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HIGH RISK HUMAN PAPILLOMAVIRUS & RISK FACTORS FOR CERVICAL CANCER

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Abstract

Cervical cancer is caused by the non-enveloped, Papillomavirus, or HPV, is an example of a double-stranded DNA virus. According to the 2020 Global Cancer Observatory (GLOBOCAN) survey, a global study of female populations, cervical cancer is associated with a relatively high fatality rate. Cervical cancer is the second most prevalent form of the disease among women in Indonesia. Over 73% of instances of cervical cancer are known to be caused by high-risk HPV strains 16 and 18. The proteins E6 and E7 significantly prevent the tumor suppressors p53 and pRb from acting, which would otherwise cause cells to proliferate and become uncontrollably large. It is necessary to identify the risk factors that lead to cervical cancer in order to necessary preventive action. This study aims to provide the latest information regarding risk factors and etiology of cervical cancer. This research uses a literature search approach from several literatures such as books, articles and journals. The results show that cervical cancer is a complex and multifaceted health problem, with multiple risk factors contributing to significant morbidity and mortality globally. It can be concluded that it is important to consider many elements in understanding and addressing the epidemiology of cervical cancer.

Keywords**:** *Human Papillomavirus, risk factors, cervical cancer***.**

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INTRODUCTION

Globally, cervical cancer continues to be a substantial concern and source of burden. The Human Papillomavirus (HPV) invades healthy cells located on the outer layer of the cervix. causing the cells to proliferate uncontrollably and form a mass known as a tumor. This is known as cervical cancer. A growth or tumor on the cervix can result from a long-term HPV infection of the cervix [1]. Cervical cancer usually occurs in older women, but statistical evidence shows that cervical cancer can also attack women aged between 20 and 30 years [2].

According to the 2020 Global Cancer Observatory (GLOBOCAN) survey, which surveyed female populations worldwide, cervical cancer is a relatively high-risk killer. Worldwide, more than half of cervical cancer's incidence (341,831 deaths) occurs in women, making it the fourth most prevalent cancer in this demographic behind breast, lung, and colorectal cancers (604,127 new cases) [1]. Indonesia is the country with the most cases fifth highest cervical cancer in the world [3]. Nearly 80% of cervical cancer cases occur in the country poor and developing, 50% end up with death. In Indonesia, more than 70% of cases cervical cancer is at an advanced stage [4]. Among female cancers in Indonesia, cervical cancer ranks second in terms of incidence. In 2020, 21.003 people lost their lives to cervical cancer, making it the second most deadly cancer in Indonesia [5]. Total cervical cancer cases in Indonesia came to 36,633 [6]. Inadequate human resources are one of the causes of high cervical cancer death rates LMICs,challenges with early detection and routine screening programs, poverty, and insufficient infrastructure. It is also difficult to accurately diagnose and treat precancerous lesions [6], [7]. The high prevalence of cervical cancer in developing nations can be attributed to a combination of factors, including limited public awareness, inadequate education and knowledge about the disease's occurrence, and the absence of effective comprehensive programs for early detection of cervical precancerous lesions [5][6][7].

A member of the Papillomaviridae family, HPV is an envelop-less, microscopic virus with two strands of DNA. There are over 200 distinct types of human papillomavirus (HPV), with 30–40 of these strains being able to infect human mucosal surfaces, including the anogenital tract epithelium [8]. A few of these are the cause of papilloma, which is another name for warts [9]. High-pressure vaginal virus (HPV) infections can only occur on the skin and in certain genital and oral mucosal linings; it cannot infect blood or internal organs like the lungs or heart. There are three different kinds of human papillomavirus (HPV) that are classified according to their cancer risk: LR-HPV, pHR-HPV, and HR-HPV. The majority of precancerous and cancerous lesions are caused by human recurrent papillomavirus infections, specifically strains 16 and 18. Common genital warts or benign hyperproliferative lesions might be caused by LR-HPV types 6 and 11, which are not always cancerous [9], [10]. HPV infection constitutes the predominant etiology of cervical cancer. Almost all cases of cervical cancer (99%) are caused by the human papillomavirus, according to the WHO [11]. Chronic HPV infections in women can lead to cervical cancer, despite the fact that the vast majority of these infections heal on their own with no symptoms [7].

