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REVIEW ARTICLE

Role of p53 in Oral Cancer-A Systematic Review

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ABSTRACT

Objective: Oral squamous cell carcinoma (OSCC) is a common tumor that develops in the mucosa of the oral cavity. Various factors such as tobacco, betel quid and alcohol are the most common causes of oral cancer. Changes at the genetic level, such as p53 mutations, have also led to cancer cell proliferation and progression. It has also been discovered that early detection and prognosis can improve if p53 is being used as a diagnostic as well as a therapeutic tool for oral cancer. In this study, a review has been done over the recent advancements of p53 as a diagnostic tool for oral cancer detection.

Methodology: This review followed the PRISMA guidelines for systematic reviews and meta-analyses. We retrieved relevant literature from 2014 to 2024 using six search engines: HEC Digital Library, PubMed/Medline, Elsevier, Wiley Online Library, Google Scholar, and Wolter Kluwer. For this review, we selected studies based on the following criteria: abstracts that included p53 and oral cancer; the 50 most cited articles; and articles investigating the role of p53 in the detection and treatment of oral cancer.

Results: In order to carry out this study, thirty studies were searched and assessed which discussed the role of p53 in tumor progression and recent advancements describing the application of these as a diagnostic tool in oral cancer detection and treatment.

Conclusion: This systematic review describes the role p53 plays in the pathophysiology of oral cancer and that it can be used as a diagnostic parameter as well as a treatment for oral cancer. This research may have missed some studies written in language other than English.

Keywords: Apoptosis, DNA repair proteins, Mutation, Oral Cancer, p53.

Authors' Contribution:
[1,2]Conception; Literature research; manuscript design and drafting; [3,4]Critical analysis and manuscript review; [5,6]Data analysis; Manuscript Editing.

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Introduction

"Oral cancer, especially oral squamous cell carcinoma (OSCC)", is fourteen prevalent malignancies around the globe in terms of mortality and morbidity. It can be fatal and teratogenic disease occurring due to a range of risk factors (such as drinking and smoking). It is exacerbated by low socioeconomic status and malnutrition.[1] There were approximately 377,713 new cases of mouth and lip cancer worldwide in 2020. Indonesia, Sri Lanka, Bangladesh and Pakistan have high rates of oral cancer. The prevalence of oral cancer progress with age, from 40 to 60 years old.[2,3]

Almost 90% of oral cancers are usually squamous cell carcinoma (OSCC). Less common oral tumors include melanoma, lymphoma and tumors of the minor salivary glands. They are often preceded by underlying oral malignant diseases (OPMD) that are linked with a higher risk of lip and oral cancer, such

as oral lichen planus, leukoplakia, oral submucosal fibrosis, andproliferativeverrucousleukoplakia.[4,5] In order to assess the probability of malignant transformation of OPMD in individuals, existence and severity associated with epithelial dysplasia is observed, a standard protocol to foresee its progression. However, this assessment is subject to the subjective variability of the observer, leading to an important limitation such that severe dysplasia may not progress to cancer, while mild dysplasia may be ignored and progress to cancer. Recent research has focused on the study of molecular biomarkers that can be used as potential predictors of malignant transformation.[6,7]

DNA damage, a recurring event in metabolism which gets triggered by endogenous and exogenous factors. When such factors accumulate, this can lead to genetic alterations and ultimately the cancer process. During carcinogenesis, alteration of certain pathways can lead tumor proliferation, apoptosis along with inducing cell transformation and clonal expansion.[8,9]

“The TP53 gene (also known as p53)” is most commonly “mutated gene in OSCC”. Most cancer-associated p53 mutations are missense mutations that encode a mutated form of p53, some of which, in addition to having the loss-of-function effect of wild-type p53, acquire oncogenic acquired functional activity.[10] In patients with head and neck cancer, carriage of a high-risk p53 mutation is often associated with poor survival and poor response to chemotherapy.[11,12]

The TP53 gene is a well-known tumor suppressor gene, also known as the "guardian of the genome". It codes for the P53 protein and is considered an important biomarker for cancer. It has roles related to apoptosis regulation, DNA damage repair and cycle control.[13] Mutations in this gene appear to be an early event in multistep process of oral cancer progression, which is necessary for the acquisition of the most relevant features of cancer, namely uncontrolled cellular proliferation and genetic instability.[14,15] A number of studies published previously using immunohistochemistry demonstrated that p53 plays a critical role in OPMD patients such as leukoplakia and stomatitis, where the results were variable.[16,17] Similarly, many research groups have also focused on p53 potential use in predicting OPMD conversions. Although the published articles have significant limitations: a) most initial studies use cross-sectional designs and cannot truly establish causal relationships b) some articles report statistical results that are inaccurate and insignificant (mainly due to smaller sample size); and type II error (false negative results).[18,19]

