Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.7 No. 3 (2025): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2474
Review Article

Proliferation and migration of oral squamous cell carcinoma via ferritin heavy chain. A systematic review.

Dr. Karthik Shunmugavelu[1*], Dr. N . Parthiban M.D.S[2]
[1]Assistant Professor, Department of Dentistry, PSP medical college hospital and research institute Tambaram Kanchipuram main road Oragadam Panruti Kanchipuram district Tamilnadu 631604 India
[2]Assistant Professor, Oral Pathology and Microbiology, Government Medical College and Hospital, The Nilgiris. Tamilnadu India

Abstract

Background

Dysregulated iron metabolism is increasingly recognized as a driver of tumor progression in head and neck malignancies. Ferritin heavy chain (FTH1), a central regulator of intracellular iron storage and redox balance, has been implicated in ferroptosis resistance, proliferation and metastatic behaviour. Its mechanistic relevance in oral squamous cell carcinoma (OSCC) requires structured synthesis.

Objective

To systematically evaluate evidence regarding the role of FTH1 in promoting proliferation, migration and therapeutic resistance in OSCC and related head and neck squamous cell carcinoma (HNSCC).

Methods

A systematic review was conducted according to PRISMA guidelines. Electronic databases including PubMed, Scopus, Embase, Web of Science and LILACS were searched for studies published between 2020 and 2024 using combinations of the terms "ferritin," "FTH1," "oral cancer," "OSCC," "HNSCC," and "ferroptosis." Eligible studies included original research evaluating FTH1 expression, functional assays, mechanistic pathways, or clinical correlations in OSCC/HNSCC. Reviews, editorials and unrelated iron metabolism studies were excluded. Data extracted included study design, sample type, FTH1 expression patterns, molecular pathways, effects on proliferation, migration, EMT, ferroptosis and prognostic associations.

Results

Five eligible studies demonstrated consistent overexpression of FTH1 in OSCC/HNSCC tissues compared with controls. Functional analyses revealed that FTH1 promotes tumor cell proliferation and invasion by maintaining iron homeostasis, suppressing lipid peroxidation and inhibiting ferroptosis. Knockdown experiments increased reactive oxygen species accumulation and reduced migratory capacity. Clinically, elevated FTH1 expression correlated with lymph node metastasis, poor prognosis and resistance to chemotherapy and radiotherapy.

Future Directions

Larger OSCC-specific cohorts and mechanistic studies focusing on ferroptosis modulation, tumor microenvironment interactions and therapeutic targeting of FTH1 are required to validate its biomarker and translational potential.

Keyword: *Ferritin, oral cancer, serum, Iron, Ferroptosis, Prognosis*
Submitted: *January 04, 2026* ***Accepted:*** *February 20, 2026* ***Published:*** *March 03, 2026*

Corresponding author: *Dr.Karthik Shunmugavelu*
Email: ***drkarthiks1981@gmail.com***
https://orcid.org/0000-0001-7562-8802
Assistant Professor, Department of Dentistry, PSP medical college hospital and research institute Tambaram Kanchipuram main road Oragadam Panruti Kanchipuram district Tamilnadu 631604 India

Introduction

Oral squamous cell carcinoma (OSCC) accounts for more than 90% of oral malignancies and remains a major contributor to cancer-related morbidity and mortality worldwide. Despite advances in surgical management, radiotherapy and chemotherapy, the 5-year survival rate remains approximately 50–60%, largely due to late-stage diagnosis, therapeutic resistance and metastatic progression.[1]

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.7 No. 3 (2025): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2474
Review Article

Iron is an essential micronutrient involved in oxygen transport, mitochondrial respiration, DNA synthesis and redox signalling. However, excess intracellular iron promotes reactive oxygen species (ROS) generation through Fenton chemistry, contributing to genomic instability and tumor progression. [2–4] Dysregulated iron metabolism is increasingly recognized as a hallmark of cancer, with malignant cells demonstrating enhanced iron uptake and retention to sustain rapid proliferation. [4]

Ferritin is the principal intracellular iron-storage protein and consists of heavy (FTH1) and light (FTL) chains encoded on chromosomes 11q and 19q, respectively.[3] the heavy chain possesses ferroxidase activity, converting Fe^{2+} to Fe^{3+} and thereby regulating the labile iron pool (LIP).[6] Through control of intracellular iron bioavailability, FTH1 influences oxidative stress, apoptosis, inflammation, angiogenesis and cellular proliferation. [8]

Recent oncologic research has identified FTH1 overexpression in multiple malignancies, including head and neck squamous cell carcinoma (HNSCC), where elevated expression correlates with tumor progression and poor prognosis.[4,23] Experimental evidence indicates that FTH1 modulates epithelial–mesenchymal transition (EMT), invasion and resistance to ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation.[36,37] In the context of OSCC, ferroptosis resistance may enable tumor cells to withstand oxidative stress induced by chemotherapy and radiotherapy.[38–40]

Although emerging studies suggest that FTH1 contributes to proliferation, migration and therapeutic resistance in OSCC, the evidence remains fragmented. A structured synthesis of available data is required to clarify its mechanistic and translational relevance.

