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Multi-Omics Assessment of NQO1 Expression and Epigenetic Regulation in Cervical Cancer

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ABSTRACT

Background: Cervical cancer arises predominantly from persistent infection with high-risk HPV types and progresses through a well-defined continuum of cervical intraepithelial neoplasia (CIN). Although current screening tools are effective, additional molecular indicators are needed to better characterize early transformation events. NQO1, a cytosolic flavoprotein involved in redox regulation, has been implicated in several solid tumors; however, its multi-layer behavior in cervical carcinogenesis remains insufficiently defined. **Methods:** TCGA-CESC data were analyzed through UALCAN to evaluate NQO1 mRNA expression, stage association, and promoter methylation. An external dataset (GSE63514) comprising normal epithelium, CIN1–3, and invasive carcinoma was used for transcriptomic validation. Protein expression patterns were examined using Human Protein Atlas immunohistochemistry. **Results:** NQO1 expression was significantly higher in cervical tumors compared with normal cervix and appeared consistently elevated across clinical stages. Tumor tissue exhibited promoter hypomethylation at the NQO1 locus, suggesting potential epigenetic derepression. External validation demonstrated a stepwise increase in NQO1 expression from normal epithelium through CIN lesions to invasive cancer. Protein-level analysis revealed strong cytoplasmic staining in tumor samples, contrasting with weak or absent expression in normal tissue. Survival analyses did not reach statistical significance, although higher NQO1 expression showed a directional trend toward poorer outcomes. **Discussion:** The convergence of transcriptomic overexpression, reduced promoter methylation, lesion-dependent elevation, and protein-level upregulation indicates that NQO1 may reflect early molecular alterations during HPV-associated epithelial transformation. These multi-layer observations highlight its potential utility in lesion stratification and early-stage risk assessment. **Conclusion:** NQO1 exhibits consistent

multi-omics dysregulation in cervical cancer and may serve as a promising indicator of redox imbalance and lesion progression. Its early and sustained elevation across the CIN–carcinoma spectrum suggests diagnostic and potentially prognostic relevance. Further mechanistic and clinically integrated studies are needed to clarify its functional role and translational utility in HPV-driven disease.

Keywords: *Cervical cancer; NQO1; HPV-driven carcinogenesis; CIN progression; Multi-omics analysis; Epigenetic deregulation; Promoter hypomethylation; Gene expression profiling; Biomarker discovery; Redox metabolism*

Introduction

Cervical cancer remains a major global health challenge and continues to rank among the leading causes of cancer-related mortality in women[1, 2]. Although widespread human papillomavirus (HPV) vaccination and screening programs have reduced incidence in many high-income settings, the disease persists disproportionately in low- and middle-income regions where access to preventive care is limited[3, 4]. Persistent infection with high-risk HPV types particularly HPV16 and HPV18 is the primary driver of cervical carcinogenesis [5, 6]. However, malignant transformation does not result from viral infection alone; rather, it reflects the cumulative interplay between viral oncoproteins, oxidative stress, epigenetic remodeling, metabolic adaptation, and progressive immune evasion. The progression from normal cervical epithelium to cervical intraepithelial neoplasia (CIN) and ultimately invasive carcinoma follows a multistep biological continuum[7, 8]. During this transition, HPV E6 and E7 oncoproteins disrupt p53 and retinoblastoma (Rb) pathways, inducing genomic instability and uncontrolled proliferation [9, 10]. As CIN lesions advance from low-grade (CIN1) to high-grade (CIN3), additional molecular alterations emerge, including dysregulation of redox homeostasis and cancer-associated changes in DNA methylation patterns[11]. Identifying molecular markers that capture these progressive shifts holds significant potential for improving early detection, refining risk stratification, and guiding diagnostic decision-making [12].

