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HUMAN PAPILLOMAVIRUS AND CERVICAL LESIONS: A COMPREHENSIVE REVIEW

PAPILOMA VÍRUS HUMANO E LESÕES CERVICAIS: UMA REVISÃO ABRANGENTE

VIRUS DEL PAPILOMA HUMANO Y LESIONES CERVICALES: UNA REVISIÓN INTEGRAL

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Ingrid Correia Bruno Estevão[1], Isabella Vilaça Ferreira[2], Natielle Cristina Silva de Oliveira[3], Lara Verônica de Araújo Lopes[4]

ABSTRACT

Cervical cancer remains a major public health challenge, especially in developing countries, and is strongly associated with persistent infection by oncogenic types of Human Papillomavirus (HPV). This article addresses the main molecular mechanisms involved in cervical carcinogenesis, highlighting the action of the viral oncoproteins E6 and E7 on tumor suppressor genes and their role in the progression of squamous intraepithelial lesions to invasive carcinoma. The relevance of the cervicovaginal cytopathological examination as a central screening tool is discussed, as well as the contribution of complementary methods, such as DNA-HPV detection tests using liquid-based cytology samples, to improve diagnostic accuracy. From a clinical perspective, the differential diagnosis of lesions is of utmost importance, as treatment is guided by the type of lesion. In the context of prevention, strategies aimed at reducing the risk of cervical cancer development are discussed, including preventive measures related to HPV infection. It is emphasized that this article focused exclusively on squamous cervical lesions, which are responsible for the majority of precursor alterations of cervical cancer.

Keywords: Human Papillomavirus. Cervical Cancer. Cervical Lesions. HPV. Prevention.

RESUMO

O câncer do colo do útero continua sendo um importante desafio de saúde pública, especialmente em países em desenvolvimento, estando fortemente relacionado à infecção persistente por tipos oncogênicos do Papilomavírus Humano (HPV). Este artigo aborda os principais mecanismos moleculares envolvidos na carcinogênese cervical, com destaque para a ação das oncoproteínas virais E6 e E7 sobre genes supressores tumorais e sua participação na progressão das lesões intraepiteliais escamosas até o carcinoma invasor. Discute-se a relevância do exame citopatológico cérvico-vaginal, como ferramenta central de rastreamento, bem como a contribuição de métodos complementares, como os testes

[1] Undergraduate student in Biomedicine. Centro Universitário UNA. E-mail: ingridd.bruno@gmail.com
[2] Undergraduate student in Biomedicine. Centro Universitário UNA. E-mail: isabellavilacaf@gmail.com
[3] Undergraduate student in Biomedicine. Centro Universitário UNA.
E-mail: natielle.biomed.com.br@gmail.com
[4] PhD in Cell Biology. Universidade Federal de Minas Gerais (UFMG). E-mail: laraveronica@gmail.com

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para detecção do DNA-HPV, a partir de amostras de citologia em meio líquido, para o aprimoramento do diagnóstico. Sob a perspectiva clínica, o diagnóstico diferencial das lesões se mostra de extrema importância, uma vez que o tratamento é norteado pelo tipo de lesão. No contexto da prevenção, são abordadas estratégias voltadas à redução do risco de desenvolvimento do câncer cervical, incluindo medidas preventivas relacionadas à infecção pelo HPV. Destaca-se que este artigo se concentrou exclusivamente nas lesões cervicais escamosas, responsáveis pela maioria das alterações precursoras do câncer do colo do útero.

Palavras-chave: Papilomavírus Humano. Câncer do Colo de Útero. Lesões Cervicais. HPV. Prevenção.

RESUMEN

El cáncer de cuello uterino continúa siendo un importante desafío de salud pública, especialmente en los países en desarrollo, y está fuertemente relacionado con la infección persistente por tipos oncogénicos del Virus del Papiloma Humano (VPH). Este artículo aborda los principales mecanismos moleculares involucrados en la carcinogénesis cervical, con énfasis en la acción de las oncoproteínas virales E6 y E7 sobre los genes supresores tumorales y su participación en la progresión de las lesiones intraepiteliales escamosas hasta el carcinoma invasor. Se discute la relevancia del examen citopatológico cérvico-vaginal como herramienta central de cribado, así como la contribución de métodos complementarios, como las pruebas de detección del ADN-VPH a partir de muestras de citología en medio líquido, para el perfeccionamiento del diagnóstico. Desde la perspectiva clínica, el diagnóstico diferencial de las lesiones resulta de suma importancia, ya que el tratamiento se orienta según el tipo de lesión. En el contexto de la prevención, se abordan estrategias dirigidas a reducir el riesgo de desarrollo del cáncer cervical, incluidas medidas preventivas relacionadas con la infección por VPH. Se destaca que este artículo se centró exclusivamente en las lesiones cervicales escamosas, responsables de la mayoría de las alteraciones precursoras del cáncer de cuello uterino.

