

Clinicopathological characterization of cervical squamous cell carcinoma with *PIK3CA* hotspot mutation: A single-institution study

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Abstract. *PIK3CA* serves a well-established role in carcinogenesis; however, although its prognostic importance in cervical squamous cell carcinoma (SCC) has been extensively studied, the results remain controversial. In the present single-institution study, the clinicopathological features of 207 cases of cervical SCC were characterized based on their *PIK3CA* hotspot mutational status. The prevalence of *PIK3CA* hotspot mutations in this cohort was 13% (27/207), with 96.3% (26/27) of mutations clustered in the helical domain (exon 9). Patients harboring *PIK3CA* mutations tended to be older, and the mutation rate was significantly higher among those aged ≥ 50 years compared with those aged < 50 years (18.4% vs. 8.3%, $P=0.031$). When stratified by stage, a trend toward a higher frequency of *PIK3CA* mutations was observed in patients with advanced-stage disease ($P=0.0575$), although this difference did not reach statistical significance. The mutation rate was 6.8% (5/74) among patients with stage I carcinoma and increased to 18.1% (19/105) among those with stage II or higher disease ($P=0.0284$). Nearly all patients with *PIK3CA*-mutant tumors (96%, 23/24) underwent chemotherapy and/or radiation therapy ($P=0.0089$). No statistically significant difference was observed between patients with *PIK3CA*-wildtype and *PIK3CA*-mutant tumors with respect to ethnicity, procedures performed at initial diagnosis or human

papillomavirus status. Programmed death-ligand 1 (PD-L1) expression (combined positive score ≥ 1) was observed in 76.3% of cervical SCC cases. However, immunohistochemical analysis did not reveal a statistically significant association between PD-L1 expression and *PIK3CA* mutation status. Furthermore, the results showed that *PIK3CA* mutations were not associated with the prognosis of patients with cervical SCC. The only factor significantly associated with the cause-specific survival and overall survival in this cohort was clinical stage. The present study highlights and expands upon the clinicopathological characteristics of cervical SCC with *PIK3CA* hotspot mutations in a single-institution cohort. Future studies should focus on evaluating the efficacy of PI3K inhibitors, alone or in combination with immunotherapy and other targeted treatments, in selected patients. This evaluation should be based on molecular alterations that may predict therapeutic benefit.

Introduction

Cervical cancer is one of the most common cancers among women globally, with an estimated 660,000 new cases and 350,000 deaths in 2022. Despite a decrease in incidence in well-developed countries due to effective preventive screening programs and vaccination, an estimated 13,360 new cases and 4,320 deaths from cervical cancer were reported in the U.S. in 2025 (1). Approximately 80-90% of cervical cancers are squamous cell carcinomas (SCCs), and more than 90-95% of these tumors are related to high-risk human papillomaviruses (HPVs), most commonly HPV16 and HPV18 (2,3). In the majority of cases, high-risk HPV DNA integrates into the host cell genome, resulting in persistent overexpression of the viral oncoproteins E6 and E7, which subsequently inactivate tumor suppressors p53 and RB1, respectively, and promote uncontrolled cell growth, genomic instability, and tumor development (4).

The evolution of invasive SCCs from their precursor lesions, namely, low-grade and high-grade squamous intraepithelial lesions (LSIL and HSIL), occurs in a stepwise fashion,

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as demonstrated in model systems (5). While HPV-related inactivation of p53 and RB1 represents the initial step of oncogenesis, somatic driver mutations accumulate as the disease progresses from precancerous stages to invasive carcinoma. Genome-wide analyses have revealed recurrent pathogenic mutations in cervical carcinomas, including *PIK3CA*, *EP300*, *FBXW7*, *PTEN*, *HLA-A/B*, *ARID1A*, *NFE2L2*, *KRAS*, *ERBB2/3*, and other less common mutations (6,7). Among these genes, *PIK3CA* mutations represent the most frequent genetic alteration in cervical SCCs (6,7).

The *PIK3CA* gene encodes the p110 α protein, which is the catalytic subunit of the phosphoinositide 3-kinase (PI3K) enzyme. PI3K is a lipid kinase generating lipid second messengers, which subsequently activate AKT and mTOR signaling cascades. This pathway is involved in numerous essential and pathogenic cellular processes, including cell proliferation and growth, survival, apoptosis, DNA damage repair, migration and motility, angiogenesis, and cancer metastasis (8,9). Mutations in *PIK3CA* lead to an overactive PI3K enzyme, potentially contributing to cancer development, metastasis, and therapeutic resistance. Notably, *PIK3CA* is one of the most frequently mutated genes in cancer (9), with most mutations occurring in the helical domain (exon 9) and the kinase domain (exon 20) (10). In cervical cancers, the reported *PIK3CA* mutation rate varies widely, ranging from 8.15% to 60.0% (11-32), underscoring its potential role in cervical cancer development and progression. While some studies suggest that *PIK3CA* mutation confers favorable survival outcomes, others have reported an association with poorer prognosis. In a meta-analysis comprising 12 articles and 2,196 women with cervical cancer, the authors demonstrated that the impact of *PIK3CA* mutations on survival outcomes remains inconclusive (33). To minimize confounding factors, we investigated the prevalence of *PIK3CA* hotspot mutations in pathology-confirmed SCCs in a single institution and correlated these mutations with clinicopathological features.

