REVIEW

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Emerging Insights into Comparative Genetic Mutations in HPV-Associated and HPV-Independent Cervical Cancer: A Systematic Review

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Abstract

Objective: Cervical cancer remains a major global health burden and is predominantly associated with human papillomavirus (HPV) infection. However, a subset of tumors develops independently of HPV, and their molecular characteristics are not fully understood. This study aimed to synthesize and compare the frequency of somatic mutations across key oncogenic pathways, *p53, PI3K-Akt-mTOR, AMPK*, and *Ras-Raf-MAPK*, in HPV-associated and HPV-independent cervical cancers. **Methods:** A systematic review was conducted following PRISMA guidelines and registered in PROSPERO (CRD420251044316). Comprehensive searches were performed in PubMed, EMBASE, LILACS, Web of Science, Scopus, CINAHL, and Cochrane Central from January 2016 to March 2025 using controlled descriptors related to cervical cancer, somatic mutations, and HPV status. Eligible studies included observational designs reporting cervical cancers with molecular HPV testing and somatic mutation profiling. Data extraction was conducted independently by multiple reviewers and validated by a senior author. Study quality was assessed using STROBE criteria. Extracted variables encompassed sample characteristics, HPV status, sequencing method, genes assessed, and mutation frequencies. **Results:** Eleven studies comprising 3,479 cervical cancer samples met the inclusion criteria, including 468 (13.4%) HPV-independent tumors. HPV-independent cancers demonstrated higher frequencies of *TP53* and *CDKN2A* mutations, reaching up to 50% and 37.5%, respectively. Alterations in the *PI3K-Akt-mTOR* pathway, particularly *PIK3CA* and *PTEN*, showed heterogeneous patterns, with some studies reporting higher prevalence in HPV-independent tumors and others in HPV-associated tumors. Mutations in *ERBB3, NTRK1, ITGB3, TSC2,* and TERT were more frequent in HPV-associated cancers, while *NTRK3* and *RICTOR* alterations appeared more common in HPV-independent tumors, although these findings were generally reported in isolated studies. Inconsistencies were also observed for *STK11* (*AMPK* pathway) and *KRAS* (*Ras-Raf-MAPK* pathway). Considerable methodological variability limited cross-study comparability. **Conclusions:** HPV-independent cervical cancers may represent a distinct molecular subgroup, particularly regarding the *p53* pathway; however, study heterogeneity limits firm conclusions. Further standardized genomic studies are needed.

Keywords: Cervical cancer, HPV-independent, Somatic mutations, Oncogenic pathways, Molecular heterogeneity

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Introduction

Cervical cancer is the fourth most common cancer in terms of both incidence and mortality in women, with an estimated 660,000 new cases and 350,000 deaths worldwide in 2022. Rates remain disproportionately high in transitioning versus transitioned countries (19.3 vs. 12.1 per 100,000 for incidence, respectively; 12.4 vs. 4.8 per 100,000 for mortality, respectively), in part reflecting the higher prevalence of chronic HPV (human Papillomavirus) infection also with limited access to screening and vaccination in transitioning countries [1].

Persistent infection with HPV, particularly high-risk oncogenic types (hrHPV), is widely recognized as the primary etiological factor in the development of cervical cancer [2, 3]. Approximately 90% of cervical cancer cases are attributable to hrHPV infection [4, 5]. Since the identification of HPV as a principal causal agent of cervical cancer in the early 1980s [6], research has predominantly focused on HPV DNA-positive tumors, with the aim of improving diagnostic tools, prophylactic vaccination, and targeted therapeutic strategies [7].

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Nevertheless, despite notable advances in the sensitivity of hrHPV testing, an estimated 5.5% to 11% of cervical cancers are reported to be HPV DNA-negative [8, 9]. The prevalence of HPV-negative tumors varies by histological subtype: while squamous cell carcinomas are rarely HPV-negative, adenocarcinomas show HPV DNA negativity in approximately 15% to 38% of cases [8, 10]. These HPV-negative tumors are currently classified by the World Health Organization (WHO) as HPV-independent cervical cancers [11] and are expected to persist even in the post-HPV vaccination era [7, 9]. At present, no therapies have been specifically developed for HPV-independent cervical cancer, and clinical management remains based on treatment protocols designed for HPV-associated disease [12].

HPV-independent cervical cancers are generally classified as either truly HPV-negative or false-negative cases [9]. Although there is no universally accepted definition, some authors propose restricting the term "HPV-independent" to primary cervical cancers for which no plausible explanation for a false-negative hrHPV test can be identified [9, 12]. Importantly, the sensitivity and specificity of HPV detection vary across testing platforms and assay types, contributing to the potential for false-negative results [9]. Additional factors that may lead to false-negativity include the integration of HPV DNA into the host genome [13, 14], low viral loads in latent infections [4], infections caused by non-high-risk HPV types not targeted by conventional assays [5, 8], and inadequate sampling or other pre-analytical limitations [15-17]. Despite these considerations, truly HPV-independent cervical cancers are hypothesized to represent a biologically distinct subgroup, associated with more aggressive clinical behavior and poorer prognosis compared to HPV-associated tumors [18, 19]. Despite these insights, the molecular and clinical characteristics of HPV-independent cervical cancers remain poorly understood [7].

