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Clinicopathological Characteristics of HPV-Related and HPV-Independent Cervical Cancer: Literature Review

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Abstract

Cervical cancer is one of the leading malignancies in women, and most cases are associated with high-risk Human Papillomavirus (HPV) infection, particularly HPV-16 and HPV-18. However, advances in classification and molecular pathology indicate that there is a group of cervical cancers that develop without HPV involvement, namely HPV-independent cervical cancer. This literature review aims to analyze the differences in clinicopathological characteristics of HPV-related and HPV-independent cervical cancer. This study uses a narrative literature review method by examining scientific articles obtained from Google Scholar, PubMed, ScienceDirect, Semantic Scholar, and SpringerLink in the publication period 2016–2026. The analyzed literature discusses clinical, histopathological, and molecular characteristics, prognosis, and therapeutic implications based on HPV status. The results of the study indicate that HPV-related cervical cancer generally occurs at a younger age, is dominated by squamous cell carcinoma, shows strong p16 expression, and has a better therapeutic response and prognosis. In contrast, HPV-independent cervical cancer is more common in older patients, is often diagnosed at an advanced stage, has histopathological subtypes such as gastric-type adenocarcinoma, clear cell carcinoma, and mesonephric carcinoma, and is associated with mutations in genes such as TP53, KRAS, PIK3CA, and PTEN. This group also exhibits higher tumor aggressiveness, more frequent lymphovascular invasion, a greater risk of recurrence, and a poorer prognosis. Therefore, HPV status plays a crucial role in determining the clinicopathological characteristics, prognosis, and therapeutic strategies of cervical cancer. Immunohistochemistry-based diagnostic approaches, molecular testing, and more individualized therapies are needed to improve diagnostic accuracy and patient outcomes.

Introduction

Cervical cancer is a major health problem for women and remains a leading cause of morbidity and mortality worldwide. It ranks fourth among the most common malignancies in women globally, particularly in developing countries with limited access to screening and vaccination. Each year, approximately 600,000 women are diagnosed with the disease, and approximately 340,000 die from it. These statistics are worst in low- and middle-income countries, where cost-effective screening and vaccination programs are lacking. Despite rapid development of early detection programs and the HPV vaccine, the burden of cervical cancer remains high, necessitating the development of more specific diagnostic and therapeutic approaches based on tumor biology (Popovici et al., 2025).

For many years, cervical cancer was understood as a malignancy almost entirely associated with persistent infection with high-risk Human Papillomavirus (HPV), particularly HPV-16

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and HPV-18. HPV infection triggers the expression of the oncoproteins E6 and E7, which inhibit the function of tumor suppressor genes, thus promoting malignant cell transformation. The strong link between HPV and cervical cancer underpins the development of vaccines and HPV-based screening methods as primary prevention strategies (Popovici et al., 2025).

HPV is a virus that infects the skin (epidermis) and human mucous membranes, such as the oral mucosa, esophagus, larynx, trachea, conjunctiva, genitalia, and anus. HPV never infects the mucosa of the gastrointestinal tract. The virus is primarily transmitted through sexual contact, including oral sex, anal sex, and hand sex. The virus can also be transmitted through nonsexual contact, such as vertical transmission from mother to child (very rare), and the use of contaminated objects such as towels, gloves, and clothing. The virus is transmitted through direct contact with infected lesions. The incubation period for HPV is 3-4 months (ranging from 1 month to 2 years). HPV replicates repeatedly when the immune response is low, for example in cases of HIV, smoking, pregnancy, and malnutrition. HPV cannot be cured; infected individuals remain carriers of the virus (Farmasi et al., 2016).

However, advances in molecular pathology and diagnostic technology have shown that not all cervical cancer cases are related to Human Papillomavirus (HPV) infection. Although most cervical cancers are caused by high-risk HPV infection, several recent studies have identified a group of cervical cancers that develop without HPV involvement and have different carcinogenesis mechanisms. Based on these developments, the World Health Organization (WHO) has updated its classification into two main categories: HPV-associated (HPV-related) and HPV-independent. This classification is based on differences in etiology, histopathological characteristics, molecular profiles, and clinical manifestations of each group. This updated classification represents a paradigm shift in understanding cervical cancer, from previously being considered to have a uniform cause to a disease with a more complex and heterogeneous biological pathway (Bhatla et al., 2025).

A study by Kır et al. (2025) showed that HPV-independent cervical cancer has distinct clinicopathological characteristics compared to HPV-related cervical cancer. HPV-independent cervical cancer is generally found in older patients and is often diagnosed at a more advanced stage. Furthermore, this group tends to have poorer clinical outcomes and a worse prognosis than HPV-associated cervical cancer. Histopathologically, HPV-independent types more frequently exhibit keratinization patterns and abnormal p53 expression, thus supporting more aggressive tumor biology (Kır et al., 2025).

HPV-independent cervical cancer has a distinct carcinogenesis pathway. Mutations in genes such as TP53, KRAS, PIK3CA, PTEN, and STK11 are more common in the HPV-independent group. Histopathological subtypes such as gastric-type adenocarcinoma, clear cell carcinoma, and mesonephric carcinoma are also reported to be more common in this group. These differences suggest that HPV status influences the clinicopathological presentation, therapy response, and even patient prognosis (Popovici et al., 2025).

Although research on cervical cancer continues to expand, studies comparing the clinicopathological characteristics of HPV-associated and HPV-independent cervical cancer in the form of a literature synthesis are still relatively limited. Therefore, this literature review was conducted to analyze various recent research results regarding the differences in the clinicopathological characteristics of the two groups of cervical cancer so that it can provide a scientific basis for improving the accuracy of diagnosis, determining prognosis, and providing more targeted therapeutic strategies.

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Method

Types of research

This study employed a literature review method. A literature review is a research method that involves identifying, reviewing, analyzing, and interpreting various research findings related to a specific topic through the collection of relevant scientific references. In this study, various literature sources, including national and international journal articles, were used as a basis for reviewing and compiling a discussion on the clinicopathological characteristics of HPV-related and HPV-independent cervical cancer. This method is expected to yield a comprehensive synthesis of information regarding the differences in clinical and pathological characteristics of these two groups of cervical cancer, based on the results of recent research..