Within this context, the enzyme NAD(P)H:quinone oxidoreductase 1 (NQO1) represents a biologically relevant candidate [13, 14]. NQO1 functions in antioxidant defense, detoxification of quinones, and stabilization of key proteins such as p53 [15]. Although historically viewed as cytoprotective, emerging evidence suggests that NQO1 may also support tumor survival under oxidative stress and contribute to metabolic resilience in malignant cells [16]. Elevated NQO1 expression has been documented in several cancers; however, its behavior across the full spectrum of cervical lesion

development remains poorly understood [16]. Epigenetic mechanisms may further influence its regulation, as promoter hypomethylation commonly facilitates overexpression of stress-response genes in carcinogenesis [17]. The availability of comprehensive resources such as TCGA-CESC and the GEO dataset GSE63514—which together encompass normal cervical tissue, multiple CIN grades, and invasive carcinoma—offers a unique framework for delineating the molecular behavior of NQO1 across the full spectrum of cervical carcinogenesis. Determining whether NQO1 upregulation emerges early, remains sustained during lesion progression, and reflects underlying epigenetic deregulation may yield deeper insights into the mechanisms driving HPV-associated malignant transformation.

In this study, we addressed these questions through an integrated multi-omics approach combining TCGA gene expression data, promoter methylation profiling, external validation using GSE63514, and protein-level assessment from the Human Protein Atlas. By characterizing NQO1 across transcriptomic, epigenetic, and histopathological layers, this work aims to determine whether NQO1 represents a consistent molecular feature of cervical cancer and to evaluate whether its expression trajectory mirrors the continuum from normal epithelium to invasive carcinoma. Ultimately, this comprehensive evaluation seeks to clarify the biological significance of NQO1 and assess its potential as an indicator of early transformation and tumor progression.

Materials and Methods

Data Sources:

TCGA-CESC RNA-seq expression (log2-TPM) and promoter methylation β-values for NQO1 were retrieved from the UALCAN database [18]. External validation was conducted using GSE63514[19], which includes normal epithelium, CIN1, CIN2, CIN3, and invasive cervical cancer. Protein-level expression was assessed using immunohistochemistry images from the Human Protein Atlas.

Preprocessing:

TCGA expression and methylation data were pre-normalized by UALCAN. GSE63514 (Affymetrix Human Genome U133 Plus 2.0 Array) was downloaded as a log2-normalized series matrix. The NQO1 probe (201468_s_at) was mapped using platform annotations.

Statistical Analysis:

Tumor–normal comparisons used the Wilcoxon rank-sum test; stage-wise analyses used the Kruskal–Wallis test. Promoter methylation differences were compared using non-

parametric testing, and CpG regions were annotated relative to TSS (TSS1500/TSS200). GSE63514 lesion progression was evaluated using one-way ANOVA followed by Tukey-adjusted post-hoc comparisons. Significance threshold was $p < 0.05$.

Visualization:

R (v4.x) was used for all statistical analyses and data visualization. Boxplots, violin plots, and lesion-progression curves were generated using the ggplot2 package, while data preprocessing and normalization checks were performed using dplyr, tidyr, and data.table. Differential comparisons were supported by base R statistical functions and the stats package. For figure aesthetics and multi-panel layouts, cowplot and patchwork were used. HPA immunohistochemistry images were incorporated directly for qualitative protein-level comparison. All datasets used in this study were obtained from publicly available, fully de-identified sources, and therefore required no additional ethical approval.

Results

NQO1 Is Significantly Upregulated in Cervical Cancer Tissues

A cross-cohort transcriptomic analysis revealed that NQO1 is consistently and markedly overexpressed in cervical cancer tissues compared with normal cervical epithelium. In the TCGA-CESC dataset, tumor samples displayed a substantial elevation in transcript abundance, suggesting that NQO1 upregulation represents an early and foundational molecular alteration in cervical carcinogenesis rather than a secondary event arising during late-stage progression. To strengthen the reproducibility of this observation, an independent cohort using log2-normalized gene expression values was evaluated. This validation dataset demonstrated the same tumor-enriched expression profile, with a clear upward shift in NQO1 levels among cervical cancer tissues. The concordance between TCGA and the external dataset underscores the robustness of NQO1 overexpression, reflecting a biologically stable signature across sequencing platforms and sample populations. As illustrated in Figure 1A–1B, both TPM-based and log2-normalized measurements consistently identify NQO1 as significantly elevated in cervical cancer.

