

Oncogenic impact of *PIK3CA*, *KRAS*, and *PTEN* mutations in cervical cancer among South Indian women

Akram Husain Rehman Syed Rasheed^{1,A–D}, Praveen Kumar Chandra Sekar^{1,A–D,E},
Anoop Sreevalsan^{2,B}, Ramakrishnan Veerabathiran^{1,C,F}, Vijaya Anand^{3,C}

¹ Human Cytogenetics and Genomics Laboratory, Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, India

² Department of Obstetrics and Gynecology, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, India

³ Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore, India

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online)

Adv Clin Exp Med. 2026;35(6):997–1008

Address for correspondence

Ramakrishnan Veerabathiran
E-mail: rkgenes@gmail.com

Funding sources

None declared

Conflict of interest

None declared

Acknowledgements

The authors thank all study participants for their participation in this study. The authors also thank the Chettinad Academy of Research and Education for its continued support and encouragement.

Received on January 21, 2025

Reviewed on July 16, 2025

Accepted on August 19, 2025

Published online on June 5, 2026

Cite as

Rehman Syed Rasheed AH, Chandra Sekar PK, Sreevalsan A, Veerabathiran R, Anand V. Oncogenic impact of *PIK3CA*, *KRAS*, and *PTEN* mutations in cervical cancer among South Indian women. *Adv Clin Exp Med*. 2026;35(6):997–1008. doi:10.17219/acem/209713

DOI

10.17219/acem/209713

Copyright

Copyright by Author(s)

This is an article distributed under the terms of the Creative Commons Attribution 3.0 Unported (CC BY 3.0) (<https://creativecommons.org/licenses/by/3.0/>)

Abstract

Background. Cervical cancer (CC) affects millions of women worldwide. This condition is strongly associated with human papillomavirus (HPV) infection. Oncogenic alterations are known to contribute to the development and progression of CC.

Objectives. This study aimed to screen for variations in selected genes associated with CC, including *PIK3CA*, *KRAS*, and *PTEN*, and to detect high-risk HPV genotypes 16, 18, 31, 45, 52, and 58 using gene-specific polymerase chain reaction (PCR), followed by single-strand conformation polymorphism (SSCP) analysis and confirmation using bidirectional DNA sequencing.

Materials and methods. The study included 414 participants, comprising 204 cases and 210 controls. Healthy controls were disease-free individuals participating in regular health checkups. Selected gene mutations were analyzed using PCR-based assays, SSCP, and sequence analysis. HPV genotyping was also performed.

Results. All study participants were analyzed for mutations in the *PIK3CA*, *KRAS*, and *PTEN* genes. The analysis revealed mutation frequencies of 6.37% for *KRAS*, 2.45% for *PTEN*, and 16.66% for *PIK3CA* in CC cases. These findings suggest that *PIK3CA* and *KRAS* mutations are more frequent in patients with CC than *PTEN* mutations. HPV infection was detected in 87.10% of patients with CC, 79.24% of participants with high-grade squamous intraepithelial lesions (HSIL), and 60.34% of participants with low-grade squamous intraepithelial lesions (LSIL). This study contributes to understanding the genetic basis of CC in South India and may facilitate the development of future targeted therapies.

Conclusions. The high prevalence of HPV underscores its etiological significance in CC. These findings contribute to a deeper understanding of the molecular mechanisms underlying CC in this population and may support the development of targeted therapeutic strategies for high-risk individuals. Future prospective studies and functional analyses are warranted to validate the clinical significance of these mutations and clarify their role in disease progression.

Keywords: genetics, cervical cancer, oncogenes, genotyping, mutations

Highlights

- This study investigates genetic mutations in the *PIK3CA*, *KRAS*, and *PTEN* genes in cervical cancer patients from South India.
- A higher prevalence of *PIK3CA* mutations (16.66%) was observed in cervical cancer cases compared with *KRAS* (6.37%) and *PTEN* (2.45%) mutations.
- High-risk HPV 16 and 18 genotypes were associated with genetic mutations and histopathological grades of cervical cancer.
- Mutation profiling using PCR, single-stranded conformation polymorphism (SSCP), and sequencing revealed potential biomarkers for personalized therapies.
- The results highlight the need for genetic testing to improve cervical cancer diagnosis and management.

Background

Cervical cancer (CC) is a major gynecological malignancy that arises in the lower part of the uterus, connecting the corpus uteri to the vagina.¹ Despite advances in screening and vaccination programs, CC remains a significant public health burden, particularly in low- and middle-income countries.² By 2026, an estimated 528,000 new cases of CC are expected, with developing nations contributing approx. 85% of the global burden.³ The disease accounts for about 266,000 deaths annually, representing 8% of all cancer-related mortality in women.⁴ In the USA alone, approx. 11,500 new cases are diagnosed each year, leading to 4,000 deaths.⁵ While CC incidence has declined in many developed countries due to effective screening programs,⁶ it remains the 4th most common malignancy among women worldwide, with 604,000 new cases and 342,000 deaths reported in 2020.⁷ India and China together account for over 1/3 of the global CC burden, with India reporting 97,000 new cases and 60,000 deaths annually. Notably, India has the highest age-standardized incidence rate in South Asia (22 per 100,000), with regional variations observed between South India (16.7–18.9 per 100,000) and the northeastern part of this country (24.3 per 100,000).⁸

Persistent infection with high-risk human papillomavirus (HPV) types is the primary cause of CC, contributing to more than 90% of cases.⁹ Among these, HPV 16 is the most oncogenic, followed by HPV 18.¹⁰ However, like many other malignancies, CC is not solely driven by viral infection but also by genetic alterations that dysregulate key signaling pathways. Mutations in oncogenes and tumor suppressor genes play a crucial role in tumor initiation and progression by disrupting cellular processes such as proliferation, metabolism, and apoptosis.¹¹ Previous studies have identified genetic variations in multiple cancer-related genes, including *AKT1*, *KRAS*, *HRAS*, *NRAS*, *PIK3CA*, *FGFR2*, *FGFR3*, *HER2*, *BRAF*, *EGFR*, *CCDC6*, and *PTEN*, in patients with CC in China.¹² However, research on the mutational profiles of *PIK3CA*, *KRAS*, and *PTEN* in South Indian patients with CC remains limited, leaving a gap in our understanding of the genetic landscape of this disease in this population.¹³

The *PIK3CA* gene, a key component of the phosphoinositide 3-kinase (PI3K) signaling pathway, is frequently mutated in various cancers, making it a potential biomarker for targeted therapies. The *KRAS* oncogene plays a critical role in tumorigenesis by regulating cell growth and proliferation, and its mutational status has clinical significance in multiple cancer types.¹⁴ The *PTEN* gene, a well-established tumor suppressor, regulates cell migration and inhibits uncontrolled tumor growth.¹⁵ Understanding the mutational status of these genes in CC could provide valuable insights into tumor biology and facilitate the development of more effective therapeutic strategies.

In regions with low socioeconomic status, the incidence and mortality of CC remain disproportionately high due to limited access to early diagnosis and personalized treatment.¹⁶ The limited availability of genetic profiling in South Indian patients with CC may complicate treatment decision-making and restrict opportunities for more individualized therapeutic approaches.¹⁷

Objectives

This study hypothesizes that mutations in *PIK3CA*, *KRAS*, and *PTEN* contribute to CC pathogenesis in South Indian women. The primary objective was to screen for genetic alterations in *PIK3CA*, *KRAS*, and *PTEN*, alongside high-risk HPV genotyping (types 16, 18, 31, 45, 52, and 58), and to assess their potential role in disease initiation and progression. By identifying specific mutations, this study aims to enhance understanding of the molecular mechanisms underlying CC in an understudied population and provide a foundation for future targeted therapeutic strategies.

