RESEARCH ARTICLE

# Expression of epigenetic marker EZH2 in squamous cell carcinoma of skin

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## Abstract

**Objective:** To assess the frequency and level of expression of enhancer of zeste homologue 2 in cutaneous squamous cell carcinoma, and compare then with normal skin.

**Method:** The retrospective, descriptive study was conducted at the Department of Morbid Anatomy and Histopathology, University of Health Sciences, Lahore, Pakistan, and comprised data from January 2016 to April 2023 related to cutaneous squamous cell carcinoma in group A and normal skin cases in group B that were evaluated and compared for enhancer of zeste homologue 2 immunohistochemistry expression and positivity. Group A cases with increased immunohistochemistry expression were tested by fluorescence in situ hybridisation for enhancer of zeste homologue 2 amplification. Data was analysed using SPSS 22.

**Results:** Of the 60 patients, 30(50%) were in group A; 19(63.3%) males and 11(36.7%) females with mean age 48±16.5 years. There were 30(50%) patients in group B; 29(96.7%) females and 1(0.3%) male with mean age 47.6±11.3 years. There were 25(83.3%) well-differentiated cases in group A. Enhancer of zeste homologue 2 positivity was noted in 25(83.3%) case in group A compared to 6(20%) in group B ($p<0.001$). The enhancer of zeste homologue 2 expression level was also significantly higher in group A than group B ($p<0.001$). Immunohistochemistry overexpression of enhancer of zeste homologue 2 was found in 13(43.3%) group A cases, and, of them, 6(46.15%) showed enhancer of zeste homologue 2 amplification.

**Conclusion:** Enhancer of zeste homologue 2 overexpression was noted in cutaneous squamous cell carcinoma cases, indicating that enhancer of zeste homologue 2 had a potential role in cutaneous squamous cell carcinoma tumourigenesis.

**Keywords:** EZH2 protein, Human, Immunohistochemistry, IHC, In situ hybridisation, Fluorescence, FISH, Squamous cell carcinoma, Skin neoplasms. (JPMA 76: 662; 2026) **DOI: https://doi.org/10.47391/JPMA.22072**

## Introduction

Skin cancer includes non-melanoma skin cancer (NMSC) and malignant melanoma (MM). NMSC is further subcategorised mainly as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Cutaneous SCC (cSCC) is the second most common skin cancer, making up 20% of all skin cancers, and is characterised by atypical growth of squamous cells or keratinocytes. Multiple risk factors can increase the chances of cSCC, but exposure to solar radiations is the most important one.[1] In Pakistan, the Punjab Cancer Registry (PCR) and the Karachi Cancer Registry (KCR) have reported a high occurrence of skin cancers and NMSCs compared to the Global Cancer Observatory (GLOBOCAN) 2018 report. In 2017, the PCR reported skin cancer as the eighth and ninth most common cancer in females and males, respectively, while the KCR documented skin cancer as the eighth most common cancer in females. Another study in Karachi listed NMSC as the second most common cancer among males and fifth among females, and noted that among NMSCs, cSCC was the m0ost frequent type leading to metastatic disease.[2] Therefore, understanding the pathogenesis and treatment of SCC has become more and more important.

Enhancer of zeste homologue 2 (EZH2), an epigenetic marker, is a catalytic subunit of polycomb repressive complex 2 (PRC2) that may change the expression of genes through trimethylation of lysine-7 in histone 3 (H3K27me3), which controls the expression of genes and is considered a very crucial epigenetic event in the development of tissue and determining the fate of stem cells.[3] EZH2 also methylates the substrate of non-histone proteins, including the GATA4 (GATA-binding protein 4, a transcriptional factor).[4] EZH2 also acts in a PRC2-independent manner (Polycomb Repressive Complex 2, a group of epigenetic proteins). and reacts directly with other proteins or methylate non-histone targets.[5] The oncogenic function of EZH2 has been attributed to transcriptional repression of tumour suppressor genes, including p16(INK4a) (Protein 16 - Inhibitor of Kinase 4a), p14(ARF) (Protein 14 - Alternate Reading Frame), E-cadherin, adrenergic receptor (AR), RUNX3 (Runt-related transcription factor 3), p57 (also called CDKN1C, Cyclin-Dependent Kinase Inhibitor 1C), Bim (Bcl-2-interacting mediator of cell death) and DAB2IP (Disabled

