Selecting the Appropriate Oral Cancer Cell Line: Characteristic-Based Recommendations from a Systematic Review

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Abstract: *Introduction*: Oral squamous cell carcinoma (OSCC) research often relies on *in vitro* models to study tumor behaviour and evaluate therapeutic agents. However, variability in cell line characteristics and limited guidance on their selection pose challenges to research consistency and translational accuracy.

Objective: To provide a comprehensive evaluation of OSCC cell lines based on anatomical origin/site, biological features and associated risk factors, offering evidence-based recommendations for their appropriate use.

Method: A systematic review was conducted in PubMed database covering the period 1972 to 2024 using the keywords "human," "oral squamous cell carcinoma," and "cell line." Inclusion criteria were English full-text publications describing human-derived OSCC cell lines. Cell lines of animal origin or with known contamination were excluded from this study.

Results: Out of 524 records, 106 publications were analyzed. Japan and the USA led in cell line development. Most cell lines originated from male patients and the tongue was the predominant anatomical site for OSCC. Highly cited lines such as HSC-3, CAL-27, and SAS were favored for studies on metastasis, immune markers, and drug testing. Cell lines were categorized based on single or multiple risk exposures, including tobacco, alcohol, betel quid, and HPV infection.

Conclusion: This review provides an evidence-based framework for selecting OSCC cell lines by anatomical origin/site, molecular features, and documented etiologic exposures. Therefore, researchers should align cell-line selection with the relevant characteristic background and the specific experimental goal (e.g., metastasis, immune-marker, or drug testing), prioritizing well-characterized models when reproducibility and translational relevance are key.

Keywords: Cell line, human, *in vitro*, oral squamous cell carcinoma, oral cancer, systematic review.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) remains the seventh most prevalent head and neck malignancy according to GLOBOCAN 2020 [1]. Geum *et al.* [2] (2013) stated that despite advancements in the treatment, the five-year survival rate of OSCC is around 75.68% which depend on the staging of tumor, largely due to late-stage diagnosis [3], local recurrence [4], and metastasis [5]. In this context, *in vitro* models such as cancer cell lines are crucial for understanding tumor behaviour and testing therapeutic agents [6]. However, due to the heterogeneity of OSCC and its microenvironment and the lack of standardization in selecting the appropriate cell lines, present significant challenges in research reproducibility and translational validity [7].

Numerous OSCC cell lines have been established over the past five decades across different countries, yet these models vary widely in terms of anatomical origin/site, differentiation, patient demographics and risk factor, and molecular features [8-12]. This diversity underscores the need to systematically evaluate and categorize these cell lines based on biological relevance and research objectives. Not all cell lines are suitable for every type of study of oral cancer, some may be more appropriate for drug screening, and others may be more appropriate for studying metastasis or specific genetic alterations.

To our knowledge, no systematic review has synthesized available OSCC cell lines according to origin, patient background, histopathological features, and specific study utility, thus leaving researchers to make high-stakes model choices with incomplete guidance. This gap impedes informed cell line selection for targeted and specific applications. A comprehensive assessment of available OSCC cell lines will enhance the relevance, reproducibility, and comparability of research findings. However, not all OSCC cell lines are interchangeable, some are better suited for drug screening, others for metastasis biology, immune-marker studies, or specific genetic alterations.

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Critically, inappropriate cell line selection could produce misleading preclinical signals (e.g., inflated drug sensitivity, artefactual pathway conclusions, or non-representative risk-factor biology), undermining reproducibility and reducing the likelihood that findings will translate into clinically useful strategies. Therefore, this systematic review provides consolidated summary and recommendation of OSCC cell lines by analyzing their characteristics, citation frequency, and risk factor associations. This study aims to guide researchers in selecting cell lines aligned with their specific experimental needs or goals and to encourage the adoption of well-characterized cell lines, specifically for biological appropriate models, thus improving translational relevance.