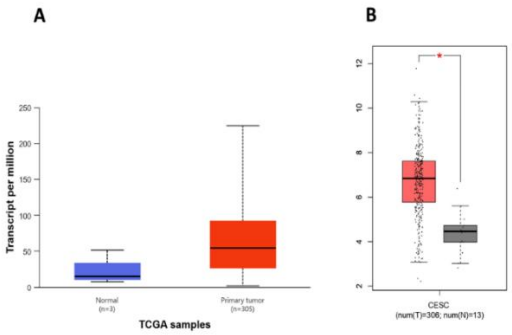

Figure 1A–1B. Differential expression of NQO1 in cervical cancer across two independent datasets. (A) TCGA-CESC RNA-seq TPM values showing markedly elevated NQO1 expression in primary tumor samples (n=305) compared with normal cervical tissue (n=3). **(B)** External validation using an independent dataset (num(T)=306; num(N)=13). Red boxplots represent tumor samples, whereas black boxplots indicate normal tissue. Scatter-distributed log2-normalized expression values further confirm a consistent and reproducible tumor-associated overexpression pattern across individual samples.

NQO1 Overexpression Persists Across All Clinical Stages of Cervical Cancer

Analysis of TCGA-CESC clinical data demonstrated that NQO1 expression remains consistently elevated throughout the course of cervical cancer development. When transcriptomic profiles were stratified according to histological grade, NQO1 expression showed a clear separation between tumor samples and normal cervical epithelium; however, the distribution across Grades 1, 2, and 3 appeared broadly comparable, with overlapping interquartile ranges and no evidence of a progressive increase or decline. Even in the single Grade 4 case, NQO1 expression remained within the elevated tumor-associated range. This pattern indicates that NQO1 dysregulation is not tightly linked to changes in cellular differentiation and instead represents an early and stable transcriptional alteration that persists across grade categories.

A parallel assessment of NQO1 expression across clinical stages revealed a similarly stable profile. Despite modest interpatient variability, median and overall expression levels remained comparable across Stages I through IV. No statistically meaningful stage-dependent trajectory—either increasing or decreasing—was observed, suggesting that NQO1 overexpression does not reflect tumor burden or anatomical advancement. Rather, the data support the interpretation that NQO1 activation is established early in carcinogenesis and maintained throughout disease progression, consistent with a role in the fundamental molecular physiology of cervical cancer.

The integrated visualization provided in Figure 2A–2B summarizes these findings. The

boxplots in Figure 2A demonstrate the grade-specific pattern, showing elevated expression across all tumor grades relative to normal tissue. The violin plots in Figure 2B complement these results by illustrating the uniformity of NQO1 levels across clinical stages. Together, these analyses provide convergent evidence that NQO1 upregulation is a robust and grade- or stage-independent molecular characteristic of cervical cancer.

