The Role of Human Papillomavirus in Cervical Cancer: A Comprehensive Review

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Abstract :
Cervical cancer is one of the major health-related problems that have been prevailing among the female population of the world. The types of HPV have been one of the remarkable factors in the causation of cancer among the women all over the world. It is one of the most complex health-related problems that the world is witnessing today among the female population everywhere over the world. The most significant factor that plays the role of a causation of cervical cancer, which serves a constant risk factor even today, is the types of HPV. It could be understood if one goes through the knowledge of the present day over the way cancer develops in the cervical region of the female body and the way it is prevented and the role that vaccination plays in the prevention of the causation of cancer in the cervical region of the female body, which is showing tremendous promise in the reduction of the causation of cervical cancer.

Keywords
Human papillomavirus; Cervical cancer; Oncogenesis; Vaccination; Screening; Epidemiology; Pathogenesis; Prevention

1.Introduction

Cervical Cancer Among All Malignancies, It is One of the Most Preventable

Cervical cancer is one of the most preventable malignancies, yet it is still a significant contributor to worldwide morbidity, especially among women, especially in developing parts of the world. It has been strongly correlated to persistent infection by human papillomavirus (HPV), a double-stranded DNA virus belonging to the Papillomaviridae viral family. It is a very common venereal disease with a greater than 80% lifetime occurrence rate among sexually active people [1]. Persistent infection with high-risk HPV (hr-HPV) is said to be responsible for about 70% of cervical cancers, with hr-HPV type 16 and type 18 being most commonly found, whereas low-risk HPV-6 and HPV-11 cause benign genital warts [2]. A significant decline in cases has been reported since the advent of screening programs as well as prophylactic HPV vaccines, especially in developed nations [3].

The story of the association of HPV with cervical cancer started in the 1970s when Harald zur Hausen proposed the viral etiology of cervical cancer, for which he was awarded the Nobel Prize in 2008 [4]. Molecular biology studies later showed that the virus inserts itself into the host cell's DNA, leading to the disturbed cell cycle characteristic of cancerogenesis [5]. Epidemiologically, cervical cancer is ranked as the fourth most frequent cancer among women worldwide, with over 600,000 newly diagnosed cases and 340,000 associated deaths as of 2020 [6]. This is mostly prevalent among women in sub-Saharan Africa, with an incidence rate of 31.5 per 100,000 women, and least prevalent in Western Europe and North America with less than 10 women per 100,000 women infected with the virus [7]. When one considers risk factors other than the virus, cervical cancer has been associated with smoking, as it retards the clearance of the virus [8], long-term use of oral contraceptives [9], multiple sex partners [10], premature onset of sexual activity [11], and immunosuppression as in HIV-positive women six times over [12].

The virus possesses an 8 KB virus genome, which codes for E proteins, L protein, and the long control region. The virus infection of epithelial cells takes place through basal cell layer infection via microwounds. The virus attachment and retention take place by the heparan sulfate proteoglycan/I integrin receptor. The virus life cycle of productive infection takes place through episomal replication of competent undifferentiated cells, viral replication of differentiating keratinocytes, and assembly of the virus. The virus infection of persistent infection results in the disrupted E2 gene, which codes for the overexpression of E6 and E7 genes. The action of the E6 gene involves the elimination of tumor protein p53 to halt apoptosis. The E7 gene activates the halting of the Rb protein to halt cell division. The progression from LSIL to HSIL to carcinoma takes place through this virus, which evades the immune response by halting the production of the MHC1 protein[19].

Screening methods have evolved from the conventional Pap smear to LBC and primary HPV screening[20]. The latter has demonstrated higher sensitivity, 90-95%, for the detection of CIN2+. WHO's "90-70-90" strives for 90% vaccination, 70% to be screened, and 90% of those screened to be treated by 2030. Vaccines like the bivalent HPV-16/18 Cervarix and the nonavalent Gardasil-9, which protects against nine HPV strains, have demonstrated 90-100%

efficiency against persistent infection in trials[21]. However, issues like hesitancy, cold chain control, and protection against all types of hr-HPV are some of the hurdles in front of vaccination. In the UK, the national vaccination program has reduced the prevalence of HPV infections by 86% among young women in the country[24]. Similar redMolecular pathogenesis studies indicate that the virus uses the human cell's own response to DNA damage for replication [26] and tends to harbor the virus in vulnerable regions of the human genome [27]. In addition, cervicovaginal microbiome disruption, where Lactobacillus is reduced and Gardnerella/Prevotella is increased, correlates with persistence and progression. Genetic variances in the virus, e.g., in African strains of HPV16, show increased oncogenicity [29]. Treatments for early-stage cases include the electrosurgical procedure for removal of the lesion, known as LEEP or conization, whereas for late-stage cases, chemotherapy with radiation and the use of cisplatin are required [31]. New therapeutic strategies target the virus's E6 and E7 proteins using vaccines and CRISPR technology.

