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Original Article

Sex differences in prognostic factors and genomic variations in oral squamous cell carcinoma: A 5-year retrospective study

Hui-Hsin Ko [a,b,c,d], Fang-Yu Wu [c,e], Ya-Syuan Chen [f], Wender Lin [f], Chun-Kai Fang [g,h], Chyi-Huey Bai [i,j], Hung-Ying Lin [a,b,c], Hsiang-Fong Kao [k,l,m*], Shih-Jung Cheng [a,b,c,n**]

[a] *Graduate Institute of Clinical Dentistry, School of Dentistry, National Taiwan University, Taipei, Taiwan*
[b] *School of Dentistry, National Taiwan University, Taipei, Taiwan*
[c] *Department of Dentistry, National Taiwan University Hospital, College of Medicine, Taipei, Taiwan*
[d] *National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan*
[e] *Department of Dentistry, National Taiwan University Hospital, Jinshan Branch, New Taipei, Taiwan*
[f] *Department of Health Care Administration, Chang Jung Christian University, Tainan, Taiwan*
[g] *Hospice and Palliative Care Center and Department of Psychiatry, MacKay Memorial Hospital, Taipei, Taiwan*
[h] *Department of Medicine, MacKay Medical College, New Taipei City, Taiwan*
[i] *Department of Public Health, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[j] *School of Public Health, College of Public Health, Taipei Medical University, Taipei, Taiwan*
[k] *Department of Medical Oncology, National Taiwan University Cancer Center, Taipei, Taiwan*
[l] *Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan*
[m] *Institute of Oncology, National Taiwan University, Taipei, Taiwan*
[n] *Graduate Institute of Oral Biology, School of Dentistry, National Taiwan University, Taipei, Taiwan*

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KEYWORDS
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Abstract *Background/purpose:* This study examined the prognostic factors and genomic variations in oral squamous cell carcinoma (OSCC) among male and female patients, focusing on the rising incidence of OSCC in women.
Materials and methods: Using data from 98 OSCC cases treated at National Taiwan University Hospital between 2013 and 2018, the study analyzed the patient cohort, clinical characteristics, and genomic profiles.

* Corresponding author. Department of Oncology, National Taiwan University Hospital, No. 1, Chang-Te Street, Taipei 10048. Taiwan.
** Corresponding author. Graduate Institute of Oral Biology, School of Dentistry, National Taiwan University, No. 1, Chang-Te Street, Taipei 10048, Taiwan.
E-mail addresses: hfkao.tw@gmail.com (H.-F. Kao), sjcheng56@ntu.edu.tw (S.-J. Cheng).

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microenvironment;
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Bioinformatics

Results: The Female patients had a higher incidence of tongue cancer, while the male patients were prone to have buccal cancer. Key prognostic factors included age over 55 years, tongue cancer, alcohol use in female patients as well as the buccal cancer, betel chewing, and smoking in male patients. Notably, women with tongue OSCC or without oral habits had poorer 5-year survival rates. Genomic analysis revealed the males with high-risk habits had elevated antigen-processing and reactive oxygen gene sets, whereas the low-risk females showed dysregulation in metabolic pathways. Immunologically, the female patients had fewer naïve B cells and higher suppressive M2 macrophages.
Conclusion: Our findings highlight distinct sex-related OSCC prognosis differences and suggest that personalized treatments targeting specific risk factors and genomic characteristics may improve the clinical outcomes, particularly for the female OSCC patients.