Materials and methods

Sample collection

Samples for the study were collected from patients attending the Department of Obstetrics and Gynecology

at Chettinad Hospital and Research Institute and Chettinad Super Speciality Hospital (CSSH) in Coimbatore, India. Patients were screened for HPV infection using type-specific polymerase chain reaction (PCR). The study protocol was approved by the Institutional Human Ethics Committee of the Chettinad Academy of Research and Education (CARE-IHEC; approval No. IHEC/D.NO:012), and informed consent was obtained from all participants prior to sample collection.

Inclusion and exclusion criteria

The study included patients diagnosed with CC across various histopathological grades, as well as healthy controls with no prior history of CC, HPV infection, or other gynecological disorders. Participants with a history of conization or hysterectomy, those who were pregnant, and individuals with severe comorbid conditions, sexually transmitted diseases, or other malignancies were excluded.

Sampling

Cervical scrapings were collected from study participants using a sterile disposable cervical cytobrush into a clean collection container (Citotest Labware Manufacturing Ltd., Haimen, China) for HPV detection and genetic analysis. Participants were also examined by trained gynecologists at Chettinad Hospital and Research Institute (Kelambakkam, India), who performed colposcopic examinations and obtained tissue samples when abnormalities were identified. The sample size was determined through power analysis using the formula $n = p(1 - p)(Z/E)^2$, with a statistical power of 0.95.¹⁸ A total of 414 individuals were included, comprising 204 cases and 210 controls. The control group consisted of healthy individuals undergoing routine health checkups who were free of disease.

Extraction of genomic DNA

Genomic DNA was extracted from cervical scrapings using the phenol-chloroform method.¹⁹ DNA quantity and quality were assessed using spectrophotometric analysis, and gel electrophoresis was performed for further evaluation.

Mutation profiling and Sanger sequencing for mutation confirmation

According to the COSMIC database, previous studies have identified somatic mutations in *PIK3CA*, *PTEN*, and *KRAS* in cervical carcinoma.²⁰ Therefore, these 3 genes were selected as targets for the present study, and gene-specific PCR primers were used to amplify mutation hotspot regions. Mutation detection within oncogenic hotspot regions was performed using gene-specific PCR.

Subsequent analyses included single-strand conformation polymorphism (SSCP) analysis and confirmation

with bidirectional DNA sequencing. The nucleotide sequences of the exonic regions of *PIK3CA*, *KRAS*, and *PTEN* were retrieved from the Ensembl genome database (<https://www.ensembl.org/index.html>).²¹ Primers were newly designed for this study using the Primer3 (v. 4.0) program (<https://primer3.ut.ee>). The quality of the designed primers was evaluated using online tools, including Primer Stats and OligoCalc (https://www.bioinformatics.org/sms2/pcr_primer_stats.html and <https://www.biosyn.com/gizmo/tools/oligo/oligonucleotide%20properties%20calculator.htm>). The designed primer sequences and their properties are presented in Table 1. Polymerase chain reaction products were separated on a 1.2% agarose gel to visualize and analyze the specific amplicon bands. The amplified fragments were excised from the agarose gel and purified using the QIAquick PCR Purification Kit (cat. No. 28104) (Qiagen, Hilden, Germany). After purification, the DNA fragments were sequenced using the Sanger sequencing method²² with the Applied Biosystems 3130 system (Applied Biosystems, Foster City, USA). The obtained sequences were then compared with the reference sequences from the Ensembl genome database to identify mutations.

Statistical analyses

All statistical analyses were performed using IBM SPSS v. 21 (IBM Corp., Armonk, USA), with statistical significance set at $p < 0.05$. The normality of continuous variables, such as age, was assessed using the Shapiro–Wilk test, and appropriate parametric tests (Student's t-test) were applied where assumptions of normality were met. Categorical variables were compared using Pearson's χ^2 test, while Fisher's exact test was applied when expected cell counts were < 5 . For ordinal variables, trend analysis was conducted using the Cochran–Mantel–Haenszel (CMH) test.

Univariate risk ratios (RRs) with 95% confidence intervals (95% CIs) were calculated for selected demographic and lifestyle variables (e.g., tobacco use, contraceptive use, parity, and family history) to assess their association with CC risk. Multivariable logistic regression models with elastic net regularization (combining L1 and L2 penalties) were used to examine associations between mutations in *PIK3CA*, *KRAS*, and *PTEN* and clinical/lifestyle predictors, including HPV status, age, parity, contraceptive use, tobacco use, and family history of cancer. Ten-fold cross-validation was used to optimize the penalty parameters. Final model results are reported as adjusted odds ratios (aORs), 95% CIs, and p-values. Model classification performance was assessed using precision, recall, and F1 score at a probability threshold of 0.3. Receiver operating characteristic (ROC) curves and areas under the curve (AUCs) are presented in the supplementary materials.

Table 1. Designed primer sequences for selected oncogenes

Sample No.	Name	Sequences of PCR primers (5'-3')	Total number of bases	GC content (%)	Size of the PCR product (bp)
1.	<i>PIK3CA</i> -Exon 1-F	GAAGTGTGGGGCATCCACTT	20	55	299
2.	<i>PIK3CA</i> -Exon 1-R	CGGTTGCCTACTGGTTCAAT	20	50	
3.	<i>PIK3CA</i> -Exon 9-F	CTGTGAATCCAGAGGGGAAA	20	50	202
4.	<i>PIK3CA</i> -Exon 9-R	TTAGCACTTACCTGTGACTC	20	45	
5.	<i>PIK3CA</i> -Exon 20-F	GCTCCAAACTGACCAAAGT	20	20	382
6.	<i>PIK3CA</i> -Exon 20-R	GGTCTTTGCCTGCTGAGAGT	20	55	
7.	<i>KRAS</i> -Exon 2-F	CTGGTGGAGATTTGATAGTG	21	43	203
8.	<i>KRAS</i> -Exon 2-R	CTCTATTGTTGGATCATATTCGTC	24	38	
9.	<i>KRAS</i> -Exon 3-F	TGTGTTTCTCCCTTCTCAGGA	21	48	275
10.	<i>KRAS</i> -Exon 3-R	GGCATTAGCAAAGACTCA	18	44	
11.	<i>KRAS</i> -Exon 4-F	TTGTGGACAGGTTTTGAAAGA	21	38	237
12.	<i>KRAS</i> -Exon 4-R	GTTACTTACCTGTCTTGTCTTTGC	24	42	
13.	<i>PTEN</i> -Exon 5-F	AGACCATAACCCACCACAGC	20	55	209
14.	<i>PTEN</i> -Exon 5-R	TGGTCTTACTTCCCATAGAA	22	45	
15.	<i>PTEN</i> -Exon 9-F	TAGAGGAGCCGTCAAATCCA	20	50	195
16.	<i>PTEN</i> -Exon 9-R	TCATGGTGTTTATCCCTCTTG	22	41	

F – forward primer; R – reverse primer; bp – base pair; PCR – polymerase chain reaction; GC – guanine and cytosine.

Results

Clinical features of the cases and controls

The demographic and baseline characteristics of the study groups are presented as mean \pm standard deviation (SD) in Table 2. The mean age of the participants was approximately normally distributed, as indicated by the Shapiro–Wilk test ($p = 0.135$ for cases; $p = 0.838$ for controls). As age was approximately normally distributed and differed modestly between groups, a 2-sample Student's *t*-test was used for comparison. The analysis showed a significant difference between the case group (mean age: 53 ± 8.90 years) and the control group (mean age: 50 ± 5.49 years) ($t = 4.14$, degrees of freedom (df) = 412, $p < 0.001$).