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Homolog 2-Interacting Protein).[6,7]

In non-cutaneous SCC, EZH2 has been reported to play a role in tumourigenesis. A study found that higher EZH2 levels were strongly associated with dysplasia and oral SCC development in patients with oral leucoplakia.[8] Another study revealed that knockout of EZH2 in basal cells of tongue epithelia results in more aggressive SCC.[9] Overexpression of EZH2 has been reported in cervical cancer patients.[10] A recent study found that expression of EZH2 in oesophageal SCC increases migration, and, thus, was associated with the poor prognosis of oesophageal SCC.[11]

Regarding cSCC, to our knowledge, scant literature is available related to EZH2. In the Catalogue of Somatic Mutations in Cancer (COSMIC) database, only 12 EZH2 mutations are mentioned in SCC of skin among 109 mutation entries in total for EZH2 in skin disorders. This indicates that the expression of EZH2 in cSCC has not been well studied.[12]

The current study was planned to investigate the role of EZH2 in cSCC pathogenesis by assessing its protein expression and determining if underlying gene amplification is a frequent mechanism, thereby identifying a potential biomarker and therapeutic target.

## Materials and Methods

The retrospective, descriptive study was conducted at the University of Health Sciences (UHS), Lahore, Pakistan, and comprised data from January 2016 to April 2023. After approval from the institutional ethics review committee, the sample size was calculated using the World Health Organisation (WHO) calculator,[13] taking anticipated proportion of skin tumours showing increased EZH2 expression as 34%.[14] Formalin-fixed paraffin embedded (FFPE) cSCC blocks were obtained from the institutional laboratory archives and placed in group A, while cases of histologically normal skin samples were collected from among the formalin-fixed leftover samples at the Cancer Care Hospital, Lahore, and placed in group B. Poorly preserved or fixed samples were excluded.

All the samples were further processed at the UHS Department of Morbid Anatomy and Histopathology and the Department of Molecular Genetics at the Chughtai Institute of Pathology, Lahore. Age, gender and pathological findings of the cases were retrieved from medical records.

The biopsy specimens were placed in 10% buffered formalin solution, embedded in paraffin wax, serially sectioned at 4µm and then mounted on slides. The slides were stained with haematoxylin and eosin (H&E), and were examined by a senior pathologist for histological diagnosis. The H&E slides were made from the available paraffin blocks.

For immunohistochemistry (IHC) detection of EZH2, antigen retrieval was done in a water bath at 97ºC for 45 minutes using a potential of hydrogen (pH) 9.0 retrieval solution of Tris base and ethylenediaminetetraacetic acid (EDTA). IHC staining was performed using EZH2 antibody (Catalogue # PA0575; Leica, China) and a universal detection kit (Envision Detection System – Peroxidase/DAB; Dako, Denmark). Nuclear staining of moderate to strong intensity was taken as positive staining for EZH2. The staining was compared with a positive control, which was a case of breast carcinoma. The IHC expression of EZH2 was scored as 0, 1, 2 and 3 if <1%, 1-10%, 10-50% and 50% of tumour cells in cSCC samples or keratinocytes in normal skin showed EZH2 positivity, respectively. The score of 0 was considered 'negative' for EZH2 IHC.

Moreover, the number of positive cells was visually estimated as a percentage based on discrete categories as per the College of American Pathologists (CAP) 2023 cancer protocol,[15] which is the most established and recognised protocol for any nuclear biomarker in a cancer that could help in semi-quantitative evaluation. No similar protocol existed regarding EZH2 or cSCC.

For fluorescence in situ hybridisation (FISH) analysis, only cSCC cases showing increased (3+) expression of EZH2 were processed. Reagents (Vysis IntelliFISH, Abbott, United States) and EZH2 probe (7q36.1; EZH2-20-OR; Empire Genomics, USA) were used to perform FISH pre-treatment and hybridisation. EZH2 gene amplification was defined as the presence of at least six gene signals. Based on EZH2 gene amplification status, the cases were reported as EZH2-positive and EZH2-negative.