Introduction

Oral cancer, the sixth most common malignant tumor worldwide, has a male-to-female incidence ratio of 3:1,[1] with over 400,000 cases diagnosed annually, predominantly in Asia.[2] Approximately 94 % of oral cancers are oral squamous cell carcinoma (OSCC), linked to betel quid (BQ) chewing and tobacco use, particularly in India. OSCC often develops on the tongue, but in Taiwan, BQ chewing leads to higher rates in the buccal mucosa.[3] Female oral cancer patients have been neglected in research, despite rising incidences of tongue cancer among women and worse recurrence and survival rates than men.[4,5] In Taiwan, oral cancer is closely linked to alcohol, BQ chewing, and smoking, with concurrent use raising the risk 123-fold.[6] BQ's arecoline and tobacco's carcinogens (e.g., nicotine and tar) are major contributors. Daily alcohol consumption significantly increases oral cancer risk in women[7–10] because of lower stomach alcohol metabolism, leading to higher blood alcohol concentrations and increased acetaldehyde in oral tissues.[11] This results in epithelial atrophy, increased carcinogen permeability, DNA mutations, and impaired DNA synthesis and repair.[12] Hormonal differences also influence alcohol metabolism, contributing to sex disparities in oral cancer risk.[13–16] Rising alcohol consumption among women in East Asia could significantly increase their risk of oral cancer. Other factors contributing to OSCC include microbial infections, such as hyperplastic candidiasis[17] and human papillomavirus,[18–20] which can promote carcinogenesis through genetic mutations and inhibition of tumor suppressor genes.

The pathogenesis of oral cancer involves multiple factors, including the activation of oncogenes (ras, myc, c-erbB) and inactivating mutations in tumor suppressor genes (p53, pRb, E-cadherin).[20,21] External influences like viral infections, radiation, and chemical carcinogens can transform proto-oncogenes into oncogenes. Overexpression of the EGFR (epidermal growth factor receptor) gene in oral cancer patients activates the Ras-MAPK, PI3K-PTEN-AKT, and PLC pathways, altering cellular gene expression and correlating with poorer survival, making EGFR a target for new therapies.[22–24]

Understanding tumor genomic variations and the tumor microenvironment (TME) is crucial for developing targeted treatments. Women demonstrate an increasing incidence of oral cancer and poorer prognosis for tongue cancer than men. Identifying risk factors improves public health advocacy and prevention. This study retrospectively analyzed patient records from National Taiwan University Hospital to examine prognostic outcomes in oral cancer, considering sex, age, primary site, stage, pathological type, treatment, and comorbid conditions. The goal was to understand treatment status and extrapolate findings on etiology, risk factors, and sex differences in female oral cancer in Taiwan.

Materials and methods

Data collection and ethical considerations

This study was approved by the Research Ethics Committee of National Taiwan University Hospital (NTUH-REC No. 202305050RINC). We retrospectively reviewed the medical records of oral cancer patients from two cohorts. The first comprised 98 consecutive OSCC patients who underwent surgery performed by Dr. S. J. Cheng in the Department of Oral and Maxillofacial Surgery at National Taiwan University Hospital (NTUH) between 2013 and 2018.

Patients included in the analysis met the following criteria: OSCC with surgical resection and complete histopathological diagnosis. Patients with distant organ metastasis were excluded because of surgical contraindications and the absence of available surgical specimens. The following patient characteristics were recorded for analysis: sex, age at diagnosis, pathological stage, histopathological grade, history of alcohol consumption, BQ chewing, cigarette smoking, date of tumor recurrence, last follow-up date, and survival status. Additionally, diagnoses of diabetes mellitus, menopause, oral ulceration, and xerostomia were extracted from medical records using ICD (International Classification of Diseases) codes.

Regular alcohol drinkers were defined as those consuming alcoholic beverages more than once a week for at least one year. BQ chewers were defined as those chewing one or more pieces of BQ per day for at least one year. Regular cigarette smokers were defined as those smoking 10 or more cigarettes per day for at least one year.

The term "alcohol-betel-cigarette" (ABC) was used to describe individuals with a history of regular alcohol consumption, BQ chewing, and cigarette smoking.

Tumor microenvironment analysis

This study compared the TME in oral cancer samples from 6 male and 6 female patients in Dr. Cheng's cohort. Female patients were prioritized, and male controls with similar lesion locations, stages, and ages were selected. Formalin-fixed paraffin-embedded (FFPE) slides were used for analysis. During surgery, Dr. Cheng microdissected tumor and non-tumor tissue sections and the evolution of TMEs was compared.