Palabras clave: Virus del Papiloma Humano. Cáncer de Cuello Uterino. Lesiones Cervicales. VPH. Prevención.

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1 INTRODUCTION

Cervical cancer is the most prevalent type in women in the world. According to the José Alencar Gomes da Silva National Cancer Institute (INCA), for the year 2025 17,010 new cases were estimated, with a death toll of 7,209. Currently, it is known that HPV has more than 200 subtypes, of which 40 are related to genital lesions, and of these, 20 are considered high risk, that is, they are more predisposed to carcinogenesis (PIRES, GOUVÊA, 2001). One of the characteristics of these viruses is the ability to remain in the body for long periods without manifesting, being able to take action at any time in life. HPV 16, 18 and 31 are the most frequent associated with cervical intraepithelial neoplasms (CIN) and invasive cancers (CARVALHO *et al;* 2000).

Lesions that develop in the squamous epithelium (squamous lesions) have different degrees of evolution, and can be histologically classified as cervical intraepithelial neoplasia (CIN), grade I, II, and III. In the Bethesda nomenclature, the terms Low *Grade Squamous Intraepithelial Lesion (LSIL)* and High-grade squamous intraepithelial lesion (*High Grade Squamous Intraepithelial Lesion – HSIL)* (LIMA, 2002).

LSILs (which correspond to CIN I) are transient viral infections that cause only minimal changes and abnormalities in the infected epithelium. This is because, generally, this type of infection has a low oncogenic risk and has high percentages of natural elimination by the host (EGAWA; DOORBAR, 2017). HSIL-type lesions, which correspond to CIN II and III), with greater potential to evolve into cervical cancer, occur when HPV infection prevents the maturation of the epithelium and leads to disordered replication of immature cells with numerous genetic abnormalities (BASEMAN; KOUTSKY, 2005).

2 STRUCTURE OF THE HPV VIRUS

Human Papillomaviruses are agents that cause tumors, both benign and malignant, on the skin and mucous membranes. They belong to the *Papillomaviridae* family, genus *Papillomavirus*, and the Human *Papillomavirus* species – HPV – is one of the eight species in this genus. HPVs are classified into genotypes based on analysis of L1 gene sequences. Its genome, consisting of approximately 8,000 base pairs, is circular and consists of two strands of DNA, containing eight genes and a non-coding region that regulates the replication and expression of transcription regulatory genes. HPV infection initially occurs in the cells of the deepest layer of the infected tissue, and the viral genome can remain in a circular (episomal) shape within the nucleus of the host cell, or integrate with DNA. This integration

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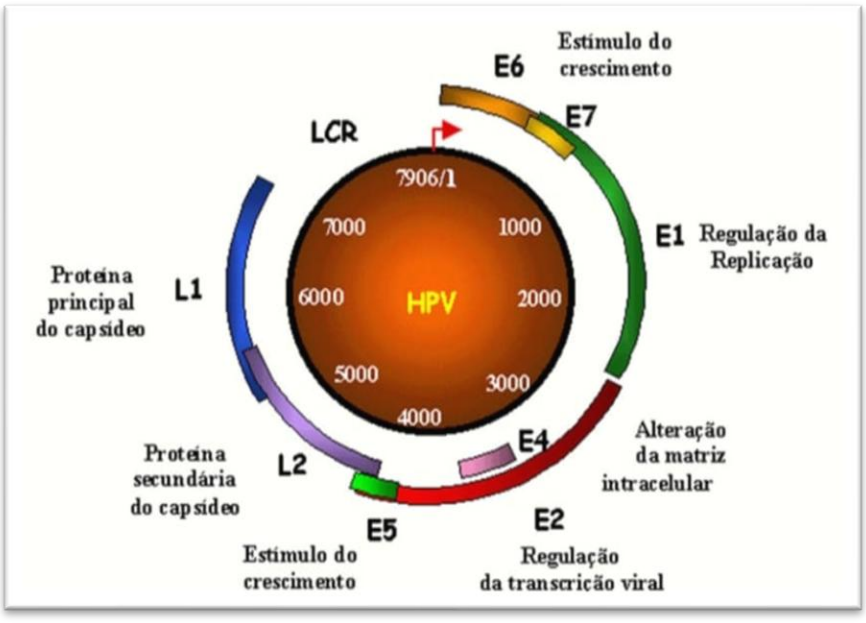
has an impact on the expression of early oncoproteins, which are responsible for cell transformation (CAMARA *et al;* 2003).