Cervical cancer does not develop overnight. The progression from initial infection to the development of aggressive cancer often spans a period of approximately 5 to 10 years. The immune system can clear HPV infection in some people before it progresses to cancer. However, in some cases, HPV has the ability to evade the immune system of the host and progress into malignancy. The persistence of HPV in each host differs, but the specific cause is unknown because cancer is complex. In order to minimize the likelihood of developing cervical cancer, it is important to comprehend the risk factors and the progression of HPV infection leading to cervical cancer [12]. We produced this review to provide the most recent updates on cervical cancer risk factors and etiology.

METHOD

This review is a literature review prepared using a literature search approach from several literatures such as books, articles and journals related to Human Papillomavirus & Risk Factors for Cervical Cancer in developing countries.

RESULTS & DISCUSSION

Cervical Cancer and Epidemiology

When abnormal cells in the lining of the cervix proliferate uncontrollably, it is referred to as cervical cancer. The cervix, an organ of the female reproductive system that creates the space between

the uterus and the vagina, is illustrated in Figure 1. Annually, cervical cancer claims the lives of over 500,000 women and is responsible for one death every two minutes; thus, it ranks among the most prevalent causes of death among women. The poorest countries suffer disproportionately from cervical cancer and its devastating effects.

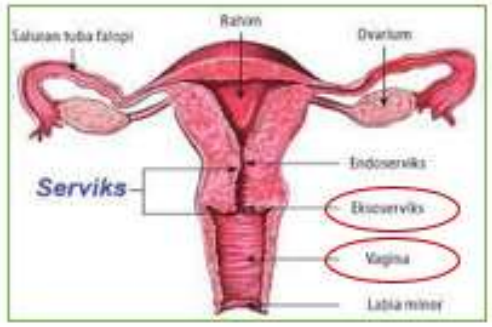

Figure 1. Female reproductive system [1].

As seen in Figure 1, the cervix is divided into two sections, the endocervix and the exocervix, each of which is lined by two distinct types of epithelial cells. Endocervix is the uterine entrance segment of the cervix; it is composed of columnar single-layered epithelial cells, whereas the exocervix or ectocervix is lined with layered flat epithelial cells. The transformation zone in the cervix is where these two types of cells meet, and it is the transition zone from flat epithelial cells to columnar epithelial cells. The majority of cervical malignancies begin in cells in the transformation zone [6][7]. Cervical epithelial tissue is divided into three layers: the base (stratum basale), middle (stratum spinosum and stratum granulosum), and suprabasal (stratum corneum). Cervical epithelial cell abnormalities are discovered in the early stages of cervical cancer CIN is a noncancerous disease that can progress to cervical cancer [13][14].

According to data from the Global Cancer Observatory (GLOBOCAN) survey in 2020, new cases of cervical cancer ranked fourth in the globe (604,127 out of 9,227,484 total new cases of cancer [6.5%]) and is the fourth leading cause of death (341,831 out of 4,429,323 deaths [7.7%]). In 2020, a study of the female population in Indonesia revealed that new instances of cervical cancer (Figure 2) ranked second (36,633 out of 213,546 new cases of cancer [17.2%]) and were the second leading cause of death (21,003 out of 109,813 deaths [19.1%]) [9].

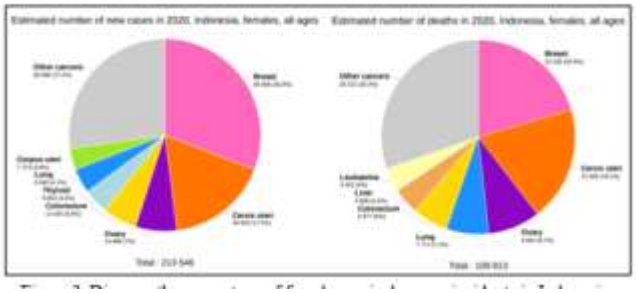

Figure 2. Diagram the percentage of female cervical cancer incidents in Indonesia: (a) New cases of cervical cancer; (b) Cervical cancer deaths (in 2020, covering all age groups in Indonesia) [9].