Gene expression analysis was performed on RNA (ribonucleic acid) extracted from FFPE biopsy samples, using NanoString technology. Total RNA was isolated and purified according to the manufacturer's protocol, using the RNeasy FFPE Kit (Qiagen, Hilden, Germany). The extracted mRNA was analyzed using the nCounter PanCancer Immune Profiling Panel (NanoString Technologies, Cold Spring Biotech Corporation, Taipei, Taiwan). Data acquisition was conducted with the nCounter Digital Analyzer (NanoString Technologies). Data processing was completed using nSolver 4.0 Analysis Software (NanoString Technologies) and R 3.5.0, with mRNA expression data normalized via log2 transformation in nSolver 4.0.

Gene Set Enrichment Analysis v4.1.0 (Broad Institute, Cambridge, MA, USA) was employed for enrichment analysis, with the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology datasets sourced from MSigDB v7.4 (https://www.gsea-msigdb.org/gsea/msigdb/). For immune cell profiling, CIBERSORTx (Stanford University, Stanford, CA, USA) and LM22 gene signatures were used to enumerate immune cell populations.

Statistical analysis

Differences in clinicopathological parameters between groups were assessed using the Student t-test, analysis of

Table 1 Correlation of clinicopathological parameters for 98 OSCCs.

	Male	Female	*P*-value
	n = 81	n = 17	
Patients' age (year)			
≤55 (n = 41)	37	4	**0.092**
>55 (n = 57)	44	13	
Cancer location			
Buccal mucosa (n = 52)	46	6	0.271
Tongue (n = 29)	22	7	
Other oral mucosal sites (n = 24)	13	4	
T Status			
T1 + T2 (n = 67)	55	12	0.345
T3 + T4 (n = 31)	26	5	
N status			
N0 (n = 76)	64	12	0.449
N1 + N2 + N3 (n = 22)	17	5	
Clinical staging			
Stage 1 + 2 (n = 55)	46	9	0.771
Stage 3 + 4 (n = 43)	35	8	
Loco-regional recurrence			
Without (n = 73)	61	12	0.685
With (n = 25)	20	5	
Histology of OSCC			
Well-differentiated (n = 58)	50	8	0.263
Moderately or poorly differentiated (n = 40)	31	9	
Oral habits			
Alcohol drinking			
Without (n = 37)	24	13	**0.0003**
With (n = 61)	57	4	
Betel quid chewing			
Without (n = 26)	13	13	**< 0.0001**
With (n = 72)	68	4	
Cigarette smoking			
Without (n = 27)	15	13	**< 0.0001**
With (n = 71)	67	4	

*OSCC: oral squamous cell carcinoma.
Values in bold indicate statistically significant results.

variance, or chi-square test. Cumulative survival was analyzed with the Kaplan–Meier product-limit method, with overall survival (OS) defined as the time from cancer diagnosis to death or last follow-up. Cumulative survival was compared between groups using the log-rank test, analyzed in GraphPad Prism 6.0 (GraphPad Software, Boston, MA, USA). A *P*-value of <0.05 was considered statistically significant.

Results

Cohort characteristics

In this study, patients were treated between 2013 and 2018. The average age was 56 for male patients and 64 for female patients, with a median follow-up of 36 months. No significant age difference was found between the male and female groups ($P = 0.092$). The most common cancer site among males was the buccal mucosa (46/81, 56.8 %), whereas that among females was the tongue (7/17, 41.2 %), followed by the buccal mucosa (6/17, 35.3 %). Most patients presented with an earlier T stage (T1/T2, 67/91, 73.6 %) and N0 stage (64/98, 65.3 %). Among male patients, the predominant histopathological grade was well-differentiated carcinoma (50/81, 62.8 %). Female patients had a slightly higher proportion of moderately or poorly differentiated carcinoma (9/17, 52.9 %). No significant differences were observed between men and women for age, tumor site, tumor size, regional lymph node metastasis, Tumor, Node, Metastasis (TNM) staging, or histopathological differentiation. However, oral habits, such as alcohol consumption, BQ chewing, and cigarette smoking, differed significantly between the sexes (Table 1) (see Table 2).

Risk factor analysis

Multivariate analyses using Cox proportional hazard regression in this cohort revealed that tumors located on the tongue or buccal mucosa, alcohol or BQ habits, and ABC habit were independent factors affecting OS ($P < 0.05$, Table).