In oral cancer, overexpression of p53 predicts chemotherapy resistance and poor prognosis. Overexpression of p53 varies in different regions of world due to various etiological factors and disease pathogenesis. The overexpression of p53 in locally advanced oral cancer in an Indian study was reported to be 85.6%.[8] Its integrity is an essential criterion that ensures the production of healthy daughter cells which eventually form healthy tissues and participate in a variety of biological functions. As a result, genetic instability can lead to diseases such as cancer. Genetic instability is recognized as an essential hallmark of carcinogenesis.[20]

However, human cells possess precise defense mechanisms sufficient to protect the genome and maintain its integrity from various internal and external factors that damage DNA. These mechanisms are collectively known as "DNA damage repair mechanisms (DDR mechanisms)."Therefore, it can be explained as a nexus of pathways that work together to identify, restore and/or eradicate a number of DNA lesions in a cell. DDR can lead to a variety of primary biological consequences, including apoptosis, DNA repair, cell cycle regression, and aging. Furthermore, undulations in DDR pathways can lead to genetic instability, which is represented by chromosomal loss or rearrangement, mutation, fusion and deletion. Furthermore, abnormal DDR can cause several diseases, such as neurodegenerative diseases, premature aging and immunodeficiency.[21] The role

that p53 plays as a tumor suppressor can be understood by its transcriptional ability by mediating and regulating genes that are directly or indirectly involved in cell cycle regulation as well as DNA repair. [22]

The aim of this review is to have a latest update on the role played by p53 as a diagnostic and therapeutic agent in oral cancer.

Methodology

In order to carry out this systematic review, Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were taken into consideration. Our aim was to scrutinize suitable studies by searching the following online databases: HEC Digital Library, Wolter Kluwer, Wiley Online Library, Google Scholar and Elsevier. The inclusion and exclusion criteria is shown in table 1.The search terms included two categories: (1) "p53," "apoptosis," "mutation" and ";" (2) "oral cancer," and "DNA repair proteins". The logical relationship was created with "OR" and "AND," and the search formula was developed afterwards. Some other databases such as lilac were not search due to inability to access the articles. To improve our search strategy, we conducted a preliminary review. Two reviewers independently read the titles and abstracts and used an initial screening to exclude documents that did not meet the inclusion criteria.If two researchers disagree, they consult a third researcher to reach a consensus. Subsequently, researchers conduct a comprehensive review of the literature to identify studies that meet the inclusion criteria. During the full-text screening process, the following information is collected: authors, publication date, study type, participant characteristics, sample size, loss to follow-up or withdrawal from follow-up, intervention methods, and measurement indicators. For studies published multiple times, only the most recent or most complete study is included.

Table I: Criteria for Inclusion and Exclusion of studies

Inclusion Criteria	Exclusion Criteria
Articles with Abstract containing p53 and Oral cancer	Articles which did not include p53 and Oral cancer in their abstract
Articles based on their citation count (Top fifty most cited articles)	Articles which were not published in the journals of following category; of dentistry, Oral Pathology, Oral surgery, Oncology and medicine
Articles containing role of p53 in Oral cancer detection and treatment	

Results

After filtering by title, abstract, and full text, only 30 studies remained. The results are shown in Figure 1 below.