METHOD

Search Strategy

This systematic review followed a structured PRISMA approach to guide the search strategy across database. The population/samples targeted in this study was human subjects with OSCC and the outcome of this review focused on the available OSCC cell lines from previous publications. Searches were conducted in the PubMed/MEDLINE database from the year of 1972 to 2024 using the following keywords, "human", "oral squamous cell carcinoma", and "cell line". One investigator (JW) performed the literature search using these terms. The literature search strategy was restricted to PubMed-indexed and English-language full-text publications, which may exclude relevant evidence from other databases and non-English sources and could introduce database, and publication bias.

Eligibility Criteria

Studies were included if they were full-text publications written in English. Eligibility was determined using the keyword “human oral squamous cell carcinoma cell line”. Studies were excluded if they reported any contaminated or misidentified cell lines or cell lines derived from non-human origins (e.g., animal models). Six investigators (IG, JJ, CL, BNJ, FKH, AR) independently screened the titles and abstracts of each publications in determining the eligibility criteria of the identified literatures. In the event of any disagreement regarding eligibility criteria or data extraction, a final investigator (RA) resolved the dispute and made the decision on whether the study or data point should be included.

Data Extraction

Six investigators (IG, JJ, CL, BNJ, FKH, AR) independently extracted and compiled data on cell line characteristics, and a final investigator (RA) adjudicated unresolved cases to achieve consensus. For each eligible cell line, the following data items were extracted when available (unreported and/or missing items were recorded as N/A or not available): (1) OSCC cell line identifier/specific name; (2) source of cell line including origin (country) and year discovered; (3) patient demographics including sex, age, and nationality/ethnicity; (4) anatomical origin/site of OSCC in the oral cavity (e.g., tongue, buccal mucosa, floor of the mouth) and tumor characteristics or cell differentiation (poor, moderate, well); (5) ATCC (American Type Culture Collection) repository availability; (6) reported biological/molecular features (antigen expression/markers); (7) specific purpose(s) of each cell line; and (8) etiological/risk-factor background (tobacco smoking, alcohol consumption, betel quid chewers, and HPV infection). Cell lines were synthesized by anatomical origin and reported etiological/risk-factor background.

Data Analysis

Due to the nature of the study, which did not involve interventional outcomes or patient-level data, no formal risk of bias analysis was performed. The data presented here are descriptive and collated from primary studies of cell line establishment and characterization.

RESULT

A total of 524 publications were obtained and identified through the PubMed database. After removing one duplicate and excluding 417 records during screening, 106 publications met the eligibility criteria. Across the study period (1972–2024), the annual number of newly established OSCC cell lines varied (ranging from 1 to 14 cell lines established per year) which showed a steady increase in the number of OSCC cell lines established annually. However, the overall linear trend suggested a gradual decline in the rate of new OSCC cell line establishment over the last 50 years. Based on the geographical distribution data of OSCC cell line establishment (total number of 149 cell line establishments with country recorded), Japan and the USA being the top contributors, followed by the United Kingdom and South Korea. Japan contributed 26.2% and the USA 25.5% for OSCC cell line establishments, followed by the United Kingdom

(14.1%), South Korea (10.7%), Germany (6.0%), Scotland (4.0%), India (2.7%), and Taiwan/Malaysia/China (2.0%).

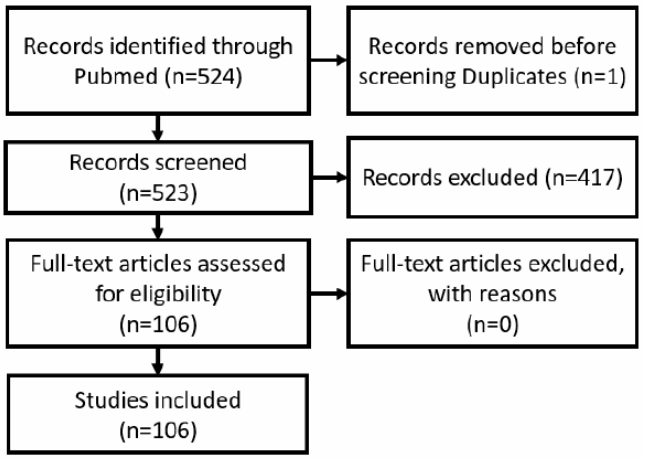

Figure 1: PRISMA flowchart.

