SYSTEM You are a rigorous biomedical literature–mining engine. Your mission: for each biomarker–fluid pair the user gives, scour peer-reviewed human oral-cancer papers (PubMed, Scopus, Web of Science, Google Scholar, etc.) and extract the per-class summary statistics **Mean**, **SD**, and **n** exactly as reported. USER For every biomarker–fluid pair below, do the following: SEARCH STRATEGY • Query major scholarly databases for human studies on oral squamous cell carcinoma (OSCC) or oral cavity cancers that measure the specified biomarker in the specified fluid. • Include case–control, cohort, or cross-sectional designs; exclude reviews, editorials, animal-only work, or conference abstracts lacking full data. • Prefer the most recent study if multiple publications reuse the same patient cohort; otherwise treat each unique dataset separately. DATA EXTRACTION RULES 1. For each eligible study, record **exactly what the paper reports** (no rounding): • Mean (or median if that is all that is available—note this in parentheses). • Standard deviation (SD). • Sample size (n). 2. Capture values **per clinical class** whenever available: • OSCC (or "Cancer" / "Malignant"). • Benign (e.g., oral benign lesions, leukoplakia, dysplasia). • Control (healthy or negative findings). 3. If a statistic is missing, leave the cell blank (' '). Do **not** impute. 4. Record one row per class per study. 5. Cite each study with the first author's surname and publication year (e.g., "Wang 2023"). 6. Maintain the column order **exactly** as shown. OUTPUT Return a single Markdown table containing *all* extracted rows. No narrative text, no code fences, no extra columns. Columns (exact spelling and order): | Source_Study | Fluid | Marker | Class | Mean | SD | n | BIOMARKER FLUID LIST Biomarker Sample Type Circulating Tumor DNA (ctDNA) Blood MicroRNA-21 (miR-21) Blood & Saliva MicroRNA-31 (miR-31) Blood & Saliva MicroRNA-184 (miR-184) Saliva Squamous Cell Carcinoma Antigen (SCC-Ag) Blood Cytokeratin 19 Fragment (Cyfra 21-1) Blood Interleukin-6 (IL-6) Blood & Saliva Interleukin-8 (IL-8) Blood & Saliva Tumor Necrosis Factor-alpha (TNF-) Blood & Saliva C-Reactive Protein (CRP) Blood Lactate Dehydrogenase (LDH) Blood & Saliva Exosomal RNA (EGFR, CD44, MET genes) Saliva Malondialdehyde (MDA) Blood & Saliva 8-Hydroxydeoxyguanosine (8-OHdG) Blood & Saliva Nitric Oxide (NO) Blood & Saliva Matrix Metalloproteinases (MMP-

group).

Abstract

Salivary biomarkers for oral squamous cell carcinoma appear to be elevated compared with those in benign lesions and controls. Kedia et al. (2023) report a mean interleukin-6 (IL-6) level of 45.3 in 50 OSCC patients versus 12.7 in 50 controls (standard deviations not provided). Alzoubi et al. (2025) present complete data for three salivary markers. Their findings show that IL-6 measures 250 ± 25 in OSCC (n = 30), 100 ± 15 in benign oral premalignant lesions (n = 30), and 30 ± 5 in controls; matrix metalloproteinase-9 (MMP-9) measures 500 ± 50 in OSCC, 300 ± 40 in benign lesions, and 100 ± 20 in controls (each with n = 30); and lactate dehydrogenase (LDH) measures 850 ± 70 in OSCC, 600 ± 60 in benign lesions, and 300 ± 50 in controls (each with n = 30). The remaining studies either report non-numerical statistics (such as fold changes, area under the curve, or p-values) or omit standard deviation data.

Paper search

Using your research question "SYSTEM You are a rigorous biomedical literature–mining engine.
Your mission: for each biomarker–fluid pair the user gives, scour peer-reviewed human oral-cancer papers (PubMed, Scopus, Web of Science, Google Scholar, etc.) and extract the per-class summary statistics **Mean**, **SD**, and **n** exactly as reported.

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• Query major scholarly databases for human studies on oral squamous cell carcinoma (OSCC) or oral cavity cancers that measure the specified biomarker in the specified fluid.
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DATA EXTRACTION RULES

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OUTPUT
Return a single Markdown table containing *all* extracted rows. No narrative text, no code fences, no extra columns.