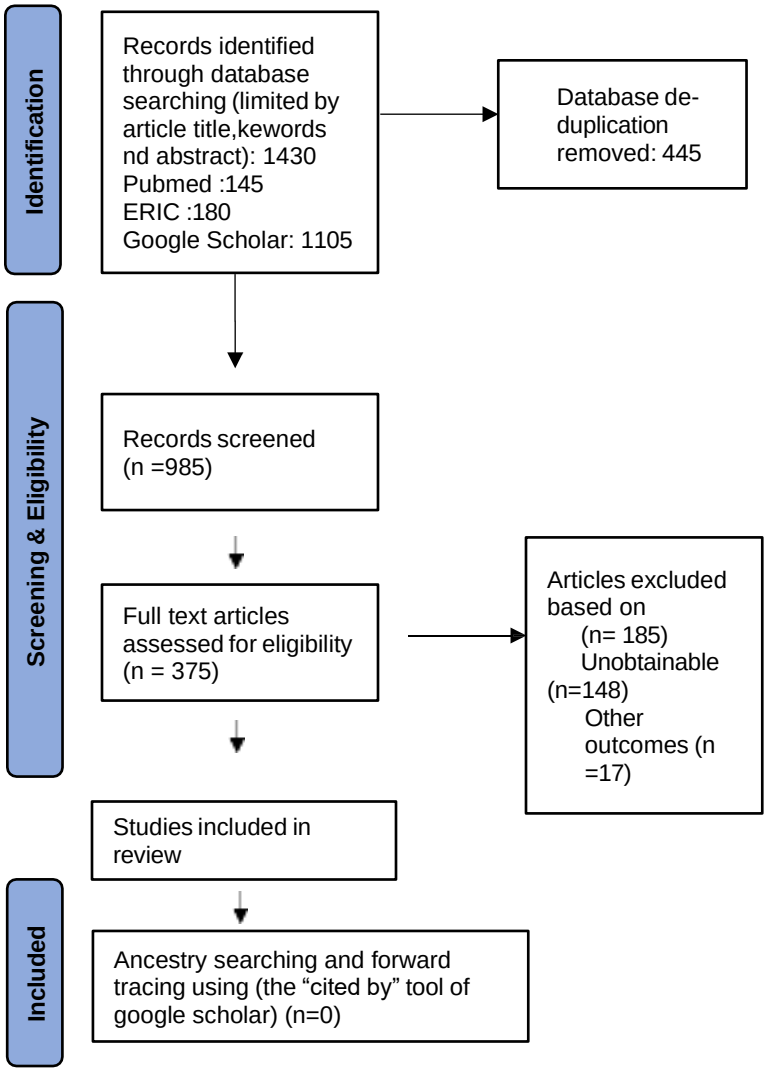

Table II: Summary of the included studies				
Sr.#	**Name of Author**	**Year**	**Design of Study**	**Study Finding**
1	Abbas S Khan et al.	2021	Case control study	Serum anti-p53 antibodies and p53 immunoreactivity can serve as sensitive and specific tests to assess the potential risk of malignant transformation in oropharyngeal cancer.
2	Hossein Daneste et al.	2022	Retrospective cross-sectional study	Immunological expression of mutant p53 has no prognostic value for relapse.
3	Shih-Wei Wang et al.	2022	Original article	Significant advances in diagnostic techniques have not significantly improved survival in secondary malignancies; However, they allow other patients to receive equivalent treatment
4	Yei-Jin Kang et al.	2022	Original article	Administration of 4-hexylresorcinol can induce conformational changes in mutated p53 peptides and increase the transcriptional activity of p53.
5	Yei-Jin Kang et al.	2021	Original article	HDAC inhibitor HR is a potential drug that can restore the function lost in p53 mutant cells. It can act as a pharmacological chaperone to induce p53 phosphorylation, or as an HDAC4 inhibitor to induce p53 acetylation.
6	Muhammed Rafi Shaik et al	2024	Original article	These nanoparticles exhibit antioxidant activity and a minimum inhibitory concentration (MIC) of 50 µg/mL against oral pathogens, indicating strong antibacterial properties. Interaction analysis revealed a high affinity for binding to oral pathogens. ZnO-PIP nanoparticles demonstrated dose-dependent anticancer activity in KB cells and increased the expression of the apoptosis genes BCL2, BAX, and p53.
7	Yewen Shi et al.	2022	Experimental study	Mutant p53 regulates the immunosuppressive mechanisms of ROC1 tumors; ROC1 cells have acquired p53 mutations. This alteration occurs in 65% to 85% of patients with oral squamous cell carcinoma.
8	Hendrik Setia Budi et al.	2023	Experimental	Natural products such as curcumin, resveratrol, melatonin, and naringin show promise in combating oral cancer and epithelial-mesenchymal transition (EMT). Studies have shown that these natural products can inhibit cancer cell proliferation, induce apoptosis, and regulate immune responses.
9	Shinjinee Sengupta et al.	2023	Original article	Higher p53 amyloid load seen in tissues from higher grades of cancer
10	Sangeetha Narasimhan Et al.	2023	Experimental	Mutated p53 expression was observed in the nuclei of dysplastic epithelial cells of oral squamous cell carcinoma
11	Guiomar Martín-Lozano et al.	2021	Experimental	A pathogenic mutation on exons of p53
12	Soumen Manna et al.	2023	Cross-sectional	Elevated calcium ion concentration, increased EGFR expression, and oxidative stress are important features of several types of cancer, including oral cancer
13	Rachel Novack et al.	2023	Experimental	Abnormal p53 oral epithelial dysplasia to emphasize the importance of p53 IHC and the strong correlation between an abnormal p53 IHC profile and an underlying TP53 mutation
14	Chen Mao et al.	2024	Cross-sectional	Resveratrol accelerates ferroptosis and inhibits malignant behavior in OSCC cells by regulating p53/SLC7A11.
15	Abbas Saleem Khan et al.	2021	Cross – sectional	Compared to normal oral mucosa, TP53 expression is increased in oral squamous cell carcinoma and oral precancerous lesions, making it a potential candidate for a predictive biomarker for oral precancerous lesions and malignant tumors.
16	Jonas Sundberg et al.	2022	Prospective longitudinal	The combined expression of p53 and p63 can serve as an independent prognostic biomarker for recurrence after oral leukoplakia surgery. Since recurrence implies an increased risk of cancer, the combined detection of these biomarkers may help identify patients at high risk of cancer.
17	Allison Nipper et al.	2023	Experimental	Mutants of p53 and Cdkn2a accelerate the development of 4-nitroquinoline-1-oxide-induced oral tumors.Mutations of p53R172H and Cdkn2a exhibit a more aggressive tumor-progression phenotype.
18	Zheng Zheng et al.	2023	Cross- sectional	MG132 upregulated p53 expression and further enhanced the CDDP-induced p53 expression levels in OSCC cells
19	He W, et al	2015	Cross-Sectional Study (Original Research)	High expression of p53 protein in oral squamous cell carcinoma tissues plays an important role in its pathogenesis.
20	Minmin Li, et al	2023	Narrative Review	The study investigates mutant p53's role in cancer of head and neck region, its effects on cancer growth, and potential therapeutic strategies to target it.