Literature Search Strategy Design

This study is a literature review with a narrative review design. This type of research was chosen because the researchers wanted to determine the clinicopathological characteristics of HPV-related and HPV-independent cervical cancer by collecting various relevant references. Literature was obtained from accredited sources such as Google Scholar, PubMed, ScienceDirect, and Semantic Scholar, as well as other scientific search sources related to the research topic.

Data Type

The data used in this study comes from research results that have been conducted and published in online journals, including theses, national and international journals, e-books, and textbooks. Reference sources were obtained from online search engines that provide free journal articles, as follows: Google Scholar, Semantic Scholar, PubMed NCBI, and Research Gate.

Inclusion and Exclusion Criteria

The inclusion criteria for references used included: (1) English and Indonesian; (2) References discussing cervical cancer; (3) References discussing HPV-related and HPV-independent cervical cancer; (4) References discussing the clinicopathological characteristics of cervical cancer based on HPV status. (5) Maximum publications from the last 10 years (period 2016–2026); (6) National and international scientific journals/articles and literature reviews; (7) Articles available in full text.

Exclusion criteria include: (1) Articles that do not match the research topic; (2) Articles that do not discuss the clinicopathological characteristics of cervical cancer based on HPV status; (3) Articles that are not available in full text; (4) Duplicate articles from other databases; (5) Articles with publication years outside the specified criteria.

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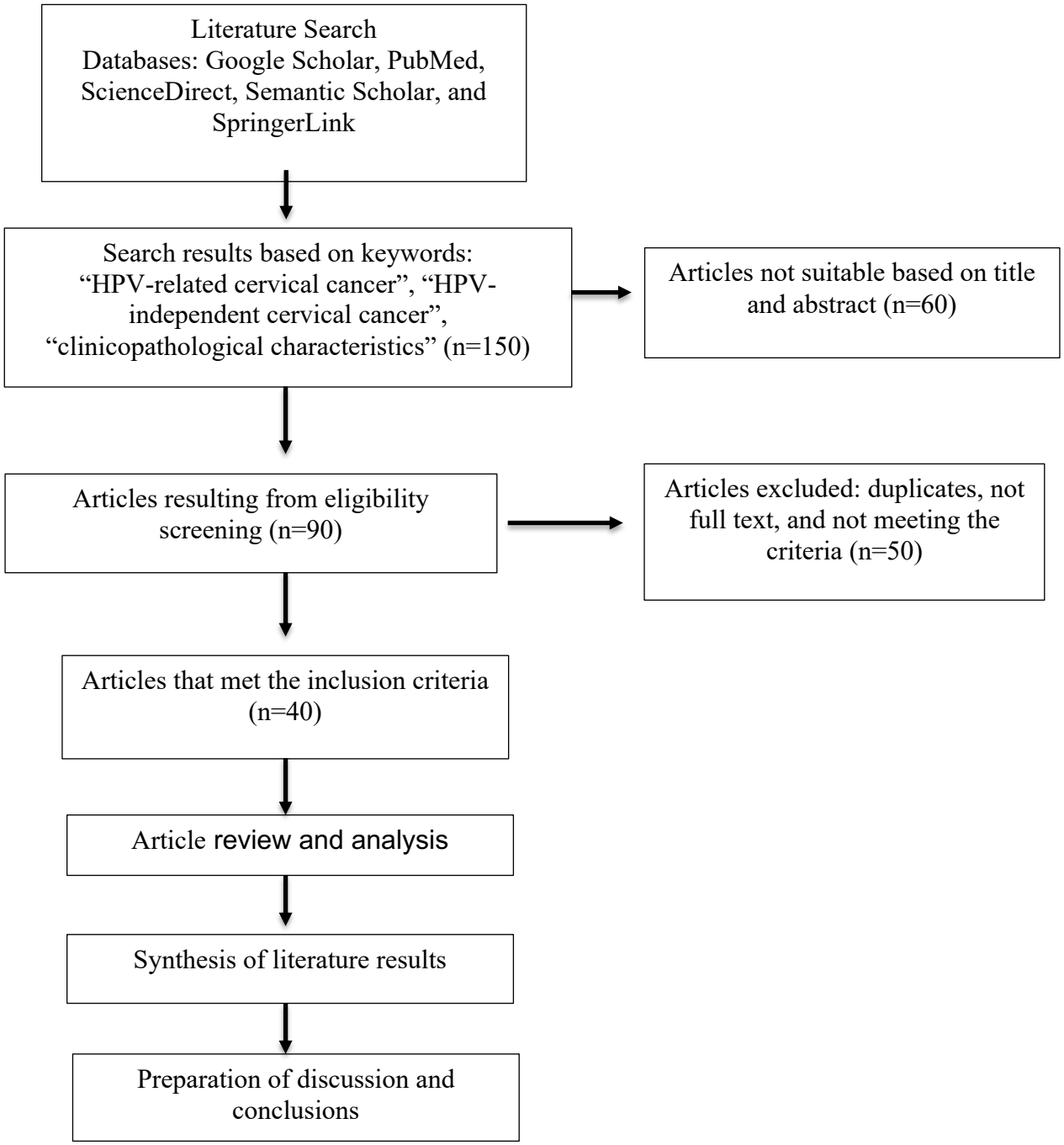
Research Flow



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Result and Discussion

To understand the differences in clinicopathological characteristics and treatment outcomes between HPV-related and HPV-independent cervical cancers, we reviewed 19 recent scientific journals containing a variety of research methodologies, including literature reviews, systematic meta-analyses, retrospective studies, case reports, and observational studies. These journals addressed the clinical, histopathological, and molecular aspects, prognosis, and treatment implications of these two subtypes of cervical cancer, providing a comprehensive overview of the biological profile and clinical challenges faced in the diagnosis and management of HPV-independent cervical cancer, which has a worse prognosis than HPV-related cervical cancer. The following table provides a summary of these studies, outlining the methods, authors, results, and key conclusions of each journal.

