Chapter 17 / Capítulo 17

Screening, Diagnosis, and Prevention in Clinical Practice: Evidence from Argentine and Latin American Medicine (English Version)
ISBN: 978-9915-704-33-3
DOI: 10.62486/978-9915-704-33-3.Ch17
Pages: 236-247

Natural history and early diagnosis of cervical cancer

Historia natural y diagnóstico temprano del cáncer cérvico-uterino

Pablo Osuna[1], René German Laurito[1]

[1]Universidad Abierta Interamericana, Facultad de Medicina y Ciencias de la Salud. Carrera de Medicina, Rosario. Argentina.

ABSTRACT

Introduction: cervical-uterine cancer was presented as a public health problem of great magnitude, especially in developing countries, where it significantly affected female morbimortality. It was explained that this malignant neoplasm originated in the cervical epithelium, with a strong relationship with persistent infection by the human papillomavirus, particularly the high-risk genotypes 16 and 18. It was recognized that, although HPV was a necessary factor, it was not sufficient on its own, since immunological, behavioral and socioeconomic factors coexisted and favored the progression of the disease.
Development: the analysis described that most HPV infections resolved spontaneously within one to two years; however, a small group of women remained infected, resulting in precursor intraepithelial lesions. These lesions, if not diagnosed and treated promptly, evolved into invasive carcinoma within 10 to 20 years. The Papanicolaou test, introduced in the 1940s, made it possible to reduce incidence and mortality in countries with organized screening programs, although its sensitivity varied according to the quality of the sample and the experience of the personnel. Therefore, complementary techniques such as colposcopy and molecular detection of HPV DNA were incorporated in certain contexts.
Conclusions: it was concluded that cervical cancer was largely preventable by controlling risk factors and implementing effective screening programs. The combination of diagnostic strategies, together with education and equitable access to health services, was essential to decrease the burden of this disease in vulnerable populations.

Keywords: Cervical Cancer; Human Papillomavirus; Papanicolaou; Prevention; Screening; Human Papilloma Virus.

RESUMEN

Introducción: el cáncer cérvico-uterino se presentó como un problema de salud pública de gran magnitud, especialmente en países en desarrollo, donde afectó significativamente la morbimortalidad femenina. Se explicó que esta neoplasia maligna se originó en el epitelio del cuello uterino, con fuerte relación con la infección persistente por el virus del papiloma humano, particularmente los genotipos de alto riesgo 16 y 18. Se reconoció que, aunque el VPH constituyó un factor necesario, no fue suficiente por sí solo, ya que coexistieron factores inmunológicos, conductuales y socioeconómicos que favorecieron la progresión de la enfermedad.
Desarrollo: el análisis describió que la mayoría de las infecciones por VPH se resolvieron espontáneamente en uno o dos años; sin embargo, un grupo reducido de mujeres mantuvo la infección, lo que derivó en lesiones intraepiteliales precursoras. Estas lesiones, si no fueron diagnosticadas y tratadas oportunamente, evolucionaron hacia carcinoma invasor en un periodo de 10 a 20 años. El test de Papanicolaou, introducido en la década de 1940, permitió reducir

la incidencia y mortalidad en países con programas organizados de detección, aunque su sensibilidad varió según la calidad de la muestra y la experiencia del personal. Por ello, en determinados contextos se incorporaron técnicas complementarias como la colposcopía y la detección molecular del ADN del VPH.
Conclusiones: se concluyó que el cáncer cérvico-uterino fue en gran medida prevenible mediante el control de factores de riesgo y la implementación de programas de tamizaje efectivos. La combinación de estrategias diagnósticas, junto con la educación y el acceso equitativo a los servicios de salud, resultó esencial para disminuir la carga de esta enfermedad en las poblaciones vulnerables.

Palabras clave: Cáncer Cérvico-Uterino; Virus Del Papiloma Humano; Papanicolaou; Prevención; Tamizaje.

INTRODUCTION

Cervical cancer (CC) is a major public health problem worldwide, especially in developing countries, where it is one of the leading causes of morbidity and mortality in women. This malignant neoplasm originates in the epithelium of the cervix, mainly in the transformation zone, where the squamous epithelium of the exocervix and the columnar epithelium of the endocervix converge. The progression of CCU can compromise not only the cervical tissue but also adjacent structures of the lower genital tract, underscoring the importance of early diagnosis and timely management.