Cancer is fundamentally a disease of molecular dysregulation, involving the alteration of numerous genes that drive carcinogenic processes. The identification of specific gene signatures holds promise for the discovery of diagnostic and prognostic biomarkers, as well as for the development of novel therapeutic targets. In this context, studies investigating the presence or absence of somatic mutations in cervical cancer may reveal associations with clinical outcomes and potential therapeutic responsiveness [20, 21]. Several signaling pathways have been extensively implicated in cervical carcinogenesis, particularly in HPV-associated tumors, including the *p53*, *PI3K-Akt, mTOR, AMPK, Ras, Raf,* and *MAPK* pathways [22-24]. These pathways regulate key cellular processes such as proliferation, survival, migration, and therapy resistance [25, 26]. For instance, *TP53* mutations are strongly associated with poor prognosis in cervical cancer [27, 28], while alterations in genes such as *PIK3CA*, *TP53*, *KRAS*, *PTEN*, and *STK11* contribute to tumor growth and metastatic potential [20, 29]. However, in HPV-independent cervical cancers, the molecular mechanisms underlying tumorigenesis and the mutational profile remain largely unexplored.

Thus, although the mutational profile of HPV-independent cervical cancers is critical for improving diagnostic accuracy, informing personalized treatment strategies, and optimizing prevention and screening efforts, to the best of our knowledge, no recent systematic review has been conducted addressing these aspects. Therefore, the aim of this systematic review is to synthesize and comparatively analyze the frequency of somatic mutations in major oncogenic pathwaysincluding *p53*, *PI3K-Akt-mTOR*, *AMPK*, and *Ras-Raf-MAPK*, in HPV-associated versus HPV-independent cervical cancers.

Materials and Methods

The review protocol was registered with the National Institutes of Health Research International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD420251044316).

Search Strategy

This systematic review was conducted following the PRISMA checklist (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [30] (Supplementary material). The review proposes to answer the question: What is the genetic mutation profile in HPV-independent cervical cancer compared with HPV-associated? For this, PICO strategy (participants, intervention, comparisons, outcomes) was proposed. (P) Patients with a diagnosis of HPV-independent cervical cancer (HPV not detectable); (I) Genetic mutations, including somatic alterations; (C) Patients with a diagnosis of HPV-associated cervical cancer (HPV detectable); (O) Frequency of somatic mutation in HPV-independent and HPV-associated cervical cancers in cancer pathways (genetic mutations for each specific gene).

Eligibility Criteria

This review did not apply language restrictions; however, only studies with an available abstract were included. Literature searches were conducted in the following databases: PubMed, EMBASE, LILACS, Web of Science, Scopus, CINAHL, and the Cochrane Central Register of Controlled Trials, covering publications from January 2016 to March 2025.

The descriptors were divided into three blocks and combined with the Boolean operator AND. Keywords and MeSH terms used for the search included: ("Uterine Cervical Neoplasms" OR "Cervical cancer") AND ("DNA Mutational Analysis" OR "Genomic Characterization") AND ("Papillomavirus Infections" OR "HPV-negative" OR "HPV-independent"). Search results were exported to a reference manager, and duplicates were removed before screening. To identify additional articles, the authors searched the references during the eligibility assessment phase of full-text articles and conducted a hand search.

Study Selection

Publications were retrieved and independently screened by title, abstract, and full-text version. Reviewers (ABCS, LEFM, LRC, and MVFS) applied predefined inclusion criteria to select potential studies including:

cervical cancer samples with an HPV molecular test; genomic profile or genetic mutation analyzed; comparison between HPV-associated group and HPV-independent group; frequency of somatic mutation in groups.

Only observational studies were included. Review articles, comments, editorials, letters, interviews, news, congress abstracts, guidelines, in vitro studies, errata publications, books and duplicates were excluded. Any disagreements were resolved through discussion with the senior author (MELC). Reference lists of the retrieved articles were also reviewed to ensure the sensitivity of the search strategy, and additional free searches were performed. To ensure that all relevant data from each study were included, a final consensus was reached after a second review by two experts (VRSS, MELC). Following this, the most relevant papers based on the study descriptors were selected for data extraction.

Data Extraction and Management

Data extraction and validation were performed by reviewers (ABCS, LEFM, LRC, and MVFS). Key information was captured, such as sample size, age, sample type, HPV status, clinicopathological features, genes studied, and the frequency of genetic mutations. All extracted data were subsequently validated by the senior author (MELC). The extracted data were analyzed and organized using Excel™ to present the relevant information in a structured format.

Quality Assessment of Included Studies

The quality of the included studies was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [31]. Based on this assessment, no studies were excluded from the review. The results of the quality assessment were presented using a plot generated by the Risk of Bias visualization tool (ROBVIS) [32].

Results

Study selection and characteristics

The study selection process is summarized in Figure 1. A total of 44 articles were retrieved after the duplicates were removed, for screening the titles and abstracts. The selected publications were retrieved for later assessment. Finally, 11 studies were included in this review [33-43].

Table 1 summarizes the main general characteristics of the cervical cancer cases, including both HPV-associated and HPV-independent tumors, reported in the included studies. A total of 3,479 cervical cancer samples were analyzed for somatic mutations, of which 468 (13.4%) were classified as HPV-independent. The majority of the cases involved tumor tissues preserved as formalin-fixed, paraffin-embedded (FFPE) specimens [33, 34, 36-41, 43]. Additionally, three studies incorporated cohorts from publicly available datasets in The Cancer Genome Atlas (TCGA), either alone or in combination with clinical patient samples [35, 42, 43].

All studies described the histopathologic classification of the tumors. Out of the 11 articles included, 6 exclusively analyzed adenocarcinomas[36-41]. Five studies investigated adenocarcinomas, squamous cell carcinomas, and/or adenosquamous carcinomas together [33-35, 42, 43].