Among the categorical variables, having more than 4 pregnancies ($\chi^2 = 11.19$, df = 1, $p = 0.001$), contraceptive use ($\chi^2 = 9.93$, df = 1, $p = 0.002$), family history of cancer ($\chi^2 = 5.70$, df = 1, $p = 0.017$), and tobacco use ($\chi^2 = 7.38$, df = 1, $p = 0.007$) were significantly more common in cases than in controls.

No significant differences between cases and controls were detected for education level ($\chi^2 = 1.65$, df = 3, $p = 0.65$), employment status ($\chi^2 = 1.79$, df = 2, $p = 0.41$), socioeconomic status ($\chi^2 = 2.01$, df = 2, $p = 0.37$), or the composite comorbidity category ($\chi^2 = 2.28$, df = 3, $p = 0.52$). In addition, risk ratios (RRs) with 95% CIs were calculated for binary variables. Having more than 4 pregnancies (RR = 2.14), contraceptive use (RR = 2.65), and tobacco use (RR = 2.27) showed strong positive associations with CC risk. Group differences in clinical and lifestyle factors were assessed using χ^2 tests, and variables

showing significant associations were considered potential confounders in the regression analysis. The normality of continuous variables, including age, was assessed using the Shapiro–Wilk test. The results are presented in Supplementary Table 1. All *p*-values in this section were derived from univariate analyses using Pearson's χ^2 test, where appropriate.

Genotyping of 6 high-risk HPVs

HPV genotyping was performed under optimized PCR conditions. Amplicons ranging from 150 to 295 base pairs indicated the presence of specific HPV genotypes in both cases and controls. Polymerase chain reaction products were analyzed using a 100 bp DNA ladder on a 1.2% agarose gel (Fig. 1). The PCR findings were subsequently correlated with histopathological grading.

Pearson's χ^2 test revealed a highly significant association between HPV infection and histopathological grade ($\chi^2 = 108.56$, df = 3, $p < 0.001$), with HPV positivity increasing from negative for intraepithelial lesion or malignancy (NILM; 10.47%) to low-grade squamous intraepithelial lesion (LSIL; 60.34%), high-grade squamous intraepithelial lesion (HSIL; 79.24%), and CC (87.10%) (Table 3). A CMH test confirmed a significant increasing trend in HPV positivity with worsening histopathological grade (p for trend < 0.001). Among HPV genotypes, HPV 16 and HPV 58 showed significant variation across histopathological grades (HPV 16: $\chi^2 = 8.10$, df = 2, $p = 0.017$; HPV 58: $\chi^2 = 9.11$, df = 2, $p = 0.033$), with higher frequencies in more advanced lesions. No statistically significant distribution patterns were observed for HPV 18, 31, 45, or 52 ($p > 0.05$ for all) (Table 4).

Table 2. Demographic characteristics of the study subjects

Sample No.	Factors	Cases (n = 204)	Controls (n = 210)	Test (statistic, df)	p-value*	RR	95% CI
1.	mean age	53 ±8.90 ^a	50 ±5.49 ^a	Student's t-test = 4.14, df = 412	p < 0.001	–	–
2.	>4 pregnancies	50 (24.50) ^b	24 (11.4) ^b	$\chi^2 = 11.19$, df = 1	p < 0.001	2.14	(1.41–4.19)
3.	usage of contraceptives	35 (17.15) ^b	14 (6.6) ^b	$\chi^2 = 9.93$, df = 1	p = 0.002	2.65	(1.33–5.04)
4.	family history of any cancer	18 (8.82) ^b	6 (2.9) ^b	$\chi^2 = 5.70$, df = 1	p = 0.017	3.04	(0.80–2.58)
5.	tobacco usage	33 (16.17) ^b	15 (7.1) ^b	$\chi^2 = 7.38$, df = 1	p = 0.007	2.27	(1.51–5.01)
level of education							
6.	primary	24 (11.76) ^b	17 (8.09) ^b	$\chi^2 = 1.65$, df = 3	p = 0.648	–	–
	high school	67 (32.84) ^b	69 (32.8) ^b				
	higher secondary	64 (31.37) ^b	70 (33.3) ^b				
	graduate	49 (24.01) ^b	54 (25.7) ^b				
work status							
7.	employed	38 (18.62) ^b	43 (20.4) ^b	$\chi^2 = 1.79$, df = 2	p = 0.409	–	–
	retired	29 (14.21) ^b	21 (10.4) ^b				
	homemaker	137 (67.15) ^b	146 (69.4) ^b				
socioeconomic status							
8.	slow	84 (41.17) ^b	6 (36.2) ^b	$\chi^2 = 2.01$, df = 2	0.367		
	middle	103 (50.49) ^b	109 (51.9) ^b				
	high	17 (8.33) ^b	25 (11.9) ^b				
other complications							
9.	hypertension	08 (3.92) ^b	05 (2.3) ^b	$\chi^2 = 2.28$, df = 3	p = 0.516	–	–
	T2DM	10 (4.90) ^b	03 (1.4) ^b				
	thyroid	14 (6.86) ^b	11 (5.2) ^b				
	obesity	20 (9.80) ^b	08 (3.8) ^b				

^adata are presented as mean ± standard deviation (SD); ^bpercentage; df – degrees of freedom; RR – risk ratio; 95% CI – 95% confidence interval; T2DM – type 2 diabetes mellitus; *p-values were derived using Pearson's χ^2 test of independence. Only applicable binary variables are presented with RR and 95% CI. Values in bold are statistically significant.

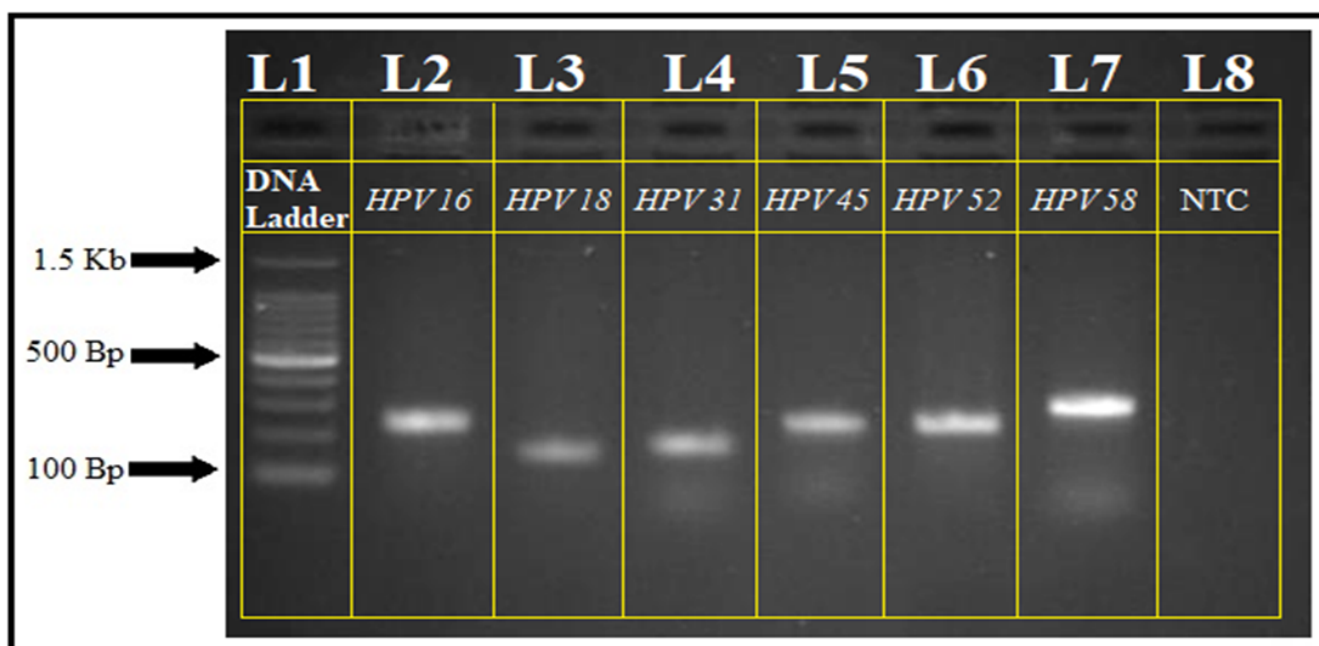


Fig. 1. Optimized polymerase chain reaction (PCR) conditions for high-risk human papillomavirus (HPV) genotypes