21	Tycho de bakker, et al	2022	Narrative Review	This review explores pharmacological manipulation of p53 for treating head and neck squamous cell carcinoma proposing subtype-specific treatments
22	Viveka TS, et al	2016	Retrospective observational study (Original article)	This review explores pharmacological manipulation of p53 for treating head and neck squamous cell carcinoma proposing subtype-specific treatments
23	Nighat Ara, et al	2017	Cross sectional study (Original article)	One of the hallmarks of oral squamous cell carcinoma is an alteration in the p53 gene, which disrupts the normal function of the p53 protein**.**
24	A. Lindermann, et al	2019	Experimental study (Original article)	COTI-2 inhibits tumor growth in head and neck squamous cell carcinoma (HNSCC) through multiple mechanisms and may be particularly effective when used in combination with other treatments for patients with TP53 mutations.
25	Singla S, et al	2018	Case control study (Original article)	This study showed that p53 and EGFR are useful biomarkers for the diagnosis of leukoplakia and for predicting its malignant transformation.
26	NMS Purwaningsih, et al	2017	Case control study (Original article)	The expression of p16 and p53 correlates with the severity of oral malignancy, making them promising diagnostic markers.
27	Vijayan AK Muthukrishnan et al	2022	Case control Genetic study (Original article)	Oral Lichen Planus's premalignant potential is linked to codon 72 p53 gene polymorphism in HPV-associated cases.
28	Krishnan RP, et al	2025	Exploratory study (Original article)	In the future, the next-generation sequencing (NGS) will be the next-generation sequencing (NGS), the molecular profielen will be the next-generation sequencing (NGS), and the next-generation sequencing (NGS) will be the next-generation sequencing (NGS).
29	Wang J, et al	2021	Experimental study (Original article)	This study found that a certain genetic mutation of p53 in oral tumors can make them resistant to a type of cancer treatment (PD-1 inhibitors). These findings endorse p53 profiling as a predictive tool for determining the effectiveness of PD-1 inhibitors in preventing Oral Premalignant Lesion progression.
30	Sawada K, et al	2022	Retrospective observational study (Original Article)	This study showed a strong link between oral epithelial dysplasia (OED), a premalignant condition and mutations in p53 gene.

Discussion

Oral squamous cell carcinoma is one of the most prevalent cause of cancer-related deaths worldwide and its global burden is increasing rapidly due to aging and population growth.[23] Early diagnosis is a significant health goal and leads to less damage and improved prognosis; Therefore, it is important to recognize potential biomarkers to improve the prognosis and treatment outcomes for such patients.[24,25] Oral cancer cases are usually diagnosed at a later stage along with metastases due to painless presentation and initial misdiagnosis. In order to deal with such patients; aggressive multimodality treatment is done, which might result in poor prognosis and can lead to mortality and morbidity.[26] In the development and progression of human malignancies, loss of p53 tumor suppressor function is a key step. The loss of tumour suppressor function occurs due to few mutations found in the wild-type TP53 gene.[27]