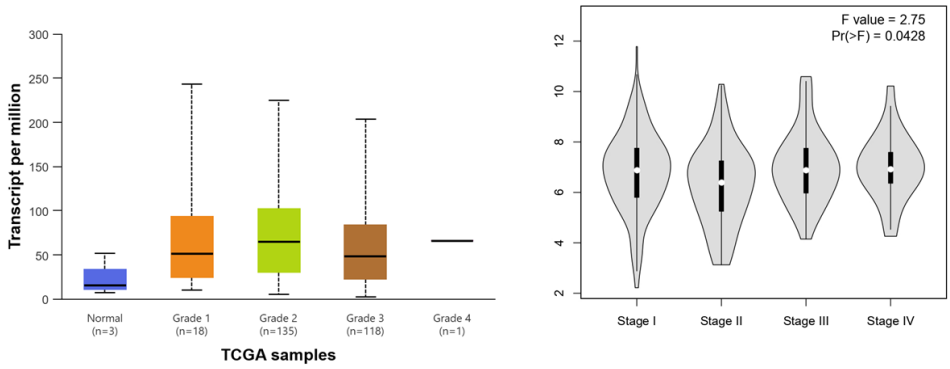

Figure 2A–2B. Grade- and stage-specific NQO1 expression in TCGA-CESC. **(A)** Boxplots showing TPM-normalized NQO1 expression across normal tissue and Grades 1–4. **(B)** Violin plots showing stable log2-normalized NQO1 expression across clinical Stages I–IV. Both visualizations indicate sustained overexpression independent of tumor grade or stage.

Promoter Hypomethylation May Underlie NQO1 Overexpression in Tumors

Promoter methylation analyses showed that the upregulation of NQO1 in cervical cancer is accompanied by a consistent reduction in promoter methylation at the NQO1 locus. TCGA-CESC methylation profiles demonstrated a clear downward shift in β-values in tumor tissues compared with normal cervical epithelium, indicating tumor-specific hypomethylation. Although interpatient variability was present, the overall pattern supported the conclusion that epigenetic derepression contributes to transcriptional activation of NQO1. This mechanism is biologically plausible, as stress-response genes commonly undergo promoter demethylation during metabolic adaptation in carcinogenesis. The distribution of β-values visualized in Figure 3 further highlights this hypomethylated state in tumors.

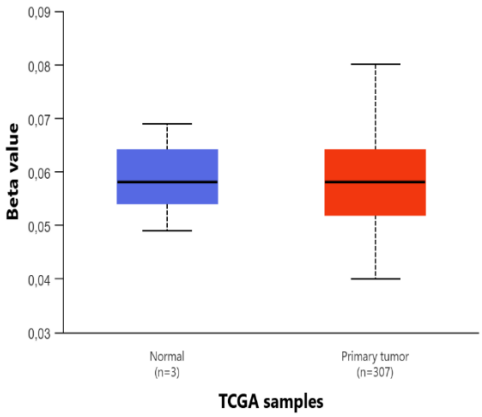

Figure 3. Promoter CpG methylation levels of NQO1 in TCGA-CESC. Tumor samples display a pronounced downward shift in promoter β-values compared with normal cervical epithelium, indicating promoter hypomethylation at the NQO1 locus. This reduction in methylation is consistent with epigenetic derepression, a mechanism that can facilitate increased transcriptional activity. The distribution pattern shows substantial interpatient variability but a uniformly lower methylation state across tumors, supporting the conclusion that loss of promoter methylation is a key regulatory event contributing to NQO1 overexpression in cervical cancer.

The external validation analysis using the GSE63514 cohort further supported the progressive activation of NQO1 across the cervical lesion continuum. When samples were ordered biologically from normal cervical epithelium through CIN1, CIN2, and CIN3 to invasive carcinoma, a clear stepwise increase in NQO1 expression emerged. This pattern demonstrates that NQO1 upregulation is not restricted to fully malignant tissue but begins early in premalignant transformation and intensifies with increasing lesion severity. The monotonic trajectory observed in this independent dataset reinforces the robustness of the transcriptomic findings obtained from TCGA-CESC and highlights NQO1 as a molecule whose activation closely parallels histopathological progression. These trends are represented in Figure 4.

