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Cervical Cancer in Women Living with HIV: A Review of the Literature

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Abstract: *Background*: The introduction of ART had a momentous impact on women living with Human immunodeficiency virus (HIV) with cervical cancer positive. The incidence of AIDS-defining cancers has decreased, but the risk is still higher than general population. Women living with (HIV) have a high prevalence of human papilloma virus (HPV) infection and correlated disease, including cervical cancer. HIV-related risk factors, such as immunodeficiency and chronic persistence of infection play an important role in its pathogenesis. HPV vaccine, screening and early antiretroviral therapies, are recommended to reduce the risk of developing cervical cancer among the WLH. *Methodology*: In this review, we considered the studies published about cervical cancer in women living with HIV between 2019 to 2022 in Kenya. We comprised only recent articles written in English, identifying 50 records. We excluded 10 articles after reading title and abstract. At the end of the assessment we included in our review the 40 full-text articles. *Results*: The normal history of HIV infection has been intensely modified by the introduction of HAART, but HIV-infected women still have a higher risk of developing HPV-related diseases, including cervical cancer. *Conclusion*: Further studies are needed to obtain data about interactions between HAART and HPV-related lesions. Lastly, psychological support for cervical cancer survivors and management of late effects are needed.

Keywords: Cervical Cancer, Human Immunodeficiency Virus (HIV), Human Papilloma Virus (HPV), Screening, Vaccination

1. Introduction

Cervical cancer is the main cause of cancer death among women in resource limited settings. It is the second most common malignancy affecting women worldwide and has been documented to be the leading cause of cancer deaths in developing countries. As at 2008, it was projected that 529,409 new cases occurred worldwide, with 274,883 of the women (52% of cases) dying, [1]. Of the total new cases each year, about 86% occur in developing countries, where unfortunately 80-90% of cervical cancer related deaths occur. With the peak age of cervical cancer being 35-45 years of age, it claims the lives of women in the prime of their life when they may be raising children, caring for the family, and contributing to the social and economic life of their community. According to The Kenya national guidelines on cervical cancer screening, (2012), it has been assessed that the average life years lost due to cancer of the cervix is 25.3 years.

The most significant risk factor for cervical cancer development is persistent Human Papilloma Virus (HPV) infection. Most sexually active women will be infected by HPV during their lifetime but for many women the infection is cleared by the immune system. However, some women can develop persistent HPV infections, which might progress into low or high-grade cervical intraepithelial neoplasia (CIN) and invasive carcinoma. As for many other cancers and diseases, people living with HIV (PLWH) have a higher risk to develop cervical cancer [2-4]. HPV infection occurs more frequently in women living with HIV than the general population: the incidence has significantly decreased after the introduction of the Highly Active Antiretroviral Therapy

(HAART) but the risk of chronic infection and progression to high-grade intraepithelial lesions and cervical cancer is still higher among HIV infected women [5]. Immunosuppression plays an important role on the natural history of HPV infection allowing its persistence: the risk of developing cancerous and pre-cancerous lesions is inversely proportional to CD4+ T-lymphocyte counts [6].

Most studies showed a prevalence of progressive disease at the time of diagnosis compared to general population and a poorer treatment outcome [7]. Additionally, the advancement from a high-grade lesion to cancer is faster in WLH than in the overall population [8]. Unusual features of HIV-related cervical disease are the high rate of extensive lesions, multimodality and the high percentage of deteriorations [9]. Furthermore, clinical appearances of invasive cancer often occur at a younger age than uninfected women [10]. In this study, we reviewed the literature available about cervical cancer, to highlight the key points of current diagnosis, management and prophylaxis.

2. Materials and Methods

On January, 2022, we did a review of the literature to detect the link existing between Cervical Cancer, Human Papilloma Virus (HPV) infection and Human Immunodeficiency Virus (HIV) infection. We searched Google scholar applying "("Cervical Cancer", "Papillomavirus", "HIV infection", "Screening", "Vaccination")". We comprised only recent articles written in English, identifying 50 records. We excluded 10 articles after reading title and abstract. At the end of the assessment we included in our review the 40 full-text articles.