Materials and methods

Case selection. In-house cases were identified from the pathology archives of The Johns Hopkins Hospital between January 2000 and August 2023 by searching for 'squamous cell carcinoma' and 'cervix'. Patient demographics (including age and ethnicity), clinical presentations and histories, procedures, gross specimen descriptions, clinical courses, and follow-up information were retrieved and reviewed from electronic medical records. Histologic sections were independently re-reviewed by a board-certified gynecologic pathologist (D.X.) to confirm the diagnosis. This study was approved by the Institutional Review Board of The Johns Hopkins Hospital (approval no. IRB00223822).

HPV in situ hybridization. *In situ* hybridization (ISH) was performed using a high-risk HPV RNA probe solution (RNAscope, Advanced Cell Diagnostics, Newark, CA; HPV types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82) and type-specific probes for HPV16 and HPV18 (RNAscope, Advanced Cell Diagnostics, Newark, CA) (34). Additionally, ISHs for wide-spectrum HPV DNA (cocktail of HPV 6, 11, 16, 18, 31, 33, 45, 51, 52, Dako, Carpinteria,

CA), type-specific DNA probes for HPV16 and HPV18 (Dako, Carpinteria, CA), and high-risk HPV DNA (Ventana INFORM HPV III family 16 probe, HPV genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 66, Ventana, Tucson, AZ) had been performed on earlier cases at the time of diagnosis (35).

DNA extraction and polymerase chain reaction (PCR) and Sanger sequencing to detect hotspot mutations of the *PIK3CA* gene. DNA extraction was performed as described previously (34). The following primers were used to amplify *PIK3CA* exon 9, which includes hotspot mutations E542K and E545K: *PIK3CA*-9F1: 5'-GGGAAAAATATGACAAAGAAAGC-3'; *PIK3CA*-9F2: 5'-CAGAGTAACAGACTAGCTAG-3'; *PIK3CA*-9R1: 5'-GAGATCAGCCAAATTCAGTT-3'; *PIK3CA*-9R2: 5'-GAATCTCCATTTTAGCACTTAC-3'. The following primers were used to amplify *PIK3CA* exon 20, which includes hotspot mutation H1047R: *PIK3CA*-20F1: 5'-CTC TGGAATGCCAGAACTAC-3'; *PIK3CA*-20F2: 5'-ACATTC GAAAGACCCCTAGCC-3'; *PIK3CA*-20R1: 5'-TGTGGA ATCCAGAGTGAGCTT-3'; *PIK3CA*-20R2: 5'-CTTTTC AGTTCAATGCATGCTG-3'. First-round PCR amplification (*PIK3CA*-9F1/*PIK3CA*-9R1; *PIK3CA*-20F1/*PIK3CA*-20R1) was performed under the following conditions: an initial denaturation at 95°C for 2 min, followed by 30 cycles of 94°C for 30 sec, 51°C for 30 sec, and 72°C for 45 sec, with a final elongation at 72°C for 7 min. PCR products from the first round were diluted 10-fold and used as templates for a second PCR amplification (nested PCR) using another pair of primers (*PIK3CA*-9F2/*PIK3CA*-9R2; *PIK3CA*-20F2/*PIK3CA*-20R2). The second round PCR was carried out under similar reaction conditions except for an annealing temperature of 56°C. Sequencing of the purified PCR products was performed using the ABI 3730 High-Throughput DNA Sequencer. Mutations and variations were analyzed using Unipro UGENE software.

PD-L1 immunohistochemistry. Immunohistochemical staining for PD-L1 (mouse monoclonal, 22C3; Dako/Agilent, Santa Clara, CA) was performed on formalin-fixed, paraffin-embedded tissue sections as previously described (36).

Semi-quantitative assessment of PD-L1 protein expression. PD-L1 protein expression was assessed using the Combined Positive Score (CPS), which is calculated as the number of PD-L1-positive cells (including tumor cells, lymphocytes, and macrophages) relative to the total number of tumor cells (36).

Although the CPS can exceed 100, the maximum score is defined as 100. PD-L1 expression was interpreted as follows: CPS <1, no PD-L1 expression; CPS \geq 1, PD-L1 expression. CPS was independently assessed by three board-certified pathologists (J.M., C.S., and D.X.), and the average score with standard deviation was calculated. PD-L1 protein expression was also evaluated using the Tumor Proportion Score (TPS), which is calculated as the number of PD-L1-positive tumor cells relative to the total number of tumor cells (36).

Statistical analysis. Statistical methods were performed as described previously (37). The χ^2 test and Fisher's exact test were used to evaluate differences between categorical variables. The Wilcoxon rank-sum test was used to compare continuous