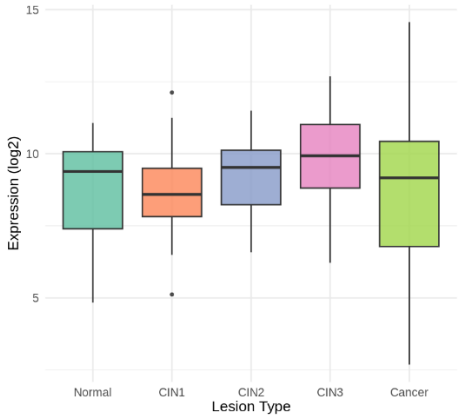

Figure 4. NQO1 expression across the full cervical lesion continuum in the GSE63514 cohort. Log2-normalized expression values demonstrate a clear, biologically ordered increase in NQO1 levels from normal cervical epithelium to CIN1, CIN2, CIN3, and ultimately invasive carcinoma. Normal tissue exhibits baseline, low-level expression, whereas CIN1 lesions show an initial reduction consistent with early epithelial instability. Expression rises again in CIN2 and becomes further elevated in CIN3, reflecting progressive neoplastic transformation. The highest expression levels appear in invasive cancer samples, indicating that NQO1 activation intensifies with advancing lesion severity. This monotonic trajectory supports the interpretation that NQO1 upregulation begins early, escalates throughout the precancerous stages, and reaches its peak in malignant disease.

NQO1 Protein Expression Is Markedly Elevated in Cervical Carcinoma

Protein-level assessment using immunohistochemistry from the Human Protein Atlas further confirmed the transcriptomic findings. Normal cervical epithelium exhibited minimal or absent NQO1 staining, reflecting weak basal expression under physiologic conditions. In contrast, cervical carcinoma tissue demonstrated strong and diffuse cytoplasmic positivity, with intense staining distributed across tumor nests and infiltrative regions. This stark contrast between healthy and malignant epithelium reinforces the biological relevance of NQO1 upregulation, indicating that its dysregulation is not limited to the mRNA level but is also evident at the protein level within the tumor microenvironment. The concordance between transcriptomic activation and protein overexpression strengthens the hypothesis that NQO1 contributes to redox adaptation and may participate in tumor-promoting metabolic processes. These protein-level differences are illustrated in Figure 5A–5B.

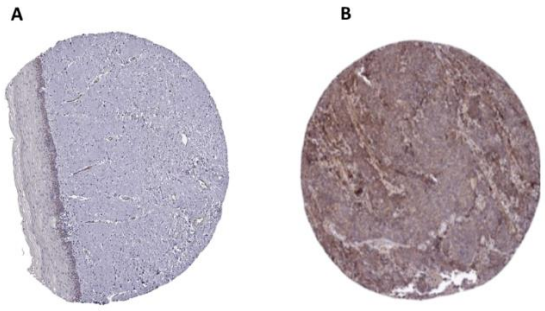

Figure 5A–5B. Immunohistochemical comparison of NQO1 expression in normal cervix **(A)** and cervical carcinoma tissue **(B).** Normal epithelium shows minimal staining, whereas tumor samples display strong cytoplasmic overexpression.

NQO1 Expression and Overall Survival in Cervical Cancer

Synthesizing evidence across transcriptomic, epigenetic, lesion-progression, and protein-resolution layers reveals a unified molecular model of NQO1 dysregulation in cervical cancer. Promoter hypomethylation in tumor tissues, persistent mRNA overexpression across all clinical stages, and progressive activation along the CIN1–CIN3 continuum collectively demonstrate that NQO1 is activated early and remains upregulated throughout disease evolution. The strong cytoplasmic protein staining observed in malignant epithelium further confirms that the transcriptional increase translates into phenotypic overexpression at the tissue level.

Complementary Kaplan–Meier survival analysis (Figure 6) showed that patients with high NQO1 expression exhibited a modest but consistent reduction in overall survival probability. Although the association did not reach strong statistical significance, the directional trend suggests that elevated NQO1 may accompany biologically aggressive tumor behavior or enhanced metabolic adaptability within an oxidative microenvironment.