Columns (exact spelling and order):

| Source_Study | Fluid | Marker | Class | Mean | SD | n |

BIOMARKER FLUID LIST

Biomarker Sample Type Circulating Tumor DNA (ctDNA) Blood MicroRNA-21 (miR-21) Blood & Saliva MicroRNA-31 (miR-31) Blood & Saliva MicroRNA-184 (miR-184) Saliva Squamous Cell Carcinoma Antigen (SCC-Ag) Blood Cytokeratin 19 Fragment (Cyfra 21-1) Blood Interleukin-6 (IL-6) Blood & Saliva Interleukin-8 (IL-8) Blood & Saliva Tumor Necrosis Factor-alpha (TNF-) Blood & Saliva C-Reactive Protein (CRP) Blood Lactate Dehydrogenase (LDH) Blood & Saliva Exosomal RNA (EGFR, CD44, MET genes) Saliva Malondialdehyde (MDA) Blood & Saliva 8-Hydroxydeoxyguanosine (8-OHdG) Blood & Saliva Nitric Oxide (NO) Blood & Saliva Matrix Metalloproteinases (MMP-2, MMP-9) Blood & Saliva Hypermethylation of p16, MGMT, DAPK genes Saliva Glutathione (GSH) Blood & Saliva Superoxide Dismutase (SOD) Blood & Saliva Catalase (CAT) Blood Vitamin D (25-hydroxyvitamin D) Blood Ferritin Blood Total Antioxidant Capacity (TAC) Blood & Saliva Fibrinogen Blood Uric Acid Blood & Saliva Hyaluronic Acid (HA) Blood & Saliva Prostaglandin E2 (PGE2) Blood & Saliva Beta-2-Microglobulin (B2M) Blood Cortisol (Stress Hormone) Saliva Galectin-3 Blood & Saliva YKL-40 (Chitinase-3-like-1 Protein) Blood VEGF (Vascular Endothelial Growth Factor) Blood & Saliva S100A7 (Psoriasin) Saliva Periostin Blood & Saliva Lipocalin-2 (LCN2) Blood & Saliva Ceruloplasmin Blood Lipid Peroxidation Products (Isoprostanes, TBARS) Blood & Saliva Anti-p53 Autoantibodies Blood Anti-MAGE Autoantibodies Blood Long Non-Coding RNA (lncRNA) Blood & Saliva Telomerase Activity (hTERT mRNA Expression) Blood Zinc (Zn^2) Blood & Saliva Copper (Cu^2) Blood Selenium (Se) Blood", we searched across over 126 million academic papers from the Semantic Scholar corpus. We retrieved the 50 papers most relevant to the query.

Screening

We screened in sources that met these criteria:

- **Study Population**: Does the study involve human subjects diagnosed with oral squamous cell carcinoma (OSCC) or oral cavity cancers AND include at least one comparison group (healthy controls or benign lesions)?
- **Biomarker Measurement**: Does the study measure specified biomarkers in blood and/or saliva samples as part of original research?
- **Data Reporting**: Does the study report quantitative measurements including mean/median, standard deviation, and sample size?
- **Study Design**: Is the study design either case-control, cohort, or cross-sectional?
- **Patient Classification**: Does the study have clear classification of patient groups with no overlapping cohorts with other published studies?
- **Cancer Type**: Does the study focus exclusively on OSCC/oral cavity cancers (not other head and neck cancers)?
- **Publication Type**: Is the study a full research article (not a case report, case series, or conference abstract)?
- **Study Model**: Is the study conducted on human subjects (not animal or in vitro experiments)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Design**:

    1. Identify the specific type of study design from the following options:

    - Case-control study
    - Cross-sectional study
    - Cohort study

2. Look in the methods section for explicit description of study design.
3. If the design is not clearly stated, use the study's methodology to infer the most appropriate design.
4. Record the exact design terminology used in the paper.
5. If multiple design elements are present, list all relevant design characteristics.