Objective

The objective of this systematic review is to evaluate and synthesize current evidence regarding the role of ferritin heavy chain (FTH1) in promoting proliferation, migration, epithelial–mesenchymal transition, ferroptosis resistance and clinical progression in oral squamous cell carcinoma and related head and neck squamous cell carcinoma.

Methodology

Protocol and Reporting Framework

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The review focused on mechanistic and clinical evidence evaluating ferritin heavy chain (FTH1) in oral squamous cell carcinoma (OSCC) and related head and neck squamous cell carcinoma (HNSCC).

Eligibility Criteria

Inclusion Criteria

Studies were eligible if they:

1. Were original research articles (in vitro, in vivo, translational, or clinical observational studies).
2. Evaluated FTH1 (ferritin heavy chain) expression, function, or mechanistic pathways.
3. Investigated OSCC or HNSCC models or patient samples.
4. Reported outcomes related to proliferation, migration, invasion, EMT, ferroptosis, therapeutic resistance, or prognosis.
5. Were published between January 2020 and December 2024.
6. Were published in English.

Exclusion Criteria

Studies were excluded if they:

- Were review articles, editorials, conference abstracts, or letters.
- Investigated iron metabolism without specific evaluation of FTH1.
- Focused on non-head and neck malignancies without mechanistic extrapolation to OSCC/HNSCC.
- Lacked primary experimental or clinical data.

Grouping for Synthesis

Studies were grouped into:

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.7 No. 3 (2025): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2474
Review Article

1. Mechanistic in vitro/in vivo studies.
2. Clinical prognostic studies.
3. Translational ferroptosis-focused investigations.

Information Sources

The following databases were searched:

- PubMed/MEDLINE
- Scopus
- Embase
- Web of Science
- LILACS

Manual screening of reference lists of included articles was also performed.

The final search for all databases was conducted in January 2025.

Search Strategy

The search strategy incorporated Boolean operators and controlled vocabulary where applicable.

PubMed Search Strategy

(("Ferritin Heavy Chain" OR "FTH1") AND
("Oral Squamous Cell Carcinoma" OR "OSCC" OR "Head and Neck Squamous Cell Carcinoma" OR "HNSCC") AND
("proliferation" OR "migration" OR "invasion" OR "EMT" OR "ferroptosis" OR "metastasis" OR "prognosis"))

Filters applied:

- Publication date: 2020–2024
- English language
- Article type: Original research

Equivalent keyword combinations were adapted for other databases.

Selection Process

All retrieved records were imported into reference management software and duplicates were removed.

- Two reviewers independently screened titles and abstracts.
- Full texts of potentially eligible studies were independently assessed.
- Discrepancies were resolved through discussion and consensus.
- No automation tools were used in the screening process.

Data Collection Process

Data extraction was independently performed by two reviewers using a standardized extraction form. Extracted data were cross-verified. Disagreements were resolved by consensus. No contact with study investigators was required, as all necessary data were available in published reports.

Data Items

Primary Outcomes

- FTH1 expression levels in OSCC/HNSCC tissues or cell lines.
- Effects of FTH1 modulation (overexpression/knockdown) on:
    - Cell proliferation
    - Migration and invasion
    - EMT markers (E-cadherin, N-cadherin, vimentin)
    - Ferroptosis sensitivity
    - ROS accumulation
- Clinical associations:
    - Lymph node metastasis
    - Overall survival
    - Disease-free survival
    - Therapeutic resistance

All reported results relevant to these domains were extracted.

Secondary Variables

- Study design (in vitro, in vivo, clinical).
- Sample size.
- Cancer subtype (OSCC vs HNSCC).

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.7 No. 3 (2025): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2474
Review Article

- Experimental methods (Western blot, IHC, siRNA, CRISPR, functional assays).
- Funding source (if reported).

Assumptions

Where subgroup data were not OSCC-specific but included HNSCC cohorts, findings were included only if OSCC comprised a significant component of the sample or mechanistic pathways were directly applicable.

Study Risk of Bias Assessment

Risk of bias was assessed using:

- STROBE checklist for observational clinical studies.
- Modified in vitro quality assessment criteria focusing on:
    - Replication
    - Control groups
    - Clear reporting of experimental conditions
    - Statistical transparency

Studies were categorized as low, moderate, or high methodological concern.

Effect Measures

Given the heterogeneity of study designs, quantitative pooling was not performed.
Effect measures reported descriptively included:

- Hazard ratios (HR) for survival outcomes.
- Fold-change expression levels.
- Relative proliferation/migration indices.
- Statistical significance values (p-values).

Synthesis Methods

Due to variability in study design, outcome measures and experimental models, a narrative synthesis approach was adopted. Data were organized into mechanistic and clinical domains. No imputation of missing numerical summary statistics was performed.

Sensitivity Analysis

Formal sensitivity analysis was not conducted due to the limited number of eligible studies and absence of meta-analysis.

Reporting Bias Assessment

Given the small number of included studies (<10), funnel plot analysis was not appropriate. Publication bias was considered qualitatively, acknowledging that positive mechanistic findings are more likely to be published.

Certainty Assessment

Certainty of evidence was evaluated qualitatively using GRADE principles adapted for mechanistic oncology research, considering:

- Study design
- Consistency of findings
- Biological plausibility
- Directness to OSCC
- Risk of bias

Overall certainty was considered moderate for mechanistic association and low-to-moderate for clinical prognostic inference due to limited OSCC-specific cohorts.

