GEORGIAN BIOMEDICAL NEWS

VOLUME 4 ISSUE 1. JAN-MAR 2026

Association of SOX2 Expression with Progression of Cervical Intraepithelial Neoplasia in Females: Whole-Slide Spatial Analysis of 135 Cases

George-Jemal Gogitidze[1,ID], Shota Kepuladze[1,ID], George Burkadze[1,ID]

DOI: 10.52340/GBMN.2026.01.01.147

ABSTRACT

Background: Sex-determining region Y-box 2 (SOX2) is a transcription factor essential for the maintenance of cellular pluripotency and epithelial stem cell renewal. Aberrant SOX2 expression has been reported in several squamous epithelial malignancies, suggesting a role in early neoplastic transformation. In the cervix, progressive cervical intraepithelial neoplasia (CIN) is characterized by increasing dysregulation of epithelial differentiation and proliferation, processes in which SOX2 may be critically involved. Emerging evidence indicates that elevated SOX2 expression correlates with higher CIN grades and may contribute to the progression from low-grade to high-grade lesions.

Objectives: To evaluate SOX2 expression across CIN grades and its association with disease progression.

Methods: In a balanced, archival cohort (n = 135; 27 per group: normal, CIN1, CIN2, CIN3, SCC), whole-slide images were analyzed using a pre-specified QuPath pipeline with fixed thresholds and area normalization. We performed immunohistochemical staining of available archival specimens to assess SOX2 protein expression. For staining, a rabbit monoclonal antibody (clone EP103) was used.

Results: By group, the cervical tissues showed the following median expression levels of SOX2: normal tissue 45 [45–55], CIN1 120 [100–130], CIN2 100 [90–150], CIN3 150 [80–180], and SCC 150 [100–200] (trend: $\rho = 0.568$, $p = 6.9 \times 10^{-13}$).

Conclusions: SOX2 expression was higher in high-grade lesions (CIN III/SCC), consistent with stem cell plasticity and the maintenance of stem cell–like properties by the cells, which, in turn, contribute to lesion progression.

Keywords: Cervical cancer; cervical intraepithelial neoplasia; Sex-determining region Y-box transcription factor 2 (SOX2); stem-cell-like parameters.

BACKGROUND

Sex-determining region Y-box transcription factor 2 (SOX2) is a key transcription factor that maintains pluripotency and self-renewal in embryonic stem cells, playing a pivotal role in stem cell biology and tissue homeostasis.[1] Beyond its physiological role, aberrant SOX2 expression has been increasingly implicated in oncogenesis across diverse solid tumors, contributing to tumor aggressiveness and poor clinical outcomes.[2,3] High SOX2 expression has been correlated with cervical intraepithelial neoplasia (CIN) progression and invasive squamous cell carcinoma (SCC), suggesting its involvement in cervical carcinogenesis.[3] Mechanistically, SOX2 regulates downstream targets involved in cell cycle control, epithelial-to-mesenchymal transition (EMT), and tumor invasion, promoting cancer stem cell (CSC) phenotypes that drive tumorigenesis and therapeutic resistance.[4,5]

In cervical cancer specifically, SOX2-positive cells exhibit enhanced self-renewal, stemness, and EMT-related gene expression compared to SOX2-negative counterparts, indicating that endogenous SOX2 expression marks CSCs within cervical carcinomas.[6] Beyond cervical cancer, SOX2 overexpression has been reported in lung, breast, colorectal, and esophageal cancers, where it is frequently associated with poor prognosis, higher tumor grade, and metastatic potential.[7] A meta-analysis across 12 studies demonstrated that high SOX2 expression is significantly associated with decreased overall survival in human solid tumors, supporting its role as a prognostic biomarker.

High SOX2 expression has also been linked to chemoresistance and radioresistance in multiple tumor types, further implicating it as a contributor to treatment failure.[8,9] Pan-cancer analyses have revealed differential SOX2 expression profiles across tumor types, with upregulation observed in cervical SCC, lung squamous carcinoma, and other cancers, underscoring its importance in tumor biology. SOX2 contributes to stem-like characteristics, EMT progression, drug resistance, and survival signaling in cancer cells, and its complex regulatory networks involve interactions with other oncogenic pathways.[9]

Collectively, these findings emphasize the significance of SOX2 in cancer development, progression, and therapeutic response, making it a promising biomarker and potential target for precision oncology.[9]

METHODS

Study design

This study is a retrospective, multicenter, observational cohort study conducted at the Teaching, Research, and Diagnostic Laboratory of Tbilisi State Medical University (TSMU), which serves approximately 25 public and private hospitals across four major cities in Georgia. The study was approved and supported by the TSMU Ethics Committee, as all materials

used were archival and fully de-identified prior to analysis; therefore, informed consent from patients was not required. The study complied with the Declaration of Helsinki and local regulations regarding the use of human tissue in research.