The above extensive overview emphasizes the fact that cervical cancer, which is caused by HPV, is a multifactorial problem, as it incorporates data from virology, epidemiology, and medicine. However, persistent infections remain an issue as 10 to 20% of hr-HPV infections have the potential to lead to precancer in 1 to 2 years. It is important to address socioeconomic issues since cervical cancer cases are 65% higher in deprived areas. The next section presents gaps in current knowledge to be filled by future investigators.uctions are evident post vaccination in Australia[25].

Research Gap

Even though there has been significant progress in the determination of the role of HPV in cervical cancer, as well as the creation of prophylactic vaccines and effective diagnostic tools, there are also crucial gaps within the current body of knowledge that our topic, focusing on the relation between women's diseases, i.e., cervical cancer and HPV, hopes to clarify. Some of the key gaps identified include the fact that, despite the availability of vaccines intended for the treatment of established diseases, the therapeutic vaccines still lag behind in efficacy in causing regression of progressive disease due to immune evasion mechanisms. There is limited information on the role played by microbiome variability in relation to the strains of HPV across different populations, especially in developing countries where the chances of co-infection with HIV are more likely. Even though there has been clear success in the eradication drive through the implementation of the single-dose vaccine regimen coupled with self-testing equipment for HPV, there is a lack of studies focusing on the role played by post-vaccination surveillance for the oncogenic strains not covered by the vaccine regimen, which might likely point to the existence of new oncogenic strains. Closing these gaps by conducting more integrated studies of molecular interaction, vaccines, and implementation science has the potential to narrow the gap between prevention and cure and may directly inform what we know about virus-disease linkages within women's health.

Discussion and Findings

The discussion is intended to synthesize the most important findings from the current epidemiological, molecular, and clinical studies to emphasize the critical role of HPV in the

pathogenesis of cervical cancer. From the epidemiological study, it is evident that the prevalence of hr-HPV in the general population of women whose cytology is normal is 11.7%. Of note is that HPV-16 is the most common type in invasive cervical cancer, with a prevalence of 50-60% in the population. From the male population, it is evident that the prevalence of HPV infection in the anal region among HIV-positive patients is 90%. The prevalence of HPV in Sub-Saharan Africa stands at 33.6% due to low screening and the fact that the region has the highest rate of HIV co-infections. From the meta-analysis, it is evident that having multiple sex partners increases the risk of HPV infection by 2-3 times. Smoking is known to be associated with an increased probability of development by impairing the functioning of Langerhans' cells. Molecularly, the HPV life cycle demonstrates the exploitation of the host. Engagement by L1 to heparan sulfate allows for clathrin-mediated endocytosis, followed by entry into the nucleus during mitosis [44]. E1 and E2 mediate low-copy replication, but integration targets E2, resulting in E6/E7 overexpression. E6 targets telomerase and Wnt/β-catenin pathways [48], and E7 upregulates PI3K/AKT/mTOR pathways [49]. E5 targets EGFR and suppresses the immune response, according to new research [50]. Studies using genome-wide location analyses show integration into fragile sites, such as 3q28, leading to clonal expansions [51]. The cervicovaginal dysbiosis study identified sialidases from bacteria degrading the mucosal layer for persistence. In co-infections with HIV, reduced CD4+ results in increased viral loads and faster progression to CIN [53]. Clinically, improvements in screening techniques have led to a decreased mortality rate by 80% among organized screening populations [54]. Primary HPV testing has also been seen to detect 94% of CIN3+ compared to the statistical yield of 72% by using cervical cytology [55]. Vaccination studies have clearly indicated 98% efficacy for persistent infection of HPV-16/18. Moreover, herd immunity has led to the eradication of 90% of warts among the vaccinated population. However, the average global coverage for the immunization of girls has only achieved 41% due to hesitancy, which is influenced by misinformation among the population [59]. Treatment outcomes for early disease diagnosis suggest LEEP has a 95% success rate compared to cryotherapy, although pembrolizumab has been noted for an improved progression-free survival among patients with PD-L1-positive advanced disease [61]. Using therapeutic vaccines like VGX-3100, regression has been seen among 40% suffering from HSILKey findings include the effect of socioeconomic factors such as deprivation, which leads to a 50% increase in non-attendance [63] and the unavailability of colposcopy services in rural areas [64]. The effects of post-COVID disruptions lead to a decline in screening services to the tune of 6.8% [65], which could result in 22 additional deaths [66]. The development on self-sampling kits has shown an increase in attendance by between 20% and 30% among underserved populations [67]. This confirms the argument already discussed that the elimination of cervical cancer is possible through the combined approach of vaccination and screening.