Five studies reported the overall mean age of the women in the analyzed cases, which ranged from 46.7 to 50.9 years [35, 36, 40, 41, 43]. Six studies compared the mean age of women across groups stratified by HPV

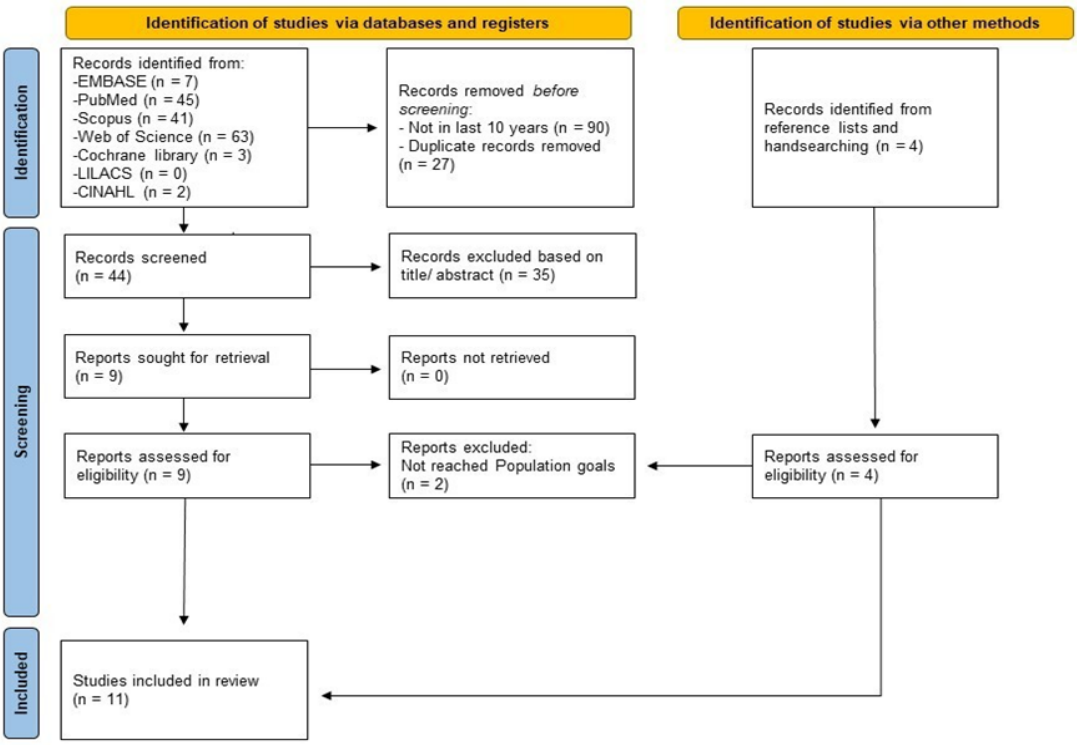

Figure 1. Workflow for the Selection of Studies, According to PRISMA Guidelines [30].

Table 1. Main Characteristics of HPV-Associated and HPV-Independent Cervical Cancer Cases Reported in the Included Studies

Author/Year/Reference	Sample type	Sample Size (n, %)	Histopathologic types (n)	HPV-independent histopathologic types (%)
Annunziata et al. 2018 [33]	Tissue tumor and FFPE	Total: 125 (100.0) HPV-independent: 31 (24.8)	SCC: 101 AD: 24	SCC: 24.8 AD: 25.0
Jiang et al. 2028 [34]	Tissue tumor	Total: 876 (100.0) HPV-independent: 245 (28.0)	SCC: NI AD: NI ASC: NI Others: NI	NI
Zhang et al. 2019 [35]	TCGA cohort*	Total: 299 (100.0) HPV-independent: 21 (7.0)	SCC: 248 AD: 46 ASC: 5	SCC: 4.8 AD: 15.2 ASC: 40
Hirose et al. 2019 [36]	FFPE	Total: 154 (100.0) HPV-independent: 15 (9.7)	SCC: NI AD: NI ASC: NI Neuroendocrine carcinoma: NI	NI
Hodgson et al. 2020 [37]	FFPE	Total: 56 (100.0) HPV-independent: 11 (20.0)	AD: 56	Gastrictype AD: 20.0
Jenkins et al. 2020 [38]	FFPE	Total: 45 (100.0)) HPV-independent: 27 (60.0)	AD: 45	Endometrioid carcinoma: 17.7 Serous carcinoma: 24 Gastric type AD: 13.3 Clear cell carcinoma: 6.6 Not other wise specified:11.1 Usual AD: 4.4
Jung et al. 2020 [39]	FFPE	Total: 18 (100.0) HPV-independent: 8 (44.4)	AD: 18	Gastric AD: 44.4
Zang et al. 2020 [40]	Tissue tumor	Total: 24 (100.0) HPV-independent: 17 (70.8)	AD: 24	NI
Ren et al. 2021 [41]	FFPE	Total: 100 (100.0) HPV-independent: 15 (15.0)	AD: 100	Gastric AD: 9.0 Mesonephric carcinoma: 4.0 Clear cell carcinoma: 1.0 Not otherwise specified: 1.0
Ruiz et al. 2021 [42]	TCGA cohort*	Total: 465 (100.0) HPV-independent: 35 (7.5)	SCC: 369 AD: 78 ASC:13 Neuroendocrine carcinoma: 1 Smallcell carcinoma: 3	SCC: 3.4 AD: 3. ASC: 0.4 Small cell carcinoma: 0.4
Wang et al. 2024 [43]	TCGA cohort*	Total: 307 (100.0) HPV-independent: 18 (5.8)	SCC: 254 AD: 48 ASC: 5	SCC: 2.9 AD: 1.9 ASC: 1.0

FFPE, paraffin-embedded specimens; TCGA, The Cancer Genome Atlas; HPV, human Papillomavirus; NI, not informed; SCC, Squamous cell carcinoma; AD, Adenocarcinoma; ASC, adenosquamous carcinoma.

status. The reported mean age for the HPV-independent group ranged from 44.2 to 60.2 years, whereas for the HPV-associated group, it ranged from 43.0 to 54.1 years [35, 37, 39-41, 43]. More specifically, five of the six studies[35, 37, 40, 41, 43] reported a higher mean age at diagnosis in the HPV-independent group compared to the HPV-associated group, which is a consistent finding across the literature [15, 44].