The early early stages of infection involve cellular transformations and DNA replication. The proteins encoded by each portion of the genome have different functions. Regarding the proteins corresponding to the "E" region of the viral genome, called early, proteins E1 to E7 stand out, which play crucial roles in viral replication and cell transformation. E1 is involved in the initiation of DNA replication, while E2 regulates DNA transcription and controls the expression of E6 and E7. The E4 and E5 proteins initiate transcription before the start of active viral replication and are expressed in increased amounts in cells in the saturation state. E6 and E7 are responsible for cell transformation, interacting with proteins such as p53 and pRb, respectively, which are important tumor suppressor genes, leading to their inactivation. The late twin genes L1 and L2 encode proteins expressed mainly in the upper epithelial layers, where the assembly of the structural proteins of the viral capsid occurs, as described in figure 1 (NARISAWA-SAITO; KIYONO, 2007).

Figure 1

Representative scheme of the HPV genome



Schematic representation of the Human Papillomavirus (HPV) genome, highlighting the main coding regions and their functions. Capsid proteins (L1 and L2) are related to viral structure; early genes (E1, E2, E4, E5, E6, and E7) play roles in the regulation of replication,

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viral transcription, intracellular matrix alteration, and stimulation of cell growth; and the LCR region corresponds to a non-coding area of control. **Source: adapted from Pereira (2011, p.16).**

2.1 HPV BIOLOGICAL CYCLE

The biological cycle of HPVs begins when viral particles invade cells in the deepest layer of the epithelium, which are still in the process of cell division. Microcracks imperceptible to the naked eye, present in this epithelium, allow the virus to reach these cells. Viral genetic material penetrates the host cell through the interaction between capsid proteins and specific receptors on the cell surface. In vitro studies have identified alpha-6 integrin as one of the cellular receptors for *Papillomaviruses* (EVANDER *et al.,* 1997; Mc MILLAN *et al.,* 1999).

Upon entry into the cell, the virus loses its protective capsule (capsid), exposing its DNA to the action of nuclear enzymes, thus facilitating the expression of viral genes. After infection, the virus enters an incubation period that can last 2 to 3 weeks, before the development of lesions begins. In addition, another mechanism of the virus allows DNA to remain inactive in the cell, both before and after a productive infection (ORIEL, 1971)

2.2 PATHOGENESIS OF CERVICAL LESIONS

According to the behavior of the virus within the nucleus of the host cell, it is possible to define the oncogenic risk of the associated lesions. Low-risk HPVs usually keep their DNA in a circular or episomal state, replicating in an extrachromosomal fashion. In contrast, high-risk HPVs suffer breakdowns from their original physical form, which allows them to integrate into the host's DNA. In this process, the E2 portion of the viral genome is lost, which is responsible for transcriptional control, functioning as a regulator of the expression of E6 and E7 oncoproteins. The overexpression of these proteins promotes cell proliferation by interacting with the p53 and pRb proteins, respectively, which regulate this process, inhibiting its functions. Thus, the uncontrolled expression of E6 and E7 proteins of HPVs with high oncogenic potential has the ability to make primary human keratinocytes immortal (ZIMMER *et al;* 2020).

Chromosomal mutations resulting from the integration of viral DNA promote significant functional modifications, such as loss of heterozygosity and activation of proto-oncogenes. In addition, there is a loss of mechanisms that are crucial for the prevention of cervical

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carcinogenesis. These genetic and functional alterations facilitate the development of cervical cancer, highlighting the critical role of high-risk HPVs in oncogenesis (ZIMMER *et al;* 2020).

In clinical practice, many HPV infections go unnoticed and regress naturally, without causing harm to the woman. Although HPV infection is an important factor in the development of cervical cancer, it alone is not enough to transform a normal cell into a neoplastic cell. Cervical carcinoma is a relatively rare occurrence even in women infected with the virus, and other factors are necessary to influence its progression, such as smoking, but also the prolonged use of contraceptives, multiple sexual partners, early initiation of sexual intercourse, among others (DERCHAIN *et al;* 2005).

Smoking has a prominent place among these factors. The carcinogens present in cigarettes induce the formation of adducts (chemical changes in DNA), causing mutations and promoting the disordered multiplication of HPV-infected cells.