Table 3. HPV identification by type-specific polymerase chain reaction (PCR)

Histopathological grade	Samples tested	HPV-positive	Percentage (%)	HPV-negative	p-value
Negative for intraepithelial lesion or malignancy (NILM)	210	22	10.47	188	–
Low-grade squamous intraepithelial lesion (LSIL)	58	35	60.34	23	<0.001
High-grade squamous intraepithelial lesion (HSIL)	53	42	79.24	11	–
Cervical cancer (CC)	93	81	87.10	12	–

*p-value derived from Cochran–Mantel–Haenszel (CMH) test ($\chi^2 = 108.56$, $df = 3$; $p < 0.001$); HPV – human papillomavirus; df – degrees of freedom.

Table 4. HPV genotype distribution among the LSIL, HSIL, and CC

HPV genotypes	LSIL, % (n)	HSIL, % (n)	CC, % (n)	χ^2 , df	p-value
16	40.00 (14)	42.80 (23)	67.90 (55)	$\chi^2 = 8.10$, $df = 2$	0.034
18	25.71 (9)	14.30 (10)	19.75 (16)	$\chi^2 = 0.59$, $df = 2$	0.786
31	5.71 (2)	4.76 (2)	–	$\chi^2 = 4.38$, $df = 2$	0.168
45	–	7.14 (3)	7.40 (6)	$\chi^2 = 2.71$, $df = 2$	0.308
52	11.42 (4)	4.76 (2)	2.46 (2)	$\chi^2 = 4.09$, $df = 2$	0.308
58	17.17 (6)	4.76 (2)	2.46 (2)	$\chi^2 = 9.11$, $df = 2$	0.033

*p-values derived from Pearson's χ^2 test of independence; p-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) correction for multiple comparisons. NILM – negative for intra-epithelial lesion (NILM); CC – cervical cancer; df – degrees of freedom; HPV – human papillomavirus. Values in bold are statistically significant.

Table 5. Elastic net logistic regression for *PIK3CA* mutations adjusted for confounding factors

Predictors	aOR (<i>PIK3CA</i>)	95% CI	p-value	aOR (<i>KRAS</i>)	95% CI	p-value
Cervical cancer	74.03	6.39–857.89	<0.001	7.44	1.41–39.36	0.018
HPV-positive	1.20	0.60–2.38	0.593	0.79	0.44–1.42	0.432
>4 pregnancies	0.84	0.51–1.37	0.488	0.26	0.17–0.40	<0.001
Contraceptive use	0.89	0.52–1.51	0.664	0.76	0.43–1.34	0.340
Family history	0.14	0.05–0.37	<0.001	0.48	0.20–1.16	0.103
Tobacco use	1.11	0.62–2.00	0.725	1.34	0.73–2.46	0.342

aOR – adjusted odds ratio. 95% CI – 95% confidence interval; HPV – human papillomavirus. Elastic net regularization (L1 + L2) was applied to logistic regression models to control for overfitting and sparse data; p-values derived from the logistic model. Bold values indicate stronger associations.

Multivariable analysis of gene mutations

To assess the independent contribution of clinical and lifestyle factors to mutation risk, elastic net-regularized logistic regression was applied for *PIK3CA* and *KRAS* mutations. This method combines L1 and L2 penalties to balance variable selection and coefficient shrinkage and is particularly suitable for small or sparse datasets. The model identified CC status as the strongest independent predictor of both *PIK3CA* (aOR = 74.03) and *KRAS* (aOR = 7.44) mutations. Other variables, including HPV positivity, tobacco use, parity, contraceptive use, and family history of cancer, were retained in the models but did not demonstrate statistically significant associations (Table 5).

Mutation profiling

Mutations in the *PIK3CA*, *KRAS*, and *PTEN* genes were analyzed among study participants using gene-specific PCR. The amplicon sizes ranged from 180 to 400 base pairs, and the PCR products were confirmed with agarose gel

electrophoresis (Fig. 2). Mutation frequency comparisons between cases and controls were assessed using univariate ORs.

The observed mutation frequencies among CC cases were 16.66% for *PIK3CA* (95% CI: 12.34–20.98, $p = 0.002$), 6.37% for *KRAS* (95% CI: 4.11–8.63, $p = 0.017$), and 2.45% for *PTEN* (95% CI: 1.12–3.78, $p = 0.042$). No significant mutations were identified in the control group, resulting in perfect separation for some outcomes. Statistical comparisons between cases and controls confirmed a strong association between *PIK3CA* mutations and CC risk (OR = 3.89, 95% CI: 2.14–7.08, $p < 0.001$).

Gene profiling of *PIK3CA*, *KRAS*, and *PTEN*

Multivariable logistic regression was performed to assess the association between gene mutations and potential confounding factors. Penalized (L2) logistic regression was applied due to sparse mutation events and perfect separation in some models. Results are presented as aORs with 95% CIs. The distribution of mutations in *PIK3CA*, *KRAS*, and *PTEN* was further analyzed in relation to HPV genotype

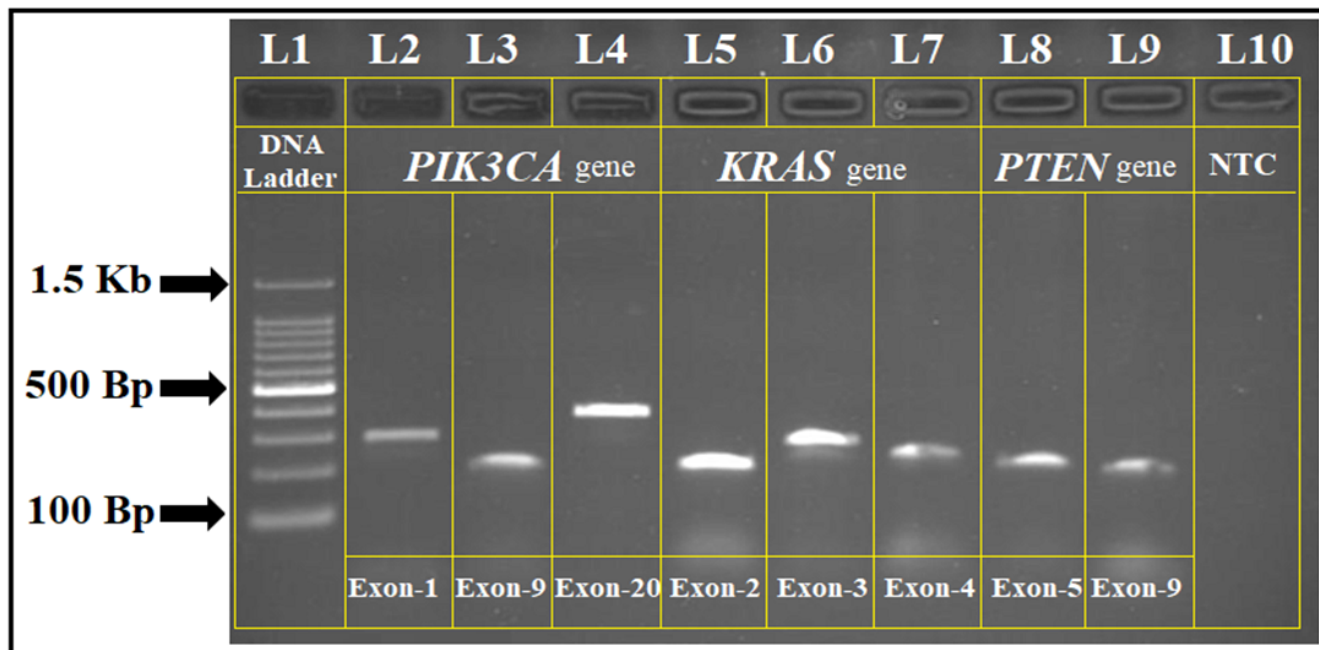


Fig. 2. Optimized polymerase chain reaction (PCR) conditions for the selected genes analyzed in this study