Assessment of study quality

Adherence to STROBE recommendations was assessed and displayed in Figure 2 and Figure 3. The methodological assessment presented varied risks between the 11 studies across the different domains analyzed. Most studies presented low risk across most domains assessed, reflecting overall good methodological quality.

Overall somatic mutations of cervical cancers

Focusing on somatic mutations, all included studies compared the frequency of mutations of different genes between HPV-associated and HPV-independent groups. Eight studies performed genomic characterization, analyzing two or more genes [35-42]. Three studies analyzed mutations in only one specific gene [33, 34, 43].

Subsequent analyses focused on comparing the frequencies of somatic gene mutations between HPV-independent and HPV-associated cervical cancer cases, emphasizing key signaling pathways implicated in cervical tumorigenesis, including *p53, PI3K-Akt/mTOR, AMPK,* and the *Ras-Raf-MAPK* cascade (Figure 4). Table 2 summarizes mutation frequencies in both groups, with the following sections presenting a detailed pathway-focused analysis and discussion of these genetic mutations.

Discussion

Somatic mutations of p53 signaling pathway

Briefly, the *p53* signaling pathway is a key tumor suppressor mechanism that orchestrates cellular responses to various stress signals, particularly DNA damage. At its

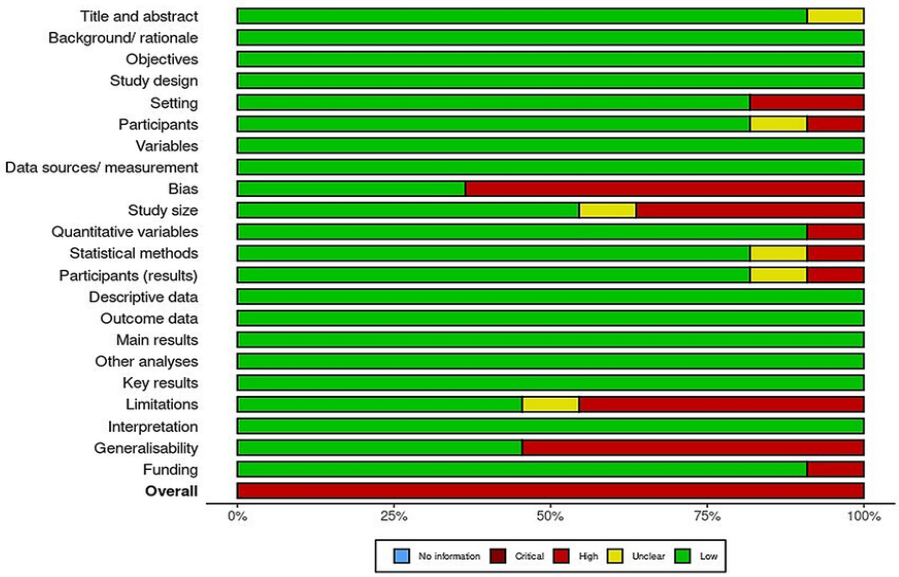

Figure 2. Adherence to STROBE Recommendations

core is the *TP53* gene, which encodes the *p53* protein, a transcription factor that regulates genes involved in cell cycle arrest (e.g., *CDKN1A/p21*), DNA repair (*GADD45*), apoptosis (*BAX, PUMA, NOXA*), and senescence. Under normal conditions, *p53* is kept at low levels through ubiquitination and degradation mediated by its negative regulators, *MDM2* and *MDM4*. In response to genotoxic stress, upstream kinases such as *ATM* and *ATR* phosphorylate *p53* and *MDM2*, leading to *p53* stabilization and activation [45, 46]. Other critical regulators include *ARF* (encoded by *CDKN2A*), which inhibits *MDM2* and enhances *p53* activation, particularly under oncogenic stress. Disruption of this pathway is a common hallmark in cancer, occurring through *TP53* mutations, overexpression of *MDM2*/*MDM4*, deletion or inactivation of *CDKN2A*, or defects in DNA damage sensors like *ATM* and *CHK2* (Figure 4). Loss of *p53* function results in impaired DNA damage response, evasion of apoptosis, and increased genomic instability, all of which contribute to tumor initiation and progression [47, 48].

Among the molecular pathways analyzed, the *p53* signaling pathway emerged as one of the most extensively examined for somatic mutations in HPV-associated and HPV-independent cervical cancers in the studies included in this systematic review (January 2016 to March 2025). Of eleven studies, seven compared *TP53* mutation status between these groups[35-39, 41, 42]. Six reported a significantly higher prevalence of *TP53* mutations in HPV-independent tumors [35-38, 41, 42]. Specifically, mutation rates in the HPV-independent group reached up to 50.0%, while in the HPV-associated group they were as high as 11.1%. Only one study [39] reported comparable