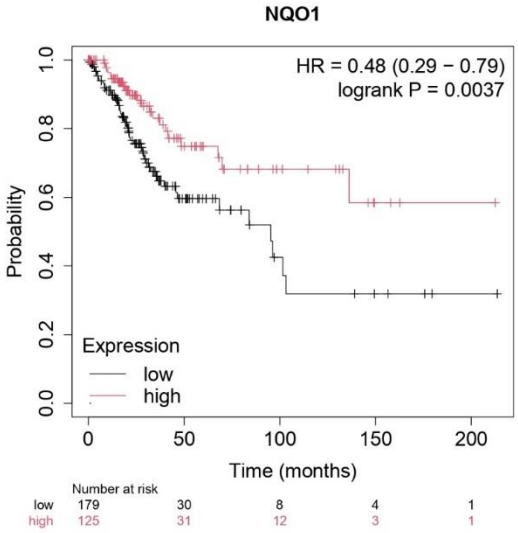

Figure 6. Kaplan–Meier overall survival analysis for NQO1 expression (TCGA-CESC). High NQO1 expression is associated with a modest trend toward reduced survival probability, indicating possible prognostic relevance.

Discussion

This study provides a comprehensive multi-omics characterization of NQO1 in cervical cancer by integrating transcriptomic, epigenetic, lesion-progression, protein-level, and survival analyses across independent cohorts. The convergent findings indicate that NQO1 appears to be upregulated during early phases of HPV-associated epithelial transformation and tends to remain elevated across malignant progression. The strong

tumor-to-normal contrast observed in both TCGA-CESC and an external dataset supports the consistency of NQO1 dysregulation in cervical cancer. Notably, the high expression detected across stages I–IV suggests that increased NQO1 levels may reflect early molecular alterations rather than late-stage tumor burden. This interpretation aligns with the oxidative stress and genomic instability induced by HPV E6/E7 oncoproteins and may also be influenced by additional viral factors such as HPV type variation, integration status, and viral load, which together contribute to a microenvironment favoring redox imbalance and sustained NQO1 expression.

Epigenetic profiling demonstrated tumor-specific promoter hypomethylation at the NQO1 locus, a pattern that may help explain the elevated transcriptional levels observed in cervical cancer. Promoter hypomethylation has been frequently associated with gene derepression in cancer, particularly among genes involved in redox regulation and metabolic adaptation. This observation is also consistent with previous reports indicating that NQO1 polymorphisms—most notably the P187S variant—have been associated with altered enzyme stability and may modify cervical cancer susceptibility by affecting cellular antioxidant defenses [20]. The concordance between decreased promoter methylation and increased expression is consistent with the possibility that epigenetic deregulation may contribute to elevated NQO1 levels in cervical cancer. The lesion-progression analysis using the GSE63514 cohort provides additional biological context, as NQO1 expression appeared to increase from normal epithelium through CIN1, CIN2, and CIN3 to invasive carcinoma, suggesting that its expression pattern may reflect histopathological advancement. This trend aligns with previous studies reporting that oxidative and metabolic stress intensify during early carcinogenic transitions, particularly as HPV16 integration—and potentially other viral factors such as HPV type variation and viral load—begin to exert functional influence on host cellular pathways [17]. The monotonic rise in NQO1 expression suggests that it may represent an indicator of early neoplastic transformation and could hold diagnostic value in distinguishing low-grade from high-grade cervical lesions. Protein-level validation using Human Protein Atlas images further supported these transcriptomic findings, demonstrating strong cytoplasmic NQO1 staining in tumor tissue and minimal expression in normal cervix. Functional studies have reported that NQO1 downregulation can reduce migration and invasion in HPV16-positive cervical cancer cell models, suggesting a possible role in malignant behavior; however, these observations are limited to specific experimental systems and should not be generalized

without broader validation [16]. This mechanistic connection has been suggested to indicate that NQO1 may not function solely as a passive biomarker but could potentially contribute to tumor-associated cellular adaptations. In the TCGA-CESC cohort, the overall survival (OS) analysis did not reach statistical significance, although patients with higher NQO1 expression exhibited a directional pattern toward reduced survival probability. This observation is consistent with reports from other solid tumors, where elevated NQO1 levels have been associated with aggressive phenotypes, enhanced stress tolerance, and poorer prognosis. While the current dataset may have limited statistical power for definitive conclusions, these preliminary findings suggest that NQO1 may hold prognostic relevance, warranting further evaluation in larger, clinically well-annotated cohorts.