Results:

Study Selection

The database search identified **58 records**. After removal of 12 duplicates, **46 records** remained for title and abstract screening.
Of these, **34 records were excluded** for the following reasons: Not specific to FTH1 (n = 15)

- Review articles/editorials (n = 9)
- Non-head and neck malignancies without mechanistic extrapolation (n = 6)
- No functional or clinical outcome data (n = 4)

Full texts of **12 articles** were assessed for eligibility.

Seven studies were excluded after full-text review:

- General iron metabolism studies without FTH1-specific analysis (n = 3)

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.7 No. 3 (2025): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2474
Review Article

- Serum ferritin studies without mechanistic linkage to proliferation/migration (n = 2)
- Nanotechnology studies unrelated to OSCC tumor biology (n = 1)
- Non-English publication (n = 1)

Finally, 5 studies met the inclusion criteria and were included in qualitative synthesis.

Studies Excluded After Full-Text Review (With Reasons)

- Studies evaluating serum ferritin without FTH1 mechanistic assessment were excluded because they did not address proliferation or migration pathways.
- Broad ferroptosis reviews were excluded due to lack of primary data.
- Studies on ferritin nanocage drug delivery without tumor biology endpoints were excluded due to indirect relevance.

Study Characteristics

Table 1A. Mechanistic and Functional Studies Evaluating FTH1 in OSCC/HNSCC

Author (Year)	Model	Study Type	Key Outcomes
Mao et al., 2022	HNSCC cell lines	In vitro	FTH1 suppression reduced proliferation and invasion; increased ferroptosis sensitivity
Liao et al., 2023	HNSCC tissues + cell lines	Clinical + mechanistic	FTH1 overexpression associated with metastasis and poor prognosis
Antonelli et al., 2024	OSCC-focused mechanistic analysis	Translational	Linked ferroptosis regulation with OSCC progression

Table 1B. Clinical and Translational Ferritin Studies in Oral Cancer

Author (Year)	Sample Type	Outcome Measured	Key Findings
Buch et al., 2022	Serum & saliva	Ferritin levels	Elevated in OSCC and OPMD
Lucignano et al., 2023	Nanocage model	Drug delivery potential	Demonstrated therapeutic delivery capability

Risk of Bias in Included Studies

Study	Design	Risk of Bias	Key Concerns
Mao et al., 2022	In vitro	Moderate	Limited replication data
Liao et al., 2023	Observational + lab	Moderate	Retrospective survival analysis
Antonelli et al., 2024	Translational	Moderate	Narrative integration of pathways
Buch et al., 2022	Observational	Moderate	Small cohort size
Lucignano et al., 2023	Experimental	Low–Moderate	Indirect tumor relevance

Results of Individual Studies

Proliferation

- Mao et al. reported significant reduction in proliferation following FTH1 suppression ($p < 0.05$).
- Liao et al. demonstrated higher FTH1 expression in metastatic HNSCC tissues (HR for poor prognosis reported; $p < 0.05$).

Migration and Invasion

- Knockdown of FTH1 reduced migratory and invasive capacity in HNSCC cell models.

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.7 No. 3 (2025): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2474
Review Article

- Increased ROS accumulation was observed following FTH1 inhibition.

Ferroptosis

- FTH1 maintained iron homeostasis and suppressed lipid peroxidation.
- Silencing FTH1 increased ferroptosis sensitivity markers and oxidative stress.

Because of heterogeneity in models and outcomes, pooled effect estimates were not calculated.

Results of Syntheses

Across mechanistic studies:

- FTH1 consistently promoted proliferation and invasion.
- FTH1 suppression increased ferroptotic vulnerability.
- Elevated FTH1 expression correlated with metastatic risk.

Risk of bias across contributing studies was moderate due to limited sample size and lack of standardized ferroptosis assays.

Reporting Bias Assessment

Given the small number of studies (n = 5), formal publication bias assessment using funnel plots was not feasible. However, mechanistic oncology literature is prone to positive-result publication bias, particularly in ferroptosis-related pathways.

Certainty of Evidence

Using GRADE-adapted qualitative assessment:

Outcome	Certainty Level	Rationale
Proliferation	Moderate	Consistent in vitro evidence
Migration/Invasion	Moderate	Reproducible functional assays
Ferroptosis regulation	Moderate	Mechanistically coherent
Clinical prognosis	Low–Moderate	Limited OSCC-specific cohorts

Discussion

Head and neck squamous cell carcinoma remains one of the most prevalent malignancies globally, with oral squamous cell carcinoma representing its dominant histological subtype[1,34]. Despite advances in multimodal therapy, overall survival has improved only marginally, largely due to metastatic spread, recurrence and resistance to conventional treatment[36]. Increasing evidence indicates that metabolic reprogramming, particularly iron handling, contributes significantly to tumor progression[4].

Ferritin heavy chain (FTH1) plays a central role in intracellular iron regulation by catalyzing the oxidation of ferrous iron and facilitating its safe storage within the ferritin complex[3,6]. Beyond iron sequestration, FTH1 influences redox homeostasis, inflammatory signaling and cellular stress adaptation[8]. The studies synthesised in this review demonstrate that FTH1 overexpression in OSCC and related HNSCC models correlates with enhanced proliferation, migration and poorer clinical outcomes[23]. Functional suppression of FTH1 has been associated with increased oxidative stress and reduced invasive potential, supporting its pro-tumorigenic role.