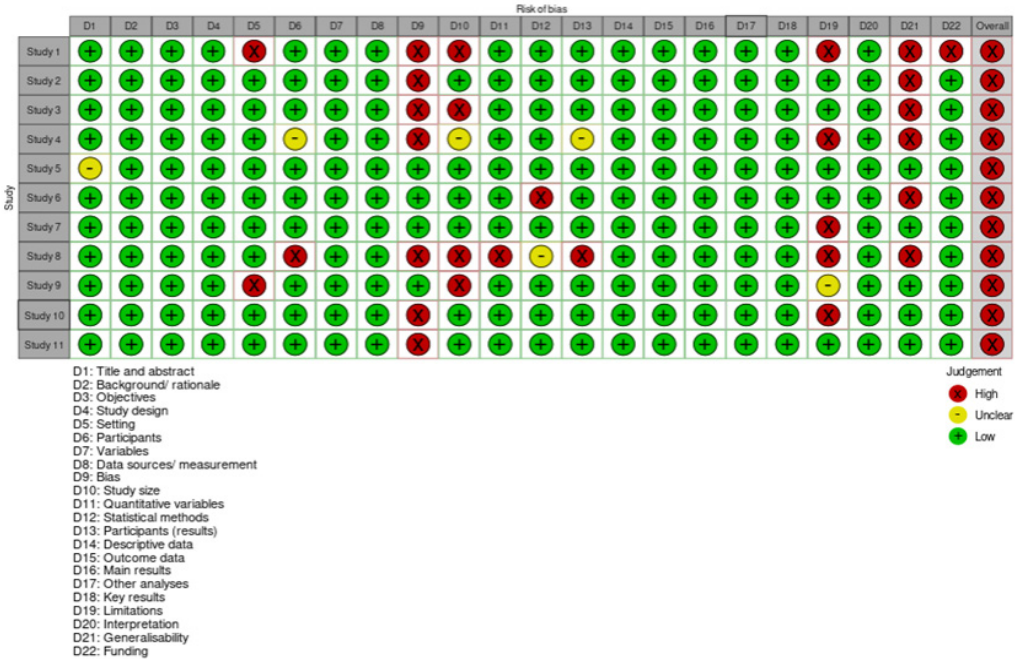

Figure 3. Adherence to STROBE Recommendations Table Format.

Table 2. Comparative Frequency of Mutated Genes between HPV-Associated and HPV-Independent Cervical Cancers

Author/Year/Reference	Studied genes classified into specific pathway				HPV-associated group mutation (%)	HPV-independent group mutation (%)
	p53	*PI3K/ Akt/ mTOR*	*AMPK*	*Ras/ Raf/ MAPK*		
Annunziata et al. 2018 [33]	NA	*TERT*	NA	NA	*TERT* (20.2)	*TERT* (12.9)
Jiang et al. 2028 [34]	NA	NA	NA	*KRAS*	*KRAS* (8.1)	*KRAS* (3.7)
Zhang et al. 2019 [35]	*TP53*	*PIK3CA*	NA	NA	*PIK3CA* (31.1) *TP53* (3.9)	*PIK3CA* (52.3) *TP53* (47.6)
Hirose et al. 2019 [36]	*TP53*	*PIK3CA* *PTEN*	*STK11*	*KRAS*	*KRAS* (7.9) *PIK3CA* (31.6) *PTEN* (6.4) *STK11* (2.1) *TP53* (7.2)	*KRAS* (6.6) *PIK3CA* (13.3) *PTEN* (0.0) *STK11* (6.6) *TP53* (46.7)
Hodgson et al. 2020 [37]	*ATM CDK-N2A CHEK2* *TP53*	*ERBB2 ERBB3* *NTRK1 NTRK3* *PIK3CA* *TSC2*	*STK11*	*KRAS MAP2K2*	*ATM* (0.0) *CDKN2A* (2.0) *CHEK2* (4.0) *ERBB2* (11.0) *ERBB3* (4.0) *KRAS* (13.0) *MAP2K2* (4.0) *NTRK1* (4.0) *NTRK3* (0.0) *PIK3CA* (16.0) *STK11* (4.0) *TP53* (11.0) *TSC2* (4.0)	*ATM* (18.0) *CDKN2A* (27.0) *CHEK2* (0.0) *ERBB2* (9.0) *ERBB3* (0.0) *KRAS* (36.0) *MAP2K2* (0.0) *NTRK1* (0.0) *NTRK3* (18.0) *PIK3CA* (18.0) *STK11* (27.0) *TP53* (46.0) *TSC2* (0.0)
Jenkins et al. 2020 [38]	*CDKN2A* *TP53*	*AKT1* *PIK3CA PTEN*	*STK11*	*KRAS NRAS*	*AKT1* (11.1) *CDKN2A* (0.0) *KRAS* (11.1) *NRAS* (5.5) *PIK3CA* (22.2) *PTEN* (0.0) *STK11* (0.0) *TP53* (11.1)	*AKT1* (7.4) *CDKN2A* (14.8) *KRAS* (18.5) *NRAS* (0.0) *PIK3CA* (33.3) *PTEN* (22.2) *STK11* (7.4) *TP53* (44.4)
Jung et al. 2020 [39]	*CDKN2A* *MDM2* *TP53*	*PIK3CA*	*STK11*	*HRAS KRAS* *NF1*	*CDKN2A* (0.0) *HRAS* (10.0) *KRAS* (0.0) *MDM2* (0.0) *NF1* (0.0) *PIK3CA* (20.0) *STK11* (0.0) *TP53* (20.0)	*CDKN2A* (37.5) *HRAS* (0.0) *KRAS* (25.0) *MDM2* (12.5) *NF1* (25.0) *PIK3CA* (0.0) *STK11* (12.5) *TP53* (25.0)
Zang et al. 2020 [40]	*HUWE1*	*ITGB3*	NA	NA	*HUWE1* (14.3) *ITGB3* (42.9)	*HUWE1* (70.6) *ITGB3* (0.0)
Ren et al. 2021 [41]	*TP53*	*AKT* *ERBB2* *PIK3CA*	*STK11*	*BRAF KRAS* *ROS1*	*AKT* (2.0) *BRAF* (2.0) *ERBB2* (4.0) *KRAS* (24.0) *PIK3CA* (20.0) *ROS1* (2.0) *STK11* (0.0) *TP53* (4.0)	*AKT* (0.0) *BRAF* (0.0) *ERBB2* (12.0) *KRAS* (12.0) *PIK3CA* (6.0) ROS1 (0.0) *STK11* (6.0) *TP53* (31.0)
Ruiz et al. 2021 [42]	*TP53*	*RICTOR* *PTEN*	NA	NA	*RICTOR* (0.6) *TP53* (3.1) (NOR-TCGA) *TP53* (3.8) (TCGA +WESW) *PTEN* (5.7))	*RICTOR* (28.8) *TP53* (50.0) *TP53* (45.5) *PTEN* (30.3)
Wang et al. 2024 [43]	*NA*	*PIK3CA*	NA	NA	*PIK3CA* (27.0)	*PIK3CA* (64.0)

TCGA,The Cancer Genome Atlas; HPV, human Papillomavirus; NA, Not analysed; TCGA + WES, Data from The Cancer Genome Atlas generated by whole exome sequencing; NOR-TCGA, Normal (non-tumor) samples from The Cancer Genome Atlas.

