LUMEN ET VIRTUS

Cervical cancer: From diagnosis to treatment

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Maria Gabryella Pereira da Silva Camarço[1]
Davi Nogueira Jales[2]
Cadidja Suzzi Oliveira Leitão[3]
Alcides Mendes da Luz Filho[4]
Isabella Kittlaus[5]
Emília Moura Silva[6]
Maria Eduarda Campêlo dos Santos[7]
Vilmar Barbosa de Sousa Junior[8]
Maria Clara Barbosa de Almeida[9]
Francisberg Dias Coêlho[10]
Antonio de Pádua Andrade Júnior[11]
Sarah Nicoly Romualdo Frota[12]
Matheus de Pádua Macedo Andrade[13]
Claudia Helena Cerqueira Mármora[14]

ABSTRACT

Introduction: Cervical cancer is primarily caused by Human Papillomavirus (HPV) infection and remains a global public health concern. Methodology: This article performs an integrative review of the literature, covering national and international scientific articles. Databases such as VHL, SciELO, LILACS and PubMed were consulted to compile the information. Discussion: Early diagnosis is essential and can be carried out through the Pap smear test and, more recently, by the detection of HPV. Treatment varies depending on the stage of the disease and may include surgery, radiation therapy, chemotherapy, or a combination of these modalities. Conclusion: Advances in research have improved the understanding of the mechanisms of cervical cancer development, influencing public health policies to promote effective prevention strategies, such as mass vaccination programs and educational campaigns.

Keywords: Cervical Cancer, Diagnosis, Treatment.

[1] Uninovafapi University Center
[2] Faculty of Technology of Teresina – CET
[3] Faculty of Technology of Teresina – CET
[4] Faculty of Technology of Teresina – CET
[5] Faculty of Technology of Teresina – CET
[6] Faculty of Technology of Teresina – CET
[7] Faculty of Technology of Teresina – CET
[8] Faculty of Technology of Teresina – CET
[9] Faculty of Technology of Teresina – CET
[10] Faculty of Technology of Teresina – CET
[11] Faculty of Technology of Teresina – CET
[12] FAMENE
[13] Faculty of Technology of Teresina – CET
[14] Professor at the Faculty of Physical Therapy of the Federal University of Juiz de Fora

INTRODUCTION

Cervical cancer (CC) is a disease characterized by slow progression and a well-documented natural history, allowing it to be screened, detected early, and treated effectively, providing a good prognosis. The practice of screening not only has great potential to save lives, but also to significantly reduce costs and burdens on health systems. (Ferreira et al., 2022)

In developed countries, a decrease in cervical cancer cases has been observed since the beginning of cytological screening programs. However, about 11,000 cases and 4,000 deaths still occur annually in the United States. On the other hand, the disease remains a significant problem in developing countries, where screening is limited. Cervical cancer is the second most common type of cancer among women worldwide, with an estimated 490,000 new cases per year. (Brazil, 2021).

There are more than 150 different types of HPV (Human Papilloma Virus) that are capable of infecting the skin or mucous membranes, of which 40 can infect the genital tract. Of these, 12 are high-risk and can cause cancers of the cervix, vulva, vagina, penis, anus, and oropharynx, and others can cause genital warts (Carvalho et al., 2018). There are 15 high-risk HPVs currently identified, but HPV-16 alone accounts for nearly 60% of cervical cancer cases, and HPV-18 another 10% of cases; other types of HPV individually contribute to less than 5% of cases. High-risk HPVs are also associated with squamous cell carcinomas that arise in many other sites, including the vagina, vulva, penis, anus, palatine tonsils, and other sites of the oropharynx (Carneiro et al., 2019; Brazil, 2021).

Non-genital HPV infection is most often identified as common and plantar warts, especially in children and adolescents, where prevalence rates range from 3% to 20%. People who are immunosuppressed or who are receiving immunosuppressive therapy can present all forms and manifestations of HPV infection (Morais et al., 2021).

The control of this malignant neoplasm is relevant in comprehensive women's health care, and the best strategy to cope with it has been screening, by identifying precursor lesions and alterations in the initial phase of the disease in asymptomatic women before progressing to invasive disease. Screening, carried out through Pap smears, recognized worldwide as efficient and safe, has as its main objective, in the long term, to impact the epidemiological profile, reducing the morbidity and mortality associated with the disease (Ferreira et al., 2022).

Thus, the main objective of this study is to understand the knowledge about cervical cancer, through the analysis of national and international scientific production indexed in electronic databases.

METHODOLOGY

It is an integrative literature review that has a broad character and proposes to describe the development of a given subject, from a theoretical or contextual point of view, through analysis and

interpretation of existing scientific production, carried out in the period of July 2024. It seeks to highlight clinical aspects of cervical cancer as well as diagnosis and treatment. For the selection of articles, the descriptors cervical cancer, diagnosis and treatment were applied, together with the AND operator, which were used in combination in searches in the electronic databases LILACS, MedLine/Pubmed and Google Scholar. Original articles with full texts in Portuguese and English, published between 2010 and 2024, were included. Duplicate articles in the databases, those not available in full text, and review articles were excluded.