The etiology of CCU is closely linked to persistent infection with human papillomavirus (HPV), particularly high-risk genotypes such as HPV-16 and HPV-18. Although HPV infection is a necessary condition for the development of the disease, it is not sufficient on its own; immunological, behavioral, socioeconomic, and environmental factors interact in carcinogenesis. These include early onset of sexual activity, multiple partners, immunosuppression, smoking, and lack of access to screening programs, all of which increase women's vulnerability to viral persistence and the progression of precursor lesions.

The natural course of HPV infection is, in most cases, self-limiting: the immune system clears the virus within 1 to 2 years. However, in a small subset of women, the infection persists, leading to cellular alterations that can progress to low- or high-grade squamous intraepithelial lesions. If these lesions are not identified and treated promptly, they can progress to invasive carcinoma over an estimated 10 to 20 years. The prolonged time frame of this progression offers a crucial window of opportunity to implement secondary prevention strategies through early detection programs.

In this context, the Pap test has historically been the most widely used screening tool worldwide. Introduced in the 1940s, this cytological method has significantly reduced the incidence and mortality of cervical cancer in countries with organized screening programs. However, its sensitivity can vary depending on the quality of the sample and the experience of the personnel, which, in some settings, has led to the incorporation of complementary techniques, such as colposcopy or molecular detection of HPV DNA.

Thus, CCU is a largely preventable disease through the control of risk factors and the proper implementation of screening programs. Understanding its definition, etiology, natural history, and the limitations of traditional diagnostic tools is essential to advancing more effective health

strategies that reduce its burden in the most vulnerable populations.

DEVELOPMENT

Cervical cancer: definition and etiology

Cervical cancer is a malignant neoplasm that originates from epithelial cells in the cervix. This neoplasm develops at the squamocolumnar junction, an area of the cervix where the stratified squamous epithelium of the exocervix meets the simple columnar epithelium of the endocervix, and extends into the transformation zone of these epithelia. As it progresses, the cancer can compromise neighboring tissues by contiguity, affecting adjacent structures of the lower genital tract (Burd, 2003).

This type of cancer is mainly caused by persistent HPV infection, especially by high-risk genotypes such as HPV-16 and HPV-18 (Cohen et al., 2019). HPV infection is a necessary but not sufficient condition for the development of this cancer, as additional factors, such as the host's immune response and environmental factors, also play a crucial role in carcinogenesis (Arbyn et al., 2020).

Several factors have been identified that are associated with an increased risk of developing OC, among which the following stand out:

- HPV infection: Main etiological factor. Persistence of infection with high-risk HPV genotypes is necessary (but not sufficient) for the development of OC (Bosch et al., 2020).
- Sexual behavior: Early onset of sexual activity and multiple sexual partners increase the risk of HPV infection (Castellsagué et al., 2018).
- Socioeconomic factors: Women of low socioeconomic status are at greater risk due to lack of access to health services and screening programs, resulting in late diagnosis and poorer control of HPV infection (Kuguyo et al., 2017).
- Immunological factors: A compromised immune system, as in the case of HIV infection, increases the risk of HPV persistence and progression to cervical cancer (Clifford et al., 2017).
- Smoking: Smoking has been associated with an increased risk of developing ASCLC (Plummer et al., 2003).

Natural history of HPV infection

HPV is a highly prevalent sexually transmitted virus, with 80 % of the general population exposed at some point in their lives. It has a double-stranded circular DNA and belongs to the Papillomaviridae family. There are more than 200 HPV types, divided into two main categories: low-risk genotypes and high-risk oncogenic genotypes (Doorbar et al., 2012).

Low-risk genotypes mainly include types 6 and 11, which are responsible for most genital warts. These genotypes are rarely associated with the development of invasive carcinoma (De Sanjosé et al., 2017).

On the other hand, high-risk oncogenic genotypes, such as types 16 and 18, are strongly associated with cervical cancer. In fact, HPV 16 and HPV 18 are responsible for approximately 70 % of cervical cancer cases (Muñoz et al., 2003).