TP53 mutation frequencies between the two groups (20.0% vs. 25.0%, respectively).

These findings indicate that *TP53* mutations are more prevalent in HPV-independent cervical cancers, highlighting their potential utility as prognostic biomarkers and possible indicators of poor prognosis. This can be attributed to the frequent mutation of *TP53* across various cancers and its established association with poor outcomes in cervical cancer [27, 28]. These mutations are linked to more aggressive disease and

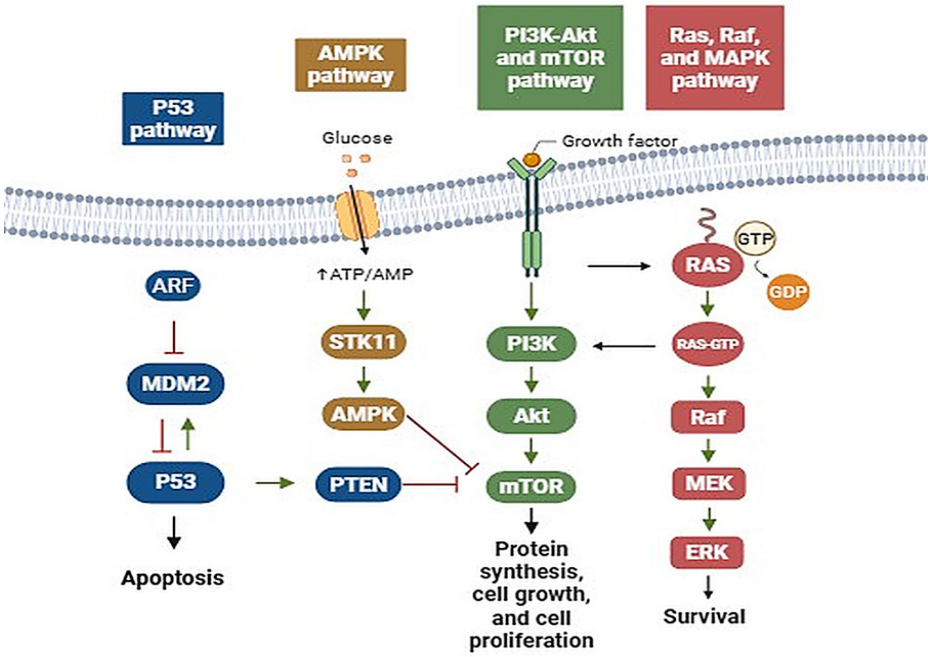

Figure 4. Simplified Schematic of Key Signaling Pathways Involved in Cervical Tumorigenesis: *p53 (TP53, CDKN2A), PI3K-Akt-mTOR (PIK3CA, PTEN), AMPK (STK11)*, and *RAS-RAF-MAPK (KRAS)* pathways.

reduced overall survival. Additionally, *TP53* mutants lose the tumor-suppressive functions of wild-type *p53* and have emerged as promising therapeutic targets due to their role in cell cycle dysregulation and tumor progression [46].

CDKN2A (cyclin-dependent kinase inhibitor 2A) or *ARF* (Alternative open reading frame) is a tumor suppressor gene that encodes p16 protein. Mutations in *CDKN2A* or dysregulation of its functional activity are frequently associated with gynecological malignant tumors [49, 50]. As a component of the *p53* signaling pathway, the frequency of *CDKN2A* mutations was comparatively assessed between HPV-independent and HPV-associated cervical cancers in three studies [37-39]. All three studies reported a higher frequency of somatic *CDKN2A* mutations in HPV-independent cases, with rates reaching up to 37.5%. In contrast, these mutations were either absent or observed at very low frequencies (≤2.0%) in the HPV-associated group.

The genes *ATM*, CHEK2, *MDM2*, and *HUWE1*, all functionally related to the *p53* signaling pathway, have also been analyzed for differences in somatic mutation frequency between HPV-associated and HPV-independent cervical cancers. Somatic mutations in *ATM*[37], *HUWE1*[40], and *MDM2*[39] were more frequently identified in HPV-independent tumors, whereas *CHEK2* mutations were more common in HPV-associated cases [37]. However, as each gene was evaluated in only one study, these findings remain inconclusive and should be interpreted with caution.

Taken together, the distinct mutation patterns of *TP53* and *CDKN2A* observed between HPV-associated and HPV-independent cervical cancers may indicate a differential involvement of the *p53* signaling pathway in the tumorigenesis of HPV-independent cases.

Somatic mutations of *PI3K-Akt* and *mTOR* signaling pathways

The *PI3K-Akt* and *mTOR* signaling pathways play central roles in regulating cell growth, proliferation, survival, metabolism, and angiogenesis, and their dysregulation is frequently implicated in cancer [51, 52]. Activation of the *PI3K* (phosphoinositide 3-kinase) pathway is commonly triggered by receptor tyrosine kinases (*RTKs*), such as *EGFR* or *HER2*, in response to growth factors. *PI3K* catalyzes the conversion of *PIP2* to *PIP3*, which subsequently recruits and activates *Akt* (also known as protein kinase B). Once activated, *Akt* phosphorylates a broad range of substrates that promote cell survival and inhibit pro-apoptotic signals, such as BAD and caspase-9 [51, 53].