Tumor microenvironment

To investigate the evolution of the TME, we compared mRNA expression profiles between tumor and non-tumor tissues. The clinicopathological characteristics of six male and female patients from the surgical patients with sex-matched cohort are listed in Table 3. We focused on female oral cancer patients without oral habits, highlighting a comparison between high-risk individuals with oral habits and low-risk individuals without any habits. Two females with a history of alcohol consumption, BQ chewing, or cigarette smoking were excluded from the analysis. The final analysis included two groups: a high-risk group of six males with oral habits and a low-risk group of four females without habits.

In the male group, KEGG gene set enrichment analysis showed higher expression of cancer-related gene sets such as pancreatic and colorectal cancer, whereas the female group exhibited higher expression of gene sets related to prion disease ($P = 0.022$) and the VEGF (vascular endothelial

Table 2 Univariate and multivariate survival analyses among clinicopathological parameters of 98 OSCCs by Cox proportional hazard regression model.

factors	Hazard ratio (95 % CI)	*P*-value
Univariate		
Age (<55 vs. ≥ 55)	0.542(0.257–1.992)	0.801
Cancer location (non-tongue vs. tongue)	1.924(1.521–2.743)	**0.034**
Cancer location (non-buccal vs. buccal)	2.342(1.723–3.543)	**0.025**
T status (T1, T2 vs. T3, T4)	1.812 (0.760–2.557)	0.694
N Status (N0 vs. N1-3)	0.955 (0.322–1.591)	0.622
Clinical staging (stage I, II vs. stage III, IV)	1.151 (0.425–1.88)	0.479
Alcohol drinking (without vs. with)	2.834 (1.005–5.377)	**0.039**
Betel quid chewing (without vs. with)	2.969 (1.687–3.558)	**0.033**
Cigarette smoking (without vs. with)	1.361 (0.715–2.000)	0.058
Alcohol-betel-cigarette (without vs. with)	3.726 (1.362–5.084)	**0.025**
Multivariate		
Age (<55 vs. ≥ 55)	0.257 (0.053–2.077)	0.976
Cancer location (non-tongue vs. tongue)	1.573 (1.554–3.723)	**0.042**
Cancer location (non-buccal vs. buccal)	1.942 (1.245–4.641)	**0.025**
T status (T1, T2 vs. T3, T4)	1.177 (0.442–3.031)	0.827
N Status (N0 vs. N1-3)	0.566 (0.231–2.879)	0.755
Clinical staging (stage I, II vs. stage III, IV)	1.014 (0.454–2.094)	0.747
Alcohol drinking (without vs. with)	2.239 (1.404–5.704)	**0.046**
Betel quid chewing (without vs. with)	1.144 (0.544–1.731)	**0.043**
Cigarette smoking (without vs. with)	1.841 (0.344–1.933)	0.090
Alcohol-betel-cigarette (without vs. with)	2.755 (1.442–3.580)	**0.033**

Values in bold indicate statistically significant results.

Table 3 Correlation of clinicopathological parameters for 12 OSCCs.

	male	female	*P*-Value
	n = 6	n = 6	
Patients' age (year)			
≦ 55 (n = 4)	3	1	0.546
>55 (n = 8)	3	5	
Cancer location			
Buccal mucosa (n = 5)	3	2	0.301
Tongue (n = 5)	3	2	
Other oral mucosal sites (n = 2)	0	2	
T Status			
T1 + T2 (n = 4)	3	1	0.546
T3 + T4 (n = 8)	3	5	
N status			
N0 (n = 7)	3	4	1.000
N1 + N2 + N3 (n = 5)	3	2	
Clinical staging			
Stage 1 + 2 (n = 55)	3	3	1.000
Stage 3 + 4 (n = 43)	3	3	
Loco-regional recurrence			
Without (n = 9)	5	4	1.000
With (n = 3)	1	2	
Histology of OSCC			
Well-differentiated (n = 3)	2	1	1.000
Moderately and poorly differentiated (n = 9)	4	5	
Oral habits			
Alcohol drinking			
Without (n = 5)	1	4	0.079
With (n = 7)	5	2	
Betel quid chewing			
Without (n = 6)	1	5	**0.021**
With (n = 6)	5	1	
Cigarette smoking			
Without (n = 5)	0	5	**0.003**
With (n = 7)	6	1	