Year	Title	Methods	Author	Result	Conclusion
2018	Cervical Cancer Not Caused by HPV—A New Challenge for Modern Oncology	The literature review method involved a systematic review of articles from PubMed and Google Scholar from 2003–2025. The selected articles included original research, molecular studies, early clinical applications, and the latest clinical guidelines on HPV-independent cervical cancer.	Ruxandra Maria Huriui, Ion Andrei Huriui, Tudor Andrei Buțurean, Diana Popović, Elena-Roxana Avÿdÿnei, Raluca Anca Balan1	Research shows that approximately 5–11% of cervical cancers are unrelated to HPV and have distinct histopathological, molecular, and clinical characteristics. The main histopathological types include gastric, clear-cell, mesonephric, and endometrioid adenocarcinomas. Mutations in genes such as TP53, PIK3CA, KRAS, STK11, and PTEN are key pathways for cancer progression. Diagnosis is often delayed due to indistinguishability from endometrial cancer and limitations in HPV detection. Many cases are found at an advanced stage and show poor response to chemotherapy and immunotherapy.	HPV-independent cervical cancer is an aggressive subtype with a worse prognosis than HPV-associated cervical cancer. Improved diagnostic methods, precision medicine-based molecular treatment approaches, and further research are needed to improve early detection, therapy effectiveness, and patient survival.
2026	Clinicopathological Features and Survival Outcomes of HPV-Independent versus HPV-Associated Cervical Adenocarcinoma: A Systematic Review and Meta-analysis	A systematic review and meta-analysis based on the 2020 PRISMA guidelines. Researchers searched PubMed, Web of Science, Scopus, Embase, and the Cochrane Library databases until March 1, 2026. Comparative studies comparing HPV-independent and HPV-associated cervical adenocarcinoma were analyzed using hazard ratios (HRs) and odds ratios (ORs) to assess survival and clinicopathological characteristics.	Dan Wu, Yun Li, Yuehua Lang, Xuan Hong, & Jianping Kong	The meta-analysis results showed that HPV-independent cervical adenocarcinoma has a worse prognosis than HPV-associated adenocarcinoma. Overall survival (OS) was lower (HR 3.37), progression-free survival (PFS) was worse (HR 2.94), and there was a higher risk of distant metastasis and local recurrence (OR 2.76). Furthermore, lymphovascular invasion (LVSI/LVI) was found more frequently in the HPV-independent group (OR	HPV-independent cervical adenocarcinoma is a more aggressive subtype clinicopathologically and has a lower survival rate than HPV-associated adenocarcinoma. These findings support the distinction between HPV-independent cervical cancer and HPV-associated adenocarcinoma, making it important for more specific risk

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				3.00), indicating a more aggressive tumor nature.	stratification, prognostic evaluation, and patient management planning.
2025	Molecular Features of HPV-Independent Cervical Cancers	This literature review method discusses previous research findings on molecular characteristics, gene mutations, molecular signaling pathways, immunohistochemical biomarkers, diagnostic implications, and targeted therapy in HPV-independent cervical cancer. This article reviews the latest scientific literature related to HPV-negative cervical cancer.	Luca Giannella, Camilla Grelloni, Leonardo Natalini, Gianmarco Sartini, Mila Bordini, Giovanni Delli Carpini, Jacopo Di Giuseppe, Erica Dugo, Francesco Piva, & Andrea Ciavattini	Studies have shown that HPV-independent cervical cancer accounts for approximately 5–11% of cervical cancer cases and is primarily characterized by gastric, mesonephric, clear cell, serous, and endometrioid adenocarcinomas. These tumors have distinct clinical and molecular characteristics from HPV-associated cervical cancer, such as mutations in the TP53, KRAS, and PIK3CA genes, activation of the PI3K/AKT/mTOR pathway, and characteristic immunohistochemical expression, such as negative or focal p16 and abnormal p53. Furthermore, HPV-independent cervical cancer is often diagnosed at an advanced stage, is difficult to detect through standard screening, and has a poorer prognosis than HPV-associated cancer.	HPV-independent cervical cancer is a distinct biological entity from HPV-associated cervical cancer due to its distinct molecular mechanisms, genetic mutations, biomarkers, and therapeutic responses. Therefore, molecular profiling-based diagnosis and the development of targeted therapies (precision medicine) are needed to improve diagnostic accuracy, treatment effectiveness, and patient prognosis.
2024	Research Progress on Human Papillomavirus-Negative Cervical Cancer: A Review	Literature review/narrative review method by reviewing various previous studies on HPV-negative cervical cancer, including causes, pathogenesis mechanisms, pathological, molecular, clinical characteristics, prognosis, as well as the latest research developments related to HPV-independent cervical cancer..	Ning Shao	Studies show that approximately 3–8% of cervical cancers are HPV-negative and have distinct characteristics compared to HPV-positive cervical cancers, such as insidious onset, advanced stage diagnosis, more aggressive invasion, and a poorer prognosis. The mechanisms of occurrence are thought to be related to the immune microenvironment, gene mutations (TP53, PIK3CA, KRAS), the PI3K/AKT/mTOR signaling pathway, and the expression of certain long non-coding RNAs (lncRNAs). Furthermore, several pathological subtypes such as gastric-type adenocarcinoma, mesonephric	HPV-negative cervical cancer is a distinct biological entity from HPV-positive cervical cancer and requires more specific diagnostic and therapeutic approaches. Increasing detection sensitivity, identifying molecular biomarkers, and developing targeted therapies and personalized medicine are needed to improve early diagnosis, therapeutic effectiveness, and patient prognosis.