One of the key downstream targets of Akt is the *mTOR* (mechanistic target of rapamycin) pathway, which integrates signals from nutrients, energy status, and growth factors to regulate protein synthesis, cell growth, and autophagy. *mTOR* exists in two distinct complexes: *mTORC1* and *mTORC2*. *mTORC1* promotes protein synthesis by phosphorylating S6K1 and 4EBP1, while *mTORC2* regulates cytoskeletal organization and contributes to full Akt activation [54]. In cancer, mutations or amplifications in genes such as *PIK3CA* (encoding the p110α catalytic subunit of *PI3K*), loss of the tumor suppressor *PTEN* (a phosphatase that degrades PIP3), or hyperactivation of *RTKs* can lead to constitutive activation of the *PI3K-Akt-mTOR* axis. This results in enhanced cell proliferation, resistance to apoptosis, metabolic reprogramming, and increased angiogenesis, all of which contribute to tumor progression and therapeutic resistance. Given its central role in oncogenesis, the *PI3K Akt mTOR* pathway is a major target for anticancer therapies, and several inhibitors targeting various components of this pathway are currently in clinical use or under investigation

[55, 56].

In the context of *PI3K-Akt* and mTOR signaling, seven of the eleven studies included in this review assessed the comparative frequency of somatic *PIK3CA* mutations in HPV-associated versus HPV-independent cervical cancers [35-39, 41, 43]. Among these, three studies reported higher *PIK3CA* mutation rates in HPV-independent tumors (33.3%–64%) compared to HPV-associated tumors (22.2%–31.1%) [35, 38, 43]. Conversely, another three studies observed higher *PIK3CA* mutation frequencies in HPV-associated tumors (20.0%–31.6%) than in HPV-independent ones (0.0%–13.3%) [36, 39, 41]. One study found comparable rates between the groups (16% vs. 18%) [37]. Overall, these findings reveal substantial heterogeneity in *PIK3CA* mutation frequencies according to HPV status, which may suggest that the oncogenic role of *PIK3CA* differs between HPV-associated and HPV-independent cervical cancers. However, further studies are needed to confirm these observations. This distinction is clinically relevant, as *PIK3CA* mutations have been consistently associated with poorer outcomes in cervical cancer [51, 52, 57, 58].

Within this pathway, *PTEN* was also analyzed for its mutation frequency in cervical cancer according to HPV status. Loss of the *PTEN* tumor suppressor is known to activate the *PI3K-Akt-mTOR* pathway [26, 59, 60]. Three studies included in this systematic review assessed *PTEN* mutation frequencies in HPV-associated versus HPV-independent cervical cancers [36, 38, 42]. Two of these reported higher mutation rates in HPV-independent tumors (22.2% and 30.3%) compared to HPV-associated tumors (0.0% and 5.7%) [38, 42], whereas one study found a higher frequency in HPV-associated tumors than in HPV-independent tumors (6.4% vs. 0.0%, respectively) [36]. Overall, these findings suggest that *PTEN* mutations may be more frequent in HPV-independent cervical cancers. However, given the limited number of studies and some conflicting results, further research is needed to clarify the role of *PTEN* alterations in cervical carcinogenesis in relation to HPV status.

Additional genes involved in the *PI3K-Akt* and *mTOR* pathways, including *ERBB3*[37], *NTRK1*[37], *ITGB3*[35], *TSC2* [37], and *TERT*[33], were reported with higher mutation frequencies in HPV-associated cervical cancers. In contrast, mutations in *NTRK3*[37] and *RICTOR*[42] were more frequently observed in HPV-independent tumors. *AKT* mutations [38, 41] occurred at similar frequencies in both groups. For *ERBB2*, one study identified mutations exclusively in HPV-independent tumors [41], whereas another found no significant difference between the two groups [37], highlighting variability in the mutational landscape across studies. Despite evidence of differential mutational frequency in HPV- associated and HPV-independent cervical cancers for genes such as *ERBB3, NTRK1, ITGB3, TSC2, TERT, NTRK3, RICTOR, AKT*, and *ERBB2*, the number of studies investigating each gene is very limited, often restricted to a single report per gene, thereby limiting the robustness and generalizability of current interpretations.

Taken together, the findings indicate that *PIK3CA* and *PTEN* mutations display inconsistent patterns between HPV-associated and HPV-independent cervical cancers. In contrast, mutations in *ERBB3, NTRK1, ITGB3, TSC2,* and *TERT* appear more frequently in HPV-associated tumors, while *NTRK3* and *RICTOR* mutations are more commonly observed in HPV-independent cases. Nonetheless, the limited number of studies assessing each gene hinders definitive conclusions and highlights the need for further research to better understand their role in cervical carcinogenesis.

Somatic mutations of AMPK signaling pathway

Among the components of the *AMPK* signaling pathway, only *STK11*, also known as liver kinase B1 (LKB1), was investigated in the studies included in this review. *STK11* is a tumor suppressor gene [61] whose activation inhibits cell proliferation and protein synthesis by stimulating *AMPK* and suppressing the mTOR pathway. Mutations in *STK11* have been implicated in various carcinomas [62] and are associated with poor prognosis, potentially serving as predictors of disease recurrence [63, 64].

The comparative frequency of *STK11* gene mutations between HPV-associated and HPV-independent cervical cancers was examined in five studies [36-39, 41]. While two studies reported no significant difference in *STK11* mutation frequency between the groups [36, 41], three studies identified higher mutation rates in HPV-independent tumors [37-39]. Reported *STK11* mutation frequencies reached up to 4.0% in HPV-associated cases, compared to as high as 27.0% in HPV-independent cases. Therefore, current evidence remains insufficient to establish a clear association between *STK11* mutation status and HPV involvement in cervical cancer.