The results demonstrated 12.8% studies did not disclose patient-specific information such as age and/or sex. Most of the cell lines were obtained from OSCC male patient, with the remaining proportion derived from female patients or not reported. Based on anatomical origin of OSCC cell lines in the oral cavity, OSCC cell lines were most frequently derived from the tongue (35.6%), followed by unspecified subsite (22.1%), floor of mouth (9.4%), buccal mucosa (9.4%), and gingiva (8.7%).

Ten most cited OSCC cell lines, including HSC-3, CAL-27, SAS, SCC-25, and HSC-2, are frequently used due to their characterized features and established relevance in metastasis studies, drug testing, and biomarker evaluation. Quantitative data for citation frequency rankings, showed citation counts ranged from 68-344 across the top-ranked cell lines. The highest-cited cell lines were HSC-3 (344 citations), CAL-27 (296 citations), SAS (279 citations), SCC-25 (212 citations), and HSC-2 (209 citations). Other highly cited cell lines included SCC-9 (185 citations), HSC-4 (125 citations), SCC-4 (102 citations), NA (89 citations), and SCC-15 (68 citations). Moreover, cell lines were categorized by etiologic exposures or risk-factor background, such as alcoho associated models (e.g., UPCI:SCC040), HPV associated models (e.g., HB96, H400, HB-2), dual exposure models such as smoking combined with alcohol (e.g., UPCI:SCC084, UPCI:SCC131, NOS-1, UPCI:SCC111) and smoking combined with betel quid chewing (e.g., ORL-115, ORL-48, ORL-136), and multi exposure models including smoking, alcohol, and HPV (e.g., UPCI:SCC154, UPCI:SCC090, 93VU147T).

DISCUSSION

A significant paradigm shift emerged in the late 1980s following the limited clinical success of compounds identified through screening models based on transplantable murine tumors [61]. In response, there was a growing impetus and demand to develop human-derived *in vitro* models that could enhance the translational relevance of anticancer drug discovery. This led to the concept of establishing a panel of human cancer cell lines designed to reflect the variability in chemotherapy responses observed in clinical settings for specific tumor types. Human cancer-derived cell lines are among the most commonly used models for investigating cancer biology and evaluating potential treatments [62]. In our study,