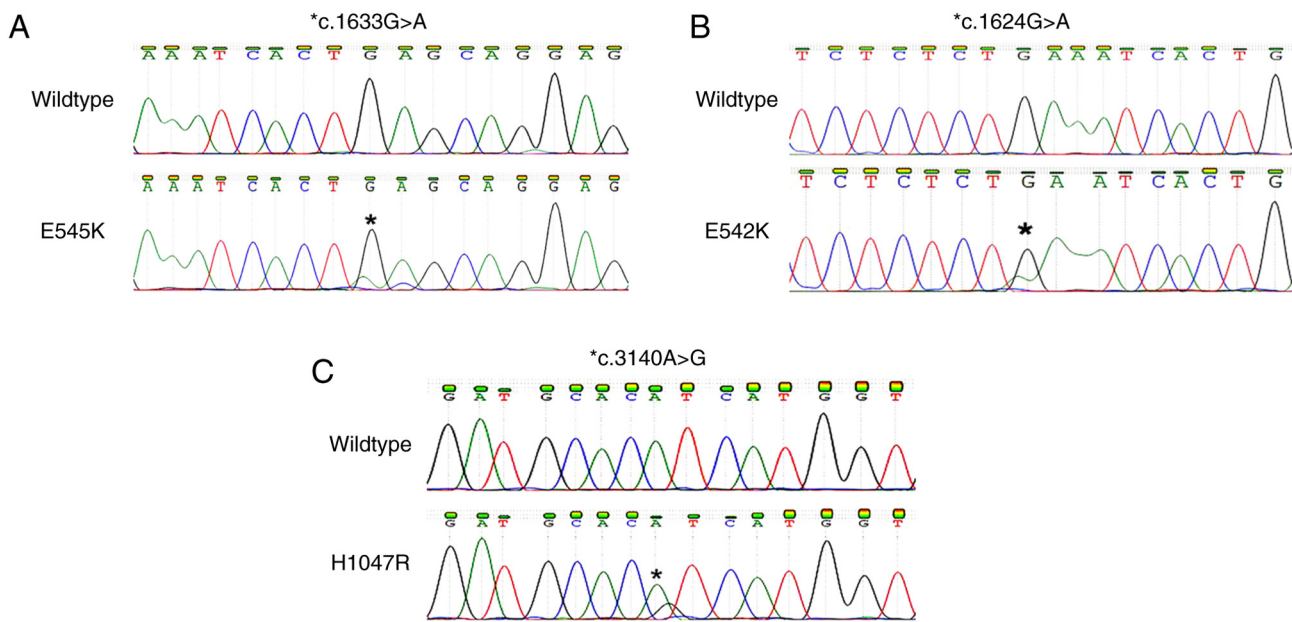


Figure 1. Representative *PIK3CA* mutations in cervical squamous cell carcinomas. (A) E545K (NM006218.4: c.1633G>A); (B) E542K (NM006218.4: c.1624G>A); (C) H1047R (NM006218.4: c.3140A>G). An asterisk (*) indicates a mutational site.

variables. Prognostic factors predictive of cause-specific survival (CSS) and overall survival (OS) were analyzed using univariate and multivariate Cox proportional hazards models. CSS and OS were calculated using the Kaplan-Meier method and compared using the log-rank test. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

***PIK3CA* hotspot mutations in cervical squamous cell carcinomas.** From 2000 to 2023, a total of 231 in-house cases of invasive cervical SCC were identified, and *PIK3CA* hotspot mutations were successfully analyzed in 207 cases. Sequencing of purified PCR products detected *PIK3CA* exon 9 mutations in 26 (12.6%) of the 207 cases, including 21 cases with an E545K mutation (Fig. 1A), 4 with an E542K mutation (Fig. 1B), and 1 with a T544I mutation. The H1047R hotspot mutation in exon 20 (Fig. 1C) was detected in only one case (0.5%). In total, 27 cases (13.0%) harbored *PIK3CA* hotspot mutations in this cohort. No case harbored two mutations.

Clinicopathological features of PIK3CA-wildtype and PIK3CA-mutant tumors. Clinicopathological features are summarized in Table I. In this cohort, patients with cervical SCC ranged in age from 23 to 86 years (median, 48 years). A similar age range was observed among patients with wild-type *PIK3CA*; in contrast, patients with mutant *PIK3CA* tended to be older (median, 54 years, $P = 0.1976$) and ranged in age from 26 to 79 years. When stratified by age, the mutation rate was significantly higher among patients aged ≥ 50 years compared with those < 50 years [18/98 (18.4%) vs. 9/109 (8.3%); $P = 0.0310$].

Of the 207 patients, clinical staging information was available in 179 cases, including 74 cases (41.3%) of stage I,

33 (18.4%) of stage II, 42 (23.5%) of stage III, and 30 (16.8%) of stage IV disease. When stratified by stage, a trend toward a higher frequency of *PIK3CA* mutations in patients with advanced-stage disease was observed ($P = 0.0575$), although the difference did not reach statistical significance. The mutation rate was 6.8% (5/74) among patients with stage I carcinoma, increasing to 18.1% (19/105) among those with stage II or higher disease ($P = 0.0284$). Chemoradiation data were available for 188 patients, and nearly all *PIK3CA*-mutant patients (96%, 23/24) underwent chemotherapy and/or radiation therapy ($P = 0.0089$).

Regarding ethnicity and procedures performed at the initial diagnosis, no statistically significant difference was observed between *PIK3CA*-wildtype and *PIK3CA*-mutant patients. Information on HPV infection was available in 197 cases, of which 90 (45.7%, Fig. 2A) were infected with HPV16, 21 (10.7%, Fig. 2B) with HPV18, and 64 (32.5%, Fig. 2C) with non-16/18 HPV subtypes. HPV signals were not detected by ISH in 22 cases (11.1%). HPV status appeared to be unrelated to *PIK3CA* mutation status ($P = 0.6816$). Specifically, 14 mutant cases were infected with HPV16, 1 with HPV18, and 8 with non-16/18 HPV subtypes.