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				adenocarcinoma, clear cell adenocarcinoma, serous carcinoma, and endometrioid adenocarcinoma are more frequently found in HPV-negative cervical cancers..	
2025	Cancer of the Cervix Uteri: 2025 Update	This article/literature review method discusses the latest developments in cervical cancer based on the FIGO 2025 report, covering epidemiology, HPV vaccination, screening, histopathological classification, cancer staging, diagnosis, surgical management, radiotherapy, immunotherapy, and current therapeutic approaches. The article synthesizes the results of clinical research, clinical trials, WHO and FIGO guidelines, and the latest scientific evidence related to the prevention, early detection, and management of cervical cancer..	Neerja Bhatla, Daisuke Aoki, Daya Nand Sharma, & Rengaswamy Sankaranarayanan	The study results demonstrate significant progress in global cervical cancer elimination through the WHO strategy of HPV vaccination, screening, and treatment. The HPV vaccine has been implemented in more than 140 countries, with both one-dose and two-dose schedules implemented. Screening has evolved through the use of DNA-based HPV tests, self-sampling, portable screening devices, artificial intelligence (AI), and the single-visit approach (SVA). Regarding diagnosis and therapy, the article highlights the importance of immunohistochemistry (PD-L1, p16, ER/PR), the classification of HPV-related and HPV-independent cervical cancers, the use of sentinel lymph nodes, conservative surgical techniques in early stages, fertility-sparing surgery, and immunotherapy (e.g., pembrolizumab) for recurrent and metastatic cancer. The article also emphasizes that HPV-independent cervical cancers have a worse prognosis and a lower response to therapy than HPV-related cancers.	Cervical cancer remains a global health problem, but advances in HPV vaccination, HPV-based screening, molecular diagnostics, minimally invasive surgical techniques, and immunotherapy offer significant opportunities for improving early detection and treatment success. Furthermore, classifying HPV-associated and HPV-independent cervical cancers is crucial because they differ in pathogenesis, prognosis, and treatment response, necessitating increasingly individualized therapeutic approaches (personalized medicine).
2025	Analysis of the Differences between HPV-Independent and HPV-Related Cervical Adenocarcinoma	Retrospective comparative research method (retrospective cohort study) with clinical data analysis of 332 cervical adenocarcinoma patients at the Xinjiang Medical University Oncology Hospital for the period October 2012–July 2023. The study compared clinicopathological characteristics, tumor markers (CEA, CA125, CA199), HPV infection	Jing He, Gulixian Tu lu Weng Jiang, & Lin Zeng	The results showed that HPV-Ind-CA had better clinicopathological characteristics and a worse prognosis than HPV-CA. HPV-Ind-CA patients tended to be ≥50 years old, postmenopausal, had lower tumor differentiation, more advanced FIGO stage, higher CA125 levels, and underwent radical surgery less frequently. HPV-Ind-CA had shorter survival (12 months and 21 months) compared to	HPV-independent cervical adenocarcinoma is a more aggressive subtype and has a worse prognosis than HPV-associated cervical adenocarcinoma. Patients with HPV negativity, age ≥50 years, FIGO stage >1, and elevated CA125 and CA199 levels require more rigorous

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		status, therapy (surgery, radiotherapy, chemotherapy), effectiveness of therapy, and survival outcomes (progression-free survival/PFS and overall survival/OS) between HPV-independent groups. cervical adenocarcinoma (HPV-Ind-CA) and HPV-related cervical adenocarcinoma (HPV-CA). Analyzes were performed using Kaplan–Meier, log-rank test, and multivariate Cox regression.		HPV-CA (26 months and 35 months). Furthermore, FIGO stage > I, elevated CA125 and CA199, age ≥50 years, and the absence of HPV infection were poor prognostic factors for patient survival. In the HPV-Ind-CA group, low tumor differentiation and elevated CA199 were independent prognostic factors for overall survival (OS).	prognostic evaluation and possibly more intensive therapy to improve the chances of treatment success and patient survival. This study also emphasizes the importance of early identification and individualized therapeutic approaches based on HPV status and clinicopathologic factors.
2025	Clinicopathological Characteristics of Cervical Carcinoma at Dr. M. Djamil Hospital, Padang, 2018–2021	This descriptive research method uses a retrospective approach using secondary data from medical records of cervical carcinoma patients at the Anatomical Pathology Laboratory of Dr. M. Djamil Padang Hospital in 2018–2021. The study used a total sampling technique, with a sample size of 108 patients with confirmed cervical carcinoma who met the inclusion and exclusion criteria. The variables analyzed included age, marital status, clinical manifestations, parity history, histopathological features, and degree of differentiation. Data were analyzed univariately and presented in frequency distribution and percentage.	Rannia Fedrivia, Aswiyanti Asri, Eka Fithra Elfi, Syamel Muhammad, Henny Mulyani, & Eka Nofita	The results showed that the majority of cervical carcinoma patients were aged ≥45 years (74.1%) and all patients were married (100%). The most common clinical manifestation was vaginal bleeding (99.1%), while the most common parity history was multiparity (>1) at 91.7%. Based on histopathological characteristics, the most common type was squamous cell carcinoma (77.8%), followed by adenocarcinoma (18.5%). The most common degree of differentiation was moderately differentiated (47.2%), then poorly differentiated (22.2%), and well differentiated (8.3%). The study showed that most patients came in the early elderly age group and were at an advanced stage, so the prognosis was influenced by clinicopathological factors and delays in early detection.	Cervical carcinoma at Dr. M. Djamil Hospital Padang during the 2018–2021 period was most commonly found in patients aged ≥45 years, with the main clinical manifestations being vaginal bleeding, a history of multiparity, and a dominant histopathological type of squamous cell carcinoma with a moderate degree of differentiation. The study emphasized the importance of early detection, screening, and education on cervical cancer prevention to reduce delays in diagnosis and improve patient prognosis.
2024	Characteristics of Clinical and Histopathological Symptoms of Cervical Cancer Patients at Ibnu Sina Hospital YW-UMI Makassar	The quantitative descriptive research method used secondary data from medical records and biopsy results of cervical cancer patients at Ibnu Sina Hospital YW-UMI Makassar for the period 2022–2023. The study used a descriptive design with medical record data sources to examine the	Ahmad Emil Zul-ayman, Sri Wahyuni Gayatri, Zulfahmidah, Syamsu Rijal, & Rizki Amalia	The results of the study showed that the most common histopathological type of cervical cancer was squamous cell carcinoma (79.1%), followed by adenocarcinoma (20.9%). The age group with the highest number of cervical cancer sufferers was 36–45 years (35.4%). The most common clinical symptoms	The majority of cervical cancer patients at Ibnu Sina Hospital YW-UMI Makassar in the 2022–2023 period had squamous cell carcinoma, were in their productive to middle adulthood (36–45 years), had lower abdominal pain