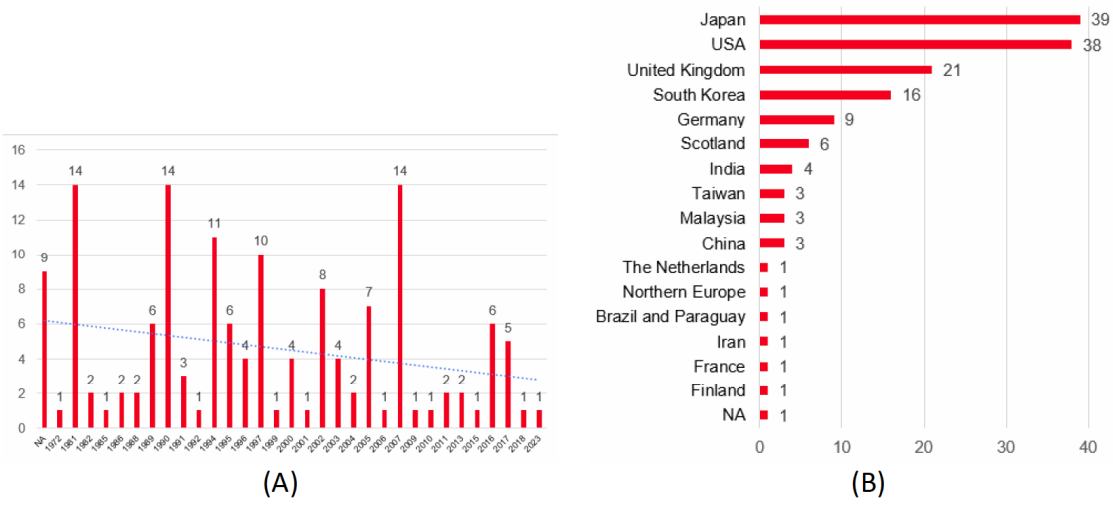

Figure 2: (**A**) Yearly total cell line established. (**B**) Country distribution of cell line establishment. (Blue line indicate linear tendency; N/A represents no information).

Table 1: Ten Most Highest Citation of OSCC Cell Line. (N/A Represents No Information)

OSCC Cell Lines	Origin, Country, Year	Gender, age	Location, Differentiation	ATCC	Total citation	Antigen expression	Specific purpose
HSC-3 [13]	Tokyo Medical and Dental University, Japan, 1989	Japanese, M, 63	Tongue, Poor	No	344	CD144, p27, RCAS1, E-cadherin, β-catenin, STAT3, SOCS1, CD47, CD36 [14-19]	HSC-3 cells used for studying mechanisms of metastasis and invasion of tongue cancer
CAL-27 [20]	Centre Antoine-Lacassagne, Nice, France, 1982	Caucasian, M, 56	Tongue, Poor	Yes	296	MHC-I, MHC-II, PD-1, PD-L1, CD47, CIP2A, p-ERK [21-25]	Cell lines constitute appropriate models for the study of human tumors
SAS [26]	Chiba University, Japan, 1989	Japanese, F, 69	Tongue, Poor, stage IIB	No	279	EPHB4, Carbonic Anhydrase (CA III), CD44v3+, CD24-, CD47, PD-L1, Human cytokeratin and epithelial membrane antigen (EMA) [27-31]	To establish a model for studying oral squamous cell carcinoma biology and evaluate drug efficacy (e.g., anticancer agents like hydroxyurea)
SCC-25 [32]	Brigham and Women's Hospital, USA, 1981	Caucasian, M, 70	Tongue, N/A	Yes	212	CIP2A, PIWIL2, CD44v6, CD9 [24,33-35]	Express tumorigenic potential in nude mice
HSC-2 [13]	Tokyo Medical and Dental University, Japan, 1989	Japanese, M, 69	Floor of mouth, Well	No	209	p53, p27, RCAS1, p130Cas, EpMab-16 [15,16,36-39]	Process of lymphatic and hematogenic metastasis
SCC-9 [32]	Brigham and Women's Hospital, USA, 1981	Caucasian, M, 25	Tongue, N/A	Yes	185	CD9, Vimentin, SNAIL1, E-Cadherin, N-Cadherin, TWIST1, MUC1, Ezrin in CD44+, HLA-G, CXCR4, EMMPRIN/CD147 [35,40]	Express tumorigenic potential in nude mice
HSC-4 [13]	Tokyo Medical and Dental University, Japan, 1989	Japanese, M, 63	Tongue, Well	No	125	Vimentin, SNAI1, E-cadherin, MMP1/2/9/13, Tie2, CD36, N-cadherin, αvβ6 integrin, STAT3, CD44v9 [40,41]	Process of lymphatic and hematogenic metastasis
SCC-4 [32]	Brigham and Women's Hospital, USA, 1981	Caucasian, M, 55	Tongue, N/A	Yes	102	CD9, CD44, E-Cadherin, Vimentin, PCNA, Hsp47/CBP2 [35,42–45]	Express tumorigenic potential in nude mice
NA [46]	Showa University, Japan, 1990	Japanese, F, 86	Tongue, N/A	No	89	Fibronectin, p53 [46,47]	NA cells may be useful for studying mechanisms of metastasis and invasion of tongue cancer
SCC-15 [32]	Brigham and Women's Hospital, USA, 1981	Caucasian, M, 55	Tongue, N/A	Yes	68	PD-L1, p21(cip1), p27(kip1), Ki67, Snail2, N-cadherin, vimentin, E-cadherin [43,48–50]	Express tumorigenic potential in nude mice