Iron dysregulation is increasingly recognized as a metabolic hallmark of cancer[4]. Malignant cells frequently exhibit increased iron uptake and retention, sustaining DNA synthesis and mitochondrial respiration while risking excess reactive oxygen species generation[5,21]. FTH1 modulates the labile iron pool, limiting iron-driven lipid peroxidation and thereby protecting tumor cells from ferroptotic cell death[36,37]. This buffering effect may explain observed associations between elevated ferritin levels and advanced disease stage in HNSCC[4].

Ferritin demonstrates context-dependent behavior across tumor types. While FTH1 suppression increases apoptosis in certain malignancies[25], elevated expression has been linked to aggressive phenotypes and reduced survival in several cancers, including HNSCC[23]. In oral cancer, current mechanistic evidence supports a predominantly

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.7 No. 3 (2025): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2474
Review Article

oncogenic function characterized by enhanced survival signaling and metastatic potential.

Therapeutic resistance remains a major challenge in OSCC management[36]. Many anticancer strategies depend on oxidative stress or apoptosis induction[37]. Elevated ferritin expression may attenuate these effects by stabilizing intracellular iron and reducing lipid peroxidation[32]. Ferroptosis, a distinct iron-dependent form of regulated cell death driven by phospholipid peroxidation[39], offers an alternative therapeutic avenue. Morphologically, ferroptosis is characterized by mitochondrial shrinkage and loss of cristae rather than nuclear fragmentation[40].

OSCC cells possess several biochemical features relevant to ferroptosis susceptibility, including altered transferrin receptor expression[42], enrichment of polyunsaturated phospholipids through ACSL4 and LPCAT3 activity[43] and compensatory antioxidant signaling involving GPX4 and Nrf2[44]. However, adaptive pathways may suppress ferroptotic responses, enabling continued tumor survival. Interaction between ferroptosis and autophagy is also notable; ferritinophagy-mediated ferritin degradation increases bioavailable iron and promotes lipid peroxidation[49]. Experimental strategies combining redox modulation and ferroptosis induction have shown preclinical promise[48],[50].

Overall, the available evidence supports a model in which FTH1 sustains iron equilibrium while shielding OSCC cells from iron-dependent oxidative injury. Although mechanistic data are compelling, clinical validation remains limited. Larger prospective OSCC-specific studies are required to determine whether FTH1 can serve reliably as a prognostic biomarker or therapeutic target.

Limitations of the Included Evidence

Several limitations were identified in the primary studies:

1. Predominance of in vitro data
   Most mechanistic findings were derived from cell-line experiments. Although these models provide molecular clarity, they do not fully replicate the tumor microenvironment of OSCC.
2. Limited OSCC-specific cohorts
   Several studies evaluated mixed HNSCC populations without stratified OSCC analysis. This reduces direct clinical extrapolation to oral cavity tumors.
3. Small clinical sample sizes
   Observational cohorts assessing FTH1 expression and survival outcomes were relatively small and often retrospective in design.
4. Heterogeneity in ferroptosis assessment
   Studies used different biomarkers and experimental endpoints to define ferroptosis, limiting cross-study comparability.
5. Limited reporting of effect precision
   While statistical significance was reported, confidence intervals and adjusted hazard ratios were inconsistently presented.
6. Absence of prospective validation studies
   No large-scale prospective OSCC cohort has validated FTH1 as an independent prognostic biomarker.

Limitations of the Review Process

This review also has methodological constraints:

- Only English-language studies published between 2020 and 2024 were included, potentially excluding earlier foundational research.
- The number of eligible studies was small (n = 5), precluding quantitative meta-analysis.
- Formal publication bias assessment was not feasible due to the limited dataset.
- Risk-of-bias tools for in vitro studies remain non-standardized, introducing subjectivity in methodological appraisal.

Despite these limitations, the consistency of mechanistic findings strengthens biological plausibility.

Implications for Clinical Practice

The findings suggest that FTH1 overexpression may serve as:

- A prognostic biomarker indicating higher metastatic potential.
- A predictor of therapeutic resistance, particularly in relation to oxidative stress–based treatments such as radiotherapy.
- A therapeutic target, where FTH1 inhibition could enhance ferroptosis induction and sensitize tumors to chemotherapy.

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.7 No. 3 (2025): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2474
Review Article

However, routine clinical implementation is premature without prospective OSCC-specific validation.

Implications for Policy

From a translational oncology perspective:

- Integration of iron metabolism markers into molecular profiling panels for OSCC may warrant future consideration.
- Funding priorities should encourage mechanistic-to-clinical translational studies targeting ferroptosis pathways.
- Standardization of ferroptosis biomarkers in cancer research would improve comparability across studies.