HPV infection can cause precursor lesions in the lower genital tract, which, if not detected and treated promptly, can progress to invasive carcinoma within 10 to 20 years (Muñoz et al., 2003). The persistence of infection and the interaction of the virus with the host's immune

system are crucial factors in the progression to cancer (Degenhardt et al., 2019).

The natural history of HPV infection begins with the acquisition of the virus, usually through sexual contact. In most cases, the host's immune system clears the infection within 1 to 2 years. However, in a minority of women, the infection persists and can cause cellular changes in the cervical epithelium. These alterations can progress to low- or high-grade squamous intraepithelial lesions and eventually to invasive cervical cancer if not detected and treated early (Castle et al., 2012). The persistence of infections caused by high-risk oncogenic genotypes is a key factor in the development of cervical cancer (Trottier & Franco, 2006).

The Pap test and its value in screening

Screening using the Pap test has proven to be an effective tool in reducing the incidence and mortality of cervical cancer in countries with organized screening programs (Arbyn et al., 2020). It was first introduced in the 1940s and uses exfoliative cytology to detect abnormal cells in the cervix early. These abnormal cells may indicate precursor lesions that, if left untreated, can progress to invasive carcinoma (Koss, 1989). The main objective of the Pap test is to detect squamous intraepithelial lesions (SILs), which are classified by degree of dysplasia (Solomon et al., 2022).

In terms of its predictive value, studies have shown that the Pap test's PPV varies widely across contexts and populations, but is generally around 60 %, underscoring the need for diagnostic confirmation by biopsy in positive cases (Meggiolaro et al., 2016). The test's sensitivity is also influenced by several factors, such as sample quality, collection technique, and pathologist interpretation (Nayar & Wilbur, 2015).

The Pap test has been the cornerstone of cervical cancer screening programs in many countries. However, its diagnostic capabilities, especially in rural settings or areas with limited infrastructure, have been questioned. A recent study conducted in a hospital in Peru compared the effectiveness of the PAP test with colposcopy and found that, although both methods are useful, colposcopy showed greater sensitivity (93,3 %) for detecting high-grade lesions than the PAP test (78,9 %) (Chacón-Byrne et al., 2024). These findings suggest that, in certain contexts, combining both methods could improve diagnostic accuracy.

Classification of Precursor Lesions of CCU

Precancerous lesions of the cervix are classified according to their degree of dysplasia, with the Bethesda system being the most used to categorize cellular abnormalities detected in cervical cytology. This system organizes cytological findings into the following categories:

- ASC-US (Atypical squamous cells of undetermined significance): This category includes cellular changes that do not meet the criteria for squamous intraepithelial lesions or malignancy, but whose nature is uncertain. Although most ASC-US cases are associated with transient HPV infections, a small proportion may present more significant lesions. This classification indicates the need for further studies to rule out low- or high-grade dysplasia.
- ASC-H (Atypical squamous cells, cannot exclude high-grade intraepithelial lesion): This diagnosis refers to atypical cellular changes that are not conclusive for high-grade intraepithelial lesions, but they cannot be ruled out either. ASC-H cases are more likely to be associated with high-grade lesions and, therefore, require a more thorough diagnostic evaluation.
- L-SIL (Low-grade squamous intraepithelial lesions): These lesions include cellular

changes associated with initial HPV infections and mild dysplasia. They represent low-risk lesions but may progress if not managed appropriately.

- HSIL (High-grade squamous intraepithelial lesions): This category includes moderate to severe dysplasia and carcinoma in situ. HSILs have a higher risk of progressing to invasive carcinoma if not treated promptly (Solomon et al., 2002).

Other older classifications have been modified over time. However, they are still relevant today, so it is important to be familiar with them and their correlation with the Bethesda System (table 1).

In 1968, the term cervical intraepithelial neoplasia (CIN) was introduced to describe the spectrum of cellular atypia confined to the epithelium. CIN was divided into grades 1, 2, and 3 (Richart, 1968). CIN 1 corresponded to mild dysplasia, CIN 2 to moderate dysplasia, and CIN 3 to severe dysplasia and carcinoma in situ (CIS). In the 1980s, more anatomopathological alterations, such as koilocytic or condylomatous atypia, associated with HPV infection were recognized. Koilocytes are atypical cells with cytoplasmic cavitation or a perinuclear halo, indicating cytopathic changes due to HPV infection. This led to the development of a simplified two-grade histological system called the "Bethesda System" (Solomon et al., 2002).