If cervical cancer is not adequately treated, the death toll from the disease is projected to reach 12 million by 2030. Indonesia has around 180,000 new cases of cervical cancer annually, with a mortality rate of 75% during the first year. Most of these fatalities occur because patients who receive a new diagnosis are already in advanced or terminal stages when they receive it [8].

Human Papillomavirus (HPV)
Classification

The International Committee on Virus Taxonomy (ICTV) classifies Papillomavirus as a member of the Papillomaviridae family (Papillomavirus and Polyomavirus were previously classified as members of the same family), and over 207 distinct HPV species have been identified. There are more than 50 genera of human papillomavirus, but only five are associated with infections in humans, namely Alphapapillomavirus, Apapillomavirus, Gammapapillomavirus, Mupapillomavirus, and Nupapillomavirus, as shown in Figure 3, which depicts the results of ICTV's phylogenetic analysis. The Alphapapillomavirus genus, as described in the table below, is the most commonly found in patients.

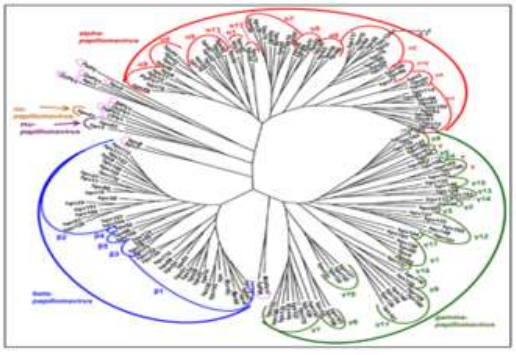

Figure 3. Phylogenetic analysis of HPV [10]

The Alphapappilomavirus genus is a form of HPV identified in humans [15]. When compared to other kinds of HPV, HPV types 16 and 18 are particularly harmful (table 1).

Table 1. Classification of the HPV virus [10]

Subfamili	Genus	Species	Type
		α-1	HPV 32, HPV 42
		α2	HPV 10, HPV 3, HPV 28, HPV 29, HPV 78
		α3	HPV 61, HPV 72, HPV 81, HPV 83, HPV 84
		α4	HPV 2, HPV 27, HPV 57
		α5	HPV 26, HPV 51, HPV 69, HPV 82
		α6	HPV 53, HPV 30, HPV 56, HPV 66
First Papilloma virinae	Alpha-papillo mavirus	α7	**HPV 18**, HPV 39, HPV 45, HPV 59, HPV 68, HPV 70
		α8	HPV 7, HPV 40, HPV 43
		α9	**HPV 16**, HPV 31, HPV 33, HPV 35, HPV 52, HPV 58, HPV 67
		α10	HPV 6, HPV 11, HPV 13, HPV 44, HPV 74
		α11	HPV 34, HPV 73
		α12	RhPV
		α13	HPV 54
		α14	canHPV 90
		α15	HPV 71

HPV is classed as LR-HPV, pHR-HPV, or HR-HPV on the basis of its correlation with precursor lesions and cervical cancer (Figure 4).

HPV infections, particularly types 16 and 18, are the primary contributors to pre-malignant and malignant lesions in cancer. LR-HPV types 6 and 11, on the other hand, are capable of inducing benign hyperproliferative lesions or common genital warts, which do not pose a risk of developing cancer [13][12].

Risk of Cervical Cancer	Type of HPV
High Risk	16, 18, 31, 32, 33, 35, 39, 45, 51, 52, 56, 58, 59,
Potential High Risk	25, 53, 66, 67, 68, 70, 73, 82
Low Risk	6, 11, 40, 42, 43, 44, 55

Figure 4. Classification of HPV based on cervical cancer risk [12]