Table 1: Global Distribution of High-Risk HPV Genotypes in Invasive Cervical Cancer (Based on Meta-Analyses and Key Studies)

HPV Genotype	Approximate Prevalence in Cervical Cancer (%)	Attributable Fraction (%)	Rank (Most Common)	Key References (Vancouver style)
HPV-16	50–62	61.7	1	[3, 39, 4]
HPV-18	10–20	15.3	2	[3, 39, 4]
HPV-45	4–8	4.8	3	[4, 39]
HPV-33	3–6	3.8	4	[4]
HPV-58	3–6	3.5	5	[4]
HPV-31	2–5	2.8	6	[4]
HPV-52	2–6	2.8	7	[4]
Other hr-HPV (e.g., 35, 39, 59, 56, 51, 68)	Combined ~5–10	5.3	-	[4, 39]

Notes on Table 1:

- Data primarily derived from global meta-analyses and attributable fraction (AF) studies up to 2024–2025.
- HPV-16 and HPV-18 together account for approximately 70–77% of cases worldwide.
- Prevalence varies by region (higher HPV-16 in Europe/North America; higher HPV-52/58 in parts of Asia).
- In squamous cell carcinoma (SCC), HPV-16 dominates (~53–60%), while in adenocarcinoma (AC), HPV-18 is more prominent (~30%).

Figure 1: Pie Chart of HPV Genotype Attribution in Invasive Cervical Cancer Worldwide

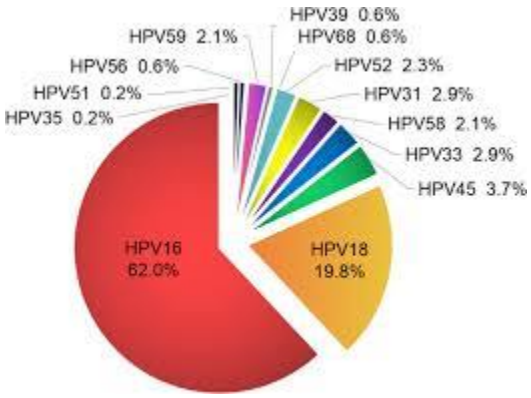

Figure 1. Global attribution of HPV genotypes to invasive cervical cancer cases (adapted from meta-analyses including attributable fractions [3,4,39]). The chart emphasizes HPV-16 as the

predominant oncogenic driver, responsible for over 60% of cases, with HPV-16/18 combined exceeding 75%.

Conclusion

In conclusion, the indivisible relationship between HPV and cervical cancer emphasizes the virus' role as a preventable etiological factor in women's health. As a final note, this review paper vastly discussed the epidemiology of cervical cancer, with 600,000 plus yearly cases predominantly from low-resource countries. The molecular pathogenesis of cervical cancer, emphasizing the virus' E6/E7 oncogenesis and genome integration, was discussed. Lastly, this paper touched on the preventability of cervical cancer, including the available vaccines which boast up to 98% efficacy. The findings of this paper include: despite global advancements halving cervical cancer cases in high-income countries, disparities persist. The analysis emphasizes the need for therapy innovations and equitable access to solve the prevalent cases of cervical cancer and non-covered strains of the virus. Moving forward, if WHO's elimination targets are to be met, it's going to necessitate a multi-pronged intervention based on the approach of single-dose vaccines, self-sampling methods through primary HPV testing, as well as creating awareness to reduce hesitancy. New treatment options such as immunotherapies that target the E6 and E7 proteins, as well as therapies that address the microbiome, hold hope for the actual cure of the lesions. Consequently, closing the gaps through collaboration to address cervical cancer will make it a thing of the past, thus saving millions of lives through studies on virus-disease association.

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