Considering the pathogenesis of HPV, smoking can exert an influence by promoting changes in viral DNA and accelerating its life cycle, thus increasing the potential for damage to the cervical epithelium. Cigarette components, such as benzopyrene, nicotine, and their derivatives, have demonstrated in studies the ability to compromise the local defense mechanisms of the cervical epithelium *(*UTAMI *et al;* 2021*).*

3 DIAGNOSIS OF CERVICAL LESIONS

3.1 CYTOLOGICAL AND MOLECULAR EXAMINATION

Among the morphological methods used to identify and classify lesions, the conventional cytological method continues to be widely used in cervical cancer screening; however, the introduction of liquid cytology (CML) has brought some benefits to the method, since it standardizes and automates the preparation of slides, reducing the number of preparation artifacts and optimizing morphological visualization by professionals. In addition, CML preserves biological material (DNA, RNA, and proteins), allowing molecular tests to be performed from the same sample collected for morphological examination, without the patient having to perform a new collection (UTAGAWA *et al;* 2004).

Among the molecular methods used to identify the presence of viruses, hybrid capture and PCR (Polymerase Chain Reaction) stand out. Both are based on the ability of complementary DNA or RNA sequences to bind to each other. Among these techniques, PCR is recognized as the most sensitive method today, being widely used in research because it

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allows the amplification of small amounts of specific sequences of the virus in millions of copies, enabling the identification of genetic material even in the absence of evident clinical signs (Rocha, 2019).

3.2 CLASSIFICATION OF CERVICAL INJURIES

The cervical-vaginal cytopathological test, popularized as the Pap smear method, represents a milestone in the secondary prevention of cervical cancer. Its main purpose is the identification of cellular morphological alterations for precursor or malignant lesions, guiding diagnostic and therapeutic work-ups (ALRAJJAL *et al;* 2021).

Initially, the cytological classification proposed by Pap smears categorized cervical smears into a system of five progressive risk classes, ranging from Class I (cytological normality) to Class V (conclusive cytology for malignancy). Subsequently, the cytohistological correlation and the understanding of the natural history of *Human Papillomavirus* (HPV) infection led to the development of the concept of Cervical Intraepithelial Neoplasia (CIN). However, the nomenclature currently adopted on a global scale is the *Bethesda* System. This system improved the diagnostic correlation and reproducibility of the reports, stratifying Squamous Intraepithelial Lesions *(SIL)* into two distinct prognostic categories (INSTITUTO NACIONAL DE CÂNCER; MINISTÉRIO DA SAÚDE, 2006).

Low-Grade Squamous Intraepithelial Lesion *(LSIL)* encompasses cytopathic manifestations of productive HPV infection, usually with a low risk of progression. In low-grade neoplastic lesions, it is common to find numerous koilocytes in the upper layers of the epithelium, indicating a possible HPV infection, as illustrated in Figure 2. Cervical cancer is known to not develop immediately in patients, but usually results from the progression of precursor lesions over several years before they become invasive (MELO, 2018).

LSIL is extremely prevalent and has a high potential for regression, especially in women under 30 years of age. It is already well described in the literature that around 47.4% of LSIL regress within 24 months and only 0.2% of women progress to invasive carcinoma. (NATIONAL CANCER INSTITUTE, 2016).

In women with LSIL and a positive test for oncogenic HPV types, there is a significant increase in the risk of developing Cervical Intraepithelial Neoplasms of grade 2 or higher, as well as with CIN of grade 3 or higher, in a period equivalent to five years compared to women with LSIL and a negative HPV-DNA test (INSTITUTO NACIONAL DO CÂNCER, 2016).

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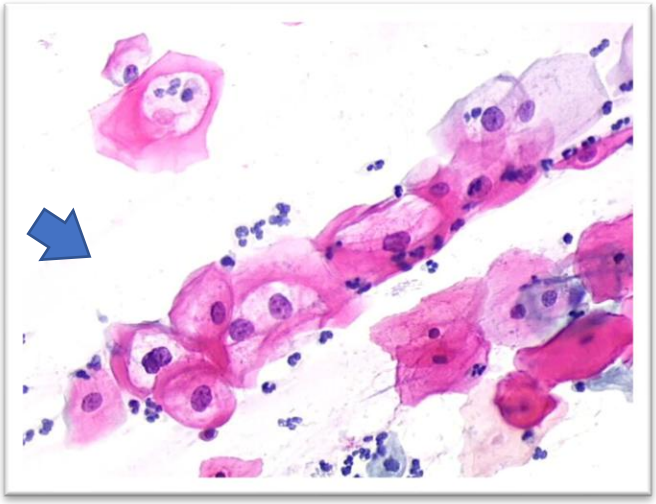
Figure 2

Low-grade intraepithelial lesion



Mature squamous cells showing accentuated perinuclear halo (arrow), thickened cytoplasmic borders, and slightly enlarged nucleus, compatible with koilocytes, associated with low-grade lesion. (obj. 20x). **Source**: adapted from Histopathology and Cytopathology of the Uterine Cervix – Digital Atlas. IARC, 2004.