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		characteristics of clinical symptoms, histopathological type, therapy, patient age, and stage of cervical cancer.		were lower abdominal pain (44.8%), followed by vaginal bleeding (33.3%) and vaginal discharge (13.8%). The most common therapy was medication (47.9%), while the most common stage of cervical cancer was stage IIB (39.6%). The study also showed that most patients presented at an advanced stage, requiring more complex management.	as the dominant symptom, and were often diagnosed at stage IIB. Research emphasizes the importance of early detection, cervical cancer screening, reproductive health education, and HPV vaccination to prevent delayed diagnosis and reduce the incidence of cervical cancer in the community.
2024	A Low-Risk HPV-Associated Well-Differentiated Squamous Cell Carcinoma of the Cervix with Low-Grade Squamous Intraepithelial Lesion Morphology: Clinical and Pathologic Diagnostic Difficulties and Review of the Literature	A case report with a literature review was conducted on a 30-year-old female patient who presented with pelvic pain, menstrual irregularities, and foul-smelling vaginal discharge with exophytic cervical lesions. Diagnosis was made through repeated biopsies, histopathology, immunohistochemistry (p16, p53, Ki-67), chromogenic in-situ hybridization (ISH), HPV PCR, CT scan, MRI, LEEP, and radical hysterectomy to evaluate the clinicopathological characteristics of low-risk HPV-associated cervical cancer..	Deniz Ates, Esra Nur Sahin, Kubra Katipoglu, & Alp Usubutun	The results showed that the patient had a well-differentiated squamous cell carcinoma of the cervix associated with low-risk HPV (HPV 6/11), a very rare case. The initial repeat biopsy showed only a low-grade squamous intraepithelial lesion (LSIL) with koilocytosis and binucleation, making it difficult to distinguish from a benign condyloma. PCR examination confirmed the absence of high-risk HPV, while ISH showed positivity for HPV 6/11. After hysterectomy, tumor infiltration was found to extend to the full thickness of the cervix, parametrium, vagina, proximal ureter, and bladder (FIGO stage IVA). The patient underwent chemoradiotherapy and remained disease-free at 36 months of follow-up.	Low-risk HPV (HPV 6/11)-associated cervical carcinoma is a very rare condition but can be invasive and mimic benign lesions such as condyloma or LSIL, potentially leading to misdiagnosis. Research emphasizes the importance of clinical, radiological, and pathological correlation, adequate biopsy, and molecular HPV testing to avoid delays in diagnosis and ensure appropriate management in cases of cervical cancer with atypical morphology.
2022	HPV-Negative Adenocarcinomas of the Uterine Cervix: From Molecular Characterization to Clinical Implications	This narrative review article discusses various studies on HPV-negative cervical adenocarcinoma, including clinical characteristics, histopathological classification, molecular basis, gene mutations, prognosis, diagnosis, and therapeutic options. This study compiles and analyzes the literature on HPV-independent cervical adenocarcinoma to	Luca Giannella, Jacopo Di Giuseppe, Giovanni Delli Carpini, Camilla Grelloni, Mariasole Fichera, Gianmarco Sartini, Serena Caimmi, Leonardo Natalini, &	Studies have shown that HPV-negative cervical adenocarcinoma accounts for approximately 15–20% of cervical adenocarcinoma cases and generally has a worse prognosis than HPV-related lesions. HPV-negative tumors tend to be diagnosed at a later stage, have lower overall and disease-free survival rates, and exhibit distinctive molecular characteristics such as mutations in genes such as TP53, STK11,	HPV-negative cervical adenocarcinoma is a more aggressive and clinically challenging subtype of cervical cancer, with a worse prognosis than HPV-associated adenocarcinoma. Diagnosis requires a combination of histopathological evaluation, molecular testing, imaging, and the latest WHO/IECC

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		understand its clinical implications and treatment.	Andrea Ciavattini	KRAS, PIK3CA, PTEN, ARID1A, and ERBB2 depending on the histopathological subtype (e.g., gastric-type adenocarcinoma, clear cell adenocarcinoma, mesonephric adenocarcinoma, and endometrioid adenocarcinoma). Furthermore, early detection is more difficult because HPV-negative lesions are less accessible to routine HPV screening and HPV vaccination.	classification to improve diagnostic accuracy and management. Research emphasizes the importance of individualized therapeutic approaches based on molecular characteristics and histologic subtype, as well as the need to develop screening strategies and targeted therapies for HPV-independent cervical cancer.
2023	Cervical cancer	This literature review/review article discusses cervical cancer from the perspectives of epidemiology, risk factors, HPV molecular pathogenesis, cancer staging, early detection, and cervical cancer therapy, based on various journal sources, health guidelines, and epidemiological reports. The study was conducted descriptively by reviewing literature on the mechanisms of HPV infection, the E6–E7 oncogenes, diagnosis, prevention, and therapy of cervical cancer.	Vera Novalia	The study results show that cervical cancer is one of the most common cancers in women and is mainly caused by infection with oncogenic types of Human Papilloma Virus (HPV), especially HPV 16 and 18, through activation of E6 and E7 proteins that deactivate the p53 and Rb tumor suppressor genes, thereby triggering abnormal cell proliferation and cervical cancer. Other risk factors include smoking, hormonal, changing sexual partners, contraception, and exposure to mutagenic substances. The article also explains that cervical cancer develops through precancerous lesions (Cervical Intraepithelial Neoplasia/CIN), has FIGO stages 0–IV, and can be prevented through HPV vaccine, early detection (Pap smear and IVA), LINAC radiotherapy, and anti-VEGF therapy to control tumor growth and metastasis.	Cervical cancer is a disease with high incidence and mortality rates, largely linked to oncogenic HPV infection. However, it is preventable through HPV vaccination, early detection, and appropriate therapy. Research emphasizes the importance of public education, increased screening awareness, and early intervention to reduce delays in diagnosis and improve the prognosis of cervical cancer patients.
2025	The Relationship of Human Papillomavirus Infection with Cervical Histopathology in Women: A Narrative Review	The narrative review/systematic literature review method was conducted with a literature search through the PubMed, ProQuest, Cochrane, and Google Scholar databases using the PRISMA approach. The study used inclusion criteria in the form of	Kelvin Florentino Kaisar, Wahida Rahmi, Asyifa Delfilaura, & Andani Eka Putra[37]	The results of the study indicate that most cervical cancers are closely related to Human Papillomavirus (HPV) infection, especially high-risk types such as HPV16 and HPV18, which can cause histopathological changes in the cervix ranging from Low-Grade Squamous Intraepithelial Lesion (LSIL),	HPV infection, particularly high-risk types (HPV16 and HPV18), is strongly associated with cervical histopathological changes and the development of cervical cancer. Research confirms