RESULTS AND DISCUSSION

RISK FACTORS, CLINICAL MANIFESTATIONS AND PREVENTION

Infection with the HPV virus (human papillomavirus), especially the oncogenic subtypes, is the main risk factor for the development of cervical cancer, with more than 97% of cervical cancer cases containing HPV DNA. Subtypes 16, 18, 31, 35, 39, 45, 51, 52, 56 and 58 are responsible for the majority of cases of invasive cancer (Bosch et al., 1995).

In addition, risk factors include early onset of sexual activity (before age 16), a high number of lifelong sexual partners, and a history of genital warts (Chichareon et al., 1998).

In addition, immunosuppressed women, especially those being treated with immunosuppressive drugs, have a higher risk of developing this neoplasm. Smoking is also a significant risk factor; Tobacco-specific carcinogens can be found in the mucus and cervical epithelium, where they can cause damage to cellular DNA, facilitating the neoplastic process (Kjellberg et al., 2000).

Cervical cancer, in its initial phase, is often asymptomatic or has mild symptoms, which means that many patients do not seek medical help early (SUNG et al., 2000). As cancer develops, it can grow locally, affecting the vagina, paracervical tissues, and parametriums, and can compromise the bladder, ureters, and rectum. Distant dissemination occurs mainly through the lymphatic route, initially involving the pelvic lymph nodes and, later, the para-aortic lymph nodes (WAGGONER, 2003).

The clinical presentation of cervical cancer depends mainly on the location and extent of the disease. Symptoms may include yellowish, foul-smelling, or bloody vaginal discharge, irregular menstrual cycles, intermenstrual spotting, postcoital bleeding, and pain in the lower abdomen. In more advanced stages, the patient may experience significant abdominal pain, anemia due to bleeding, low back pain due to ureteral involvement, hematuria, voiding changes due to bladder invasion, and changes in bowel habits due to rectum invasion. Patients may also experience pain in the lumbar spine and pelvic region due to pelvic wall involvement (PRETORIUS et al., 1991)

The prevention of invasive cervical cancer is based on education, vaccination, screening,

diagnosis, and treatment of subclinical lesions. The disease usually begins at the age of 30, with cervical intraepithelial lesions that can progress to invasive carcinomas, with increasing incidence until the age of 50. The main risk factor is human papillomavirus (HPV) infection, although more than 90% of new HPV infections regress spontaneously in six to 18 months. There are 13 HPV types recognized as oncogenic by the IARC, with HPV-16 and HPV-18 types being the most common. Persistence of HPV infection is the greatest risk factor, with factors such as smoking, use of immunosuppressants, and HIV immunosuppression contributing to this.

The HPV vaccine is an effective tool in the prevention of cervical cancer. In Brazil, the Ministry of Health incorporated the tetravalent HPV vaccine into the vaccination schedule in 2014, initially for girls aged 9 to 13 years. From January 2017, vaccination was extended to boys aged 12 to 13, with the age range being gradually broadened through 2020 to include boys aged 9 to 13. The vaccination schedule consists of two doses, with an interval of six months for girls and boys (Universidade Aberta do SUS, 2017). The vaccine protects against HPV subtypes 6, 11, 16 and 18, the first two being responsible for genital warts and the last two for about 70% of cervical cancer cases. It is important to emphasize that even vaccinated women should undergo the preventive exam at the recommended age, as the vaccine does not offer protection against all oncogenic subtypes of HPV.

In Brazil, cervical cancer screening, recommended by the Ministry of Health, is done through cytopathological testing in women aged 25 to 64 years. The routine involves repeating the Pap smear every three years, after two consecutive normal exams with an interval of one year (INSTITUTO NACIONAL DE CÂNCER, 2023). The effectiveness of the cervical cancer control program depends on the organization, comprehensiveness, and quality of services, as well as the treatment and follow-up of patients.

DIAGNOSIS AND TREATMENT

According to the Ministry of Health, cervical cancer screening should be carried out through the cytological test, known as the Pap smear. This exam should be started at the age of 25 for women who have already started sexual activity, regardless of whether they are pregnant or not. After two consecutive negative tests with an interval of one year, the following tests can be performed every three years. Screening in women under 25 years of age is not recommended to avoid the diagnosis and treatment of asymptomatic precursor lesions (INSTITUTO NACIONAL DE CÂNCER (NATIONAL CANCER INSTITUTE, 2016).

For women over the age of 64, screening can be stopped if there are at least two consecutive negative tests in the last five years and no history of cervical pathology. In postmenopausal women, estrogenization prior to test collection may improve the quality of the smear. Those who have

undergone total hysterectomy for benign lesions, with no history of high-grade cervical lesions, may also be excluded from screening, as long as their previous examinations have been normal (INSTITUTO NACIONAL DE CÂNCER, 2016).