Values in bold indicate statistically significant results.

growth factor) signaling pathway ($P = 0.053$) (Table 4). Gene Ontology analysis revealed that high-risk patients had high expression in antigen presentation, integrins, and reactive oxygen species gene sets ($P < 0.05$), whereas low-risk females showed higher expression in metabolism-related gene sets, such as reactive nitrogen metabolic process, fat cell differentiation, and protein modification by small protein conjugation (Table 4). These results showed distinct effects on tumor carcinogenesis and the TME.

Using CIBERSORTx to compare immune cells, mRNA data analysis indicated no significant differences in T-cell (Fig. 1A) or myeloid lineages but suggested higher expression of M2-type macrophages in females (Fig. 1B). Additionally, B-cell lineage analysis showed a higher proportion of naïve B cells in the high-risk group compared to low-risk females ($P = 0.044$) but with no significant difference for memory B cells (Fig. 1C). These findings suggest that oral habits and sex differences may influence tumor carcinogenesis and the TME.

Discussion

This study explored the epidemiological characteristics, clinical manifestations, treatment patterns, and TME of oral cancer in Taiwanese women compared to men. Female oral cancer patients aged over 55 accounted for 73.7 % in the this study, compared to 62.2 % of males in the same age group. The predilection site for females was the tongue, whereas for males, it was the buccal mucosa. Prognostic factors for females included age over 55, tongue cancer, alcohol consumption, oral ulcers, and xerostomia. For males, they included age over 55, buccal cancer, BQ chewing, cigarette smoking, and ABC habit. These findings underscore key sex differences in age distribution, predilection sites, oral risk factors, oral environments, and comorbidities.

We simultaneously evaluated gene expression levels in tumors and their microenvironments. We previously identified predictive biomarkers for immunotherapy through

Table 4 Comparison between female patients without oral habitats and male patients with oral habitats.

	No ABC[a] history (n = 4)				ABC history (n = 6)			
KEGG	No.	Gene set	Normalized enrichment score	Normalized *P*-value	No	Gene set	Normalized enrichment score	Normalized *P*-value
	1	Prion diseases	1.57	0.022	**1**	Pancreatic cancer	1.6	0.058
	2	VEGF signaling pathway	1.49	0.053	**2**	Colorectal cancer	1.57	0.051
	3	Complement and coagulation cascades	1.29	0.072	**3**	Regulation of actin cytoskeleton	1.54	0.094
	4	Fc Epsilon RI signaling pathway	1.14	0.228	**4**	Endocytosis	1.33	0.166
	5	Small cell lung cancer	0.95	0.596	**5**	Focal adhesion	1.33	0.21
Gene ontology biological process	**No.**	**Gene set**	**Normalized enrichment score**	**Normalized *P*-value**	**No**	**Gene set**	**Normalized enrichment score**	**Normalized *P*-value**
	1	Reactive nitrogen species metabolic process	1.86	<0.001	**1**	Antigen processing and presentation of peptide antigen via MHC class I	1.81	0.008
	2	Regulation of small molecule metabolic process	1.84	<0.001	**2**	Cell adhesion mediated by integrin	1.56	0.019
	3	Developmental maturation	1.79	<0.001	**3**	Antigen processing and presentation	1.56	0.019
	4	Anatomical structure maturation	1.75	<0.001	**4**	Antigen processing and presentation of peptide antigen	1.54	0.032
	5	Fat cell differentiation	1.72	<0.001	**5**	Antigen processing and presentation of endogenous antigen	1.52	0.029
	6	Protein modification by small protein conjugation	1.72	0.058	**6**	Response to reactive oxygen species	1.51	0.014
	7	Regulation of post translational protein modification	1.71	<0.001	**7**	Striated muscle cell differentiation	1.48	0.104
	8	Negative regulation of transcription by RNA polymerase II	1.71	0.026	**8**	Cardiocyte differentiation	1.42	0.146
	9	Connective tissue development	1.7	<0.001	**9**	T cell apoptotic process	1.42	0.124
	10	Regulation of peptidase activity	1.68	<0.001	**10**	Integrin mediated signaling pathway	1.41	0.122

[a] ABC: alcohol-betel-cigarette; KEGG: kyoto encyclopedia of genes and genomes; VEGF: vascular endothelial growth factor; MHC: major histocompatibility complex; RNA: ribonucleic acid.