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		primary English-language journals from 2015–2020, journals indexed by SCOPUS Q1–Q2, and an observational design (cohort, cross-sectional, retrospective, case-control). The study examined the relationship between HPV infection and cervical histopathological changes, HPV genome types, and the effectiveness of cytology screening and HPV genome detection in cervical cancer.		High-Grade Squamous Intraepithelial Lesion (HSIL), Cervical Intraepithelial Neoplasia (CIN), to invasive cervical cancer. A review of 16 studies showed that the prevalence of HPV infection in cervical tissue with dysplasia or cancer is very high (around 98%), with combined detection of cytology (Pap smear) and HPV genome examination having a higher sensitivity than cytology alone. In addition, HPV-based cervical cancer screening is more effective in detecting infection at an early stage before the appearance of histopathological changes in the cervix.	that early detection through a combination of cytology and HPV-based screening, along with HPV vaccination, is an important strategy to prevent the progression of dysplasia to invasive cervical cancer and reduce cervical cancer morbidity and mortality.
2025	A Review of the Carcinogenic Potential of Human Papillomavirus (HPV) in Urological Cancers	This literature review discusses the carcinogenic role of Human Papillomavirus (HPV) in various urological cancers, including prostate, penile, bladder, testicular, and kidney cancers. The study was conducted by reviewing previous research on the molecular mechanisms of HPV, oncoproteins E5, E6, and E7, HPV involvement in chronic inflammation, cancer progression, molecular pathways, and the role of HPV vaccines in urological cancer prevention.	Ehsan Zolfi, Farhood Khaleghi Mehr, Nikoo Emtiazi, & Yasaman Moradi.	The study results indicate that HPV, particularly high-risk types such as HPV-16 and HPV-18, plays a role in the carcinogenesis of several urological cancers, especially penile cancer, with the highest prevalence of HPV-16 (68.3%), followed by HPV-6 (8.1%) and HPV-18 (6.9%). In addition, HPV infection is also associated with an increased risk of prostate, bladder, testicular, and kidney cancer, through mechanisms of chronic inflammation, DNA damage, activation of the E6/E7 oncoprotein, inactivation of the p53 and Rb tumor suppressor genes, and activation of molecular pathways such as PI3K/Akt/mTOR, EGFR, Wnt/β-catenin, and MAPK that trigger abnormal cell proliferation and cancer progression. The study also shows that HPV vaccination in men has the potential to reduce the incidence of HPV-related urological cancers.	HPV has significant carcinogenic potential in urologic cancers, particularly penile cancer, and may contribute to prostate, bladder, testicular, and kidney cancers through molecular changes and chronic inflammation. Research emphasizes the importance of HPV vaccination, early screening, and the development of molecular-based preventive strategies, particularly in men, to reduce the incidence of HPV-related urologic cancers and improve future disease prevention.
2022	Untold Story of Human Cervical Cancers: HPV-	This literature review method discusses HPV-negative/HPV-independent cervical cancer, examining	Jae-Eun Lee, Yein Chung, Siyeon Rhee,	The study results show that HPV-negative cervical cancer accounts for approximately 3–8% of	HPV-negative cervical cancer is an important but under-researched subtype,

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	Negative Cervical Cancer	epidemiological data, clinical characteristics, molecular mechanisms, diagnostic limitations, research models, gene mutations, and future research and therapy directions for HPV-negative cervical cancer. This study uses an analysis of various previous studies, clinical data, and molecular findings regarding HPV-negative versus HPV-positive cervical cancer.	& Tae-Hyung Kim	cervical cancer cases, but has a worse clinical prognosis than HPV-positive, characterized by more advanced FIGO stage, higher lymphatic metastasis, and lower overall survival (OS) and disease-free survival (DFS) rates. The study also found that HPV-negative cervical cancer has different biological characteristics, including mutations in genes such as TP53, KRAS, PTEN, PIK3CA, ARID1A, and is predominantly adenocarcinoma-type. Furthermore, there are still limitations in diagnostic methods, a lack of research models, and the absence of specific targeted therapies for HPV-negative.	despite its serious clinical impact and poorer prognosis than HPV-positive cervical cancer. Research emphasizes the need to develop more accurate diagnostic methods, research models (e.g., organoids), understand molecular mechanisms, and develop specific therapies based on the biological characteristics of HPV-negative cancers to improve patient outcomes.
2023	Impact of HR-HPV Infection on Oncological Outcomes in Early Cervical Cancer	This multicenter retrospective observational study (real-world study) used secondary data from the cervical cancer diagnosis and treatment database at 37 hospitals in China since 2004. The study involved 2061 patients with early stage FIGO IA1–IIA2 cervical cancer who underwent laparotomy, consisting of 153 HR-HPV negative patients and 1908 HR-HPV positive patients. All patients were examined using polymerase chain reaction (PCR) for HPV detection, and HR-HPV negative patients were re-examined twice. Analysis used Kaplan–Meier survival analysis, Cox proportional hazard regression, and propensity score matching (PSM) 1:1 to compare overall survival (OS) and disease-free survival (DFS) between HR-HPV positive and negative groups.	Xiaoqiang Su, Pan Liu, Hongwei Zhao, Lixin Sun, Wuliang Wang, Shuanglin Jin, Hui Wang, Ping Liu, Chunlin Chen, & Min Hao.	The results showed that before PSM matching, there was no significant difference in 5-year Overall Survival (OS) between the HR-HPV negative and positive groups (p=0.900), but there was a significant difference in Disease-Free Survival (DFS) (p=0.025) where HR-HPV negative patients had worse DFS. Cox analysis showed that HR-HPV status was an independent factor in DFS (p=0.022). However, after 1:1 PSM was performed to control for confounding factors (histopathology, LVSI, adjuvant therapy, stage, etc.), no significant difference was found in OS or DFS between the HR-HPV negative and positive groups. This indicates that the clinical prognosis of the two groups is relatively similar after clinicopathological factors are controlled.	The study concluded that early-stage HR-HPV-negative cervical cancer had similar oncological outcomes to HR-HPV-positive cervical cancer after controlling for clinicopathological factors that influence prognosis, suggesting that the therapeutic approach for HR-HPV-positive cervical cancer can also be applied to HR-HPV-negative cases. The study also emphasized that although HR-HPV-negative cervical cancer is rare, careful diagnostic approaches and clinical evaluation still require careful consideration because biological characteristics and other molecular factors can influence patient prognosis.
2021	Significance of p16 and HPV Genotype in HPV-Associated	This retrospective cohort study used data from 348 HPV-associated cervical	Sara da Mata, Joana Ferreira,	The results showed that HPV16 was the most common genotype (69%),	The study concluded that overexpression of p16, HPV16, and the