The etiology of cervical cancer has been linked to HPV, which is transferred sexually. HPV High-risk oncogenic (HR-HPV) is present in nearly all cervical cancer patients, according to nearly all retrospective investigations. HPV is a diverse family of viruses, with around 180 forms of HPV infection documented in humans, with approximately 30-40 types in animals. Some of them are capable of infecting the vaginal tract. IARC has classified thirteen forms of HR-HPV as carcinogenic in the cervix, namely HPV types 16, 18, 31, 32, 33, 35, 39, 45, 51, 52, 56, 58, and 59. In the cervix, HPV strains 16 and 18 are the most active and carcinogenic. LR-HPV types 6, 11, 40, 42, 43, 44, and 45 are not carcinogenic but can cause condyloma or genital warts. A global meta-analysis of the spread of HPV on 30,000 cases of invasive cervical carcinoma (ICC) showed HPV 16 as the most prevalent strain of HPV throughout the world, followed by HPV 18. It is possible that strains 16 and 18 of HPV are responsible for 73% of all ICC cases [16].

Virion Structure

Papillomavirus is classified within the Papillomaviridae family of icosahedral DNA viruses, characterized by their 52–55 nm in diameter. The viral particle consists of a capsid protein composed of 72 pentameric capsomeres enclosing a single 8000-bp double-stranded DNA molecule that is bound to cellular histones. As illustrated in Figure 5, two structural proteins make up the capsid, late L1 (55 kDa), which constitutes 80% of the total viral protein, and L2 (70 kDa). There is a single circular dsDNA molecule within this capsid. By means of L1 expression alone or in conjunction with L2, VLPs can be generated in expression systems that are not specific to mammals. Density 1.34 g/mL and sedimentation coefficient (S 20, W) 300 are the properties of intact virions in cesium chloride [17].

Figure 5. Internal and external structure of human papillomavirus (HPV) (Illustration with enlarged schematic representation) [18]

Genome

Every human papillomavirus (HPV) genome is composed of a single strand of DNA and has eight open reading frames (ORFs). There are three distinct functional components to the ORF, as demonstrated in Figure 6: Proteins needed for virus replication are encoded in the early region (E), which is blue in color. Proteins needed for virion assembly are coded in the late region (L), which is green in color. LCR or URR, which is predominantly non-coding and is colored yellow, contains cis elements that are critical for viral DNA replication and transcription. The E protein of the virus is mostly produced by an early promoter (for example, P97 in HPV 31) and the L protein by a late promoter (for example, P742 in HPV 31) [19]. E1, E2, E4, E5, E6, and E7 are the six ORFs found in the early region, which comprises 45% of the HPV genome. Open reading frames L1 and L2 are encoded by the late region, which makes up 40% of the HPV genome. Table 2

displays the function of the genes responsible for producing the early HPV genome's proteins. URR URR makes up 15% of the total HPV genome and consists of promoter and enhancer elements. In contrast to enhancer elements, which encourage transcription and viral genome replication, promoters also called ori are locations that biological transcription factors may detect [20][21][22].

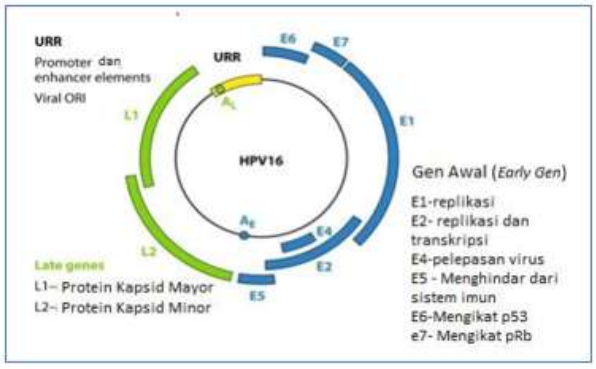

Figure 6. Structure of the HPV 16 Genome [23]

Table 2. Genes coding for proteins in the Early region [18][22]