Case selection and histopathological classification

Formalin-fixed, paraffin-embedded (FFPE) cervical tissue samples were sequentially retrieved from the laboratory archive to create a balanced cohort encompassing the full histological spectrum: normal cervix, CIN1, CIN2, CIN3, and invasive squamous cell carcinoma (SCC). Inclusion criteria were: (I) adequate epithelium with intact basal membrane (BM); (II) availability of blocks for immunohistochemistry (IHC); (III) absence of cauterization or processing artifacts that could affect results; and (IV) availability of serial sections. Exclusion criteria included: (I) prior neoadjuvant therapy; (II) extensive necrosis >50%; (III) tissue autolysis; and (IV) poor-quality histological slides after scanning.

The final histological diagnosis was confirmed by two independent pathologists using H&E staining and standard criteria. To minimize subjective bias, a final dataset of n = 135 samples was collected, with 27 per diagnostic group.

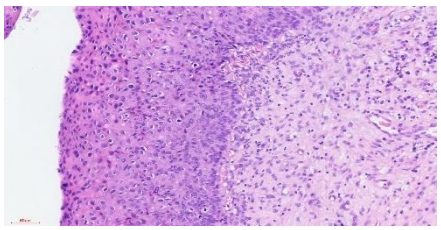
Tissue processing and immunohistochemistry

FFPE blocks were sectioned at 3–4 µm for positively charged slides. Routine H&E staining was performed according to standard laboratory protocols. IHC was performed using Leica/Novocastra primary antibodies and polymer-based HRP/DAB detection systems according to the manufacturer's instructions, with heat-induced epitope retrieval (HIER) in citrate buffer (pH ~6.0) or Tris-EDTA (pH ~9.0), depending on the antibody. Each IHC run included a positive control (tonsil, appendix, or a known positive tumor) and a negative control (an isotype or reagent control). Target antibodies and typical Leica/Novocastra clones included SOX2 (rabbit monoclonal, e.g., EP103).

Whole-slide imaging (WSI)

All stained slides were scanned using a Motic whole-slide scanner (Motic, Xiamen, China) at 40–800× equivalent magnification (pixel size ~0.25–0.27 µm/pixel) with automated focus and exposure normalization. Quality control (QC) criteria included the absence of gross blurring, <2% of the tissue area with insufficient focus, and no striping or other artifacts in the analysis region (Fig.1).

FIGURE 1. Digitized whole-slide image of the study case (WSI) cervical intraepithelial neoplasia 3 (CIN3)



RESULTS

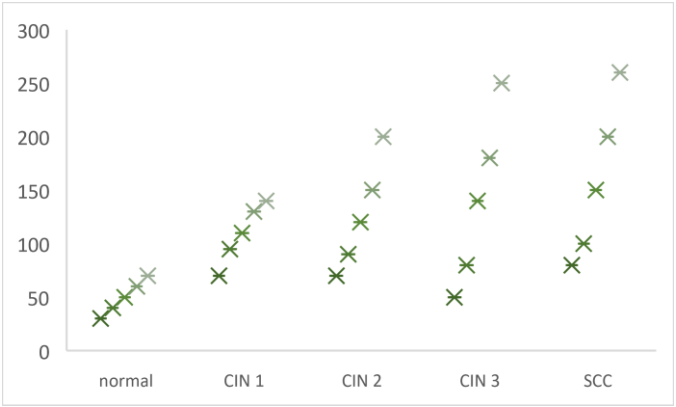
SOX2 expression was assessed across a spectrum of cervical tissue samples, including normal cervix, cervical intraepithelial neoplasia (CIN) grades 1-3, and invasive squamous cell carcinoma (SCC). Analysis revealed a clear trend of increasing SOX2 expression with lesion severity. The median expression levels in each group were as follows: normal cervical tissue, 45 [45-55]; CIN1, 120 [100-130]; CIN2, 100 [90-150]; CIN3, 150 [80-180]; and SCC, 150 [100-200]. Statistical analysis demonstrated a significant positive trend across these diagnostic categories (Spearman's $\rho=0.568$, $p=6.9\times10^{-13}$).

SOX2 expression was markedly higher in high-grade lesions (CIN3) and invasive SCC compared to normal and low-grade lesions, suggesting a role in lesion progression. Although CIN2 samples exhibited slightly lower median expression than CIN1, the overall upward trend remained strongly positive, reflecting heterogeneity in mid-grade dysplastic lesions. The progressive increase in SOX2 expression from normal tissue to high-grade lesions and carcinoma supports its involvement in maintaining stem-like properties and promoting cellular plasticity, which may facilitate neoplastic progression.