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	Cervical Cancer—A Large Cohort of Two Tertiary Referral Centers	cancer patients from two tertiary referral centers in Portugal and Spain. The study analyzed the relationship between p16 expression, HPV genotype, HPV genera, FIGO stage, histopathological characteristics, recurrence, and patient survival. The examinations were performed using HPV genotyping (SPF10 PCR-DEIA-LiPA25 system), p16 immunohistochemistry, histopathological evaluation, Kaplan–Meier survival analysis, univariate and multivariate Cox regression analysis, with a median follow-up period of 111.6 months..	Inmaculada Nicolás, Susana Esteves, Gonçalo Esteves, Sofia Lérias, Fernanda Silva, Adela Saco, Daniela Cochicho, Mário Cunha, Marta del Pino, Jaume Ordi, & Ana Félix.[40]	followed by HPV18 (14%), and the majority of patients had advanced stages (68%). Five percent of HPV-associated cervical cancer cases were p16-negative, which was more common in older patients, at more advanced stages, and with a poorer prognosis. Univariate analysis showed that HPV16 (p=0.0198), α-9 genera (p=0.0106), and p16 overexpression (p=0.032) were associated with better survival rates. Patients with HPV16 tumors had higher disease-free survival (DFS) and disease-specific survival (DSS) compared to other HPV types. However, in multivariate analysis, only initial FIGO stage was an independent prognostic factor for survival and recurrence.	α-9 genera were associated with a better prognosis in HPV-related cervical cancer, although they were not independent prognostic factors after controlling for FIGO stage and patient age. Furthermore, p16-negative HPV-related cervical cancers tended to be found in older patients, at a more advanced stage, and had a worse prognosis, thus requiring further clinical attention in the evaluation of prognosis and therapy of cervical cancer patients.
2019	Pathogenesis of Human Papillomavirus (HPV) in Cervical Cancer	The literature review method uses a literature search approach from various sources, such as books, articles, and scientific journals, related to the pathogenesis of HPV in causing cervical cancer in humans. The study was conducted by analyzing the mechanism of HPV infection, genome structure, viral life cycle, molecular mechanisms of the E6 and E7 proteins, and the development of cervical lesions into cervical cancer.	Paulina Rosa Evriarti & Andi Yasmon.[41]	The study results show that Human Papillomavirus (HPV), especially high-risk types (HR-HPV) such as HPV16 and HPV18, is the main cause of cervical cancer through persistent infection in cervical epithelial cells. The pathogenesis process begins with microabrasions in the cervical epithelium that allow HPV to enter the basal layer of the epithelium, replicate, and integrate viral DNA into the host cell genome. The integration of viral DNA causes disruption of the E2 gene, resulting in overexpression of the oncogenic proteins E6 and E7. The E6 protein inhibits the function of the p53 tumor suppressor protein, while E7 inactivates the retinoblastoma protein (pRb), so that apoptosis fails and cell division becomes uncontrolled (immortal cells). In addition, HPV is also able to evade the immune system by inhibiting interferon, macrophage	Research concludes that the mechanism by which HPV causes cervical cancer is complex, involving various viral proteins, particularly E6 and E7, which disrupt cell cycle regulation, fail apoptosis, and continuously proliferate abnormal cells. Persistence of HR-HPV infection is a major factor in the progression of precancerous lesions to cervical cancer, making understanding HPV pathogenesis crucial for developing strategies for prevention, early detection, and treatment of cervical cancer.

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				activity, NK cells, and dendritic cells, so that the infection becomes persistent and develops into Cervical Intraepithelial Neoplasia (CIN I–III) and invasive cervical cancer.	
2025	Comparison of Risk Factors and Clinical Manifestations of HPV 16 and HPV 18 in Cervical Carcinoma Patients	The analytical research method with a retrospective cohort approach uses secondary data from the research of Dr. dr. Andani Eka Putra, M.Sc and dr. Syandrez Prima Putra collected in the research master table. The sampling technique uses nonprobability sampling with convenience sampling of 38 respondents (19 HPV 16 and 19 HPV 18) with specimens stored in the Laboratory of the Diagnostic Center and Infectious Disease Research, Faculty of Medicine, Andalas University. Data analysis was carried out using Fisher's Exact Test to compare risk factors and clinical manifestations between HPV 16 and HPV 18 sufferers.	Aura Putri Anavelda, Andani Eka Putra, Defrin, Netti Suharti, Puja Agung Antonius, dan Elmatris.	The results of the study showed that women aged >45 years, early marriage (<20 years), low education, working as a housewife, and multiparity are characteristics that are often found in cervical carcinoma sufferers both HPV 16 and HPV 18. The results of statistical tests showed that there was no significant difference in risk factors between HPV 16 and HPV 18 ($p>0.05$), except for the age of marriage with a value of $p=0.038$. Clinical manifestations such as abnormal vaginal bleeding, bleeding after coitus, bleeding after menopause, abnormal vaginal discharge, pelvic pain, and swollen legs were also found in both groups without significant differences ($p>0.05$). Thus, sufferers of HPV 16 and HPV 18 have relatively similar risk factor characteristics and clinical manifestations	The study concluded that there was no significant comparison between the risk factors and clinical manifestations of HPV 16 and HPV 18 in cervical carcinoma patients, so that both HPV types had relatively similar clinical features. Significant differences were only found in the age of marriage factor, where early marriage (<20 years) was more common in HPV 16 patients. These findings indicate that although HPV 16 and HPV 18 are both high-risk HPVs, the clinical manifestations and risk factors in cervical carcinoma patients do not differ significantly.