the available models are not evenly representative of OSCC populations, in which cell line establishment was concentrated in a small number of countries (Japan 26.2% and the USA 25.5%, followed by the UK 14.1% and South Korea 10.7%), most lines with reported sex were derived from male patients (66.4%), and the tongue was the dominant anatomical source (35.6%) compared with other subsites. Since the establishment of the first cancer cell line, concerns have persisted regarding their clinical relevance due to the variability

of basic characteristics, such as the origin of the cell line itself. The most frequently used models in the collected literatures were a small subset with high citation counts, HSC-3 (344), CAL-27 (296), and SAS (279), which likely reflects their accessibility and accumulated characterization, but also underscores the risk of over reliance on a narrow set of lines when study aims involve different subsites or etiologic backgrounds. These challenges was probably due to OSCC arises from region and behavior specific carcinogenic exposures (e.g., tobacco, alcohol, betel quid chewing, HPV) that are associated with distinct molecular alterations and tumor behavior. Thus, choosing a cell line without considering its origin and etiologic background could impose bias in biological interpretability and translational relevance.

Based on geographical distribution, institutions in Japan and the USA were the most prolific in establishing OSCC cell lines, supporting existing literature that identifies these countries as global leaders in cancer research and biomedical innovation. Importantly, the genomic and molecular characteristics of these cell lines are likely influenced by the demographic and regional profiles of the patients from whom they were derived [63-65]. As OSCC arises from a complex interplay of etiological factors, including tobacco use, alcohol consumption, and infection with high-risk human papillomavirus (HPV) [66]. In South Asian regions, the high incidence of OSCC is frequently associated with the habitual use of betel quid (areca nut) [67], with or without tobacco, and in some parts of India, the addition of slaked lime (calcium hydroxide) [64], is also a contributing risk factor. These region specific carcinogenic exposures may lead to distinct molecular alterations, tumor behaviors, and therapeutic responses.

Moreover, based on Table **1**, a hypothesis could be proposed that region specific carcinogens exposure translate into measurably distinct molecular fingerprints in corresponding cell lines. For example, betel quid associated models (e.g., ORL series) may relate transcriptomic/proteomic patterns consistent with chronic mucosal injury (oxidative stress signalling), persistent inflammation, and stromal remodelling/EMT programs which are implicated in areca related carcinogenesis and commonly observed in buccal/tongue disease where these exposures predominate. In contrast, HPV positive OSCC cell lines would be expected to reflect viral oncogene biology and integration-driven effects (e.g., HPV16 integration reported in an oral carcinoma derived line), with downstream differences in cell cycle control and immune related signalling compared with classic tobacco/alcohol driven cell lines. Therefore, cell lines originating from different geographical and etiological backgrounds are not only valuable for understanding OSCC pathogenesis but also essential for developing region specific prevention strategies and targeted therapies. Highlighting and utilizing these diverse cellular models enables more precise, population relevant oral cancer research and supports the advancement of personalized medicine approaches in oncology.