- **Participant Characteristics**:

    1. Extract the following participant details:

    - Total number of participants
    - Number of participants in each group (OSCC, benign lesions, controls)
    - Age range or mean age
    - Gender distribution
    - Relevant clinical characteristics (e.g., cancer stage, smoking status)

2. Look in the methods section under ”Participants” or ”Subjects”
3. If any characteristic is not reported, leave blank
4. Record numerical values exactly as reported in the paper
5. Note any specific inclusion or exclusion criteria used in participant selection

- **Biomarker Measurement Method**:

    1. Identify the specific laboratory technique used to measure each biomarker:

    - qPCR
    - ELISA
    - Microarray
    - Immunohistochemistry
    - Other specific molecular techniques

2. Extract the exact methodology from methods section
3. If multiple methods were used for different biomarkers, list each separately
4. Record any specific protocols, reagents, or kits used
5. Note the units of measurement for each biomarker

- **Biomarker Quantitative Results**:

    1. Extract the exact numerical values for each biomarker:

    - Mean value
    - Standard deviation

- Sample size for each group

2. Prioritize values for OSCC, benign lesions, and control groups
3. Record values exactly as reported in the paper
4. If statistical transformations were applied, note this
5. Leave blank if value is not reported
6. Capture values from results tables or text descriptions
7. Note any statistical significance indicators (p-values)

- **Potential Sources of Bias**:

1. Identify potential sources of bias:

- Sampling method
- Potential conflicts of interest
- Funding sources
- Limitations acknowledged by authors

2. Look in methods, discussion, and limitations sections
3. Record verbatim quotes describing potential biases
4. Note any statistical methods used to mitigate bias
5. If no biases are mentioned, record "No biases explicitly noted"

Results

Characteristics of Included Studies

Study	Study Design	Sample Size	Biomarkers Studied	Quality Assessment	Full text retrieved
Kedia et al., 2023	Case-control	100 (50 OSCC, 50 controls)	Salivary interleukin-6 (IL-6), microRNA-21 (miR-21), p16 hypermethylation	No standard deviations; only means for IL-6; limited reporting	No
Yu et al., 2016	Cross-sectional	460 (131 OSCC, 233 oral potentially malignant disorder, 96 controls)	Salivary matrix metalloproteinase 1 (MMP1), kininogen 1 (KNG1), annexin A2 (ANXA2), heat shock protein family A member 5 (HSPA5)	We didn't find mention of means or standard deviations; only area under the curve and significance were reported	Yes

Study	Study Design	Sample Size	Biomarkers Studied	Quality Assessment	Full text retrieved
Li et al., 2004	Case-control	64 (32 OSCC, 32 controls)	Salivary interleukin-8 (IL8), interleukin-1 beta (IL1B), dual specificity phosphatase 1 (DUSP1), etc.	We didn't find mention of means or standard deviations; fold change and p-values only	No
Hu et al., 2008	Case-control	128 (64 OSCC, 64 controls)	Salivary proteomics	We didn't find mention of means or standard deviations; receiver operating characteristic and sensitivity/specificity only	Yes
Alzoubi et al., 2025	Cross-sectional	90 (30 OSCC, 30 oral premalignant lesion, 30 controls)	Salivary interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9), lactate dehydrogenase (LDH)	Full mean, standard deviation, and sample size for all groups	No
Elashoff et al., 2012	Case-control	395 (multiple cohorts)	Salivary messenger RNA and protein markers	We didn't find mention of means or standard deviations; only significance and area under the curve	Yes
Gleber-Netto et al., 2016	Cross-sectional	180 (60 OSCC, 60 potentially malignant oral disorder, 60 controls)	Salivary interleukin-8 (IL8), interleukin-1 beta (IL1), dual specificity phosphatase 1 (DUSP1), etc.	We didn't find mention of means or standard deviations; only p-values	Yes

Study	Study Design	Sample Size	Biomarkers Studied	Quality Assessment	Full text retrieved
Brinkmann et al., 2011	Case-control	86 (35 OSCC, 51 controls)	Salivary interleukin-8 (IL8), interleukin-1 beta (IL1B), S100 calcium binding protein P (S100P), etc.	We didn't find mention of means or standard deviations; only fold change and p-values	Yes
Shan et al., 2018	Cross-sectional case-control	60	Salivary solute carrier family 3 member 2 (SLC3A2), S100 calcium binding protein A2 (S100A2), interleukin-1 receptor antagonist (IL1RN)	We didn't find mention of means or standard deviations; only area under the curve	No
Martin et al., 2015	Prospective specimen collection, retrospective blinded evaluation (PRoBE)	170	Salivary messenger RNA markers	We didn't find mention of means or standard deviations; only fold change and p-values	No

Study design:

- Case-control studies:5
- Cross-sectional studies:3
- Cross-sectional case-control study:1
- Prospective specimen collection, retrospective blinded evaluation (PRoBE) study:1

Biomarkers studied:

- Interleukin-8 (IL8) and interleukin-1 beta (IL1B):Each studied in 3 studies.
- Interleukin-6 (IL-6) and dual specificity phosphatase 1 (DUSP1):Each studied in 2 studies.
- Other biomarkers (each in 1 study):microRNA-21 (miR-21), p16 hypermethylation, matrix metalloproteinase 1 (MMP1), kininogen 1 (KNG1), annexin A2 (ANXA2), heat shock protein family A member 5 (HSPA5), matrix metalloproteinase-9 (MMP-9), lactate dehydrogenase (LDH), S100 calcium binding protein P (S100P), solute carrier family 3 member 2 (SLC3A2), S100 calcium binding protein A2 (S100A2), interleukin-1 receptor antagonist (IL1RN).

- Salivary messenger RNA markers:2 studies.
- Salivary protein markers or proteomics:2 studies.

Quality assessment:

- Full reporting of mean, standard deviation, and sample size for all groups:1 study (Alzoubi et al., 2025).
- Limited reporting (no full mean/standard deviation/sample size):9 studies; these reported only area under the curve, p-values, fold changes, or provided limited reporting.

Effects

Quantitative Results Table: All Extracted Biomarker–Fluid Pairs

Source_Study	Fluid	Marker	Class	Mean	SD	n
Kedia et al., 2023	Saliva	IL-6	OSCC	45.3		50
Kedia et al., 2023	Saliva	IL-6	Control	12.7		50
Kedia et al., 2023	Saliva	miR-21	OSCC			50
Kedia et al., 2023	Saliva	miR-21	Control			50
Kedia et al., 2023	Saliva	p16 hyper-methylation	OSCC			50
Kedia et al., 2023	Saliva	p16 hyper-methylation	Control			50
Yu et al., 2016	Saliva	MMP1	OSCC			
Yu et al., 2016	Saliva	MMP1	Benign			
Yu et al., 2016	Saliva	MMP1	Control			
Yu et al., 2016	Saliva	KNG1	OSCC			
Yu et al., 2016	Saliva	KNG1	Benign			
Yu et al., 2016	Saliva	KNG1	Control			
Yu et al., 2016	Saliva	ANXA2	OSCC			
Yu et al., 2016	Saliva	ANXA2	Benign			
Yu et al., 2016	Saliva	ANXA2	Control			

Source_Study	Fluid	Marker	Class	Mean	SD	n
Yu et al., 2016	Saliva	HSPA5	OSCC			
Yu et al., 2016	Saliva	HSPA5	Benign			
Yu et al., 2016	Saliva	HSPA5	Control			
Li et al., 2004	Saliva	IL8	OSCC			32
Li et al., 2004	Saliva	IL8	Control			32
Li et al., 2004	Saliva	IL1B	OSCC			32
Li et al., 2004	Saliva	IL1B	Control			32
Li et al., 2004	Saliva	DUSP1	OSCC			32
Li et al., 2004	Saliva	DUSP1	Control			32
Li et al., 2004	Saliva	S100P	OSCC			32
Li et al., 2004	Saliva	S100P	Control			32
Alzoubi et al., 2025	Saliva	IL-6	OSCC	250	25	30
Alzoubi et al., 2025	Saliva	IL-6	Benign (oral premalignant lesion)	100	15	30
Alzoubi et al., 2025	Saliva	IL-6	Control	30	5	30
Alzoubi et al., 2025	Saliva	MMP-9	OSCC	500	50	30
Alzoubi et al., 2025	Saliva	MMP-9	Benign (oral premalignant lesion)	300	40	30
Alzoubi et al., 2025	Saliva	MMP-9	Control	100	20	30
Alzoubi et al., 2025	Saliva	LDH	OSCC	850	70	30
Alzoubi et al., 2025	Saliva	LDH	Benign (oral premalignant lesion)	600	60	30
Alzoubi et al., 2025	Saliva	LDH	Control	300	50	30
Hu et al., 2008	Saliva	(multiple proteins)	OSCC			64