Somatic mutations of Ras, Raf, and MAPK signaling pathway

The Ras–Raf, andMEK–ERK (MAPK) signaling pathway is a key regulator of cell proliferation, survival, and differentiation. Upon activation of receptor tyrosine kinases (RTKs) by growth factors, the small GTPase Ras, particularly *KRAS*, one of its most frequently mutated isoforms in cancer, is activated and recruits Raf kinases (such as *BRAF*) to the plasma membrane. Raf then phosphorylates and activates *MEK1/2*, which in turn activates *ERK1/2*. Once phosphorylated, ERK translocates to the nucleus, where it regulates transcription factors and gene expression to control cellular outcomes. This pathway is tightly regulated by feedback mechanisms and is commonly dysregulated in cancers, especially through activating mutations in *KRAS* and *BRAF*, leading to uncontrolled cell growth [65-68].

Six studies assessed the comparative frequency of *KRAS* mutations in HPV-associated versus HPV-independent cervical cancers [34, 36-39, 41]. Of these, three studies reported higher *KRAS* mutation frequencies in HPV-independent tumors, with rates reaching up to 36% [37-39]. In contrast, two studies observed higher *KRAS* mutation frequencies in HPV-associated tumors, with rates up to 24% [34, 41]. One study reported comparable *KRAS* mutation frequencies between the two groups [36]. These findings once again highlight the variability in

KRAS mutation frequencies across studies, underscoring the lack of consensus regarding its association with HPV status in cervical cancer and reinforcing the need for further investigation.

Within the same signaling pathway, mutations in *MAP2K2*[37], *NRAS*[38], *HRAS* and *NF1*[39], and *BRAF* and *ROS1*[41] were each assessed in a single study. *NF1* mutations were more frequently observed in HPV-independent tumors (25%) compared to HPV-associated cases (0.0%). In contrast, mutations in *NRAS* (5.5%), *HRAS* (10%), *BRAF* (2%), *ROS1* (2%), and *MAP2K2* (4%) were reported exclusively in HPV-associated tumors.

Relevance and Limitations

To our knowledge, this is the most recent systematic review to identify and synthesize current evidence on the frequencies of somatic mutations, comparing HPV-associated and HPV-independent cervical cancers. Given that systematic reviews represent the highest level of scientific evidence, this study holds substantial relevance for both academic research and clinical practice. The findings may contribute to the refinement of diagnostic classification frameworks and inform the development of molecularly guided therapeutic protocols and clinical management strategies tailored to the distinct biological characteristics of these tumor subtypes.

The findings of this review should be interpreted considering its limitations. We did not include conference abstracts, books and reviews, so our findings may not fully represent the full body of the literature on HPV-independent cervical cancers. Furthermore, the retrospective nature of the included studies may have introduced bias in the results. Additionally, several important gaps in existing literature were identified during the execution of this systematic review. A major challenge in data interpretation stemmed from the heterogeneity across studies regarding sample types, HPV detection methods, histopathological subtypes analyzed, and study objectives. This variability compromises the ability to accurately differentiate truly HPV-negative cervical cancers from false-negative cases. Furthermore, there is a notable lack of comprehensive clinical and diagnostic data, which limits deeper insights into the molecular characteristics of HPV-independent tumors. Most studies assessed somatic mutations in small cohorts using heterogeneous methodologies, thereby constraining both comparability and generalizability of findings. In addition, many reports did not stratify somatic mutation data by histopathological classification, hindering correlations between molecular profiles and tumor subtypes. The exclusive focus on somatic mutations also overlooks other relevant layers of molecular dysregulation, such as copy number alterations, epigenetic modifications, and transcriptomic changes. Collectively, these limitations underscore the urgent need for large-scale, well-designed studies to better define the genomic landscape of HPV-independent cervical cancers and support the development of more precise diagnostic and therapeutic strategies.

In conclusions, this systematic review compared the frequency of somatic mutations between HPV-associated and HPV-independent cervical cancers across key oncogenic pathways, including *p53*, *PI3K-Akt-mTOR*, *AMPK*, and Ras-Raf-MAPK. The *p53* pathway, particularly mutations in *TP53* and *CDKN2A*, showed a consistently higher mutation frequency in HPV-independent tumors, suggesting a potentially distinct molecular trajectory. In contrast, mutation patterns in the *PI3K-Akt-mTOR* pathway were more heterogeneous, with *PIK3CA* and *PTEN* showing variable frequencies across studies and HPV groups. Certain mutations, such as *ERBB3* and *TERT*, appeared more common in HPV-associated tumors, while others like *NTRK3* and *RICTOR* were more frequently observed in HPV-independent cases, though often reported in single studies. Mutations in *STK11* (*AMPK* pathway) and *KRAS* (*Ras-Raf-MAPK* pathway) also showed conflicting or inconclusive results. Overall, these findings underscore the molecular heterogeneity of cervical cancer according to HPV status and highlight the need for further large-scale studies to elucidate these differences and support the development of prognostic, diagnostic, and therapeutic strategies specifically designed for HPV-independent cervical cancer.

Author Contribution Statement

ABCS: Conceptualization, database searching, data extraction, statistical analysis, and manuscript drafting. LRC, LEFM, and MVFM: Database searching, data extraction, manuscript review. VRSS: Supervision, validation of methodology, review and editing of the manuscript. MELC: Conceptualization, study design and procured funding. All authors discussed the results and contributed to the final manuscript.

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Study Registration

The study was registered using the National Institutes for Health Research (NIHR) PROSPERO tool (International Prospective Register of Systematic Reviews) (CRD420251044316).

Ethical Compliance

All procedures performed in this study involving human participants data were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of Interest

The authors declare that there is no conflict of interest.

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