Overall, the findings position NQO1 as a multi-dimensional molecular feature of cervical cancer. Its early elevation, epigenetic alterations, the observed stepwise increase in expression across CIN grades, strong protein-level signal, and possible prognostic associations collectively suggest that NQO1 may represent a consistent molecular characteristic throughout cervical carcinogenesis. Future research integrating multi-omics approaches with mechanistic experimentation will be important to clarify whether NQO1 acts primarily as a biomarker of redox imbalance, a contributor to metabolic adaptation and tumor survival, or a potential targetable vulnerability.

Conclusion

This integrated multi-omics investigation demonstrates that NQO1 is a consistently elevated molecular feature of cervical carcinogenesis, with increased mRNA expression, reduced promoter methylation, stepwise elevation across the CIN-to-cancer spectrum, and strong protein-level accumulation collectively suggesting that NQO1 may represent an early and recurrent molecular alteration during HPV-associated epithelial transformation. The relative stability of its expression across clinical stages supports the possibility that NQO1 upregulation emerges early in neoplastic development and remains detectable throughout tumor evolution, while the graded rise from normal epithelium to high-grade lesions indicates that NQO1 may reflect lesion severity and potentially complement existing diagnostic markers. Although the overall survival analysis did not reach statistical significance, the directional pattern aligns with observations in other tumor types, underscoring the need for validation in larger, clinically annotated cohorts. Together, these findings position NQO1 as a biologically meaningful indicator of cervical cancer development, while the question of whether it

functions primarily as a biomarker of oxidative stress or may contribute to redox adaptation and tumor-associated processes remains to be clarified through future mechanistic and prospective clinical studies.

Conflict of Interest

The authors declare that there are no conflicts of interest related to this study. No commercial, financial, or personal relationships influenced the design, execution, or interpretation of the analyses presented.

Limitations

This study is based entirely on publicly available datasets, which limits access to certain clinical variables (e.g., treatment details, HPV subtype, long-term follow-up). Functional experiments were not performed, and therefore mechanistic roles of NQO1 cannot be directly inferred. Although external validation was conducted using the GSE63514 dataset, additional cohorts—particularly from diverse ethnic and clinical backgrounds are needed to generalize the findings. Immunohistochemical observations relied on image resources from the Human Protein Atlas; dedicated tissue microarray validation would further strengthen the histopathological conclusions. Finally, survival associations were modest and should be interpreted as exploratory rather than definitive.

Data Availability

All datasets used in this study are publicly accessible.

• TCGA-CESC transcriptomic and methylation data were obtained from the UALCAN platform (https://ualcan.path.uab.edu).

• GSE63514 microarray data were downloaded from the Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/).

• Immunohistochemistry images for NQO1 were sourced from the Human Protein Atlas (https://www.proteinatlas.org/).

All scripts used for plotting and analysis are available from the corresponding author upon reasonable request.

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Ethical Approval

This study utilized only fully anonymized, publicly available data. Therefore, institutional review board (IRB) approval and informed consent were not required, in

accordance with international ethical guidelines for secondary data analysis.

Author Contributions

• (S.E.): Conceptualization; study design; acquisition and preprocessing of TCGA and GEO datasets; execution of transcriptomic, epigenetic, and cross-cohort validation analyses; data visualization and figure generation; primary drafting of analytical sections; contribution to the interpretation of integrated multi-omics findings.

• (M.Ö.): Comprehensive literature review; identification and synthesis of relevant scientific evidence; preparation of preliminary manuscript drafts; refinement of background and contextual framing of the study.

• (M.H.K.): Support in data curation; assistance with statistical verification and methodological cross-checking; review of analytical outputs for internal consistency; contribution to manuscript refinement.

• (E.S.A.): Supervision of the analytical workflow and study methodology; oversight of data interpretation and multi-layer integration; critical revision of the manuscript for scientific accuracy, coherence, and rigor; senior authorship approval of the final version.

All authors interpreted the results, contributed to the writing process, and approved the final version of the manuscript.

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