and histopathological grade (Fig. 3). *PIK3CA* mutations were predominantly identified in exons 9, 20, and 1, with hotspot mutations located in the helical domain (*E542K*, *E545K*) and catalytic domain (*H1047R*). The overall frequency of these mutations was 2.94%. Patients harboring *PIK3CA* mutations had a significantly higher likelihood of HPV 16 infection ($p = 0.004$). Detailed information regarding *PIK3CA* mutations in relation to HPV genotypes and histopathological grading is presented in Table 6. *KRAS* mutations were primarily detected in exon 2, followed by exons 3 and 4 (Table 7). These mutations were significantly associated with a family history of breast cancer and consanguineous marriage ($p = 0.016$). As shown in Table 8, logistic regression analysis demonstrated that *KRAS* mutations were significantly associated with HPV positivity (OR = 2.47, 95% CI: 1.32–4.21, $p = 0.022$) and CC (OR = 3.80, 95% CI: 2.01–6.88, $p < 0.001$). An interaction term between HPV status and cancer status was also statistically significant.

PTEN gene variants were predominantly identified in exon 5, followed by exon 9. These mutations were detected exclusively in CC cases and were not observed in any control subjects. Patients harboring *PTEN* mutations did not report a family history of cancer or consanguinity, suggesting that these variants may represent somatic alterations contributing to carcinogenesis. A novel *PTEN* mutation identified in this study has not previously been reported in HPV-associated CC (Table 9).

Model performance evaluation

To further evaluate the classification performance of the mutation prediction models, various probability thresholds (e.g., 0.3) were tested. However, due to extreme

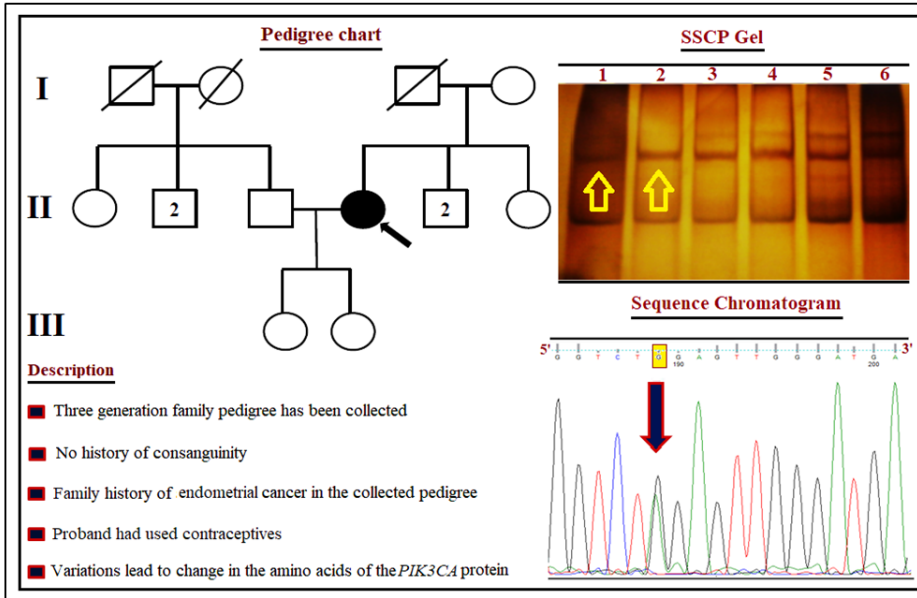
class imbalance, the models failed to identify mutation-positive cases (zero true positives). Despite this limitation, overall accuracy remained relatively high (91.8% for *PIK3CA* and 96.9% for *KRAS*), largely driven by the high number of correctly classified negative cases. These results are presented in Supplementary Table 2. Nevertheless, ROC analysis indicated that both models retained moderate-to-strong discriminatory ability, with AUC values of 0.825 for *PIK3CA* and 0.881 for *KRAS* (Supplementary Table 3). The corresponding ROC curves are shown in Supplementary Fig. 4.

Discussion

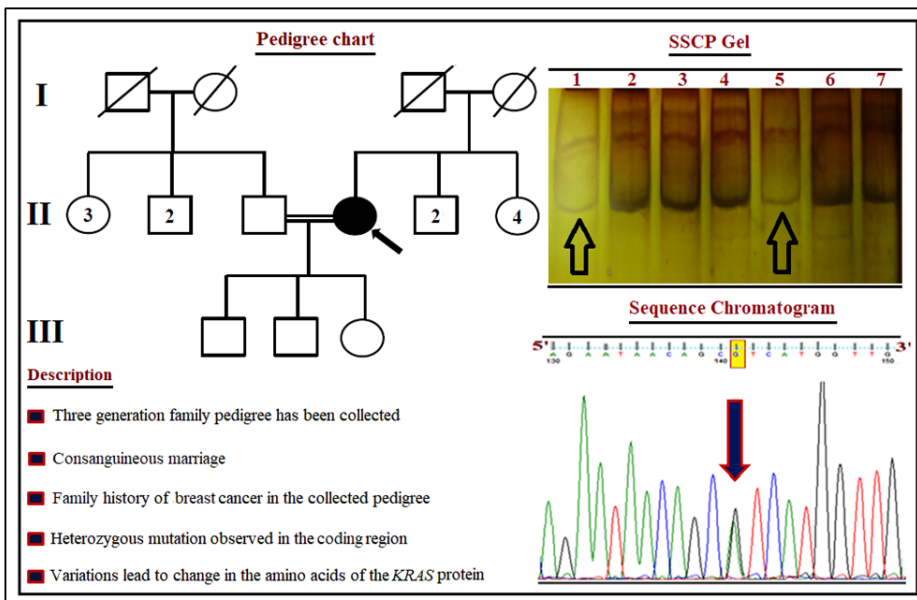
Advances in high-throughput sequencing technologies have enabled the identification of novel genetic variants and somatic mutations with high depth of coverage, contributing to the transition toward precision medicine. The fundamental principle of mutation profiling is the detection of genetic alterations in candidate or disease-associated genes. This approach may facilitate the identification of predictive biomarkers and improve the effectiveness of therapeutic strategies.