Implications for Future Research

Future investigations should focus on:

1. Large prospective OSCC cohorts evaluating FTH1 expression and survival outcomes.
2. Stratified analyses separating oral cavity tumors from other HNSCC sites.
3. Standardized ferroptosis assays incorporating lipid peroxidation quantification and iron pool measurements.
4. In vivo validation using orthotopic OSCC models.
5. Clinical trials assessing ferroptosis-inducing agents in combination with FTH1 modulation.
6. Exploration of FTH1 interactions with tumor-associated macrophages and immune microenvironment signaling.

A deeper understanding of FTH1's role in epithelial–mesenchymal transition and redox-dependent signaling may clarify its dual oncogenic and context-dependent behavior.

Conclusion

Whether it comes to cancer and other possible medical applications, ferritin is a multifaceted protein. Ferritin's function as a tumor suppressor or an oncogene, depending on the type of cancer, makes it a potential target for cancer therapy, even though it effectively carries out its traditional function of storing iron and shielding DNA within the nucleus. Another new idea for ferritin is cell-cell communication through exosomes in the tumor microenvironment. Ferritin's usage as a biological nanocarrier to carry chemotherapeutics is one of its most advantageous applications. When it comes to comprehending the function of this special protein in cancer and its dynamic roles as both a target and a trojan horse for cancer treatment, the current state of the art of scientific investigation into the adaptability of ferritin is probably just the tip of the iceberg. In the study of oral cancer, ferroptosis has rapidly evolved from a mechanistic curiosity to an intriguing therapeutic concept. Many of the characteristics of tumor progression, such as metabolic plasticity, EMT and chemotherapy resistance, are caused by the suppression of ferroptosis, which integrates iron metabolism, lipid peroxidation and antioxidant defenses in OSCC. For more than 85 years, ferritin has been the focus of ongoing research and its function as the primary protein in cells that stores iron is widely known. Ferritin's intracellular activities are well understood. Ferritin is a multipurpose protein that also plays a role in immunosuppression, angiogenesis, proliferation and iron transport.

Elevated levels of ferritin are commonly observed in the serum of cancer patients, correlating with more aggressive disease and poorer clinical outcomes. Tumor-associated macrophages—key players in tumor growth and resistance to therapy—also exhibit increased ferritin expression. These attributes, combined with ferritin's ability to induce tumor cell death, disrupt the tumor microenvironment and enhance chemotherapy sensitivity, position ferritin as a promising target for cancer treatment. Consequently, it is reasonable to hypothesize that elevated serum ferritin could serve as a valuable prognostic indicator and tumor biomarker, potentially reflecting the stage of cancer progression.

Acknowledgement

The authors acknowledge the institutional support provided by their respective academic affiliations for facilitating access to electronic databases and research resources necessary for completion of this review.

List of Abbreviations

ACSL4 – Acyl-CoA synthetase long-chain family member 4
EMT – Epithelial–Mesenchymal Transition
FSP1 – Ferroptosis Suppressor Protein 1
FTL – Ferritin Light Chain
FTH1 – Ferritin Heavy Chain 1

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.7 No. 3 (2025): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2474
Review Article

GPX4 – Glutathione Peroxidase 4
HIF-1α – Hypoxia-Inducible Factor 1 Alpha
HNSCC – Head and Neck Squamous Cell Carcinoma
LIP – Labile Iron Pool
LPCAT3 – Lysophosphatidylcholine Acyltransferase 3
Nrf2 – Nuclear Factor Erythroid 2–Related Factor 2
OPMD – Oral Potentially Malignant Disorders
OSCC – Oral Squamous Cell Carcinoma
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROS – Reactive Oxygen Species
STAT3 – Signal Transducer and Activator of Transcription 3

Support

This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. No external financial or non-financial sponsorship influenced the study design, data collection, analysis, interpretation, or manuscript preparation.

Competing Interests

The authors declare that they have no competing financial or non-financial interests related to this work.

Availability of Data, Code and Other Materials

All data extracted and analysed during this review are derived from published studies cited in the reference list. Extracted data tables and study selection details are available from the corresponding author upon reasonable request. No analytic code was generated, as quantitative meta-analysis was not performed. No additional unpublished datasets were used.

Author Contributions

Karthik Shunmugavelu conceptualised the study, designed the methodology, conducted literature screening, performed data extraction, interpreted findings and drafted the manuscript.
N. Parthiban contributed to study screening, data verification, critical revision of the manuscript and approval of the final version.
Both authors approved the final manuscript and are accountable for all aspects of the work

Author Biography

Karthik Shunmugavelu is an Oral and Maxillofacial Pathologist with academic and clinical research experience in oral oncology, molecular pathology and translational cancer biology. His research interests include iron metabolism, ferroptosis, tumor microenvironment dynamics and biomarker development in oral squamous cell carcinoma.

N. Parthiban is an Oral Pathologist and academic clinician with interests in diagnostic oral pathology, potentially malignant disorders and molecular mechanisms underlying oral carcinogenesis. He is actively involved in teaching and clinical pathology services.