Gen	Protein Produced
E1	The 73 kDa Non-Structural E1 protein is involved in HPV replication and is encoded by the E1 gene. Through its interaction with the E2 protein, this protein binds to particular DNA regions and helps construct the hexamer complex. Oligomerization is facilitated by the helicase activity present in this complex when coupled. In order to keep the creation of single-strand DNA stable, the E1 protein interacts with replication protein A (RPA).
E2	The E2 protein, encoded by the E2 gene, ranges in size from 40 kDa to 45 kDa (type dependent). When human cells express the E2 protein, the viral promoter is transcribed. In the process of viral DNA synthesis during host cell mitosis, the E2 protein is also crucial. The viral DNA is amplified when E2 binds to L2.
E4	Oligomerization, phosphorylation, and proteolytic cleavage are all aided by the E4 protein, which is encoded by the E4 gene. Virus maturase or maturation control, late gene expression modulation, and aiding viral genome expansion are all functions of the E4 protein. Epithelial cells undergo koilocytotic alterations when this protein is expressed. After viral genome integration into the DNA of the host cell, the E4 gene will cease to be expressed.
E5	The cytoplasmic membrane incorporates a little protein encoded by the E5 gene, which has around 44 amino acids. An EGFR (Epidermal Growth Factor Receptor) amplifier is what this protein does. In order to prevent cell death, the E5 protein and EGFR can interfere with signal transduction pathways, such as the kinase pathway's mitogen-activated protein (MAP).
E6	The E6 gene produces an oncoprotein that inhibits the action of the tumor inhibitor protein, namely the p53 protein, through the E6 protein ligase. As a result, the transcription process of p53 and the apoptosis process are hampered. The protein produced by the E6 gene also induces the expression and activation of telomerase, causing cells not to die (to grow abnormally because there is no cell death process).
E7	The retinoblastoma protein (pRb), which functions as a tumor suppressor protein, is bound to an oncoprotein encoded by the E7 gene. As a result, pRb loses control of the E2F transcription factor. In addition, the oncoprotein of the E7 gene is also able to bind p107 and p130. These interactions cause cells to not die (immortal) and eliminate the cell's response to DNA damage.

Viral replication

The first step of the HPV life cycle begins with the virus being exposed to host cells. This exposure happens as a result of ulcers or lesions in the host cells' epithelial layer. After being introduced to cells, the virus will adhere to host cells via receptors present on the cell surface in the epithelial basal layer [24].

In general, HPV will first bind to the primary receptor Syndecan-1 (the Heparan Sulfate Proteoglycans (HSPGs) isoform that is dominant on the surface of epithelial cells), and then change its capsid and bind to a secondary receptor, particularly the integrin group receptor [21]. The link created between the virus and the host cell's particular receptor will signal the host cell to endocytoze the virus [25][26]. The initial step in viral endocytosis is the formation of indentations in the plasma membrane around the site where the virus attaches. These indentations eventually develop into vesicles, which enclose the virus. After viruses have been endocytosed by cells, they become uncoated. The removal of intra-capsomer sulfide bonds speeds up the uncoating process and allows the capsid to open. This takes place within the host cell environment [25][26][27].

Following uncoating, the viral DNA will exit the vesicle and connect to the microfilaments via

the interaction of the L2 region with the dynein complex motor protein, assisting in its transport in the cytoplasm and cell nucleus [26][28][29].

The HPV genome will reach the nucleus of the cell and start the viral gene expression cascade. First, the virus will express replication factors, specifically proteins E1 and E2. The E2 protein attaches to the viral replication origin located in viral DNA. This link signals the E1 helicase protein to separate the viral DNA double strands and form a replication complex. This replication complex will notify the polymerase enzyme and host cell auxiliary proteins to begin viral DNA replication [24][21][25][26].

Late promoter activity will rise in tandem with epithelial cell differentiation. The HPV virus's last promoter will start the production of two genes that code for the virus's structural (capsid) proteins, L1 and L2. The DNA particles will next be combined with viral proteins to produce infectious particles at the top of the epithelial layer. The L2 protein is responsible for encapsulating the viral DNA, whereas the L1 protein is responsible for building the virus's icosahedral capsid. The HPV virus will then undergo exocytosis and leave the cell to infect uninfected cells (non-lytic) [27][29].