The present study aimed to identify and characterize CC-associated mutations using gene-specific PCR, followed by SSCP analysis and confirmation by DNA sequencing. According to our findings, mutations in *PIK3CA* (16.66%), *KRAS* (6.37%), and *PTEN* (2.45%) were associated with CC in South Indian patients. *PIK3CA* is one of the genes frequently implicated in human malignancies. The PI3K signaling pathway plays a critical role in multiple cellular processes, including cell survival, metabolism, growth, and proliferation. *PIK3CA* mutation

A. *PIK3CA*



B. *KRAS*



C. *PTEN*

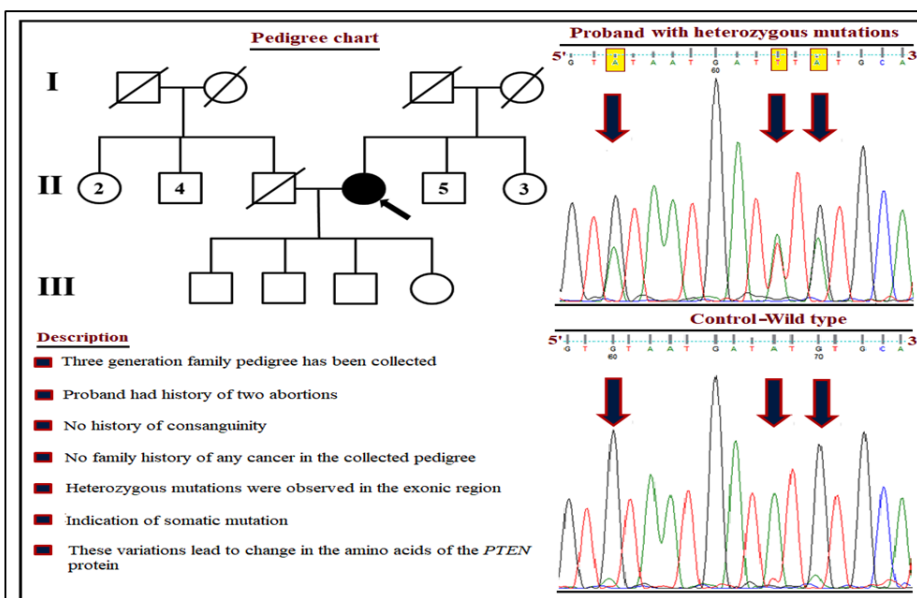


Fig. 3. A. Genetic analysis of *PIK3CA* mutations in cervical cancer (CC); B. Genetic analysis of *KRAS* mutations in CC; C. Genetic analysis of *PTEN* mutations in CC

Table 6. Histological characteristics, human papillomavirus (HPV) status, and *PIK3CA* mutations of study subjects

Sample No.	Histological grading	HPV genotype	Exonic region	Nucleotide change	Amino acid change
1.	CC	16	01	c.35 G > T	p.G12C
2.	CC	16		c.70 T > A	p.C24S
3.	HSIL	16		c.223 C > G	p.Q75E
4.	CC	18		c.100 T > C	p.L34L
5.	CC	16		c.241 G > A	p.E81K
6.	LSIL	18		c.115 G > A	p.E39K
7.	CC	16	09	c.1633 G > A	p.E545K
8.	CC	18		c.1624 G > A	p.E542K
9.	CC	16		c.1633 G > A	p.E545K
10.	CC	16		c.1624 G > A	p.E542K
11.	HSIL	18		c.1633 G > A	p.E545K
12.	CC	45		c.1624 G > A	p.E542K
13.	CC	18		c.1634 A > C	p.E545A
14.	CC	16		c.1633 G > A	p.E545K
15.	HSIL	16		c.1624 G > A	p.E542K
16.	LSIL	58		c.1634 A > C	p.E545A
17.	CC	16		c.1624 G > A	p.E542K
18.	CC	18		c.1633 G > C	p.E545Q
19.	HSIL	16		c.1633 G > A	p.E545K
20.	CC	16		c.1634 A > C	p.E545A
21.	HSIL	18		c.1624 G > A	p.E542K
22.	LSIL	16		c.1633 G > C	p.E545Q
23.	CC	16		c.1635 G > T	p.E545D
24.	CC	45		c.1633 G > A	p.E545K
25.	CC	18	20	c.3140 A > T	p.H1047L
26.	CC	16		c.3140 A > G	p.H1047R
27.	CC	16		c.3140 A > T	p.H1047L
28.	LSIL	58		c.3146 G > C	p.G1049A
29.	HSIL	18		c.3140 A > G	p.H1047R
30.	CC	45		c.3140 A > T	p.H1047L
31.	CC	18		c.3140 A > G	p.H1047R
32.	LSIL	16		c.3146 G > C	p.G1049A
33.	HSIL	16		c.3140 A > T	p.H1047L
34.	CC	16		c.3140 A > G	p.H1047R

NILM – negative for intra-epithelial lesion (NILM); LSIL – low-grade squamous intra-epithelial lesion; HSIL – high-grade squamous intra-epithelial lesion; CC – cervical cancer.

and amplification are among the most common mechanisms leading to aberrant activation of the PI3K pathway in various cancers.²³ The mutation frequency of *PIK3CA* in our study was 16.66% among patients with CC. When compared with previous studies, a cohort from the Netherlands including 301 patients with CC of Caucasian ancestry reported *PIK3CA* mutations in 20% of cases. Similarly, a study of 213 Chinese patients with CC reported a mutation frequency of 12.3%.²⁴ Another study involving Chinese patients of Asian ancestry that screened 16 genes also reported a *PIK3CA* mutation frequency of 12.3%.²⁵ Our observed *PIK3CA* mutation frequency was therefore

somewhat higher than that reported in Chinese cohorts, despite both populations being of Asian ancestry. These differences may reflect variation in mutation spectra, patient characteristics, HPV subtype distribution, or methodological differences between studies. A study from the USA involving 67 patients with CC reported *PIK3CA* mutations in 27.1% of cases, which is substantially higher than the frequency observed in our cohort.²⁶ The higher prevalence of *PIK3CA* mutations in some Western populations may reflect differences in environmental exposures, lifestyle factors, genetic background, or interactions with high-risk HPV variants.

Table 7. Histological characteristics, human papillomavirus (HPV) status, and *KRAS* mutations of study subjects

Sample No.	Histological grading	HPV genotype	Exonic region	Nucleotide change	Amino acid change
1.	CC	16	02	c.111 G > A	p.G38D
2.	CC	16		c.168 C > T	p.D57C
3.	CC	45		c.174 A > T	p.A59C
4.	CC	16	03	c.299 T > G	p.I100K
5.	HSIL	16		c.349 A > T	p.N117Y
6.	CC	18		c.310 A > G	p.I104K
7.	HSIL	16	04	c.362 G > T	p.P121P
8.	HSIL	45		c.453 G > A	p.G151G
9.	CC	16		c.470 A > T	p.L157L
10.	LSIL	16		c.491 G > A	p.R171S
11.	CC	18		c.453 G > A	p.G151G
12.	HSIL	18		c.480 T > A	p.C167S
13.	CC	16		c.491 G > A	p.R171S

NILM – negative for intra-epithelial lesion (NILM); LSIL – low-grade squamous intra-epithelial lesion; HSIL – high-grade squamous intra-epithelial lesion; CC – cervical cancer.

Table 8. Logistic regression model for predicting *KRAS* mutations based on human papillomavirus (HPV) status and cervical cancer (CC)

Predictor	OR	95% CI	SE	p-value
HPV-positive	2.47	1.32–4.21	0.45	0.022
Cervical cancer	3.80	2.01–6.88	0.49	<0.001
HPV * CC interaction	1.95	1.01–3.45	0.52	0.38

OR – odds ratio; 95% CI – 95% confidence interval; SE – standard error.