The consistent elevation of SOX2 in CIN3 and SCC underscores its potential as a biomarker for identifying high-risk lesions and as a possible contributor to tumor aggressiveness. These results align with SOX2's established role in other solid tumors, underscoring its relevance as both a prognostic marker and a potential therapeutic target.

Graphical representation of the data was prepared using box-and-whisker plots, illustrating the median, interquartile range, and overall distribution of SOX2 expression in each diagnostic group. The plot clearly depicts the upward trend in expression from normal tissue through CIN1–CIN3 to SCC, providing a visual summary of the correlation between SOX2 levels and lesion severity. This graphical analysis reinforces the statistical findings and highlights the potential clinical significance of SOX2 in cervical neoplastic progression (Fig.2).

FIGURE 2. Expression of the Sox2 gene product in 5 different groups from normal to SCC



Abbreviations: CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma.

Georgian Biomedical News
ISSN (Online): 2720-8796 ISSN (Print): 2720-7994

DISCUSSION

In this study, we evaluated SOX2 expression across a spectrum of cervical lesions, ranging from normal cervical tissue to low- and high-grade cervical intraepithelial neoplasia (CIN1-3) and invasive squamous cell carcinoma (SCC). Our results demonstrate a clear trend of increasing SOX2 expression with lesion severity, with the highest median levels observed in CIN3 and SCC. These findings are consistent with previous reports implicating SOX2 as a critical regulator of stemness and cellular plasticity in both premalignant and malignant tissues. The observed increase in SOX2 expression suggests that this transcription factor may contribute to the acquisition of stem cell–like properties, promoting proliferation, survival, and resistance to apoptotic signals, all of which are essential mechanisms in cervical carcinogenesis.

Interestingly, we noted a slight decrease in median SOX2 expression in CIN2 compared to CIN1; however, the overall trend remained positive. This pattern may reflect the biological heterogeneity of mid-grade dysplastic lesions, which are known to include both regressive and progressive cases. The heterogeneity observed underscores the complexity of cervical lesion progression and highlights the potential utility of SOX2 as a marker to stratify lesions by their likelihood of progressing to higher-grade dysplasia or invasive carcinoma. Such stratification could be valuable for clinical decision-making, particularly in determining whether close surveillance or early therapeutic intervention is needed.[12]

Our findings align with broader evidence from other solid tumors, including lung, breast, esophageal, and colorectal cancers, where SOX2 overexpression has been associated with poor prognosis, increased tumor grade, and metastatic potential. Mechanistically, SOX2 is known to regulate genes involved in cell cycle control, epithelial-to-mesenchymal transition (EMT), and chemoradiation resistance, further underscoring its role in tumor progression.[13] In cervical cancer specifically, elevated SOX2 expression in high-grade lesions and SCC may facilitate the maintenance of cancer stem cell populations, which are critical drivers of tumor growth, recurrence, and therapy resistance.[14] These characteristics reinforce the relevance of SOX2 as a potential prognostic biomarker and a therapeutic target.

From a translational perspective, the significant positive correlation between SOX2 expression and lesion severity observed in our study suggests that SOX2 immunohistochemical assessment could complement existing histopathological evaluation. This approach may help identify patients at higher risk of progression from low- or mid-grade lesions to invasive carcinoma, guiding personalized management strategies. Furthermore, the availability of reliable antibodies, such as the rabbit monoclonal clone EP103 used in this study, facilitates reproducible assessment of SOX2 in routine diagnostic practice, allowing integration into both research and clinical workflows.

Limitations of our study include its retrospective design and the use of archival tissue, which may be subject to pre-analytical variability. However, strict inclusion criteria, standardized immunohistochemistry protocols, and rigorous whole-slide imaging (WSI) quality control minimized potential biases. Additionally, although our sample size provided sufficient power to detect statistically significant trends, further studies with larger, multicenter cohorts and longitudinal follow-up are warranted to confirm the prognostic significance of SOX2 and to explore its potential as a therapeutic target in cervical neoplasia.

CONCLUSIONS

In conclusion, our study demonstrates that SOX2 expression increases progressively with cervical lesion severity, reaching its highest levels in CIN3 and invasive SCC. These findings support the role of SOX2 in promoting stem cell–like phenotypes and lesion progression, consistent with its functions in other solid tumors. The results highlight the potential utility of SOX2 as a biomarker for risk stratification and as a candidate for targeted therapeutic strategies. Future prospective studies are needed to further elucidate the mechanistic role of SOX2 in cervical carcinogenesis and to evaluate its integration into clinical practice for early detection, prognosis, and therapy guidance.