PD-L1 expression in PIK3CA-wildtype and PIK3CA-mutant cases. A total of 59 cases (32 *PIK3CA*-wildtype and 27 *PIK3CA*-mutant) were tested for PD-L1 expression and then evaluated using both CPS and TPS. PD-L1 expression (CPS ≥ 1) was observed in 45 of 59 (76.3%) cervical SCCs (Fig. 3A and B), while 14 tumors showed no PD-L1 expression. In the *PIK3CA*-wildtype group, CPS values ranged from 0 to 95 (mean, 18.50), whereas in the *PIK3CA*-mutant group, scores ranged from 0 to 85 (mean, 12.07). No statistically significant difference was observed between the two groups ($P = 0.2784$; Fig. 3C). Similarly, TPS values did not differ significantly between *PIK3CA*-wildtype and *PIK3CA*-mutant cases (mean TPS: 13.31 vs. 8.67; $P = 0.3907$; Fig. 3D).

Table I. Clinicopathological characteristics.

Variable	Total	<i>PIK3CA</i> -wildtype	<i>PIK3CA</i> -mutant	P-value
N	207	180	27	
Median age at diagnosis, years (range)	48 (23-86)	48 (23-86)	54 (26-79)	0.1976
Age, n				0.0310
<50 years	109	100	9	
≥50 years	98	80	18	
Ethnicity, n				0.9485
White	106	92	14	
Black	74	64	10	
Other	27	24	3	
Clinical stage, cases with available information, n	179	155	24	
I	74	69	5	
II	33	28	5	
III	42	36	6	
IV	30	22	8	0.0575
I	74	69	5	
II + III + IV	105	86	19	0.0284
Procedure at diagnosis, n				0.4666
Biopsy	101	85	16	
Excision	25	23	2	
Hysterectomy	81	72	9	
Chemo and/or radiation, cases with available information, n	188	164	24	0.0089
Yes	139	116	23	
No	49	48	1	
HPV infection, cases with available information, n	197	171	26	
HPV16	90	76	14	
HPV18	21	20	1	
HPV-non16/18	64	56	8	
Not detected	22	19	3	0.6816
Follow-up				
N of available follow-up	198	173	25	
Median follow-up time, months (range)	30 (1-250)	32 (1-250)	24 (1-228)	0.1972

χ^2 , Fisher's exact test or Wilcoxon rank-sum test were applied to the P-value calculation.

Prognostic factors. Among the clinicopathological variables analyzed in this cervical SCC cohort, the only factor significantly associated with CSS by both univariate and multivariate analyses was clinical stage (Table II). Age, ethnicity, and HPV subtype were not associated with clinical outcome or prognosis. Although the presence of a *PIK3CA* mutation was correlated with older age and higher disease stage, it was not an independent prognostic factor for CSS. Similarly, both univariate and multivariate analyses indicated that clinical stage, but not age, HPV subtype, or *PIK3CA* mutation, was associated with OS (Table III). While Black patients showed poorer OS in the univariate analysis [hazard ratio (HR), 1.689; 95% confidence interval (CI), 1.047-2.724], ethnicity was no longer an independent prognostic factor in the multivariate analysis (HR, 1.242; 95% CI, 0.717-2.152). Consistently, Kaplan-Meier plots (Fig. 4) demonstrated significant differences in both CSS and OS according to clinical stage. However, no statistically

significant differences were observed between *PIK3CA* mutation status and either CSS or OS.

Discussion

In this study, we characterized the clinicopathological features of cervical SCC with *PIK3CA* mutations at a single institution, focusing primarily on the most common *PIK3CA* mutations in the helical domain (exon 9, E542K and E545K) and the kinase domain (exon 20, H1047R) (10,33). We found that the prevalence of *PIK3CA* hotspot mutations in this cohort was 13%, consistent with findings from several previous studies (6,11,20,24). However, our reported mutation rate is relatively lower than that observed in most other studies. The reasons for these differences remain unclear; however, Sanger sequencing of *PIK3CA* hotspot mutations, unlike next-generation sequencing, may underestimate the overall mutation rate, as these hotspot

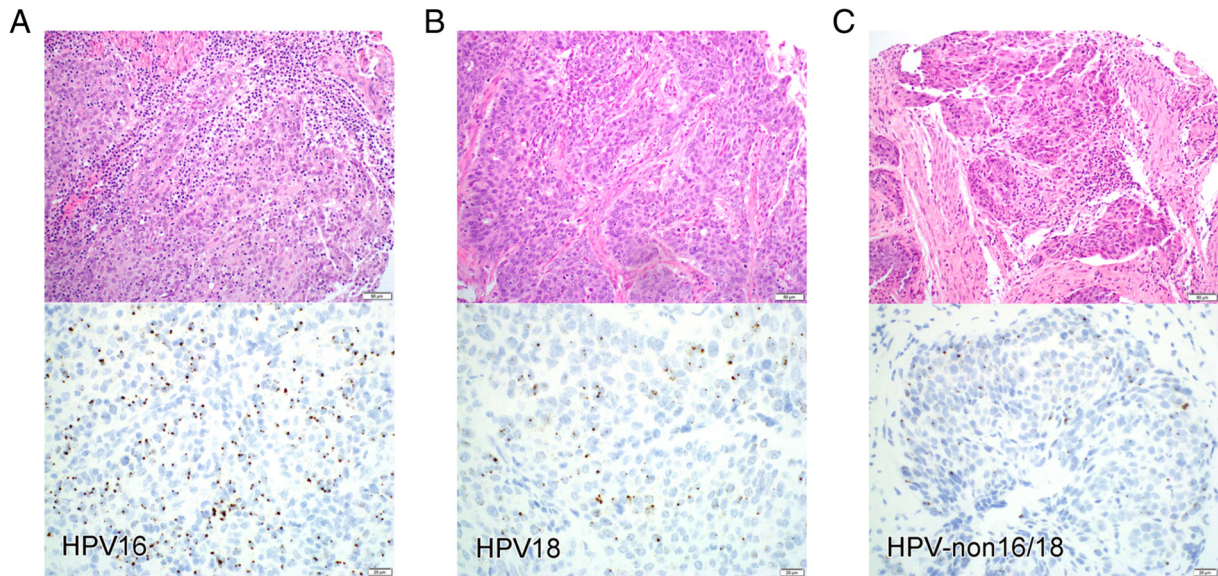


Figure 2. In situ hybridization detection of HPV infection in cervical squamous cell carcinoma. (A) HPV16; (B) HPV18; (C) non-16/18 HPV.