In high-grade squamous intraepithelial lesion (HSIL), it corresponds to the alterations previously classified as cervical intraepithelial neoplasia (CIN) grades II and 3III. The current terminology for HSIL was introduced by the *Bethesda* System for Cervical Cytology Reporting (TBS) and later also adopted for histological samples by the LAST *(Lower Anogenital Squamous Terminology*) Consensus Conference and the World Health Organization (WHO) in 2012 and 2014, respectively (DARRAGH, 2015).

Among the high-risk genotypes, HPV 16 and 18 are the most frequently identified, being found in more than 70% of cases of HSIL and cervical squamous cell carcinomas. These viral types are strongly related to persistent infection and have a higher risk of progression to invasive cervical cancer. The estimated risk of a patient developing HSIL when she has a positive HPV test associated with an abnormal Pap smear is approximately 20%, increasing to 33% when HPV positivity is observed in more than one test (MASSAD *et al.*, 2013).

From a diagnostic point of view, about 60% of women with HSIL-compatible cytology will have at least CIN 2 on biopsy, while approximately 2% will be diagnosed with invasive cancer, the latter being more frequent in older women. In addition, in women over the age of

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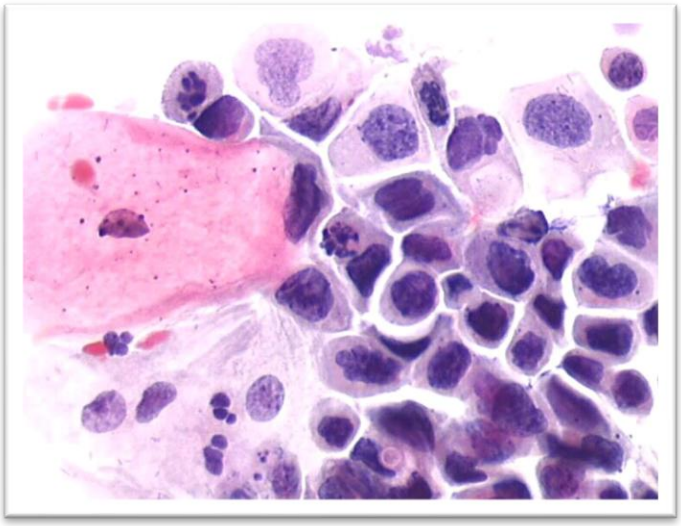
30, the cumulative risk of cervical cancer within five years of HSIL diagnosis is approximately 8%. Diagnostic confirmation is performed by means of biopsies obtained during colposcopy, which are later histologically analyzed (KHIEU; BUTLER, 2023).

Morphologically, these cells are smaller in size and with lower cytoplasmic maturity than those of LSIL, the cytoplasm can be keratinized and must present a high ratio between the nucleus and the cytoplasm, as illustrated in image 3. In addition, they are often hyperchromatic and the nuclear contours must be distinctly irregular (KHIEU; BUTLER, 2023).

For differentiation criteria from HSIL to LSIL, the reduction in cell maturation, the increase in the nucleus-cytoplasmic ratio, the disorganization of the epithelial layers, with loss of polarity, in addition to nuclei more varied in shape and size, with irregular contours, represented in image 5 (KHIEU, BUTLE, 2023) stand out.

Figure 3

High-grade intraepithelial lesion



Immature cells agglomerated, with enlarged, hyperchromatic nucleus and irregular contour (obj. 40x). **Source**: adapted from Histopathology and Cytopathology of the Uterine Cervix – Digital Atlas. IARC, 2004.

Invasive Cervical Carcinoma corresponds to an established malignant neoplasm of the cervix, characterized by the invasion of the cervical stroma by neoplastic cells, representing the progression of high-grade squamous intraepithelial lesions when not properly diagnosed or treated.