3. Etiology

Human Papilloma Virus (HPV) is a small, non-enveloped deoxyribonucleic acid (DNA) virus with a marked tropism for epithelial cells of skin or mucosal membrane, causing lesions anywhere on the cutaneous and mucosal surface. Its capsid composed of 72 capsomers, which comprise of at least two capsid proteins, L1 and L2, and the genome consists of a single molecule of double-stranded, circular DNA30. The genome is alienated into three regions: the first one is a non-coding regulatory region which contains the p97 core promoter with enhancer and silencer sequences. They control DNA replication by regulating the transcription of the ORFs. The second is an early region consisting of ORFs E1, E2, E4, E5, E6, and E7 which involved in viral replication and oncogenesis. Lastly the third is a late region, which encodes the L1 and L2 structural proteins for the viral capsid. There are over 80 different HPV subtypes, divided into high-risk HPV (subtypes -16; 18; 31; 33; 35) most frequently linked with a persistent infection leading to invasive cancer, and low-risk HPV (subtypes 6, 11, 40, 42, 43) 19. HPV-16 and HPV-18 responsible for most of the neoplastic lesions but also cause other neoplasms, including vaginal, anal and oropharyngeal cancers [11].

3.1. Immunological Markers for Cervical Cancer

3.1.1. Risk Factors

Perseverance of high-risk HPV infection is necessary for the development of cervical cancer and it represents the most important known risk factor [12]. Other risk factors included: smoking, the use of combined oral contraceptives, sexual behavior and immunosuppression [13]. HIV induced immune deficiency increases the risk of cancer with a permissive mechanism, stimulating the buildup of genetic damage and progression from dysplasia to cancer [5]. HPV-DNA is found integrated into the host's genome in many HPV associated cancers [14]. HPV-16 and -18 encode for three oncoproteins (E5; E6; and E7): these oncoproteins stimulate growth and have transforming properties. The integration of HPV-DNA within the host genome results in chromosomal instability and favors the progression from CIN to invasive carcinoma. Immunosuppression caused by HIV infection prevents the clearance of HPV, leading to a gradual loss of control over HPV replication [15].

3.1.2. Symptoms

Invasive carcinoma is asymptomatic in an initial stage. When tumor deeply invades the tissues, the most common symptom is post-coital, occasional often blood loss, unrelated to the menstrual cycle and leucoxantorrhea. Signs and symptoms of advanced disease includes vaginal bleeding, unilateral pelvic pain, lower limbs edema, anemia, loss of urine and / or feces from the vagina [16].

3.2. Primary Prophylaxis and Screening

HPV is detected in nearly all cases of cervical cancer and is the common vulvar, head and neck, vaginal, and anal cancers [7]. Cervical cancer can be prevented through anti-HPV vaccination and appropriate screening agendas [17]. Vaccination against high-risk HPV subtypes is suggested for females starting at age 11 or 12 years [18]. The three anti-HPV vaccines based on virus-like particles of the L1 capsid protein are available, that is Cervarix™ (GlaxoSmithKline), which is the bi-valent vaccine against HPV-serotypes 16 and 18; the quadrivalent Gardasil (Merck & Co., Inc., Kenilworth, NJ, USA), which is against HPV-serotypes 6, 11, 16 and 18 and lastly the nine-valent Gardasil-9 (Merck & Co., Inc., Kenilworth, NJ, USA), which is against HPV-serotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58. Numerous data from HIV negative population have established vaccine safety and efficacy [19, 20].