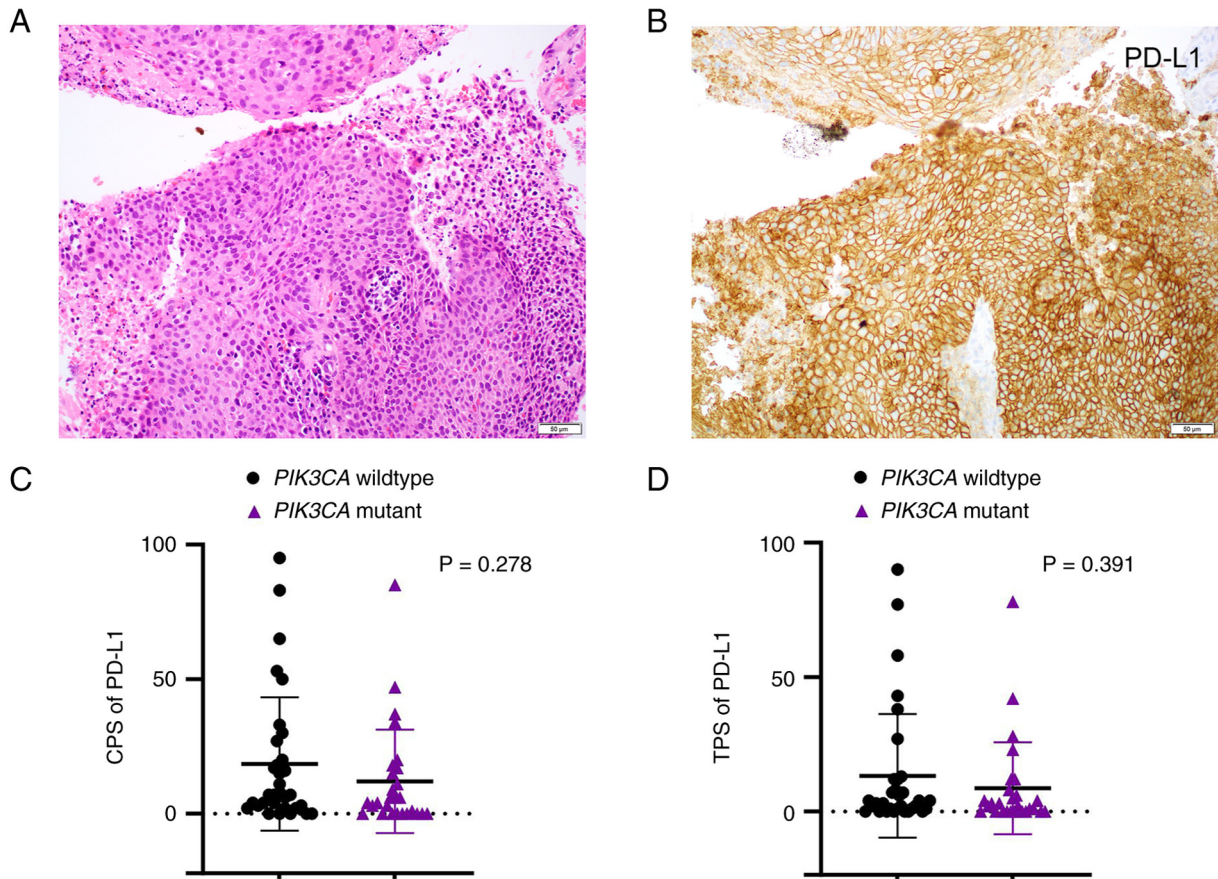


Figure 3. Semi-quantitative evaluation of PD-L1 expression in *PIK3CA*-wildtype and *PIK3CA*-mutant cervical SCC. Representative pictures show a (A) cervical SCC (B) with PD-L1 expression. (C) CPS and (D) TPS show no statistically significant difference between the two groups. CPS, combined positive score; SCC, squamous cell carcinoma; TPS, tumor proportion score.

mutations account for approximately 80% of all mutations in the gene (10,24,38,39). Other possible contributing factors include age distribution, ethnic heterogeneity, differences in tumor stage, and degradation of genomic material in archival formalin-fixed, paraffin-embedded (FFPE) tissues (11).

As an oncogene regulating the PI3K/AKT/mTOR pathway, *PIK3CA* is one of the most frequently mutated genes in human cancers. Consistent with previous investigations (11,16-18,24,38), we found that 96.3% (26/27) of mutations were clustered in the helical domain (exon 9),

Table II. Univariate and multivariate analysis of hazard ratio of cause specific survival.