The *KRAS* gene is a well-established oncogene, and multiple point mutations have been identified across various malignancies, including breast, cervical, endometrial, liver, and myeloid cancers.²⁷ The *KRAS* protein plays a crucial role in regulating the MAPK signaling pathway and may also influence cellular proliferation through interactions with the PI3K–AKT pathway. Our study demonstrated an association between *KRAS* mutations and high-risk HPV 16/18 genotypes. The integration of *KRAS* mutational analysis with HPV genotyping may improve risk stratification and potentially inform prognostic assessment in patients with CC. The mutation frequency of *KRAS* in this study was 6.37% among patients with CC. In comparison, a previous study from Boston analyzing 80 Caucasian patients across 139 cancer-related genes reported an overall mutation rate of 60%, with *KRAS* mutations accounting

for 8.8% of cases.²⁸ In a Chinese study (n = 876), *KRAS* mutations were detected in 3.4% of CC cases,²⁹ whereas another Chinese study focused on cervical adenocarcinoma reported *KRAS* mutations in 16.6% of patients.³⁰ These differences may reflect variation in histological subtype, study population, sequencing methodology, or sample composition.

Although *KRAS* mutations have been reported across diverse populations, current evidence remains insufficient to conclude that they represent a conserved oncogenic event in CC irrespective of ethnicity. In addition to mutation-driven signaling pathways, targeted gene-silencing approaches such as *MCT1* inhibition have shown promise in enhancing dendritic cell-mediated immune responses against CC, suggesting potential synergy between immunotherapeutic and molecular targeting strategies.³¹ However, our observed association between *KRAS* mutations and HPV 16/18 infection highlights the potential value of integrating viral and genetic profiling in CC risk assessment.

PTEN is a well-established tumor suppressor gene implicated in the development of multiple cancer types and plays an important role in regulating cellular proliferation, survival, and migration. The phosphatase encoded by *PTEN* negatively regulates the PI3K signaling pathway through dephosphorylation of phosphoinositide substrates, thereby

Table 9. Histological characteristics, HPV status, and *PTEN* mutations of study subjects

Sample No.	Histological grading	HPV genotype	Exonic region	Nucleotide change	Amino acid change	Prediction
1.	CC	16	05	c.397 G > A	p.V133L	damaging
				c.405 A > T	p.I135I	silent
				c.407 G > A	p.C136Y	damaging
2.	CC	16	05	c.466 G > T	p.R160H	pathogenic
3.	HSIL	45	05	c.1044 A > T	p.K234B	pathogenic

HPV – human papillomavirus; CC – cervical cancer; HSIL – high-grade squamous intra-epithelial lesion; CC – cervical cancer.

limiting uncontrolled cellular growth and proliferation.³² In our study, the mutation frequency of *PTEN* was 2.45% among patients with CC. Compared with previous studies, cohorts from Mexico and Norway analyzing 115 CC and control samples reported a *PTEN* mutation frequency of approx. 6%, which is higher than the frequency observed in our cohort.³³ A Japanese study (n = 50) reported *PTEN* mutations in 4.2% of cases,³⁴ while a study from the USA reported *PTEN* alterations in 8% of CC cases.³⁵ Another study in Mexican patients (n = 155) identified *PTEN* mutations in 5% of cases.³⁶

Observed differences in *PTEN* mutation frequency across studies may reflect variation in study population characteristics, sequencing methodology, histological subtype composition, or sample size rather than ethnicity alone. The reasons for these discrepancies remain uncertain. In addition, the identification of a novel *PTEN* mutation in our study raises the possibility of previously unrecognized genetic alterations in South Indian patients with CC, warranting further investigation.

Limitations of the study

One important limitation of this study is its focus on a specific population from South India, which may limit the generalizability of the findings to other populations or ethnic groups. Additionally, the relatively small sample size, particularly for mutation frequency analyses, may have reduced the statistical power to detect less common genetic variants. Although techniques such as SSCP and bidirectional DNA sequencing were employed, these methods may not detect all potentially relevant genetic alterations, including large structural variants or epigenetic changes. Furthermore, the use of conventional PCR and Sanger sequencing rather than next-generation sequencing (NGS) may have limited the ability to detect rare, novel, or non-hotspot mutations more comprehensively. A major limitation of the mutation prediction models was their inability to accurately identify mutation-positive cases because of the low frequency of mutation events and severe class imbalance. This resulted in zero sensitivity and F1 scores at the evaluated classification thresholds. Therefore, further large-scale studies using more comprehensive genomic approaches are needed to better understand the genetic landscape of CC in South Indian patients and its relationship to other populations.

Conclusions

Our findings underscore the importance of understanding population-specific genetic variation in CC. The higher mutation frequency of *PIK3CA* compared with *KRAS* and *PTEN* suggests that alterations in the PI3K pathway may play a prominent role in cervical carcinogenesis in South Indian women. These results provide

valuable insights into the molecular landscape of CC in this population and add to the growing body of evidence suggesting that genetic alterations, together with HPV infection, may influence disease progression and therapeutic response. This study highlights the potential relevance of *PIK3CA*, *KRAS*, and *PTEN* mutations in CC among South Indian women. A higher mutation frequency was observed for *PIK3CA* (16.66%) compared with *KRAS* (6.37%) and *PTEN* (2.45%), suggesting that alterations in the PI3K/AKT/mTOR pathway may play an important role in cervical carcinogenesis in this population. The observed association between *KRAS* mutations and high-risk HPV 16/18 infection warrants further investigation into the biological and potential clinical significance of this finding. Although *PTEN* mutations were less frequent, their established role in tumor suppression suggests potential relevance to disease biology. Integrating genetic profiling with HPV testing may improve molecular characterization and risk stratification in CC. However, the clinical utility of mutation-guided therapeutic strategies, including PI3K-targeted therapies, alternative approaches for *KRAS*-mutant tumors, or the predictive relevance of *PTEN* alterations for immunotherapy response, requires further validation in larger prospective studies. Future research should focus on further investigating these mutations and clarifying their potential clinical relevance. Our findings suggest that more individualized therapeutic strategies for CC warrant exploration. Although current management strategies do not routinely incorporate molecular stratification beyond standard clinicopathological classification, our study suggests that identifying distinct molecular subpopulations within CC may offer opportunities to improve patient stratification and potentially enhance outcomes in both early- and advanced-stage disease.

Supplementary data

The supplementary materials are available at <https://doi.org/10.5281/zenodo.16919759>. The package contains the following files:

Supplementary Table 1. Normality test results for continuous variables.

Supplementary Table 2. Performance metrics and confusion matrix for elastic net logistic regression models.

Supplementary Table 3. Performance metrics for elastic net logistic regression models.

Data Availability Statement

Data sharing does not apply to this article, as all data are already included in the manuscript.

Consent for publication

Not applicable.

Use of AI and AI-assisted technologies

Not applicable.