Data was analysed using SPSS 22. Descriptive statistics for continuous variables were presented as mean ± standard deviation. Categorical data was characterised by frequencies and percentages. The data was subjected, as appropriate, to chi-square test and independent sample *t*-test. P<0.05 was considered statistically significant.

## Results

Of the 60 patients, 30(50%) were in group A; 19(63.3%) males and 11(36.7%) females with mean age 48±16.5 years. There were 30(50%) patients in group B; 29(96.7%) females and 1(0.3%) male with mean age 47.6±11.3 years. Ear was the commonest site 6(20%) in group A, and head-and-neck was the commonest region (Table 1). In group B, the breast was the commonest site in 29(96.7%), while perianal region was the only other site 1(3.3%). Regarding the tumour

**Table-1:** Demographic characteristics of cutaneous squamous cell carcinoma (cSSC) cases (n=30).

| | n (%) |
|---|---|
| **Age Distribution** | |
| ≤30 years | 6 (20.0) |
| 31-40 years | 4 (13.3) |
| 41 - 50 years | 6 (20.0) |
| 51 - 60 years | 9 (30.0) |
| 61 - 70 years | 4 (13.3) |
| ≥ 71 years | 1 (3.3) |
| **Gender Distribution** | |
| Female | 11 (36.7) |
| Male | 19 (63.3) |
| **Site of Lesion** (cSCC) | |
| Arm | 1 (3.3) |
| Chest | 1 (3.3) |
| Ear | 6 (20.0) |
| Face: Cheek | 2 (6.7) |
| Face: Eye | 1 (3.3) |
| Face: Forehead | 1 (3.3) |
| 0Face: Lip | 1 (3.3) |
| Face: Mouth | 1 (3.3) |
| Face: Nose | 2 (6.7) |
| Forearm | 1 (3.3) |
| Head | 3 (10.0) |
| Hip | 2 (6.7) |
| Knee | 1 (3.3) |
| Leg | 1 (3.3) |
| Unknown | 6 (20.0) |

grade in group A, 25(83.3%) cases were well-differentiated, 4(13.3%) were moderately-differentiated, and 1(3.3%) case was poorly-differentiated.

EZH2 positivity was noted in 25(83.3%) case in group A compared to 6(20%) in group B ($p$<0.001). Among group A case, 21(84%) had well-differentiated tumour, 3(12%) had moderately-differentiated tumour and 1(4%) was a poorly-differentiated case (Figure). Among EZH2-positive cases, 3+ positivity was not found in any group B case (Table 2).

The EZH2 expression level was significantly higher in group A than group B ($p$<0.001) (Table 3).

**Table-3:** Quantification of immunohistochemical expression of EZH2 in SCC and normal skin (NS) cases.

| Parameter | Group | n | Mean±SD | Standard Error of Mean |
|---|---|---|---|---|
| EZH2% | cSCC | 30 | 36.50±29.77 | 5.43 |
| | Normal Skin | 30 | 2.27±8.01 | 1.46 |

Independent sample $t$-test = 6.083, $p$≤0.001;
EZH2: Enhancer of zeste homologue 2, cSCC: Cutaneous squamous cell carcinoma.

IHC overexpression of EZH2 was found in 13(43.3%) group A cases, and, of them, 6(46.15%) showed EZH2 amplification (Figure, Table 4).

## Discussion

In the current study, EZH2 expression was analysed using IHC and FISH. There were 30 samples in the cSCC group selected for the study of IHC expression of EZH2 and related molecules. The mean age of patients in the study was 48±16.5 years, indicating a higher frequency in the older age group. This finding is consistent with local and international literature.[16-18] Further, cSCC was found more frequently in males (63.3%) than in females (33.7%) in the current study, and this finding is compatible with the available local and international literature.[16,19,20] Regarding types of cSCC, literature favours well-differentiated or conventional cSCC to be more frequent[16,18] and the same was found in this study, with well-differentiated SCC constituting 83.3% of total cSCCs. In the present study, SCC was found mostly on exposed parts, and these results match the WHO findings.[1] Also, cSCC commonly occurs on the face, neck, bald scalp, extensor forearms, dorsal hands, and shins[20] and that same was found in this study, with the face as the site in 33.3% of cSCC cases.