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Invasive cervical carcinoma is a malignant neoplasm of the cervix caused, in more than 99% of cases, by persistent infection by oncogenic types of the Human Papillomavirus (HPV), especially genotypes 16 and 18 (WANG *et al.,* 2018). Progression to cancer occurs when there is viral persistence associated with additional risk factors, such as smoking, immunosuppression, and co-infection with multiple HPV types (MILANO *et al.,* 2023). At the molecular level, viral oncoproteins E6 and E7 interfere with cell cycle control mechanisms by inactivating tumor suppressor proteins p53 and pRB, promoting genomic instability and malignant transformation of cervical cells (ROMERO-MASTERS *et al.,* 2022).

Squamous cell carcinoma is the most frequent histological subtype of invasive cervical carcinoma, while Adenocarcinoma, which corresponds to cancer that develops within the endocervical canal, represents a smaller proportion, although its incidence is increasing in some countries (FOWLWE *et al.,* 2023).

In the early stages, invasive cervical carcinoma can be asymptomatic, which reinforces the importance of screening through Pap smears and testing for high-risk HPV. The definitive diagnosis is established by biopsy, usually performed after colposcopic evaluation of cytological alterations (BURNESS; SCHROEDER; WARREN, 2020).

From the morphological point of view, invasive cervical carcinoma presents evident alterations in cytology and colposcopy. Cytologically, the presence of immature malignant cells with varied shapes (pleomorphism), marked anisocytosis, hyperchromasia, irregular nuclei with macronucleoli, typical and atypical mitoses, as illustrated in Figure 4, is observed. On colposcopy, invasive carcinoma manifests itself as hypertrophic leukoplakia, gross punctation, atypical large vessels, and frankly carcinomatous proliferation, findings compatible with tumor invasion (FILIPPIN, 2004).

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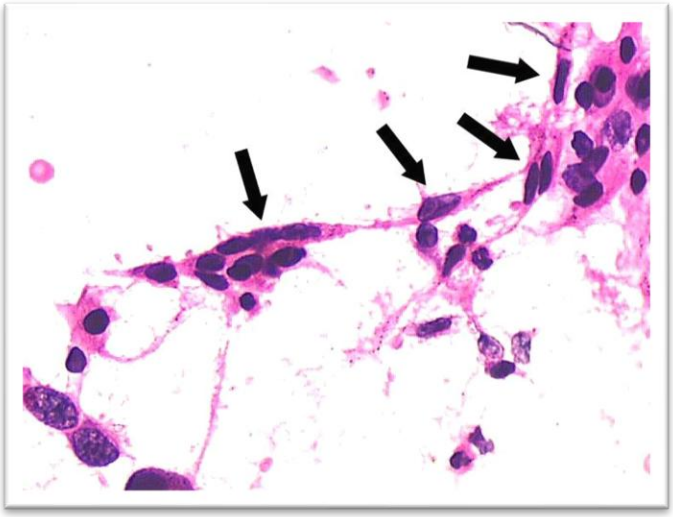
Figure 4

Squamous cervical carcinoma



In the arrows, pleomorphic malignant cells (elongated) can be observed, a morphological characteristic distinct from normal squamous cells (obj. 40x). **Source:** adapted from Histopathology and Cytopathology of the Uterine Cervix – Digital Atlas. IARC, 2004.

The system also includes categories of atypical *Squamous Cells of Undetermined Significance (ASC-US) and Atypical Squamous Cells of Undetermined Significance (ASC-H) in which Atypical Squamous Cells, Cannot Exclude a High-Grade Lesion*, which direct specific clinical conducts according to the risk stratum (INSTITUTO NACIONAL DE CÂNCER; MINISTÉRIO DA SAÚDE, 2006).

5 EPIDEMIOLOGY

Human Papillomavirus (HPV) infection is considered the most common sexually transmitted infection in the world and has a high prevalence among sexually active women, with rates varying according to age group and other population characteristics. Epidemiological studies have shown that the prevalence of HPV can be significant in young women, remaining relevant in age groups up to around 50 years of age, indicating that most sexually active women are exposed to the virus throughout their lives (DUNNE *et al.,* 2007).

In longitudinal studies of prolonged follow-up, progression of low-grade to high-grade lesions is observed in only about 11% of cases. This scenario presents a significant clinical dilemma: while any therapeutic intervention may be considered exaggerated, adding unnecessary stress and additional costs, the absence of treatment for persistent lesions may

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increase the increased risk of developing invasive cancer. After a period of 24 months, the rate of regression of lesions decreases, indicating that persistent lesions should be approached therapeutically. Unfortunately, the absence of an ideal marker to identify women at higher risk of progression makes it difficult to stratify and select the best course of action. As a result, several therapeutic modalities, including ablative therapies such as electrical cauterization, laser, or cryotherapy, as well as excisional interventions such as excision of the transformation zone or conization with a diathermic loop or cold scalpel, can be performed (DERCHAIN *et al;* 2005).