Its main feature was the creation of the term "squamous intraepithelial lesion" (SIL), with two grades: low-grade lesions (LSIL) and high-grade lesions (HSIL). The Bethesda classification combines flat condylomatous changes (HPV) and low-grade CIN (CIN 1) in LSIL, while HSIL covers the more advanced CIN, CIN 2, and CIN 3. The term lesion was used to emphasize that the morphological changes on which a diagnosis is based do not necessarily indicate a neoplastic process (Nayar & Wilbur, 2015).

Table 1. Correlation between Cervical Intraepithelial Lesion Classifications

Precursor Lesion	Bethesda System	Old Classification (CIN)	Reference
Low-grade squamous intraepithelial lesion grade	LSIL	CIN 1 (Cervical intraepithelial neoplasia grade 1)	Solomon et al., 2002
High-grade squamous intraepithelial lesion intraepithelial lesion grade	HSIL	CIN 2 AND CIN 3 (Cervical intraepithelial neoplasia grades 2 and 3)	Wright et al., 2001
Carcinoma in situ	Carcinoma in situ	CIN 3	Sherman et al., 2003

As shown in figure 1, low-grade lesions (LSIL/CIN 1) affect only the lower third of the cervical epithelium. In contrast, high-grade lesions (HSIL/CIN 2 and CIN 3) affect the upper two-thirds of the epithelium and are more likely to progress to invasive carcinoma if left untreated (Solomon et al., 2002).

The long interval between initial infection and the onset of obvious disease suggests that several cofactors (genetic differences, hormonal effects, micronutrient deficiencies, smoking, or chronic inflammation) may be necessary for the disease to progress. Spontaneous regression of precursor lesions also suggests that many women may not be exposed to these cofactors. Several studies have addressed the natural history of HPV lesions, emphasizing regression, persistence, and progression of the disease (Holowaty et al., 1999; McIndoe et al., 1984; Melinkow et al., 1998; Mitchell et al., 1994; Ostor et al., 1993). They have revealed that most low-grade lesions

are transient; in most cases, they return to normal within a relatively short period of time or do not progress to more severe forms.

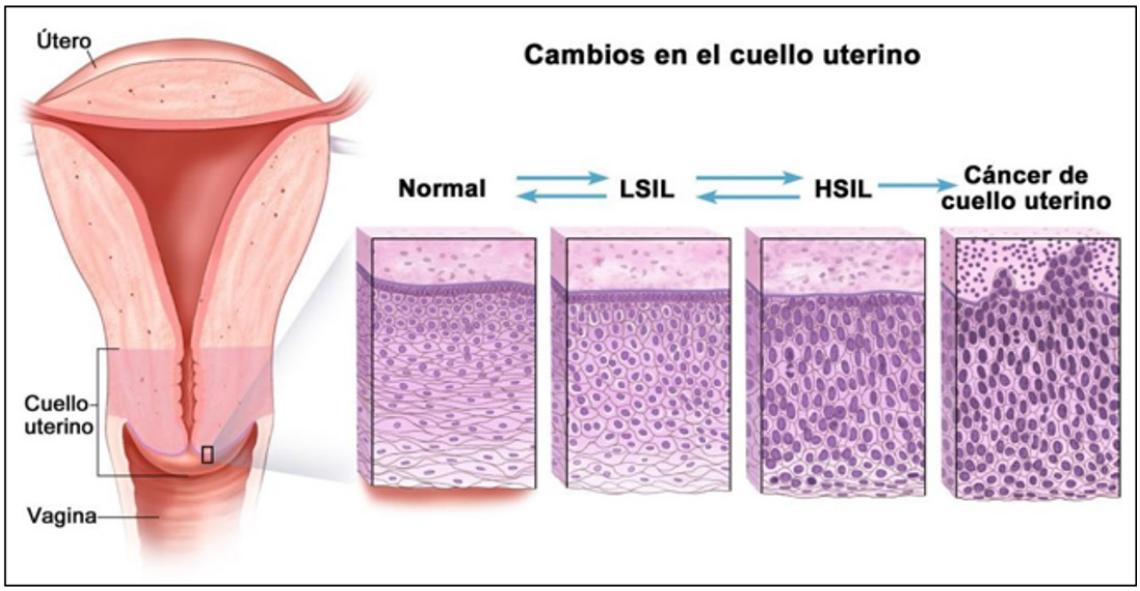

Figure 1. Changes in the cervix (National Cancer Institute, n.d.)