Based on gender distribution, a greater proportion of OSCC cell lines were derived from male patients compared to female patients (66.4% vs 12.8%) (Figure **3A**). This aligns with previous cohort study by Lee *et al*., who reported that males are more prone to developing OSCC than females [68]. In their study, significant differences were observed ($p<0.01$), with female patients being diagnosed at an older average age (57.1 vs 50.2 years) and at an earlier local stage compared to males. This disparity may be attributed to lower exposure among females to known risk factors such as cigarette smoking, alcohol consumption, and betel quid chewing ($p<0.01$). In terms of tumor location, the tongue was identified as the most frequent subsite

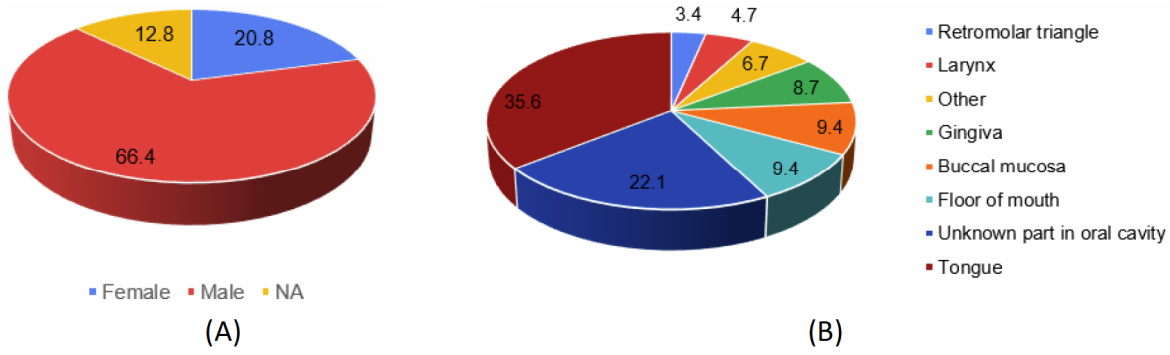

Figure 3: (**A**) Percentage of OSCC subject (N/A represents no information). (**B**) Anatomical origin of OSCC cell line in percent.

(35.81%), followed by the floor of the mouth and buccal mucosa, each accounting for 9.4% of cases. This pattern reflects the typical anatomic distribution of OSCC observed in clinical practice. The tongue remains the most frequent source of cell line origin, consistent with OSCC epidemiology [66].

The most widely cited OSCC cell lines (HSC-3, CAL-27, SAS, and SCC-25), that exhibits diverse antigen expression profiles, which reflect their suitability for distinct research applications (Table **1**). HSC-3, is characterized by markers such as E-cadherin, β -catenin, CD144 (Vascular-endothelial cadherin), and STAT3, all of which are involved in epithelial-mesenchymal transition (EMT) [69], metastasis [70], and immune evasion [71]. This profile underpins its widespread use in studies investigating invasion and lymphatic spread in tongue cancer. Similarly, CAL-27 expresses MHC-I, MHC-II, PD-L1, and p-ERK, indicating a model for immunological and signalling studies, especially those involving immune checkpoint pathways [72]. The expression of PD-L1, in particular, highlights its relevance in evaluating anti-PD-1/PD-L1 therapeutic strategies. SAS was another well-cited line with expression of PD-L1, CD44v3+, and EMA, indicating its utility in both immune regulation and epithelial differentiation research [73,74]. Its poor differentiation and stage IIB origin further position it as a model for aggressive OSCC phenotypes. SCC-25 and SCC-9, both established from tongue tumors in the United States, express CD44 variants and markers such as CIP2A and PIWIL2, reflecting their roles in tumorigenicity and stem-like features. These lines have been demonstrated to form tumors in nude mice, thus serving as reliable preclinical models for tumor growth and metastasis.