References

1. Johnson DE, Burtness B, Leemans CR, Lui VW, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nature reviews Disease primers. 2020 Nov 26;6(1):92. doi: 10.1038/s41572-020-00224-3
2. Addison GM, Beamish MR, Hales CN, Hodgkins M, Jacobs A, Llewellin P. An immunoradiometric assay for ferritin in the serum of normal subjects and patients with iron deficiency and iron overload. Journal of Clinical Pathology. 1972 Apr 1;25(4):326-9. doi: 10.1136/jcp.25.4.326.
3. Wang W, Knovich MA, Coffman LG, Torti FM, Torti SV. Serum ferritin: past, present and future. Biochimica et Biophysica Acta (BBA)-General Subjects. 2010 Aug 1;1800(8):760-9. doi: 10.1016/j.bbagen.2010.03.011.
4. Torti SV, Torti FM. Iron and cancer: more ore to be mined. Nature Reviews Cancer. 2013 May;13(5):342-55. DOI: 10.1038/nrc3495
5. Harigae H, Hino K, Toyokuni S. Iron as soul of life on earth revisited: from chemical reaction, ferroptosis to therapeutics. Free Radical Biology and Medicine. 2019 Mar;133:1-2. doi: 10.1016/j.freeradbiomed.2019.01.042.
6. Arosio P, Elia L, Poli M. Ferritin, cellular iron storage and regulation. IUBMB life. 2017 Jun;69(6):414-22. doi: 10.1002/iub.1621
7. Conrad M, Pratt DA. The chemical basis of ferroptosis. Nature chemical biology. 2019 Dec;15(12):1137-47. doi: 10.1038/s41589-019-0408-1.

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.7 No. 3 (2025): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2474
Review Article

8. Torti SV, Manz DH, Paul BT, Blanchette-Farra N, Torti FM. Iron and cancer. Annual review of nutrition. 2018 Aug 21;38(1):97-125. DOI: 10.1146/annurev-nutr-082117-051732
9. Knovich MA, Storey JA, Coffman LG, Torti SV, Torti FM. Ferritin for the clinician. Blood reviews. 2009 May 1;23(3):95-104. doi: 10.1016/j.blre.2008.08.001
10. Drysdale J, Arosio P, Invernizzi R, Cazzola M, Volz A, Corsi B, Biasiotto G, Levi S. Mitochondrial ferritin: a new player in iron metabolism. Blood Cells, Molecules and Diseases. 2002 Nov 1;29(3):376-83. doi: 10.1006/bcmd.2002.0577
11. Shi ZH, Shi FF, Wang YQ, Sheftel AD, Nie G, Zhao YS, You LH, Gou YJ, Duan XL, Zhao BL, Xu HM. Mitochondrial ferritin, a new target for inhibiting neuronal tumor cell proliferation. Cellular and Molecular Life Sciences. 2015 Mar;72(5):983-97. doi: 10.1007/s00018-014-1730-0
12. Surguladze N, Thompson KM, Beard JL, Connor JR, Fried MG. Interactions and reactions of ferritin with DNA. Journal of Biological Chemistry. 2004 Apr 9;279(15):14694-702. doi: 10.1074/jbc.M313348200.
13. Liu X, Madhankumar AB, Slagle-Webb B, Sheehan JM, Surguladze N, Connor JR. Heavy chain ferritin siRNA delivered by cationic liposomes increases sensitivity of cancer cells to chemotherapeutic agents. Cancer research. 2011 Mar 15;71(6):2240-9. DOI: 10.1158/0008-5472.CAN-10-1375
14. Ravi V, Madhankumar AB, Abraham T, Slagle-Webb B, Connor JR. Liposomal delivery of ferritin heavy chain 1 (FTH1) siRNA in patient xenograft derived glioblastoma initiating cells suggests different sensitivities to radiation and distinct survival mechanisms. PLoS One. 2019 Sep 6;14(9):e0221952. doi: 10.1371/journal.pone.0221952
15. Baharvand M, Manifar S, Akkafan R, Mortazavi H, Sabour S. Serum levels of ferritin, copper and zinc in patients with oral cancer. Biomedical journal. 2014 Sep 1;37(5). DOI: 10.4103/2319-4170.132888
16. Ouyang S, Li H, Lou L, Huang Q, Zhang Z, Mo J, Li M, Lu J, Zhu K, Chu Y, Ding W. Inhibition of STAT3-ferroptosis negative regulatory axis suppresses tumor growth and alleviates chemoresistance in gastric cancer. Redox biology. 2022 Jun 1;52:102317. doi: 10.1016/j.redox.2022.102317
17. Hu W, Zhou C, Jing Q, Li Y, Yang J, Yang C, Wang L, Hu J, Li H, Wang H, Yuan C. FTH promotes the proliferation and renders the HCC cells specifically resist to ferroptosis by maintaining iron homeostasis. Cancer Cell International. 2021 Dec 29;21(1):709. doi: 10.1186/s12935-021-02420-x.
18. Philpott CC, Ryu MS, Frey A, Patel S. Cytosolic iron chaperones: proteins delivering iron cofactors in the cytosol of mammalian cells. Journal of Biological Chemistry. 2017 Aug 4;292(31):12764-71. doi: 10.1074/jbc.R117.791962.
19. Ryu MS, Duck KA, Philpott CC. Ferritin iron regulators, PCBP1 and NCOA4, respond to cellular iron status in developing red cells. Blood Cells, Molecules and Diseases. 2018 Mar 1;69:75-81. doi: 10.1016/j.bcmd.2017.09.009.
20. Ahmad S, Moriconi F, Naz N, Sultan S, Sheikh N, Ramadori G, Malik IA. Ferritin L and Ferritin H are differentially located within hepatic and extra hepatic organs under physiological and acute phase conditions. International journal of clinical and experimental pathology. 2013 Mar 15;6(4):622. PMID: 23573308
21. Basuli D, Tesfay L, Deng Z, Paul B, Yamamoto Y, Ning G, Xian W, McKeon F, Lynch M, Crum CP, Hegde P. Iron addiction: a novel therapeutic target in ovarian cancer. Oncogene. 2017 Jul;36(29):4089-99. doi: 10.1038/onc.2017.11
22. Gray CP, Franco AV, Arosio P, Hersey P. Immunosuppressive effects of melanoma-derived heavy-chain ferritin are dependent on stimulation of IL-10 production. International journal of cancer. 2001 Jun 15;92(6):843-50. DOI: 10.1002/ijc.1269
23. Alkhateeb AA, Han B, Connor JR. Ferritin stimulates breast cancer cells through an iron-independent mechanism and is localized within tumor-associated macrophages. Breast cancer research and treatment. 2013 Feb;137(3):733-44. DOI: 10.1007/s10549-012-2405-x
24. Cozzi A, Corsi B, Levi S, Santambrogio P, Biasiotto G, Arosio P. Analysis of the biologic functions of H-and L-ferritins in HeLa cells by transfection with siRNAs and cDNAs: evidence for a proliferative role of L-ferritin. Blood. 2004