TME and genomic analysis, leading to a Phase II clinical trial.[25] We found that combining afatinib, an EGFR-targeting tyrosine kinase inhibitor, with the PD-1 (programmed death-1) antibody pembrolizumab significantly improved immunotherapy effectiveness in head and neck cancer patients. The addition of afatinib increased antigen presentation, whereas genomic analysis revealed that the loss of the MTAP (methylthioadenosine phosphorylase) gene predicted poorer outcomes.[25]

This study revealed that female oral cancer patients exhibit distinct gene expression patterns in their TMEs compared to males. KEGG analysis showed that high-risk male patients with a history of alcohol, BQ, and cigarette habits had higher expression of cancer-related gene sets like pancreatic ($P = 0.058$) and colorectal cancer ($P = 0.051$). This suggests that the carcinogenic mechanisms in these patients may resemble those of pancreatic and colorectal cancers.

Conversely, low-risk female patients had different highly expressed gene sets like prion disease ($P = 0.022$) and the VEGF ($P = 0.053$) signaling pathway, which warrants further research in females. The potential of vascular inhibitors as a first-line treatment for females should be validated. These differences suggest that oral habits result in significant sex differences in carcinogenesis and the TME.

In the gene set analysis of Gene Ontology Biological Processes, high-risk patients showed elevated expression of gene sets related to antigen processing and presentation,