Despite their research value, some cell lines lack complete clinical metadata such as tumor stage or differentiation status (e.g., SCC-4, SCC-9). This absence limits their contextual relevance and highlights the need for standardized cell line reporting to enhance reproducibility and cross-study comparisons. At the same time, these models remain highly established in the OSCC literature (e.g., SCC-9 showed 185 citations and SCC-4 showed 102 citations) and have demonstrated tumorigenicity in nude mice, supporting their continued utility as robust preclinical platforms for tumor growth, EMT-related biology, and migration/invasion assays [32]. In practice, SCC-4/SCC-9 are appropriate when the research question is primarily cell-autonomous (e.g., EMT programs, adhesion/motility markers, or general tumorigenicity screening) and does not depend on matching tumor stage/grade or exposure history [32]. However, when translational interpretation depends on clinicopathologic context, for example, when modelling aggressive behavior stratified by grade or stage, comparing treatment responses across clinically defined subgroups, or selecting models that reflect specific etiologic exposures, preference should be given to cell lines with more complete characterization,

Table 2: OSCC Cell Line Based on their Risk Factor. (N/A Represents Not Specified; FOM Represents Floor of the Mouth; M Represents Male; F Represents Female, BQC Betel Quid Chewing; HPV Human Papilloma Virus)

Risk factor	OSCC cell line
Alcohol	UPCI:SCC040 (M, 50, Tongue, Stage III (T2N2M0)) [51]
HPV	HB96 (N/A) [52]; H400 (F, 55, Alveolar, Moderate, Stage II) [53]; HB-2 (N/A) [52]
Smoking + Alcohol	UPCI:SCC084 (M, 52, retromolar, Stage III (T2N2b)) [54]; UPCI:SCC131 (M, 73, FOM, Stage III (T2N2M0)) [54]; NOS-1 (M, 47, Gingiva) [55]; UPCI:SCC111 (F, 69, FOM, Poor, Stage II (T1N1M0)) [56]
Smoking + BQC	ORL-115 (F, 75, Buccal, Well, T2NxM0) [57]; ORL-48 (F, 79, Well, T4N2aMx) [57]; ORL-136 (M, 57, Tongue, Well, T1N0M0) [57]
Alcohol + BQC	OC3 (M, 57, Buccal) [58]
Smoking + BQC + HPV	OC2 (M, 51, Buccal) [59]
Smoking + Alcohol + HPV	UPCI:SCC154 (M, 54, Tongue) [56]; UPCI:SCC090 (M, 46, Tongue, Grade 3, T2N0) [56]; 93VU147T (M, 58, FOM, Moderate, Stage III (T4N2M0)) [60]

such as HSC-3 (344 citations), CAL-27 (296), and SAS (279 citations; stage IIB), or to risk-factor–annotated cell lines summarized in Table **2**.

From a risk factor perspective, Table **2** showed a compelling framework for aligning OSCC models with environmental and behavioral carcinogenic exposures. Cell lines derived from patients with a history of alcohol consumption alone (e.g., UPCI:SCC040) may help isolate ethanol-related mechanisms of carcinogenesis, such as acetaldehyde-mediated DNA damage [51]. In contrast, those exposed to combined risk factors, such as smoking and alcohol (e.g., UPCI:SCC084, UPCI:SCC131), may offer insight into synergistic carcinogenic effects and mutational landscapes that more closely resemble real-world OSCC pathology. Betel quid chewing (BQC), particularly prevalent in South and Southeast Asia, is another major etiological factor represented by cell lines such as ORL-115 and ORL-136. These lines are crucial for understanding alkaloid and arecoline-induced molecular damage [75], especially in the buccal and tongue subsites. The inclusion of HPV-positive models (such as HB96, HB-2, and OC2), reflects the growing importance of viral oncogenesis in oral cancer research, especially in younger or non-smoking populations. Cell lines like UPCI:SCC154 and 93VU147T, derived from patients exposed to triple risk factors (smoking, alcohol, and HPV), are invaluable for dissecting multifactorial oncogenesis and for testing therapeutic agents in highly aggressive, mutation phenotypes. Overall, aligning cell line selection with both biological markers and etiological background enhances experimental precision. It allows for more relevant modelling of tumor biology, increases the translational potential of preclinical findings, and supports the development of personalized therapeutic strategies.