Our study demonstrates that SOX2 expression progressively increases with cervical lesion severity, reaching the highest levels in CIN3 and invasive squamous cell carcinoma. This pattern supports the role of SOX2 in maintaining stem cell–like properties, promoting cellular plasticity, and facilitating neoplastic progression. The strong correlation between SOX2 expression and lesion grade highlights its potential as a prognostic biomarker for identifying high-risk cervical lesions and guiding clinical management. Furthermore, SOX2 may serve as a promising therapeutic target. Future prospective studies are warranted to validate its clinical utility and to explore targeted interventions aimed at modulating SOX2-driven pathways in cervical cancer.

AUTHOR AFFILIATIONS

[1]Department of Pathology, Tbilisi State Medical University, Tbilisi, Georgia.

ACKNOWLEDGEMENTS

The authors would like to sincerely thank the staff of the Teaching, Research, and Diagnostic Laboratory at Tbilisi State Medical University (TSMU) for their invaluable support in sample preparation and immunohistochemical analyses. We also extend our gratitude to the TSMU Biostatistics Team for their expert assistance with data analysis and statistical interpretation, which was essential to completing this study.

REFERENCES

1. Zhu Y, Huang S, Chen S. SOX2 promotes chemoresistance, cancer stem cell properties, and epithelial–mesenchymal transition by β-catenin and

ISSN (Online): 2720-8796 ISSN (Print): 2720-7994

Beclin1/autophagy signaling in colorectal cancer. Cell Death Dis. 2021;12:449. doi:10.1038/s41419-021-03733-5.
2. The role of SOX2 overexpression in prognosis of patients with solid tumors: A meta-analysis and systematic review. PubMed. https://pubmed.ncbi.nlm.nih.gov/32221082/. Published 2020. Accessed January 9, 2026.
3. Cervical cancer cells with positive SOX2 expression exhibit the properties of cancer stem cells. PubMed. https://pubmed.ncbi.nlm.nih.gov/24489842/. Published 2014. Accessed January 9, 2026.
4. Clinical significance of OCT4 and SOX2 protein expression in cervical cancer. BMC Cancer. https://doi.org/10.1186/s12885-015-2015-1. Published 2015. Accessed January 9, 2026.
5. SOX2 in cancer stemness: Tumor malignancy and therapeutic potentials. J Mol Cell Biol. https://pubmed.ncbi.nlm.nih.gov/30517668/. Published 2018. Accessed January 9, 2026.
6. SOX2 expression associates with stem cell state in human ovarian carcinoma. Cancer Res. https://doi.org/10.1158/0008-5472.CAN-12-4177. Published 2013. Accessed January 9, 2026.
7. Pan-cancer analysis of SOX2: Prognostic implications and potential as a therapeutic target in immune checkpoint modulation. Heliyon. https://doi.org/10.1016/j.heliyon.2025.e42200. Published 2025. Accessed January 9, 2026.
8. The role of SOX2 and SOX9 in radioresistance and tumor recurrence. Cancers. 2024;16(2):439. doi:10.3390/cancers16020439.
9. Exosomal lncRNA UCA1 modulates cervical cancer stem cell self-renewal through microRNA-122-5p/SOX2 axis. J Transl Med. https://doi.org/10.1186/s12967-021-02872-9. Published 2021. Accessed January 9, 2026.
10. Sung H, Lee SY, Oh SY, et al. SOX2 regulates self-renewal and tumorigenicity of stem-like cells of head and neck squamous cell carcinoma. https://doi.org/10.1038/bjc.2014.528. Published 2014. Accessed January 9, 2026.
11. Zhang L, Poh CF, Williams M. Predicting low-grade oral dysplasia progression. Cancer Prev Res (Phila). 2021;14(11):1067-1078. doi:10.1158/1940-6207.CAPR-21-0017.
12. Moshi JM, Ummelen M, Broers JLV, et al. SOX2 expression in the pathogenesis of premalignant lesions of the uterine cervix: Its histo topographical distribution distinguishes between low and high grade CIN. Histochem Cell Biol. 2022;158(6):545-559. doi:10.1007/s00418-022-02145-6.
13. Basu Roy U, Bayin NS, Rattanakorn K. Impact of SOX2 function and regulation on therapy resistance in cancer. Front Oncol. 2022;12:1020675. doi:10.3389/fonc.2022.1020675.
14. Gao H, Teng C, Huang W, Peng J, Wang C. SOX2 promotes the epithelial to mesenchymal transition of esophageal squamous cells by modulating Slug expression through STAT3/HIF-1α signaling. Int J Mol Sci. 2015;16(9):21643-21656. doi:10.3390/ijms160921643.

ISSN (Online): 2720-8796 ISSN (Print): 2720-7994