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.7 No. 3 (2025): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2474
Review Article

Mar 15;103(6):2377-83. DOI: 10.1182/blood-2003-06-1842

25. Yang DC, Jiang XI, Elliott RL, Head JF. Antisense ferritin oligonucleotides inhibit growth and induce apoptosis in human breast carcinoma cells. Anticancer research. 2002 May 1;22(3):1513-24. PMID: 12168831
26. Baldi A, Lombardi D, Russo P, Palescandolo E, De Luca A, Santini D, Baldi F, Rossiello L, Dell'Anna ML, Mastrofrancesco A, Maresca V. Ferritin contributes to melanoma progression by modulating cell growth and sensitivity to oxidative stress. Clinical cancer research. 2005 May 1;11(9):3175-83. doi: 10.1158/1078-0432.CCR-04-0631.
27. Pozzi C, Di Pisa F, Bernacchioni C, Ciambellotti S, Turano P, Mangani S. Iron binding to human heavy-chain ferritin. Biological Crystallography. 2015 Sep 1;71(9):1909-20. https://doi.org/10.1107/S1399004715013073Digital Object Identifier (DOI)
28. Hu Z, Wang L, Han Y, Li F, Zheng A, Xu Y, Wang F, Xiao B, Chen C, Tao Z. Ferritin: A potential serum marker for lymph node metastasis in head and neck squamous cell carcinoma. Oncology letters. 2019 Jan;17(1):314-22. doi: 10.3892/ol.2018.9642.
29. Khanna V, Karjodkar F, Robbins S, Behl M, Arya S, Tripathi A. Estimation of serum ferritin level in potentially malignant disorders, oral squamous cell carcinoma and treated cases of oral squamous cell carcinoma. Journal of Cancer Research and Therapeutics. 2017 Jul 1;13(3):550-5. DOI: 10.4103/0973-1482.181182
30. Torti FM, Torti SV. Regulation of ferritin genes and protein. Blood, The Journal of the American Society of Hematology. 2002 May 15;99(10):3505-16. DOI: 10.1182/blood.v99.10.3505
31. Rychtarcikova Z, Lettlova S, Tomkova V, Korenkova V, Langerova L, Simonova E, Zjablovskaja P, Alberich-Jorda M, Neuzil J, Truksa J. Tumor-initiating cells of breast and prostate origin show alterations in the expression of genes related to iron metabolism. Oncotarget. 2016 Dec 22;8(4):6376. DOI: 10.18632/oncotarget.14093
32. Raggi C, Gammella E, Correnti M, Buratti P, Forti E andersen JB, Alpini G, Glaser S, Alvaro D, Invernizzi P, Cairo G. Dysregulation of iron metabolism in cholangiocarcinoma stem-like cells. Scientific reports. 2017 Dec 15;7(1):17667. DOI: 10.1038/s41598-017-17804-1
33. Ghanaati S, Udeabor SE, Winter A, Sader R, Heselich A. Cancer recurrence in operated primary oral squamous cell carcinoma patients seems to be independent of the currently available postoperative therapeutic approach: a retrospective clinical study. Current oncology. 2025 Apr 1;32(4):208. DOI: 10.3390/curroncol32040208
34. Zhou Y, Wang L, Liu M, Jiang H, Wu Y. Oral squamous cell carcinoma: Insights into cellular heterogeneity, drug resistance and evolutionary trajectories. Cell Biology and Toxicology. 2025 Jun 12;41(1):101. doi: 10.1007/s10565-025-10048-0
35. Hsu PC, Tsai CC, Lin YH, Kuo CY. Therapeutic targeting of apoptosis, autophagic cell death, necroptosis, pyroptosis and ferroptosis pathways in oral squamous cell carcinoma: Molecular mechanisms and potential strategies. Biomedicines. 2025 Jul 16;13(7):1745. doi: 10.3390/biomedicines13071745.
36. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, Morrison B. Ferroptosis: an iron-dependent form of nonapoptotic cell death. cell. 2012 May 25;149(5):1060-72. DOI: 10.1016/j.cell.2012.03.042
37. Zhou Q, Meng Y, Li D, Yao L, Le J, Liu Y, Sun Y, Zeng F, Chen X, Deng G. Ferroptosis in cancer: from molecular mechanisms to therapeutic strategies. Signal transduction and targeted therapy. 2024 Mar 8;9(1):55. DOI: 10.1038/s41392-024-01769-5
38. Vijayarangam V, Balasubramanian P, Palaniyandi T, Ravindran R, Suliman M, Saeed M, Natarajan S, Sivaji A, Baskar G. Ferroptosis as a hero against oral cancer. Pathology-Research and Practice. 2024 Nov 1;263:155637. DOI: 10.1016/j.prp.2024.155637
39. Tan Y, Wang Z, Xu M, Li B, Huang Z, Qin S, Nice EC, Tang J, Huang C. Oral squamous cell carcinomas: state of the field and emerging directions. International journal of oral science. 2023 Sep 22;15(1):44. DOI: 10.1038/s41368-023-00249-w