Variable	Univariate		Multivariate	
	Hazard ratio	P-value	Hazard ratio	P-value
Age at diagnosis	0.994 (0.976, 1.013)	0.5272	0.985 (0.965, 1.005)	0.1379
Ethnicity				
White	Reference		Reference	
Black	1.464 (0.876, 2.448)	0.1459	1.069 (0.592, 1.931)	0.8249
Other	0.821 (0.352, 1.917)	0.6488	0.381 (0.128, 1.134)	0.0830
Clinical stage				
I	Reference		Reference	
II	8.171 (2.981, 22.393)	<0.0001	5.131 (1.445, 18.218)	0.0114
III	8.239 (3.010, 22.555)	<0.0001	5.519 (1.530, 19.914)	0.0091
IV	14.130 (5.460, 36.567)	<0.0001	7.279 (2.181, 24.293)	0.0012
HPV infection				
HPV16	Reference		Reference	
HPV18	0.301 (0.077, 1.170)	0.0830	0.433 (0.094, 1.997)	0.2828
HPV-non16/18	1.117 (0.667, 1.868)	0.6742	1.132 (0.590, 2.169)	0.7097
<i>PIK3CA</i>				
Wildtype	Reference		Reference	
Mutant	1.497 (0.761, 2.947)	0.2425	1.309 (0.610, 2.808)	0.4887

For the multivariate model, the N has decreased to 164 women.

Table III. Univariate and multivariate analysis of hazard ratio of overall survival.

Variable	Univariate		Multivariate	
	Hazard ratio	P-value	Hazard ratio	P-value
Age at diagnosis	1.002 (0.986, 1.019)	0.7877	0.996 (0.977, 1.015)	0.6688
Ethnicity				
White	Reference		Reference	
Black	1.689 (1.047, 2.724)	0.0316	1.242 (0.717, 2.152)	0.4398
Others	0.817 (0.348, 1.915)	0.6413	0.394 (0.129, 1.200)	0.1010
Clinical stage				
I	Reference		Reference	
II	5.791 (2.497, 13.427)	<0.0001	3.110 (1.213, 7.977)	0.0182
III	5.707 (2.399, 13.574)	<0.0001	3.102 (1.176, 8.180)	0.0221
IV	11.100 (5.198, 23.705)	<0.0001	4.672 (1.974, 11.059)	0.0005
HPV infection				
HPV16	Reference		Reference	
HPV18	0.282 (0.073, 1.095)	0.0675	0.433 (0.100, 1.876)	0.2631
HPV-non16/18	1.108 (0.676, 1.818)	0.6836	1.057 (0.567, 1.969)	0.8625
<i>PIK3CA</i>				
Wildtype	Reference		Reference	
Mutant	1.498 (0.790, 2.842)	0.2157	1.229 (0.615, 2.456)	0.5591

The N for multivariate model is 164.

whereas only one case (3.7%) harbored H1047R, a mutation in the kinase domain (exon 20). Our findings in cervical

cancer, as well as the findings in previous investigations (7), are similar to results reported in bladder cancer (40) and

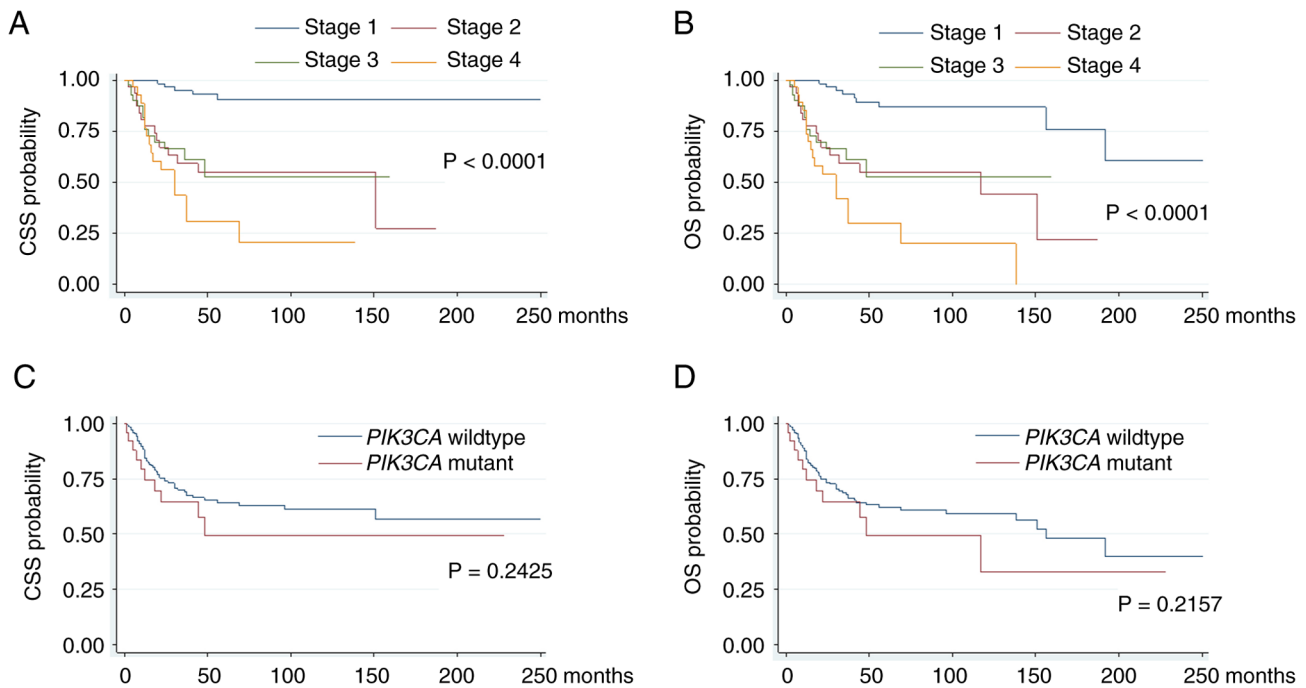


Figure 4. CSS and OS in cervical squamous cell carcinoma. Kaplan-Meier plots demonstrate significant differences in both (A) CSS and (B) OS according to clinical stage. However, no statistically significant differences were observed between *PIK3CA* mutation status and either (C) CSS or (D) OS. CSS, cause-specific survival; OS, overall survival.