Pathogenesis

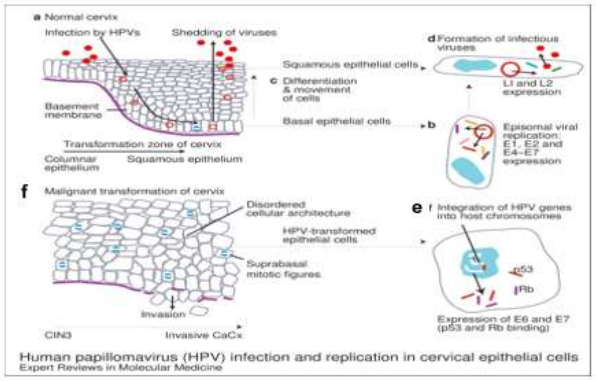

Figure 7. Cervical epithelial cell infection and replication of the human papillomavirus (HPV) [30]**.**

(a) In a healthy cervix, that can see a transition zone where the columnar and squamous epithelium meet. (b) When a human papillomavirus (HPV) reaches a cervix through the vagina, it replicates episomally (in the cytoplasm, outside of the host chromosomes) and expresses its viral genes (early) E1, E2, E4, E5, E6, and E7. This process might occur, for instance, during sexual intercourse. (c) When basal cells are infected with a virus, they suffer cell damage, differentiation, and Translocation to the surface of epithelial cells. (d) Squamous cells express the HPV genes LI and L2, which are expressed late. Virus particles can reproduce and spread throughout the vaginal lumen. (e) Upon integration of the HPV genes into the host genome, the two cancer-causing proteins, E6 and E7, interact with the tumor suppressor proteins p53 and pRb by forming a binding connection. (f) When a person is infected with an HPV, particularly a human retrovirus (HR-HPV), it can induce mild dysplasia, advanced CIN3, and, finally, invasive CaCx.

A complex known as Ubiquitin Ligase is formed when the 150-amino acid E6 protein interacts with the E6-AP found in cells. It is the job of this enzyme complex to break down p53. Common p53 functions, such as apoptosis, DNA repair inhibition, and cell cycle termination during G1 phase, are disrupted when p53 is degraded (Figure 8) [30]. In addition, the E6 protein helps activate telomerase by interacting with the c-myc protein. Therefore, cells will become immortal due to the fact that their telomeres will not shorten [31][30].

The E7 protein, consisting of 100 amino acids, interacts to the hypophosphorylated RB protein to disrupt the pRB complex and the cellular transcription factor E2F-1. Transcription of the genes needed to enter the phase can then take place once the E2F-1 transcription factor is released from the DNA strand. S stops host cells from dying and is involved in the cell cycle (Figure 8). The host cells undergo immortality and uncontrolled cell division [13].

The progression of lesions to more invasive stages (II and III) is a symptom of a persistent HPV infection. In stage I CIN, The HPV genome is integrated, either partially or entirely, into the genome of the host cell. depending on the specific case. But in advanced CIN, The totality of the HPV DNA is integrated into the genome of the host cell [32]. This integration results in the disruption or deletion of the E2 protein coding gene. Consequently, the E2 protein is unable to regulate the E6 and E7 proteins' transcription. The expression of E6 and E7 proteins is consequently increased. These two proteins inhibit cell cycle regulation by binding to and deactivating two tumor suppressor proteins, p53 and retinoblastoma (pRb) (Figure 8) [13][32].

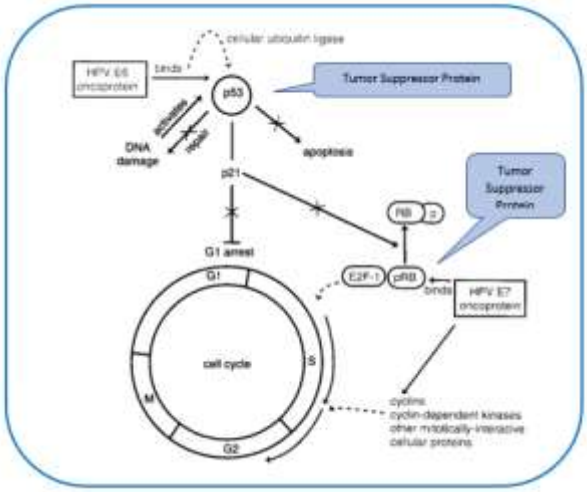

Figure 8. Role of Oncogenic HPV E6 and E7 Proteins [33]