ORCID iDs

Akram Husain Rehman Syed Rasheed

<https://orcid.org/0009-0004-2561-3601>

Praveen Kumar Chandra Sekar <https://orcid.org/0009-0008-5346-9597>

Ramakrishnan Veerabathiran <https://orcid.org/0000-0002-9307-5428>

Vijaya Anand <https://orcid.org/0000-0001-7485-1586>

References

- Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri: 2021 update. *Int J Gynecol Obstet.* 2021;155(Suppl 1):28–44. doi:10.1002/ijgo.13865
- Ganesan S, Subbiah VN, Michael JJC. Associated factors with cervical pre-malignant lesions among the married fisher women community at Sadras, Tamil Nadu. *Asia Pac J Oncol Nurs.* 2015;2(1):42–50. doi:10.4103/2347-5625.146223
- Chandra Sekar PK, Thomas SM, Veerabathiran R. The future of cervical cancer prevention: Advances in research and technology. *Explor Med.* 2024;5:384–400. doi:10.37349/emed.2024.00226
- Ramamoorthy T, Kulothungan V, Sathishkumar K, et al. Burden of cervical cancer in India: Estimates of years of life lost, years lived with disability and disability adjusted life years at national and subnational levels using the National Cancer Registry Programme data. *Reprod Health.* 2024;21(1):111. doi:10.1186/s12978-024-01837-7
- Division of Cancer Prevention and Control, Centers for Disease Control and Prevention (CDC). Cervical Cancer Statistics. Atlanta, USA: Centers for Disease Control and Prevention (CDC); 2023. <https://www.cdc.gov/cancer/cervical/statistics/index.htm>. Accessed July 27, 2025.
- Hull R, Mbele M, Makhafole T, et al. Cervical cancer in low and middle-income countries (Review). *Oncol Lett.* 2020;20(3):2058–2074. doi:10.3892/ol.2020.11754
- Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209–249. doi:10.3322/caac.21660
- Nath A, Sathishkumar K, Das P, Sudarshan KL, Mathur P. A clinicoepidemiological profile of lung cancers in India: Results from the National Cancer Registry Programme. *Indian J Med Res.* 2022;155(2):264–272. doi:10.4103/ijmr.ijmr_1364_21
- Okunade KS. Human papillomavirus and cervical cancer. *J Obstet Gynaecol.* 2020;40(5):602–608. doi:10.1080/01443615.2019.1634030
- Da Silva RL, Da Silva Batista Z, Bastos GR, et al. Role of HPV 16 variants among cervical carcinoma samples from Northeastern Brazil. *BMC Womens Health.* 2020;20(1):162. doi:10.1186/s12905-020-01035-0
- Purushothaman P, Uppal T, Verma SC. Human DNA tumor viruses and oncogenesis. In: *Animal Biotechnology.* Amsterdam, the Netherlands: Elsevier; 2020:131–151. doi:10.1016/B978-0-12-811710-1.00007-0
- Xiang L, Li J, Jiang W, et al. Comprehensive analysis of targetable oncogenic mutations in Chinese cervical cancers. *Oncotarget.* 2015; 6(7):4968–4975. doi:10.18632/oncotarget.3212
- Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K pathway in human disease. *Cell.* 2017;170(4):605–635. doi:10.1016/j.cell.2017.07.029
- Janakiraman M, Vakiani E, Zeng Z, et al. Genomic and biological characterization of exon 4 KRAS mutations in human cancer. *Cancer Res.* 2010;70(14):5901–5911. doi:10.1158/0008-5472.CAN-10-0192
- Milella M, Falcone I, Conciatori F, et al. PTEN: Multiple functions in human malignant tumors. *Front Oncol.* 2015;5:24. doi:10.3389/fonc.2015.00024
- Cetina-Pérez L, Luvián-Morales J, Delgadillo-González M, et al. Sociodemographic characteristics and their association with survival in women with cervical cancer. *BMC Cancer.* 2024;24(1):161. doi:10.1186/s12885-024-11909-3
- Burmeister CA, Khan SF, Schäfer G, et al. Cervical cancer therapies: Current challenges and future perspectives. *Tumour Virus Res.* 2022; 13:200238. doi:10.1016/j.tvr.2022.200238
- Sobha SP, Kesavarao KE. Prognostic effect of GSTM1/GSTT1 polymorphism in determining cardiovascular diseases risk among type 2 diabetes patients in South Indian population. *Mol Biol Rep.* 2023;50(8):6415–6423. doi:10.1007/s11033-023-08514-1
- Chu TY, Hwang KS, Yu MH, Lee HS, Lai HC, Liu JY. A research-based tumor tissue bank of gynecologic oncology: Characteristics of nucleic acids extracted from normal and tumor tissues from different sites. *Int J Gynecol Cancer.* 2002;12(2):171–176. doi:10.1046/j.1525-1438.2002.01085.x
- Sharmin S, Zohura FT, Islam MdS, et al. Mutational profiles of marker genes of cervical carcinoma in Bangladeshi patients. *BMC Cancer.* 2021;21(1):289. doi:10.1186/s12885-021-07906-5
- Flicek P, Amode MR, Barrell D, et al. Ensembl 2014. *Nucl Acids Res.* 2014;42(D1):D749–D755. doi:10.1093/nar/gkt1196
- Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. *Proc Natl Acad Sci U S A.* 1977;74(12):5463–5467. doi:10.1073/pnas.74.12.5463
- Yang J, Nie J, Ma X, Wei Y, Peng Y, Wei X. Targeting PI3K in cancer: Mechanisms and advances in clinical trials. *Mol Cancer.* 2019;18(1):26. doi:10.1186/s12943-019-0954-x
- Spaans VM, Trietsch MD, Peters AAW, et al. Precise classification of cervical carcinomas combined with somatic mutation profiling contributes to predicting disease outcome. *PLoS One.* 2015;10(7):e0133670. doi:10.1371/journal.pone.0133670
- Femi OF. Genetic alterations and *PIK3CA* gene mutations and amplifications analysis in cervical cancer by racial groups in the United States. *Int J Health Sci (Qassim).* 2018;12(1):28–32. PMID:29623014. PMID:PMC5870313.
- Voutsadakis IA. *PIK3CA* mutations in uterine cervix carcinoma. *J Clin Med.* 2021;10(2):220. doi:10.3390/jcm10020220
- Jančík S, Drábek J, Radzich D, Hajdúch M. Clinical relevance of KRAS in human cancers. *J Biomed Biotechnol.* 2010;2010:150960. doi:10.1155/2010/150960
- Wright AA, Howitt BE, Myers AP, et al. Oncogenic mutations in cervical cancer: Genomic differences between adenocarcinomas and squamous cell carcinomas of the cervix. *Cancer.* 2013;119(21):3776–3783. doi:10.1002/cncr.28288
- Jiang W, Xiang L, Pei X, et al. Mutational analysis of *KRAS* and its clinical implications in cervical cancer patients. *J Gynecol Oncol.* 2018; 29(1):e4. doi:10.3802/jgo.2018.29.e4
- Loong HHF, Du N, Cheng C, et al. KRAS G12C mutations in Asia: A landscape analysis of 11,951 Chinese tumor samples. *Transl Lung Cancer Res.* 2020;9(5):1759–1769. doi:10.21037/tlcr-20-455
- Sui X, Xi X. *MCT1* gene silencing enhances the immune effect of dendritic cells on cervical cancer cells. *Adv Clin Exp Med.* 2024;33(7):739–749. doi:10.17219/acem/171446
- Guo CY, Xu XF, Wu JY, Liu SF. PCR-SSCP-DNA sequencing method in detecting *PTEN* gene mutation and its significance in human gastric cancer. *World J Gastroenterol.* 2008;14(24):3804. doi:10.3748/wjg.14.3804
- Ojesina AI, Lichtenstein L, Freeman SS, et al. Landscape of genomic alterations in cervical carcinomas. *Nature.* 2014;506(7488):371–375. doi:10.1038/nature12881
- Harima Y, Sawada S, Nagata K, Sougawa M, Ostapenko V, Ohnishi T. Mutation of the *PTEN* gene in advanced cervical cancer correlated with tumor progression and poor outcome after radiotherapy. *Int J Oncol.* 2001;18(3). doi:10.3892/ijo.18.3.493
- Shin J, Kim SH, Yoon J. PTEN downregulation induces apoptosis and cell cycle arrest in uterine cervical cancer cells. *Exp Ther Med.* 2021; 22(4):1100. doi:10.3892/etm.2021.10534
- Lou H, Villagran G, Boland JF, et al. Genome analysis of Latin American cervical cancer: Frequent activation of the PIK3CA pathway. *Clin Cancer Res.* 2015;21(23):5360–5370. doi:10.1158/1078-0432.CCR-14-1837