In the normal skin group, mean age was 47.6±11.3 years, which is comparable to the mean age of the cSCC group. Regarding gender distribution, almost all normal skin cases

**Table-2:** Immunohistochemical expression of EZH2 in cSCC and normal skin (NS) cases (n+60).

| Sample | | Total | IHC Expression of EZH2 | | | | |
|---|---|---|---|---|---|---|---|
| | | | Negative (0) [n(%)] | Positive [n(%)] | 1+ | 2+ | 3+ |
| cSCC | Moderately differentiated | 4 | 1 (25) | 3 (75) | 0 | 1 | 2 |
| | Poorly differentiated | 1 | 0 (0) | 1 (100) | 0 | 1 | 0 |
| | Well-differentiated | 25 | 4 (16) | 21 (84) | 4 | 6 | 11 |
| | Total | 30 | 5 (16.7) | 25 (83.3) | 4 | 8 | 13 |
| Normal Skin | 30 | 24 (80) | 6 (20) | 4 | 2 | 0 | |

Pearson Chi-square = 24.093, $p$-value ≤0.001 (for EZH2 positivity in cSCC and NS); EZH2: Enhancer of zeste homologue 2, cSCC: Cutaneous squamous cell carcinoma, IHC: Immunohistochemistry.

**Table-4:** FISH analysis of EZH2 in cSCC.

| SCC Grade | No. of Cases with 3+ EZH2 [n(%)] | FISH Analysis | | EZH2 Amplification | |
|---|---|---|---|---|---|
| | | Signals Found [n(%)] | Signals Not Found [n(%)] | Positive [n(%)] | Negative [n(%)] |
| Moderately differentiated | 2 (15.4) | 2 (100) | 0 (0) | 1 (50) | 1 (50) |
| Well-differentiated | 11 (84.6) | 8 (72.7) | 3 (27.3) | 5 (62.5) | 3 (37.5) |
| TOTAL | 13 (100) | 10 (76.9) | 3 (23.1) | 6 (60) | 4 (40) |

EZH2: Enhancer of zeste homologue 2, cSCC: Cutaneous squamous cell carcinoma, FISH: Fluorescence in situ hybridisation.

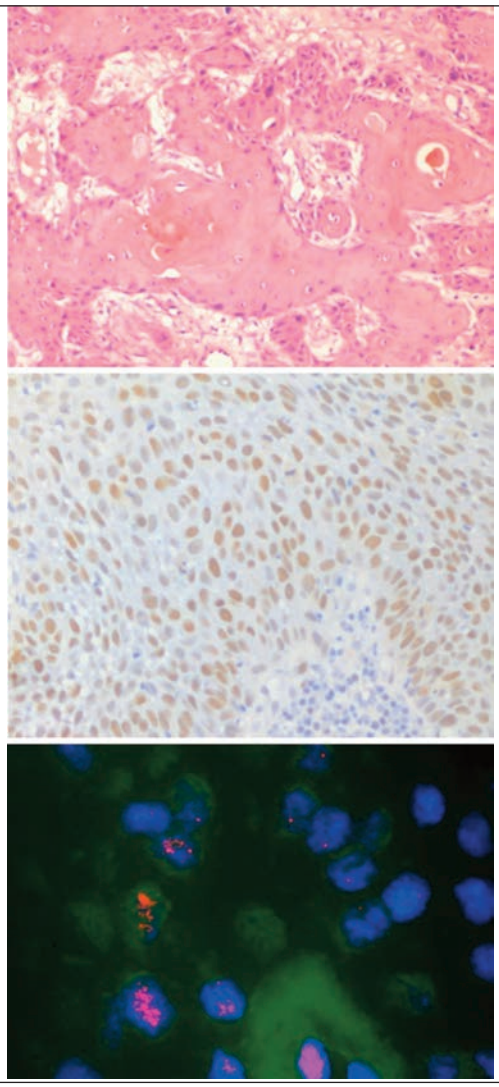

**Figure:** SCC evaluation by IHC and FISH. (a) Well-differentiated histology (H&E, 10x); (b) EZH2 expression with 3+ score and 90% positivity (IHC, 20x); (c) Positive for EZH2 amplification, with >6 orange signals in some tumour cells (FISH, 40x).