Clinicopathological Characteristics of HPV-Related and HPV-Independent Cervical Cancer

Cervical cancer is one of the most common types of cancer in women worldwide, with the majority of cases associated with Human Papillomavirus (HPV) infection, particularly high-risk types such as HPV16 and HPV18. However, approximately 5–11% of cervical cancer cases are unrelated to HPV, known as HPV-independent cervical cancer. These two subtypes have significantly different clinicopathological characteristics, including clinical, histopathological, molecular, and prognostic aspects. HPV-related cervical cancer is usually found in women of reproductive age (around 35–44 years), with typical symptoms such as abnormal vaginal bleeding, pelvic pain, and vaginal discharge. In contrast, HPV-independent cervical cancer is more common in older women, particularly postmenopausal women (>50 years), with diagnosis often delayed due to less specific clinical symptoms and the limitations of standard HPV screening methods, which are insensitive to detecting HPV-negative lesions (Loayza et al., 2025).

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Histopathologically, HPV-related cervical cancers are predominantly squamous cell carcinoma (SCC) and usual-type adenocarcinoma, which exhibit strong and diffuse p16 expression as a biomarker of HPV infection. In contrast, HPV-independent cervical cancers are more often gastric, clear-cell, mesonephric, serous, and endometrioid adenocarcinomas, with negative or focal p16 expression and characteristic genetic mutations. Furthermore, HPV-independent cancers also exhibit more frequent lymphovascular invasion (LVSI), which is associated with a higher risk of metastasis and recurrence than HPV-related cancers (Shao, 2024; Wu et al., 2026).

The clinical prognosis of these two types of cervical cancer differs significantly. A recent meta-analysis showed that HPV-independent cervical cancer has a lower overall survival (OS) with a hazard ratio (HR) of 3.37 and worse progression-free survival (PFS) (HR 2.94), as well as a higher risk of metastasis and local recurrence (odds ratio/OR 2.76). Lymphovascular invasion is also more common in HPV-independent cancers (OR 3.00), indicating that this cancer is a more aggressive subtype and has a worse prognosis than HPV-related cancers. Patients with HPV-related cervical cancer tend to respond better to platinum-based chemotherapy and radiotherapy, while patients with HPV-independent cancers require a more specific and individualized therapeutic approach, including targeted therapy based on molecular mutations (precision medicine) (Shao, 2024; Giannella et al., 2025). The underlying molecular mechanism of HPV-related cervical cancer is the integration of HPV DNA into the host cell genome, leading to overexpression of the E6 and E7 oncoproteins. The E6 protein inactivates the tumor suppressor protein p53, while E7 inactivates the retinoblastoma protein (pRb), thereby inhibiting apoptosis and allowing abnormal cell proliferation. HPV-independent cervical cancer, on the other hand, develops without the involvement of HPV DNA, through mutations in genes such as TP53, KRAS, PIK3CA, and PTEN, which activate cell proliferation and survival signaling pathways. These differences in mechanisms explain the differences in therapeutic response and clinical aggressiveness between the two types of cervical cancer (Lee et al., 2022; Giannella et al., 2025; Wu et al., 2026).

The clinical implications of these differences are crucial for diagnosis and treatment. HPV-independent cervical cancer requires a more complex and comprehensive diagnostic approach, including immunohistochemistry (p16, p53), genetic mutation testing, and advanced imaging techniques for early detection and prognosis evaluation. The development of targeted therapies and precision medicine approaches are key to improving treatment outcomes in HPV-independent cancer patients, who are generally less responsive to standard therapies. In contrast, HPV-related cervical cancer can be effectively prevented through HPV vaccination and is more easily detected through HPV-based screening, which has significantly reduced the incidence of HPV-related cervical cancer in many countries. These differences in clinicopathological characteristics also emphasize the importance of risk stratification and treatment planning tailored to HPV status to achieve optimal clinical outcomes (He et al., 2025).

The limitations of conventional HPV screening methods in detecting HPV-independent cervical cancer pose a significant challenge in early detection. Therefore, the development of new biomarkers and advanced imaging technologies is urgently needed to improve the sensitivity of HPV-independent cancer diagnosis. 3,36 Meanwhile, HPV-related cervical cancer benefits greatly from widespread vaccination programs and routine HPV-based screening. Therefore, a thorough understanding of the differences in clinicopathological characteristics between HPV-related and HPV-independent cervical cancer is crucial for improving future strategies for cervical cancer prevention, diagnosis, and therapy (Shao, 2024; Kaisar et al., 2025).

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Conclusion

HPV-related cervical cancer is generally caused by high-risk HPV types such as HPV16 and HPV18. Its clinical characteristics include earlier onset, frequent diagnosis at an early stage, and a better prognosis compared to HPV-independent cervical cancer. Major risk factors include persistent HPV infection, early sexual activity, and multiparity. HPV-independent cervical cancer is a rarer subtype (3–20% of cases) and is often diagnosed at an advanced stage. Its clinical characteristics include higher lymphovascular invasion, greater tumor aggressiveness, and a poorer prognosis. Specific risk factors are not fully understood, but genetic mutations such as TP53, KRAS, and PIK3CA are characteristic. HPV-related cervical cancer is predominantly squamous cell carcinoma (SCC) with high p16 expression, while HPV-independent cervical cancer is more often gastric, mesonephric, clear cell, or endometrioid adenocarcinoma with negative or focal p16 expression. Different genetic mutations and molecular pathways are the main distinguishing features between these two subtypes. HPV-independent cervical cancer has a worse prognosis than HPV-related cervical cancer, with lower overall survival (OS) and disease-free survival (DFS). Furthermore, HPV-independent cervical cancer is more common in older patients and has a higher recurrence rate. HPV status influences cervical cancer prognosis. Patients with HPV-related cancer have a better response to chemotherapy and immunotherapy than patients with HPV-independent cancer. Furthermore, HPV-independent cancer is often difficult to detect through HPV-based screening, resulting in delayed diagnosis.

Suggestion

The development of more sensitive and specific diagnostic methods to differentiate between HPV-related and HPV-independent cervical cancer, especially in early stages, is essential to improve early detection and therapeutic effectiveness. Furthermore, further research into the molecular mechanisms and specific biomarkers of HPV-independent cervical cancer is crucial to support the development of targeted therapies and more personalized treatment approaches. HPV vaccination and HPV-based screening programs also need to be expanded to reduce the incidence of HPV-related cervical cancer, along with public education to raise awareness of the importance of early detection and prevention.

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