Due to the increase in the incidence of preneoplastic cervical lesions among adolescents, the importance of studying the behavior of these alterations in the age group corresponding to this period of women's lives is highlighted. A better understanding of these changes can contribute to the development of intervention strategies that reduce the morbidity and mortality rates associated with this neoplasm (PEDROSA *et al.,* 2008).

The prevalence of cervical cancer varies significantly between countries, being higher in developing nations. This disparity is attributed to social factors, such as levels of education and awareness of self-care, which are generally lower in these regions. In addition, household income and access to prevention resources play a crucial role. In the United States, for example, the incidence of cervical cancer is higher among black women and immigrants. This highlights the relevance of social factors within the same country, when analyzing the prevalence of the disease in the population (MENDES, 2018).

6 PREVENTION

Primary prevention refers to the measures taken to avoid contact with the virus, preventing lesions from developing. This prevention is carried out through immunization, specifically vaccination, which confers protection against the virus (INTERAMINENSE *et al.,* 2016; GUEDES *et al.,* 2017). In the last ten years, significant advances in the understanding of the body's response to HPV infection have resulted in the development of highly immunogenic vaccines, which require reduced doses of antigens and have the ability to induce the production of genotype-specific neutralizing antibodies. Highly available vaccines mainly target types 16 and 18, which are primarily responsible for cervical carcinomas, as well as types 6 and 11, which are associated with most cases of condylomas. The most recently developed vaccine covers nine types of HPV (6,11,16,18,31,33,45, 52 and 58), known as Nonavalente (DERCHAIN *et al;* 2005).

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Currently, Brazil has three types of HPV vaccines: bivalent, quadrivalent and nonavalent. Scientific evidence shows that the bivalent vaccine (Cervarix®) induces high titers of antibodies against HPV genotypes 16 and 18, being able to prevent infection by these types for a period of at least ten years. In addition, it is more than 60% effective in preventing precancerous cervical lesions, regardless of the type of HPV involved or the previous presence of viral infection (Oliveira *et al*., 2023).

The quadrivalent vaccine (Gardasil®) confers protection against HPV genotypes 6, 11, 16 and 18, demonstrating excellent efficacy in the prevention of cervical HPV infections, precursor lesions of cervical cancer and genital warts associated with the covered viral types. Additional studies indicate that the use of Gardasil® significantly reduces HPV infections in other anatomical regions, such as the anus, vulva, penis, and oral cavity, related to the types included in the vaccine (MOURA *et al*., 2021).

In turn, the nonavalent vaccine, which is not yet offered by the SUS, (Gardasil® 9) expands coverage by including, in addition to the genotypes already contemplated in the quadrivalent, types 31, 33, 45, 52 and 58. The nonavalent vaccine was approved by ANVISA in March 2023 and has demonstrated high efficacy in preventing infections and precursor lesions of cervical cancer, reaching rates above 95% when administered before exposure to HPV. In addition, there was an approximate reduction of 90% in the incidence of vulvar diseases and 80 to 85% in vaginal diseases (TOH *et al.,* 2019). In the Brazilian public health network, the vaccine available free of charge is the quadrivalent Gardasil® (Oliveira *et al.,* 2023).

In Brazil, vaccination began in 2014, initially aimed at girls aged 11 to 13 years, with the administration of two doses at an interval of six months. In 2016, the MINISTÉRIO DA SAÚDE approved the expansion of the program, and in 2017, vaccination was also released for boys (GUEDES *et al.,* 2017; HINO *et al.,* 2016; SILVA, 2015, KRABBE *et al.,* 2016). In 2025, the MINISTÉRIO DA SAÚDE expanded the campaign to include young people aged 15 to 19 who missed the immunization in the recommended period

Secondary prevention of cervical cancer consists of the early detection of lesions before they evolve to an invasive condition. This early prevention can be carried out through screening techniques , which include oncotic colpocytology (Pap smear), colposcopy and histopathological tests (PINHO, JUNIOR, 2003). Cervicovaginal cytology is used by most successful screening programs in the world. The Pap smear, the main tool for secondary prevention globally, consists of the study of exfoliated cells of the ectocervix, JEC and

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endocervix, which are subsequently examined by microscopic visual inspection (MENDES, 2018).

Tertiary prevention is carried out after the diagnosis of the disease, seeking to limit damage, control progression and offer rehabilitation, and may include ablative surgery, radiotherapy and/or chemotherapy. Ideally, these services should be integrated with primary care, facilitating the rapid referral of patients diagnosed with cancer and post-treatment follow-up (MENDES, 2018).

