutics and precision medicine methods by elucidating the molecular pathways associated with P53 dysregulation and their consequences in OSCC. Exploring P53 as a diagnostic biomarker also has the potential to enhance early detection tactics, leading

to better patient outcomes.

Although this research has made great efforts in bringing together the available material, it does have some caveats. Some heterogeneity in the meta-analysis can be attributed to differences in study designs, patient groups, and definitions of P53 dysregulation found throughout the examined literature. More standardized procedures and larger, well-defined patient groups should be used in future studies to overcome these restrictions.

Future Directions.

Moving forward, there are several promising directions for further research in the context of P53 and OSCC:

- Precision Medicine Approaches: The molecular profiling of OSCC patients, including the characterization of P53 status, should be integrated into clinical practice. This can enable the development of tailored treatment regimens based on the genetic makeup of individual tumors.
- Functional Studies: In-depth functional studies are needed to elucidate the precise mechanisms by which P53 dysregulation influences OSCC pathogenesis. This could lead to the identification of specific targets for therapeutic intervention.
- Advanced Biomarker Discovery: Research should continue to explore other potential biomarkers in conjunction with P53, aiming to refine diagnostic and prognostic tools for OSCC.
- Clinical Trials: Conducting clinical trials targeting P53-associated pathways in OSCC is essential to evaluate the therapeutic potential of drugs that modulate P53 activity.
- Risk Assessment and Prevention: Investigating the influence of environmental and lifestyle factors on P53 dysregulation in OSCC development can contribute to effective risk assessment and prevention strategies.

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