For immunosuppressed women, cytologic testing should be performed after initiation of sexual activity at six-monthly intervals in the first year and, if normal, continue with annual follow-up for as long as immunosuppression factor persists. HIV-positive women should undergo the cytological examination every six months. Some national and international guidelines recommend the use of HPV detection tests, associated with cytology, for women aged 30 years or older, due to the higher sensitivity and high negative predictive value of these tests, allowing the interval between collections to be extended from three to five years when both tests are negative (PEIRSON et al., 2013; GIRIANELLI et al., 2016).

The success of the screening program depends on its organized performance, including the periodic performance of the test (every three years) in women aged 25 to 64 years, the sending of invitations to perform the test to 95% of women, the collection of the cytological test in 85% of women, the appropriate management of altered results in 85% of women, and the maintenance of good quality control of the tests and treatments performed (INSTITUTO NACIONAL DE CÂNCER, 2016).

The Pap smear remains the most widely used method in Brazil and in the world for screening cervical cancer and its precursor lesions (INSTITUTO NACIONAL DE CÂNCER, 2016; NAYAR; WILBUR, 2015). This test aims to detect negative or positive cells for intraepithelial neoplasia or malignancy in the ectocervix and endocervix of women with apparently normal cervix, based on changes in the degree of cytoplasmic maturation, presence of abnormal mitotic figures, and changes in the shape and size of the nucleus.

Currently, the most widely used classification for cytological results is the Bethesda classification, updated in 2014, which categorizes results as negative cytology for intraepithelial lesion and malignancy, or with squamous or glandular cell abnormalities, with progressive degrees of atypia, from indeterminate atypia to cytological alterations suggestive of invasive carcinoma (NAYAR; WILBUR, 2015). The most common collection method is conventional cytology, although liquid-based cytology is increasingly used in developed countries. Liquid-based cytology offers advantages in sample quality, reducing artifacts and allowing the detection of HPV in the same material collected (HODA et al., 2013). Comparative studies have shown that the accuracy of liquid-based cytology is comparable to that of conventional cytology, although its large-scale implementation in Brazil depends on cost-benefit analyses.

Colposcopy is a complementary technique recommended for women with positive cervical cytology results in screening programs (INSTITUTO NACIONAL DE CÂNCER, 2016). This test

must be conducted by qualified and trained professionals, and is inappropriate as a primary screening method for cervical cancer (INSTITUTO NACIONAL DE CÂNCER, 2016). Colposcopy enables several important functions:

- Evaluation of pre-invasive and invasive lesions of the cervix;
- Complementation to conventional screening methods;
- Determination of the extent of the lesions;
- Guidance for biopsies of suspicious areas;
- Assistance in treatment with procedures such as cryotherapy or LEEP;
- Monitoring after treatment of pre-invasive lesions of the cervix.

Chart 1: Recommendations from the Febrasgo Manual for the initial conduct of altered cytopathological test results.

DIAGNÓSTICO CITOPATOLÓGICO		FAIXA ETÁRIA	CONDUTA INICIAL
Células escamosas atípicas de significado indeterminado (ASCUS)	Possivelmente não neoplásticas (ASC-US)	< 25 anos	Repetir em 3 anos
		Entre 25 e 29 anos	Repetir a citologia em 12 anos
		≥ 30 anos	Repetir a citologia em 6 anos
	Não se podendo afastar lesão de alto grau (ASC-H)		Encaminhar para colposcopia
Células galndulares atípicas de significado indeterminado (AGC)	Possivelmente não neoplásicas ou não se podendo afastar lesão de alto grau		Encaminhar para colposcopia
Células atípicas de origem indefinida (AOI)	Possivelmente não neoplásicas ou não se podendo afastar lesão de alto grau		Encaminhar para colposcopia
Lesão de Baixo Grau (LSIL)		< 25 anos	Repetir em 3 anos
Lesão de Alto Grau (HSIL)		≥ 25 anos	Repetir a citologia em 6 anos
Lesão intraepitelial de alto grau não podendo excluir microinvasão			Encaminhar para colposcopia
Carcinoma escamoso invasor			Encaminhar para colposcopia
Adenocarcinoma *in situ* (AIS) ou invasor			Encaminhar para colposcopia

Source: Manual of Recommendations Screening, diagnosis and treatment of cervical cancer FEBRASGO, 2017.

FINAL CONSIDERATIONS

The literature on cervical cancer highlights Human Papillomavirus (HPV) infection as its main causal factor, emphasizing the importance of vaccination and screening in preventing the disease. In addition to HPV, other risk factors are discussed, emphasizing the multifactorial complexity of this condition. Advances in research have improved our understanding of the mechanisms of cervical cancer development, guiding public health policies to promote effective prevention and treatment strategies.

Therefore, cervical cancer remains a significant public health concern globally, despite progress in prevention through vaccination and screening. It remains one of the leading causes of

cancer mortality among women in various parts of the world. Awareness and universal access to vaccination programs and preventive screenings are essential to reduce their incidence and mortality, providing better health outcomes for women.

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