HPV-associated head and neck cancers (41) but differ from observations in breast (42), endometrial (43), and many other cancers, which predominantly harbor *PIK3CA* mutations in the kinase domain. This distinct mutation profile may reflect the difference in etiology, cell-of-origin, and oncogenic mechanisms across different cancers (44,45). The helical domain of the *PIK3CA* protein (p110 α) has been shown to function as a scaffold that biochemically interacts with the inhibitory p85 α protein. Somatic mutations in this domain disrupt the inhibitory interface between the p110 α catalytic subunit and the p85 α regulatory subunit, releasing the enzyme from normal inhibitory control and resulting in enzymatic overactivity. This overactivity mimics a growth-factor-activated state and is highly dependent on the Ras-binding domain. In contrast, mutations in the kinase domain alter the protein's conformation, enhancing its affinity for substrates on the cell membrane, which increases kinase activity. This pathway functions independently of Ras. Regardless of the mutation sites, these variants directly affect the PI3K enzyme, leading to overactive AKT and subsequent mTOR activity, which promotes tumor growth, proliferation, and resistance to certain therapies. Given their different oncogenic potential and context-dependent crosstalk, mutations in the helical domain and kinase domain may respond differently to inhibitors (46-48), a factor that should be considered when designing targeted therapies for cervical SCC.

In this cohort, patients with mutant *PIK3CA* tended to be older, and the mutation rate was significantly higher among those aged ≥ 50 years compared with those < 50 years (18.4% vs. 8.3%, $P=0.031$). Because more than half of the patients were younger than 50 years, this age distribution may partly explain the relatively low *PIK3CA* mutation rate observed in this study. A similar correlation between age and

PIK3CA mutational status has been consistently reported in several studies (11,24), although the reason for this association remains unclear. Interestingly, although less common than the H1047R kinase domain mutation, helical domain hotspot mutations in breast cancer have also been associated with older age at diagnosis ($P=0.004$) (49). These observations in cervical SCC and breast cancer may highlight an age-associated link in the pathogenesis of *PIK3CA* helical domain hotspot mutations.

Although most studies have reported no correlation between *PIK3CA* mutations and tumor stage (16,20,24), our results showed that patients with higher-stage disease tended to harbor mutant *PIK3CA* ($P=0.0575$). When stratified by stage, patients with stage II or higher tumors had a significantly higher frequency of *PIK3CA* mutations than those with stage I tumors ($P=0.0284$). Consistent with their higher stage, nearly all *PIK3CA*-mutant patients (96%) in this cohort underwent chemotherapy and/or radiation therapy ($P=0.0089$). Another study also observed a similar trend between *PIK3CA* mutations and pT2-T3 staging, although the difference did not reach statistical significance ($P=0.078$) (23). *PIK3CA* somatic mutations have been postulated to represent a late event in cervical carcinogenesis, as these mutations are rarely detected in cervical intraepithelial neoplasia (38).

Some studies have reported an association between *PIK3CA* mutations and HPV16 infection (50). Consistent with previous studies (7), HPV16 was the most common HPV subtype among cervical SCCs in this cohort. However, our results indicated that HPV status was not associated with *PIK3CA* mutations. Although one study reported that American Indian and Alaska Native populations have the highest rate of *PIK3CA* mutations in cervical cancer (32), statistical analyses have shown no significant differences in *PIK3CA* mutation frequency by ethnicity, consistent with our findings.

Compared with single-agent chemotherapy, PD-1-blocking antibody-based immunotherapy significantly improves survival among patients with recurrent cervical cancer following first-line platinum-containing treatment (51). One study reported that *PIK3CA* mutations lead to increased mRNA and protein expression of PD-L1 in cervical cancer (52). To investigate the relationship between PD-L1 expression and *PIK3CA* mutation, we analyzed 59 cases of cervical SCC (32 *PIK3CA* wild-type and 27 *PIK3CA*-mutant). Consistent with previous studies (51), PD-L1 expression (CPS \geq 1) was observed in 76.3% of cervical SCCs. However, immunohistochemical analysis did not reveal a statistically significant association between PD-L1 expression and *PIK3CA* mutation. These findings suggest that *in vivo* PD-L1 expression may be regulated by complex mechanisms involving diverse genetic and epigenetic alterations. Notably, although PD-L1 expression was observed in more than 75% of samples in our series, the lack of correlation with *PIK3CA* mutational status may reflect the limited sample size (n=59), resulting in an underpowered subset analysis. Future studies involving all cases, with evaluation of PD-L1 expression and assessment of its relationship with clinical outcomes, are warranted.