Risk factor–based categorization offers a practical, exposure-aligned guide or framework for researchers in selecting suitable OSCC cell lines according to the carcinogenic context under investigation. In particular, multi-exposure models (e.g., UPCI:SCC154 [56], UPCI:SCC090 [56], and 93VU147T [60]) are well suited for interrogating the combined and potentially synergistic biology of smoking, alcohol use, and HPV infection, whereas single-exposure models (e.g., UPCI:SCC040 [51] for alcohol; HB96 [52], H400 [53], and HB-2 [52] for HPV-associated biology) that allow for clearer mechanistic interpretation and may enable cleaner attribution of downstream molecular effects to a single etiologic driver. This multi-risk stratification aligns with the paradigm of precision oncology. To enhance practical implementation, we propose a simplified objective-to-model selection aid (in the form of decision-tree and/or summary table) that maps the common OSCC research aims to etiologic-annotated cell lines (e.g., for HPV-driven oncogenesis consider HB96/H400/HB-2; for betel quid–associated mechanisms consider ORL-115/ORL-48/ORL-136; for multi-exposure interactions consider UPCI:SCC154/ UPCI:SCC090/93VU147T). This tool is intended to support exposure-aligned model selection and improve the translational relevance and interpretability of preclinical OSCC studies.

This systematic review has several limitations. First, the review was limited to studies indexed in PubMed and written in English, which may have excluded relevant cell line data reported in other databases or non-English publications. This could potentially introduce publication, language and selection bias. Second, several studies undisclosed demographic or clinical information, such as patient age, gender, tumor stage, and exposure to risk factors, which limited a more detailed stratification and analysis of OSCC cell lines. Lastly, although citation frequency was used as an indicator of relevance, it may not fully reflect the biological validity or experimental reliability of a given cell line. Some widely cited lines may be outdated or misused, while newer, potentially more relevant models might be underrepresented due to low citation frequency. Additionally, this review did not include a formal quality or risk of bias assessment, as it focused on descriptive characteristics rather than outcome data. There was also no experimental validation or genetic profiling comparison among the cell lines, which would have strengthened the recommendations.

For future research, we recommend expanding the search to include other databases such as Scopus, Web of Science, and Embase to capture a broader set of studies. Researchers should be encouraged to provide complete and standardized metadata when publishing new cell line descriptions, including clinical background, anatomical origin, risk factor exposure, and genetic or molecular profiles. Moreover, future studies should focus on genomic characterization and authentication of existing cell lines using standardized methods such as short tandem repeat profiling to prevent cross contamination and misidentification. In addition, it is also essential to develop region specific cell line panels/models that reflect the unique etiological patterns of OSCC across different populations, particularly in regions like South Asia where habits such as betel quid use are prevalent.

Incorporating multi omics approaches and co culture models may further enhance the translational relevance of *in vitro* findings. Finally, establishing a global, publicly accessible OSCC cell line registry with quality control benchmarks would be a valuable initiative to support reproducibility and standardization in oral cancer research.

CONCLUSION

This systematic review presents a comprehensive evaluation of OSCC cell lines based on anatomical origin, citation frequency, and associated risk factors. Investigators should prioritize using well characterized cell lines for studies requiring reproducibility and translational relevance. Moreover, selecting models based on specific carcinogen exposures could enhance the biological validity of mechanistic and therapeutic investigations.

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CONFLICT OF INTEREST

All authors declared no conflict of interest.

AUTHOR CONTRIBUTION

JW and IG were responsible for conceptualization, design of the study, writing original draft, review and editing manuscript. JW, JJ, IG, CL, BNJ, FKH, and AR were responsible for data acquisition and investigation. IG also did administration for projects, resources, and visualization of charts and tables. JW and IG were responsible for analysis and interpretation of data. Meanwhile, RA were responsible for supervision and validation of collected data. All authors have participated to drafting the manuscript, IG and EFS revised it critically. All authors have read and agreed to the published version of the manuscript.

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