In contrast, HSIL is much more likely to develop into invasive cancer, although some of these lesions also persist as such or regress. The average interval for precursors to progress to invasive cancer ranges from 10 to 20 years. Some studies have attempted to summarize the rates of regression, persistence, and progression of SILs. Only about 10 % will have a persistent infection with a high-risk viral type, which may contribute to the development of the disease. In 90 % of cases, these are transient infections that, if they cause lesions, have a high rate of spontaneous regression related to the host's immune response. Thus, low-grade intraepithelial lesions (L-SIL) have a regression rate without treatment of 75 % in those over 25 years of age and 90 % in those under 25 years of age (Toziano et al., 2022).

Cytological-histological correlation in the diagnosis of precursor lesions

Cytological-histological correlation is a key process in validating PAP test results and confirming the diagnosis of precursor lesions of cervical cancer. This correlation compares cytological findings from PAP tests with histological results from cervical biopsies, which are considered the gold standard for definitive diagnosis (Nayar & Wilbur, 2015).

The accuracy of the Pap test in detecting precursor lesions depends on multiple factors, including the quality of the sample, the cytotechnician's ability to identify abnormal cells, and the pathologist's interpretation. Cytological-histological correlation allows evaluation of the consistency between the cytological preliminary diagnosis and the histological confirmation, which is crucial for validating the effectiveness of the Pap test as a screening method (Bishop et al., 2019).

The literature shows that cytological-histological correlation is variable. In some studies, high concordance between cytological and histological results has been observed, with rates

ranging from 70 % to 90 % for HSIL diagnoses (Reeves et al., 2018). However, agreement tends to be lower in diagnosing LSIL due to the greater difficulty in distinguishing these lesions from benign changes such as inflammation or atrophy (Stoler & Wright, 2020). These differences underscore the importance of confirming cytological findings with biopsy, especially in LSIL, where variability in interpretation can lead to false positives or false negatives (Sherman et al., 2021).

Several studies have investigated cytological-histological correlation in different clinical settings. For example, a study by Sherman et al. (2021) at a referral center showed that cytological-histological concordance for HSIL diagnoses reached 85 %, while for LSIL, concordance was 65 %. These differences highlight the importance of accurate diagnosis in cervical cytology and the need for histological confirmation, particularly in LSIL cases.

Another study, conducted by Arbyn et al. (2017), reviewed cytological-histological correlation in different patient cohorts in Europe, noting that variability in results was influenced by factors such as staff training, interpretation guidelines used, and HPV prevalence in the study population. These findings suggest that implementing uniform standards and providing ongoing training are essential to improve diagnostic accuracy and, therefore, cytological-histological correlation.

Cytological-histological correlation is not only important for validating Pap test results but also has direct clinical implications. A high correlation indicates that the test is reliable for correctly identifying precursor lesions, allowing for appropriate patient management. On the other hand, low correlation can lead to overtreatment or, in the worst case, to a lack of adequate treatment in patients with significant lesions (Sasieni et al., 2009).

Factors influencing cytological-histological correlation

- Sample quality: Proper sample collection is essential to ensure that cells representative of the transformation zone of the cervix, where most precursor lesions originate, are obtained. Poorly collected or insufficient samples can lead to false-negative results, decreasing concordance with histological findings (Miller et al., 2003).
- Cytological interpretation: The experience of the cytotechnician and pathologist in interpreting samples is crucial. Low-grade lesions, in particular, can be difficult to identify and differentiate from benign reactive changes, leading to lower cytological-histological correlation (Bishop et al., 2019).

In addition, the subjectivity inherent in cytological interpretation can lead to variations between observers, affecting the consistency of diagnoses (Sherman et al., 2003).