*EZH2: Enhancer of zeste homologue 2, SCC: Squamous cell carcinoma, FISH: Fluorescence in situ hybridisation, IHC: Immunohistochemistry, H&E: Haematoxylin and Eosin staining.*

belonged to females. This bias is because histologically, normal skin samples were conveniently available in the routine mastectomy specimens of female breast cancer patients. This also explains the finding that the breast was the most common site in normal skin samples in the group.

IHC is a useful tool in understanding the pathogenesis of the disease as well as providing diagnostic and therapeutic details.[21] Thus, the current study chose IHC as the procedure of choice to assess protein expression of EZH2. Athanassiadou et al. reported expression of EZH2 for the first time in SCC and found EZH2 positivity in all the studied cSCC samples.[22] In normal skin, Xie et al. reported minimal nuclear staining for EZH2 in their tissue microarray sample.[23] In the current study, similar results were found with positive EZH2 expression in 20% normal skin cases and 83.3% cSCC cases.

In this study, the mean value of EZH2 positive cell percentage per 100 skin cells was 36.5±29.77 and 2.27±8.01 for SCC and normal skin samples, respectively. Athanassiadou et al. reported similar findings in normal skin with mean EZH2+ cells percentage of 1.3, but that study found higher mean EZH2+ cell percentage in cSCC samples, ranging from 53.8 to 64.9 in different grades of SCC.[22]

Among EZH+ cases of cSCC in the study, more than half of well-differentiated and moderately-differentiated SCCs showed 3+(>50%) positivity. These findings were consistent with those of a similar study which reported >50% EZH positivity in both the above-mentioned SCC types.23 The current study found significantly higher expression of EZH2 in cSCC samples, and similar results were found in another study.[23] This clearly indicates that overexpression of EZH2 is associated with cSCC.

FISH analysis for EZH2 in SCC, to our knowledge, has not been reported by any study. The current study is the first to assess EZH2 amplification in SCC by FISH analysis, and for that purpose, all SCC cases (n=13) showing EZH2 overexpression (3+ staining) were chosen. FISH analysis was informative in 10(76.9%) of the selected samples. Samples without a FISH signal were the main reason for the non-informative cases. FISH results demonstrated that the amplification of EZH2 was detected in 6(46%) of the studied SCC cases. Out of the total 6 SCC cases showing EZH2 amplification, 5 were well-differentiated SCC, and 1 was moderately-differentiated. No comparable study was available regarding skin/SCC samples. However, Hu et al. and Rao et al. studied EZH2 amplification by FISH in oesophageal SCCs and ovarian carcinomas. respectively. Among the ovarian cancer cases, 8.8% showed EZH2 amplification, while among the oesophageal SCC cases, EZH2 amplification was observed in 12% cases.[24,25]

Putting together, increased EZH2 IHC and FISH expression indicates a possible role of EZH2 in cSCC formation. EZH2 is an important marker to be considered in skin tumourigenesis. In future studies, DNA sequencing yield and results can be improved by taking fresh frozen samples and by doing whole exome sequencing, which is a limitation of the current study due to its scope and financial constraints.

## Conclusion

The expression of EZH2 was significantly higher in cSCC cases compared to normal skin both in terms of the frequency of positive cases and the expression level, as indicated by the IHC score and the number of IHC-positive cells per 100 tumour cells. FISH analysis revealed EZH2 amplification in 46% of the shortlisted cSCC cases. These findings highlight the potential role of EZH2 as an important marker in cSCC development.

**Disclaimer:** The text is based on a PhD thesis.

**Conflict of Interest:** One of the authors was member of the ethics review committee which approved the study.

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**Author Contribution:**
**MUS:** Concept and design.
**AHN:** Critical review and final approval.
**SM:** Critical review.
**NH**: Sampling and data acquisition.