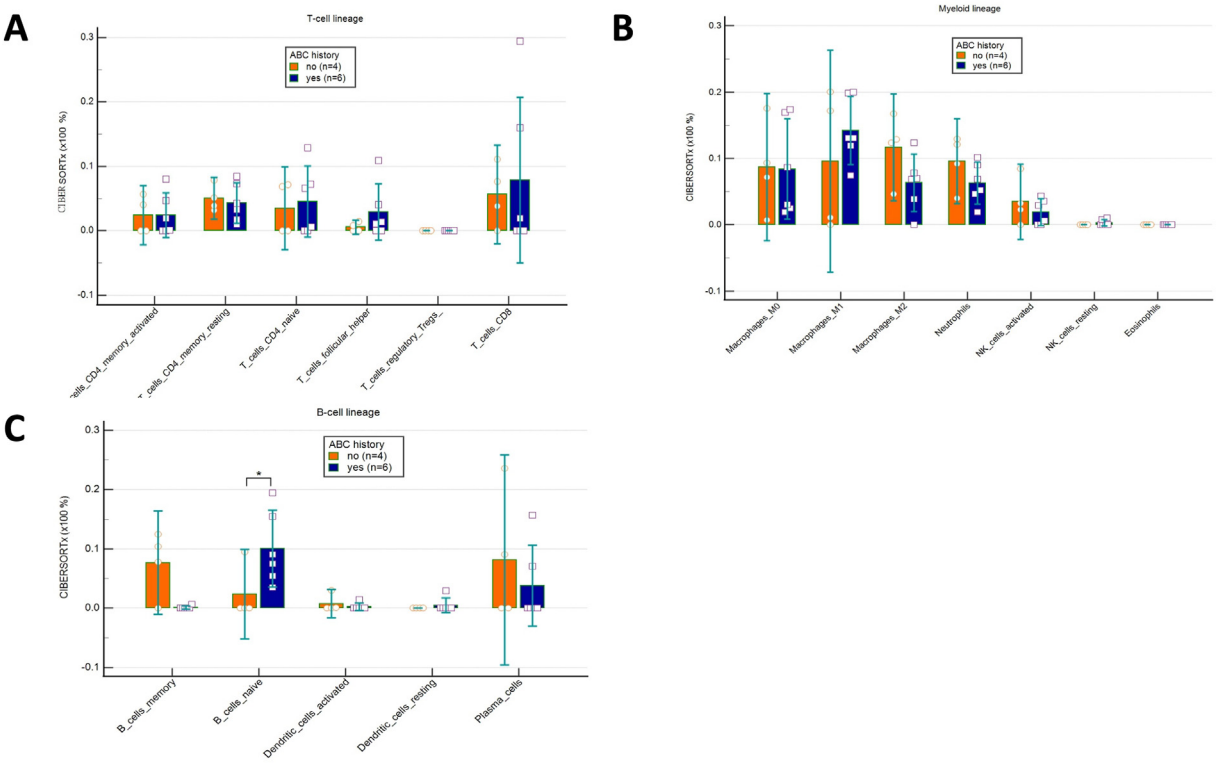

Figure 1 Expression of immune cells in high- and low-risk oral squamous cell carcinoma patients with and without oral habits
(A) The mRNA data analysis indicated no significant differences in T-cell lineages or (B) myeloid lineages but suggested higher expression of M2-type macrophages in females (C) B-cell lineage analysis showed a higher proportion of naïve B cells in the high-risk group compared to low-risk females ($P = 0.044$), but with no significant difference in memory B cells.

integrins, and reactive oxygen species—pathways associated with better outcomes in immunotherapy. This aligns with previous observations that male lung cancer patients or those with a smoking history tend to respond better to immunotherapy.[26] By contrast, low-risk patients exhibited biological pathways distinct from males and lacked substantial antigen processing and presentation, instead showing higher expression in gene sets related to metabolic dysregulation (e.g., reactive nitrogen metabolic processes, fat cell differentiation, protein modification). CIBERSORTx revealed that females had fewer naïve B cells but higher levels of suppressive M2-type macrophages, whereas the high-risk group had more naïve B cells. This may promote tumor antigen presentation within tertiary lymphoid structures, potentially improving immunotherapy outcomes in high-risk groups compared to low-risk groups.[27,28]

Another critical finding is that female tongue cancer patients without a history of oral habits had poorer prognoses, suggesting the need to investigate whether this is linked to dysregulation of metabolism-related genes or suppressed immune function. Research indicates that hormonal changes during the menopause affect women's oral health, leading to thinner, more atrophic oral mucosa, increased infections, and oral ulcers. Post-menopausal status may also play a role, as hormonal deficiencies can compromise immune function and lead to atrophic oral mucosa, making it more susceptible to injury.[29] Stress and chronic oral ulcers can cause oral cancer, and prolonged stress may lead to endocrine disorders and reduced immunity.[30,31] These findings suggest that differences in submucosal lymphoid organs between males and females with oral cancer may help guide future design of personalized immunotherapy.

Our study had limitations, including a small sample size that limits generalization to all female oral cancer patients in Taiwan. We will use the Health and Welfare Data Science Center (Taiwan) for a larger analysis to reduce bias in the future. The study focused on oral cancer alone, without comparison to other head and neck cancers, possibly leading to incomplete understanding of carcinogenesis and the TME. Additionally, few female patients consumed alcohol, complicating study of its effects. We compared survival outcomes between female and male patients in our cohort. However, this cohort included only 17 female patients, which restricted the scope of the analysis and precluded a meaningful survival outcome comparison. Lastly, genomic and TME analysis involved only 12 tissue samples, necessitating further investigation with larger sample sizes.

In conclusion, understanding tumor genomic variations and the TME is critical for developing targeted therapies and personalized treatments for different sexes (Fig. 2). Key prognostic factors include age, tumor predilection site, alcohol consumption, BQ chewing, cigarette smoking. However, common mucosal issues in women, such as oral ulcers, xerostomia, and comorbid conditions, may also play