Overexpression of mutant p53 proteins can accumulate in the nuclei of tumour cells and is associated with more aggressive behaviour in almost all types of cancer.[29,30] In almost 50% of all human cancers, increased immunoreactivity of the p53 protein is observed.[30]

Protein synthesis/function is affected by mutations, which can vary according to their location and context. One of the ways to detect inactivated p53 is Immunohistochemistry, which is a simple and inexpensive method.[31] It can detect directly by the mutations in the TP53 gene or indirectly via binding to viral proteins and cellular oncogenes. Although,

changes in p53 have not been assessed in previous studies.[32]

The majority of mutations in p53 are missense mutations capable of producing a full-length p53mt protein with a single amino acid substitution in the DNA-binding domain, differences in p53wt protein though, but nonsense mutations or loss of both alleles may so result in the absence/detection of p53 protein.[33] Thus, identification of the type of inactivated p53 protein is significant and may explain the limited prognostic importance of p53 immuno-expression in some cancers.[34,35]

One of the viable therapeutic strategy is to look into wild-type p53, which is overexpressed in cancer and is a potent promoter of apoptosis and senescence in tumor cells can be reactivating the wild-type properties of p53 mutants.[36] Another way is gene therapy, in which aim is to restore normal expression and function of p53 by transfection of cancer cells with plasmids expressing wild-type p53. This can induce apoptosis and/or growth arrest. There are several clinical studies being done by using viral and non-viral vectors that deliver the p53 gene, either alone or in combination with other therapeutic agents.[36,37]

Some tumor-derived mutations that cause loss of wild-type p53 function can be stabilized by point mutations which indicate that structural changes are reversible. [37]

There are small molecules with the name of PhiKan083 and PK7088, which bind to p53 and generate the Y220C mutant, which stabilizes and increases the amount of wild-type p53. There are few molecules such as PRIMAmet/APR-246, PRIMA-1, CP-31398, and SCH29074 which interact with the DNA-binding domain and bind to the mutant p53 protein in order to promote mutant protein folding and restoration of p53 function. In order to achieve proper folding of wild-type p53, zinc-binding domain is required, which is absent in the R175H p53 mutant.[38]

There are currently numerous therapeutic agents available that target specific genes, proteins and enzymes associated with OSCC. The p53-targeted agents include COTI-2, MIRA-1, PRIMA-1, PRIMA-1MET (APR-246) and STIMA-1. These compounds are responsible for restoring p53 to its wild-type conformation, therefore reactivating the transcriptional activity of wt-p53.[39] The PRIMA-1 and APR-246 are cysteine-binding and they induce apoptosis by caspase activation. Many studies have been done in the past which demonstrated the efficacy of PRIMA-1 and APR-246 but only a few studies have applied it to the treatment of OSCC/HNSCC.[40] The p53-restorative ability of PRIMA-1 and APR-246 is confirmed by various studies, experimental results have suggested that their anti-cancer properties may be independent of p53 restoration.[41] Tumor suppressor protein, p53 may prevent the development of OSCC by stopping the cell cycle by p21, regulation of BER activity for DNA repair, and activation induced apoptosis the internal and external pathways.[42]

However, despite showing promising results in preclinical studies, adenovirus is not always a suitable vector and therefore gene therapy may be limited by the lack of effective delivery mechanisms later in clinical trials.[43] The use of nanoparticles (NPs), which can increase the stability of a given particle and exhibit higher uptake by cancer cells, may provide a method to more effectively deliver the p53 gene.[44] In order to make p53 gene delivery system effective, several requirements are must such as the vector should not be toxic or immunogenic and allow multiple injections if needed.[45] Because the p53 protein is highly efficient but unstable, sustained expression of the gene in tumors is required to achieve durable therapeutic effects.

Because transfected cells can influence non-transfected parts of a tumor, achieving high levels of transfection may not be necessary to slow tumor growth. This is because p53 has a strong bystander effect. Currently, work is underway to administer peptide activators of the p53 protein into cells, which could offer an alternative to gene therapy.

Ideally, gene vectors should be administered systemically and precisely target both primary and metastatic malignancies.[46,47]

Conclusion

This review encapsulates the central role p53 has in regards to a tumor suppressor gene and its dysregulation in various cancers. In order to understand the molecular process significant progress has been made but clinical translation remains limited. Further research is needed to develop effective therapeutic strategies to restore or modulate p53 activity. This review also offers a thorough examination and description of p53 mutations in oral cancer as well as a diagnostic and therapeutic tool. However, certain studies might have been missed which were in languages other than English.

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