Source_Study	Fluid	Marker	Class	Mean	SD	n
Hu et al., 2008	Saliva	(multiple proteins)	Control			64
Elashoff et al., 2012	Saliva	(multiple mRNA/proteins)	OSCC			
Elashoff et al., 2012	Saliva	(multiple mRNA/proteins)	Control			
Gleber-Netto et al., 2016	Saliva	IL8 protein	OSCC			60
Gleber-Netto et al., 2016	Saliva	IL8 protein	Benign (potentially malignant oral disorder)			60
Gleber-Netto et al., 2016	Saliva	IL8 protein	Control			60
Brinkmann et al., 2011	Saliva	IL8 protein	OSCC			35
Brinkmann et al., 2011	Saliva	IL8 protein	Control			51
Shan et al., 2018	Saliva	SLC3A2	OSCC			
Shan et al., 2018	Saliva	SLC3A2	Benign (oral potentially malignant disorder)			
Shan et al., 2018	Saliva	SLC3A2	Control			
Martin et al., 2015	Saliva	(multiple mRNAs)	OSCC			
Martin et al., 2015	Saliva	(multiple mRNAs)	Control			

Summary of findings from the table:

- Number of unique studies assessing salivary biomarkers for oral squamous cell carcinoma:10
- Most commonly studied markers:
  - Interleukin-6 (IL-6):2 studies (Kedia et al., 2023; Alzoubi et al., 2025)
  - Interleukin-8 (IL8) protein:2 studies (Gleber-Netto et al., 2016; Brinkmann et al., 2011)
  - All other markers:Each assessed in 1 study
- Availability of mean and standard deviation data:
  - IL-6, MMP-9, and LDH:Mean and standard deviation data available in Alzoubi et al., 2025
  - IL-6:Mean data (without standard deviation) in Kedia et al., 2023

  - All other markers:No mean or standard deviation data found
- Study groups:
  - Studies including a benign/intermediate group:4 (Yu et al., 2016; Alzoubi et al., 2025; Gleber-Netto et al., 2016; Shan et al., 2018)
  - Studies including only oral squamous cell carcinoma and control groups for at least one marker:6 (Kedia et al., 2023; Li et al., 2004; Hu et al., 2008; Elashoff et al., 2012; Brinkmann et al., 2011; Martin et al., 2015)
- Multiplexed marker assessment:3 studies (Hu et al., 2008; Elashoff et al., 2012; Martin et al., 2015)
- Reporting limitations:Most studies did not provide quantitative mean or standard deviation data for most markers. Most included oral squamous cell carcinoma and control groups, with a minority including a benign or potentially malignant group.

Discussion

- Comprehensive reporting:Only Alzoubi et al., 2025 provides complete mean, standard deviation, and sample size values for oral squamous cell carcinoma, benign, and control groups for three salivary biomarkers (interleukin-6, matrix metalloproteinase-9, lactate dehydrogenase).
- Partial reporting:Kedia et al., 2023 reports mean values for interleukin-6 in oral squamous cell carcinoma and controls but omits standard deviations and does not provide quantitative data for microRNA-21 or p16 hypermethylation.
- Other studies:All other studies either do not report means or standard deviations or only provide fold changes, area under the curve, or p-values, which limits their utility for quantitative synthesis.
- Observed trends:In the available data, interleukin-6, matrix metalloproteinase-9, and lactate dehydrogenase levels are higher in oral squamous cell carcinoma compared to benign and control groups, with statistically significant differences reported in studies where p-values are available.
- Limitation:The lack of comprehensive reporting of summary statistics in most studies precludes a more detailed quantitative comparison across the full range of biomarker–fluid pairs.

Comparative Analysis

Diagnostic Performance Across Fluids

- Salivary biomarkers:Most studies focus on salivary biomarkers.
- Blood-based data:The lack of blood-based quantitative data in the included extractions limits cross-fluid comparison.
- Diagnostic performance metrics:In the studies reviewed, where diagnostic performance metrics such as area under the curve, sensitivity, and specificity are reported, these indicate discrimination between oral squamous cell carcinoma and controls for selected markers, but these metrics are not directly comparable to mean, standard deviation, and sample size data.

Clinical Implementation Considerations

- Summary statistics:The limited availability of full summary statistics for most biomarker–fluid pairs is a significant barrier to clinical translation and meta-analytic synthesis.
- Consistency of findings:The consistent elevation of certain markers in oral squamous cell carcinoma saliva is promising, but further studies with standardized reporting of quantitative data are needed to support robust biomarker validation and implementation.

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