In our study, *PIK3CA* mutations were not associated with the prognosis of cervical SCCs. The only factor significantly correlated with the CSS and OS in this cohort was clinical stage. *PIK3CA* plays a well-established role in carcinogenesis; although its prognostic significance in cervical SCC has been extensively investigated, the results remain controversial. Some studies, including the largest to date (771 cases), have reported that the presence of *PIK3CA* mutations is associated with significantly better clinical outcomes (11-15), whereas others have identified *PIK3CA* mutations as a poor prognostic factor linked to unfavorable survival (16-20). In contrast, several investigations, including the present study, have demonstrated no association between *PIK3CA* mutations and survival outcomes (21-25). Multiple factors, including tumor stage, patient demographics, mutation subtype, and treatment modalities, may contribute to these discrepancies. Interestingly, in a phase II study evaluating the long-term efficacy and survival outcomes of sintilimab (a monoclonal antibody targeting PD-1) in combination with anlotinib (a multikinase inhibitor with broad inhibitory effects on tumor angiogenesis and growth) in patients with PD-L1-positive recurrent or metastatic cervical cancer, *PIK3CA* mutation was identified as an independent favorable prognostic factor for OS (15). Similarly, another phase II study demonstrated that patients with *PIK3CA* mutations treated with camrelizumab (a PD-1 inhibitor) in combination with apatinib (a vascular endothelial growth factor receptor-2 inhibitor) experienced significantly improved progression-free survival and OS (12,14). These clinical trial-based studies suggest that activation of the PI3K/AKT/mTOR pathway through *PIK3CA* mutation may represent a promising indicator for response to immunotherapy.

However, our study has certain limitations. First, as mentioned above, targeted Sanger sequencing of *PIK3CA* hotspot mutations may underestimate the overall mutation rate. This Sanger sequencing-based analysis is limited by its sensitivity in detecting mutant allele frequencies of approximately 80 to 85%, which may miss a subset of low-level mosaic mutations below 15 to 20% (53,54). Ideally, next-generation sequencing should be

used to investigate the mutational profile in these tumors. The application of advanced molecular techniques not only allows for a thorough investigation of all possible pathogenic mutations across the entire *PIK3CA* gene but also helps identify a mutational landscape that may involve other key genes in the PI3K/AKT/mTOR pathway or crosstalk with other carcinogenic pathways (21,26). Second, although a single-institution study with a sizable case number and centralized pathology review helps minimize heterogeneity in patient population and tumor characteristics, our findings may still be influenced by local variations in patient demographics and treatment approaches, thereby reducing generalizability. Regional and demographic differences may affect mutation frequencies and clinical outcomes. Notably, 41.3% of patients in this cohort had stage I disease, and most were cured after treatment at our tertiary care center. The high proportion of stage I patients and the relatively low frequency of *PIK3CA* mutations in this group may have confounded the analysis of survival outcomes. Third, in addition to somatic mutations, *PIK3CA* gene expression and copy number variation may also affect the downstream pathway. These alterations were not investigated in our cases. Although the relationship between *PIK3CA* gene expression and mutation has been reported, the findings remain inconclusive (55,56). Given its clinicopathological focus, the functional validation of *PIK3CA* gene expression and mutations was not performed in this study. Future studies incorporating these analyses may provide a more comprehensive understanding of the role of the PI3K/AKT/mTOR pathway in cervical cancer development, progression, and treatment. Finally, as with other retrospective studies, selection bias may be present in our cohort due to reliance on existing clinical data. In particular, therapeutic strategy may have varied over time, contributing to treatment heterogeneity.

In summary, despite certain limitations, our study highlights and expands upon the clinicopathological characteristics of cervical SCCs with *PIK3CA* hotspot mutations within a single-institution cohort. We further demonstrate that *PIK3CA* helical domain mutations are more frequently observed in tumors from older patients and are associated with higher tumor stage. Nearly all patients harboring *PIK3CA* mutations underwent chemoradiation therapy; however, the mutation was not an independent prognostic factor in this cohort. Additionally, PD-L1 expression appears to be unrelated to *PIK3CA* mutational status. Future studies should focus on evaluating the efficacy of PI3K inhibitors alone or in combination with immunotherapy and other targeted treatments in selected patients, based on molecular alterations that may predict therapeutic benefit.

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Availability of data and materials

The *PIK3CA* gene mutational profile data generated in the present study may be found in the NCBI ClinVar database under accession numbers SCV007346396, SCV007346397, SCV007346398 and SCV007346399 or at the following URLs: <https://www.ncbi.nlm.nih.gov/clinvar/variation/13655/?term=SCV007346396>; <https://www.ncbi.nlm.nih.gov/clinvar/variation/31944/?term=SCV007346397>; <https://www.ncbi.nlm.nih.gov/clinvar/variation/4690213/?term=SCV007346398>; <https://www.ncbi.nlm.nih.gov/clinvar/variation/13652/?term=SCV007346399>. The other data generated in the present study may be requested from the corresponding author.

Authors' contributions

JM, HK, CS, TCW and DX conceived and designed the study, and participated in acquisition of data. JM, HK, CS, AAW, LSF, YCT, CFH, TCW and DX participated in ancillary analysis (Sanger sequencing and immunohistochemistry) and interpretation of data. DX wrote the draft of the manuscript. JM, HK, CS, LSF, TCW and DX reviewed and revised the manuscript. TCW and DX supervised the study. JM and DX confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board at The Johns Hopkins University/Hospital (approval no. IRB00223822). Patient consent was waived by JHU IRB policy since this is minimal-risk research using/involving secondary material for which consent is not required.

Patient consent for publication

Not applicable.

Competing interests

Not applicable.

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