Among HIV-negative women, the quadrivalent HPV vaccine confirmed 98% efficacy for preventing CIN and 100% of genital warts, related results were also reported with 9-valent HPV vaccine [21]. Kojic et al [22] observed safety and serostatus of HPV types 6, 11, 16, and 18 in HIV-infected women which presented the quadrivalent HPV vaccine safe and immunogenic among women aged 13-45 years who were seronegative, with a percentage of seroconversion >75% for all the 4 HPV types included in the vaccine. In HPV-seropositive women, vaccination

encouraged a significant increase in antibody levels. Additionally, seroconversion proportions were higher among women with baseline CD4 cell counts >200 cells/μL. HPV vaccination can possibly prevent cervical cancer and this is the reason why HPV vaccination must be suggested not only for young girls, but also for boys and HIV-infected people [7], hence it is important certifying an appropriate antibody response to HPV vaccine to establish long-term immunity. Women LWH have a high risk of developing precancerous lesions and invasive carcinomas, but a timely screening allows early detection and treatment hence leading to a significant reduction in mortality [17]. Screenings are systematic examinations that aim at finding the pathology at an early stage allowing better options of treatment and prognosis. Screening test must satisfy some criteria in that it must be safe without side effects furthermore it should be well tolerated by the patient and sustainable from an economic point of view.

There are now three chief options for cervical cancer screening which are cytology, HPV testing, and cytology-HPV co-testing. Cytology-based screening (Pap-Test) is still the most frequent one and it is a cervical cytological examination that can be performed with conventional smear or with liquid preparation systems in which if any abnormality is detected colposcopy is needed. Cervical cancer screening for general population is recommended every 3 years for women aged 25 to 64. According to the new 2017 Guidelines screening for HIV positive women must start at the diagnosis, the second test should be repeated at 12 months and if 3 annual Pap smears are negative it should be repeated every 3 years [23]. New recommendations support HPV testing strategies like hours HPV infection is needed for developing cancer and hours HPV DNA is present in the context of lesions. For these reasons molecular test is a good approach to identify women with high grade CIN [24]. Co-testing is currently recommended as the best screening option in the US, while it is not in Africa, Europe or Australia [25].

3.3. Management and Therapy

Controlling of cervical cancer provides adherence to ART monitoring drugs interaction during cancer therapy and psychological support of the women [7, 25]. Staging of cervical cancer consists in a combination of pelvic exam, chest x-ray and abdominal ultrasound to omit metastasis [26]. The relations between ART, HPV and cervical lesions in HIV infected women are poorly understood and the effect of ART on the lesions is not well established [27]. A number of studies have revealed that effective therapy associated with a reduction in high-risk HPV persistence [26]. Management of Cervical Cancer include surgery, radiotherapy and chemotherapy [28] where surgery plays an important role in the management of early stage cervical cancer, radical hysterectomy and lymphadenectomy are often needed. Treatment of locally advanced cervical cancer includes RT (external RT and brachytherapy) and chemotherapy [27]. In People Living with HIV (PLWH) the extended CD4+ T-cell suppression induced by chemotherapy could negatively influence the course of HIV disease [28]. Value of life of cervical cancer survivors can be prejudiced by late effects such as bladder and bowel dysfunction, sexual dysfunction, lymphedema and psychosocial problems [29]. Surgical treatment and radiation therapy can lead to long-term sequelae such as atonic bladder, hydroureteronephrosis, incontinence, dysuria, hematuria, hemorrhagic cystitis. Diarrhea, steatorrhea, tenesmus, fecal incontinence and rectal bleeding represent some of the other complications that can occur. Fatigue, anxiety and depression are the most frequent psychosocial problems. For all these reasons, management of cervical cancer must include psychological support during and after treatment and evaluation of long-term sequelae, improving quality of life.

4. Conclusions

The normal history of HIV infection has been intensely modified by the introduction of HAART, but HIV-infected women still have a higher risk of developing HPV-related diseases, including cervical cancer. Screening and Vaccination programs are essential weapons to fight cancer burden. Further studies are needed to obtain data about interactions between HAART and HPV-related lesions. Lastly, psychological support for cervical cancer survivors and management of late effects are needed.

Competing Interests

The authors declare no competing interests.

Data Availability Statement

All the data has been shared in the manuscript.

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