- Type of lesion: The nature of the lesion also influences cytological-histological correlation. High-grade lesions (HSIL) tend to show greater concordance between cytology and histology because of their more distinct cellular characteristics. In contrast, low-grade lesions (LSIL) and glandular lesions may show less concordance due to their greater morphological variability (Nayar & Wilbur, 2015).
- Complementary techniques: The use of complementary techniques, such as immunocytochemistry or HPV DNA detection, can improve cytological-histological correlation by providing additional information on the presence of high-risk infections or markers of cell proliferation (Sankaranarayanan et al., 2003).

All these factors can influence cytological-histological correlation, affecting both the

sensitivity and specificity of the Pap test.

Challenges in implementing screening in developing countries

Despite the widely recognized effectiveness of the Pap test in the early detection of precursor lesions of cervical cancer, its implementation in developing countries faces several significant challenges. Among the main obstacles are a lack of access to adequate health services, scarcity of organized screening programs, and insufficient follow-up of positive cases. These limitations not only reduce the effectiveness of the PAP as a screening tool but also underscore the urgent need to adapt detection strategies to local realities (Sankaranarayanan et al., 2001).

Variability in PAP sensitivity across settings is a critical factor that underscores the need to consider complementary approaches. In many developing countries, where health infrastructure is limited and access to trained personnel is scarce, PAP alone may not be sufficient to ensure early and accurate diagnosis. A recent study in Peru, for example, revealed that although PAP remains a commonly used practice, its sensitivity may not be adequate to detect all high-grade intraepithelial lesions, which could lead to late diagnoses and, consequently, less effective treatments (Chacón-Byrne et al., 2024). These challenges highlight the importance of integrating new technologies and complementary methods, such as colposcopy and HPV testing, which could overcome some of the inherent limitations of PAP. Adapting screening programs to the specific conditions of each region would not only improve the detection of precursor lesions but also enhance the effectiveness of screening. However, it could also significantly reduce cervical cancer mortality in these areas (Arbyn et al., 2020).

CONCLUSIONS

Cervical cancer (CC) is a complex and persistent challenge for global public health, especially in developing countries where social and economic inequalities and unequal access to healthcare services increase women's vulnerability. Throughout this work, it has been shown that the etiology of CCU is closely linked to persistent infection with human papillomavirus (HPV), particularly high-risk genotypes such as HPV16 and HPV18. However, the mere presence of the virus is not sufficient for cancer to develop, as multiple cofactors—immunological, behavioral, and environmental—condition the progression to precursor lesions and, eventually, to invasive carcinoma.

The natural history of HPV infection, characterized by its generally self-limiting course, offers a significant window of opportunity for intervention. This 10- to 20-year interval between initial infection and the onset of invasive cancer underscores the importance of early diagnosis and sustained preventive strategies. The Pap test, despite its limitations in sensitivity and variability in interpretation, has proven to be a fundamental tool in reducing incidence and mortality in countries with organized programs. Its historical contribution is undeniable, although evidence suggests that its effectiveness is optimized when combined with complementary techniques such as colposcopy or molecular detection of HPV DNA.

Likewise, the classification of precursor lesions, whether using the CIN or Bethesda system, has enabled a more systematic approach to cellular alterations, distinguishing risk and guiding clinical management. Cytological-histological correlation, although subject to variability, is an essential process for validating diagnostic accuracy and avoiding both overdiagnosis and undertreatment. However, the effectiveness of these tools depends largely on the quality of the sample, the staff's experience, and access to complementary techniques.

The analysis has also highlighted the challenges developing countries face in implementing effective screening programs. Lack of infrastructure, shortage of trained personnel, and insufficient follow-up limit the effectiveness of PAP and lead to late diagnoses. Given this situation, it is urgent to adapt screening strategies to local conditions, integrate new technologies, promote continuous training, and strengthen health systems.

In summary, CCU is largely preventable when comprehensive public health policies, community education, and accessible, effective screening programs are combined. The challenge lies in reducing gaps between countries and within regions themselves, ensuring that women, regardless of their context, have access to quality diagnostic tools. Only then will it be possible to sustainably reduce the burden of this disease and move toward health equity.

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