For screening programs to be fully effective in reducing mortality, it is essential that Pap smears are widely known and accepted by the population, in addition to being performed at appropriate intervals to detect the disease in its early stages. Many authors state that the early detection of cervical cancer depends on comprehensive population coverage, in addition to an organized program. This indicator, defined as the proportion of the population at risk that was screened, is one of the crucial aspects to be evaluated in the screening process (MINISTÉRIO DA SAÚDE; INCA, 2016).

7 TECHNICAL CONDUCTS

According to the guidelines of the Ministério da Saúde and the *Bethesda* system, it is essential that Pap smear reports contain detailed information on the quality of the sample, and the collection should be repeated whenever the sample collected is not adequate. In addition, laboratories can provide reports that include information about the sample collected by each professional. This information is crucial to guide the need to change the collection technique, aiming to improve quality indicators. When a smear does not provide adequate visualization of cervical lesions, there are no interventions available to reduce false negatives (FRANCO *et al*; 2006).

During colposcopy, it is possible to target the biopsy specifically to the lesion. Patients who do not undergo biopsy should be followed up with cytology and semiannual colposcopy, adopting a specific action according to the following results (INSTITUTO NACIONAL DO CÂNCER, 2011).

8 TREATMENT

The decision about how to treat women with whiplash injuries varies depending on several factors. The therapeutic approach for patients with cervical intraepithelial neoplasms is a widely debated topic in clinical practice. Failure to treat these conditions can result in

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progression to more severe lesions or an invasive carcinoma. This progression is partly associated with the degree of the lesion, i.e., the more pronounced the degree of abnormality analyzed in the histological results, the greater the probability of progression to a more severe lesion, thus accelerating its development. Therefore, while Low-Grade Intraepithelial Lesions (CIN1) can be monitored by observation and depending on the woman's age, High-Grade Intraepithelial Lesions (CIN2 and CIN3) require an intervention aimed at the complete destruction of the abnormal epithelium, preferably through cervical excision. It is important to emphasize that many patients diagnosed with CIN2 may express spontaneous regression of their lesions, not requiring immediate treatment (OLIVEIRA *et al.,* 2011).

High-frequency surgery (LEEP) has several advantages over cold conization, since it is an outpatient procedure performed under local anesthesia, has a low risk of complications, and is simplified to perform. The primary goal of this procedure is the complete removal of the cervical intraepithelial neoplasia (CIN) along with the squamocolumnar junction (SCJ). Indications for LEEP include grade 2 and 3 neoplasms, persistent high-grade cytology with poor colposcopy or negative biopsy, and discrepancies between cytology and histology. On the other hand, it is not indicated for invasive carcinoma and adenocarcinoma, for which more invasive procedures are recommended (Lima *et al;* 2011)

Due to reports of considerable thermal damage complicating the analysis of surgical margins, the use of electrosurgical techniques in the excisional treatment of preinvasive glandular diseases is controversial. In addition, scalpel conization is associated with a higher proportion of free margins compared to electrosurgery (INSTITUTO NACIONAL DO CÂNCER (NATIONAL CANCER INSTITUTE, 2006).

For patients diagnosed with cervical cancer or precancerous lesions, surgery is the primary therapeutic modality. According to recommendations from the *National Comprehensive cancer Network (NCCN)* and the European Society of Medical Oncology *(EMSO),* in cases of advanced, invasive or metastatic cancer, surgical options include simple or radical hysterectomy, trachelectomy (removal of the uterine cervix) and radical pelvic surgical approach.

The choice of procedure depends on factors such as the histological nature of the tumor, its size, the staging of the disease, and the patient's clinical history. In addition to the surgical approach, in more advanced stages, radiotherapy, chemotherapy and immunotherapy can be used, with the aim of promoting apoptosis of neoplastic cells and facilitating their elimination by the immune system (BOON *et al;* 2022).

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9 CONCLUSION

Based on the content presented, it is concluded that cervical cancer is closely related to persistent infection by oncogenic HPV types, especially genotypes 16 and 18, being the result of a progressive process that involves well-characterized cytomorphological and molecular alterations. Early recognition of squamous intraepithelial lesions, together with the appropriate use of cytopathological examination, molecular methods, and correct classification by the Bethesda System, is essential to prevent progression to invasive forms of the disease. In addition, HPV vaccination and organized population screening programs stand out as essential strategies for reducing the incidence and mortality associated with cervical cancer, reinforcing the importance of integrating primary and secondary prevention and appropriate clinical conduct.

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