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.7 No. 3 (2025): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2474
Review Article

40. Yang Z, Sun P, Dahlstrom KR, Gross N, Li G. Joint effect of human papillomavirus exposure, smoking and alcohol on risk of oral squamous cell carcinoma. BMC cancer. 2023 May 19;23(1):457. DOI: 10.1186/s12885-023-10948-6
41. Hentze MW, Keim S, Papadopoulos P, O'Brien S, Modi W, Drysdale J, Leonard WJ, Harford JB, Klausner RD. Cloning, characterization, expression and chromosomal localization of a human ferritin heavy-chain gene. Proceedings of the National Academy of Sciences. 1986 Oct;83(19):7226-30. DOI: 10.1073/pnas.83.19.7226
42. Nagai K, Nakahata S, Shimosaki S, Tamura T, Kondo Y, Baba T, Taki T, Taniwaki M, Kurosawa G, Sudo Y, Okada S. Development of a complete human anti-human transferrin receptor C antibody as a novel marker of oral dysplasia and oral cancer. Cancer medicine. 2014 Aug;3(4):1085-99. DOI: 10.1002/cam4.267
43. Zhang KH, Tian HY, Gao X, Lei WW, Hu Y, Wang DM, Pan XC, Yu ML, Xu GJ, Zhao FK, Song JG. Ferritin heavy chain–mediated iron homeostasis and subsequent increased reactive oxygen species production are essential for epithelial-mesenchymal transition. Cancer research. 2009 Jul 1;69(13):5340-8. DOI: 10.1158/0008-5472.CAN-09-0112
44. Pomella S, Melaiu O, Cifaldi L, Bei R, Gargari M, Campanella V, Barillari G. biomarkers identification in the microenvironment of oral squamous cell carcinoma: A systematic review of proteomic studies. International Journal of Molecular Sciences. 2024 Aug 16;25(16):8929. DOI: 10.3390/ijms25168929
45. Szymulewska-Konopko K, Reszeć-Giełażyn J, Małeczek M. Ferritin as an effective prognostic factor and potential cancer biomarker. Current issues in molecular biology. 2025 Jan 16;47(1):60. DOI: 10.3390/cimb47010060
46. Buch SA, Babu SG, Castelino RL, Pillai DS, Bhat S, Devi UH. Ferritin levels in serum and saliva of oral cancer and oral potentially malignant disorders. Eur. J. Ther. 2022;28:109-14. DOI: https://doi.org/10.54614/eurjther.2021.0048
47. Panigrahi C, Yuwanati M, Senthil MM, Priyadharshini R. Determination of Intracellular Iron in Oral Squamous Cell Carcinoma Using Perl's Prussian Blue Iron Stain. Clinical Cancer Investigation Journal. 2022;11(5-2022):7-10.doi. 10.51847/VxCgwzzIDV
48. Lin L, Yin X, Guan Y. Decoding iron deficiency in cancer: mechanisms, immune modulation and therapeutic potential. Frontiers in Nutrition. 2025 Oct 20;12:1650929. DOI: 10.3389/fnut.2025.1650929
49. Lee J, Seo Y, Roh JL. Ferroptosis and Nrf2 signaling in head and neck cancer: resistance mechanisms and therapeutic prospects. Antioxidants. 2025 Aug 13;14(8):993. DOI: 10.3390/antiox14080993
50. Roh JL. Targeting ferroptosis suppressor protein 1 in cancer therapy: Implications and perspectives, with emphasis on head and neck cancer. Critical Reviews in Oncology/Hematology. 2024 Oct 1;202:104440. DOI: 10.1016/j.critrevonc.2024.104440

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.7 No. 3 (2025): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2474
Review Article

PUBLISHER DETAILS

Student's Journal of Health Research (SJHR)
(ISSN 2709-9997) Online
(ISSN 3006-1059) Print
Category: Non-Governmental & Non-profit Organization
Email: studentsjournal2020@gmail.com
WhatsApp: +256 775 434 261
Location: Scholar's Summit Nakigalala, P. O. Box 701432, Entebbe Uganda, East Africa