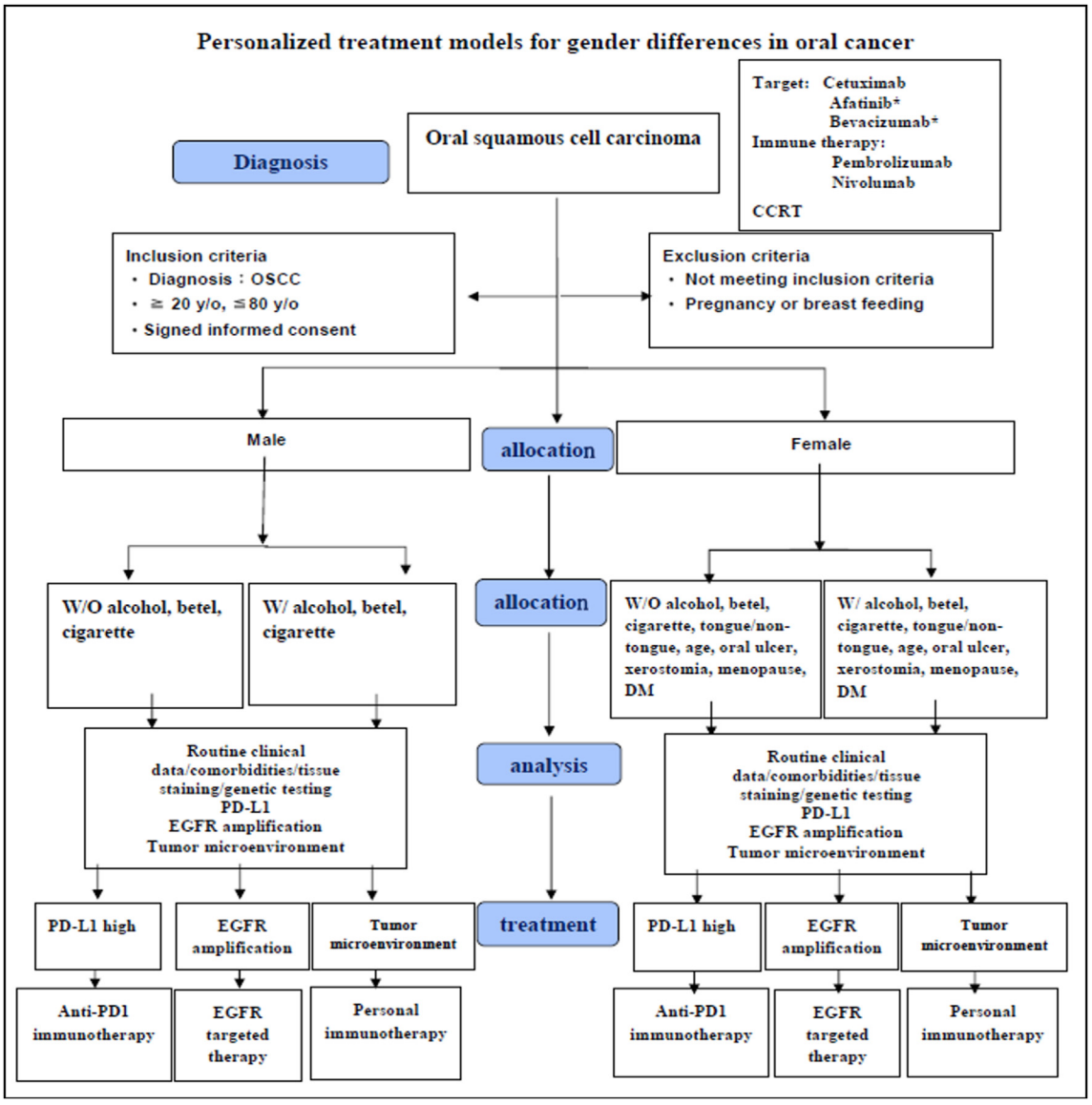

Figure 2 Personalized treatment models for sex differences in oral cancer Abbreviation: OSCC: oral squamous cell carcinoma; CCRT: concurrent chemoradiotherapy; PD-L1: programmed cell death-ligand 1; EGFR: epidermal growth factor receptor.

an important role. In females, the TME exhibits dysregulation in metabolism- and immunosuppression-related genes, possibly explaining their distinct treatment responses and prognoses. These findings highlight the importance of sex-specific factors in diagnosis and treatment decisions. Future research will expand the sample size and further investigate the pathogenic mechanisms and biological characteristics of oral cancer in women to develop more effective prevention strategies, early intervention approaches, and educational guidelines for disease management.

Conflict of interest statement

There are no conflicts of interest to declare.

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