Multiple articles state that HPV can infect cervical epithelial wounds or micro-abrasions in order to connect to basal cells. Within a few weeks of infection, the virus replicates and exhibits its early genes (E1, E2, E4, E5, E6, and E7). The expression of the late genes L1, L2, and E4 occurs in the upper epithelium, where replication is ongoing. The transmitted virus can cause new infections, but after two years, 90% of the afflicted tissue will have recovered. Integration of The integration of the HPV genome into the host DNA takes place 10 to 30 years subsequent to the disruption of E2 and the emergence of the E6 and E7 oncogenes. This integration is associated with persistent infections and untreated lesions [33].

Risk Factors for Cervical Cancer

Immunity

Some women are more prone to get cervical cancer if they are taking immune suppressing medication. Women getting therapy for autoimmune illnesses or who have received an organ transplant are included. The development of colorectal cancer is, on the one hand, correlated directly with HPV infection. On the flip side, cancer growth is greatly aided by immune system defects. T helper cells have been implicated in the regression of lesions, providing support for the notion that HPV infection predominantly induces a cellular immune response. There was an increase in Langerhans cells in women whose HPV was eliminated, according to one study [34].

HPV is classified into two types based on its ability to cause cancer: low-risk and high-risk. It is surprising that they acquired separate illnesses and cellular targets, despite stimulating a comparable cellular milieu and immune response. Although the exact process is not known, one theory is that the HPV E7 protein at low risk has a lower binding affinity [35]. Immunosurveillance is a method by which tumors can be detected and treated or prevented. While mucosal immunity serves as the primary barrier against disease progression, cellular and humoral immunity play an equally significant role in the initiation of cancer and the spread of illness. We are driven to explore the correlation between cervical cancer and immunology by the tumor microenvironment and patients' peripheral blood [36].

Human Immunodeficiency Virus (HIV)

Those infected with the HIV are more likely to get HPV, which is responsible for the AIDS epidemic. Unvaccinated females with HIV are more susceptible to acquiring high-risk HPV strains [37]. Research examining the association between HIV and cervical cancer, individuals who are HIV-positive have an increased risk of developing chronic HPV infections that comprise a multitude of viral oncogenes, more Pap screen abnormalities, and higher rates of cervical intravenous leakage (CIN) and invasive cervical carcinoma [9]. Prevalence of cervical cancer is higher among women living with HIV, and the virus is most commonly contracted between the ages of 13 and 18. Cervical cancer in women who are HIV + is detected at a younger age (1549 years) compared to women who are not infected. An important part of the immune system's job is to kill cancer cells and stop them from spreading. Women who have HIV are more likely to develop severe cervical carcinoma from precancerous lesions. HIV-positive women face a 2–12 times higher chance of developing cervical cancer [38].

Syphilis, HBV, HCV and Chlamydia

Syphilis, HBV, and HCV sexually transmitted infections (STIs) have been identified as necessary factors for the progression of cervical HPV infection to cancer. HPV infection is associated with heightened vulnerability to other sexually transmitted diseases such as syphilis, hepatitis B and C viruses, as well as vaginal infections [39].

Some forms of immunological dysfunction may be associated with the hidden mechanism that causes cancer patients infected with HBV to have a poor prognosis [40], Oncogenic hepatitis B virus (HBV) reaction or the presence of hepatitis B X-interacting protein [41]. The fact that HPV can be transmitted from person to person via sex raises

the possibility that it may work in tandem with HPV to accelerate the onset and spread of cervical cancer. Yet, whether or whether HBV infection affects cervical cancer clinicopathological features and prognosis, and if so, to what degree, remains unknown.

The reproductive system is vulnerable to the effects of the common bacterium chlamydia. Sexual interaction is the main means of transmission. Chlamydia infections in women are often asymptomatic and go undiagnosed unless a pelvic check reveals the illness. Infertility can be caused by inflammation in the pelvis, which can be induced by a Chlamydia infection.

According to several research, women who have tested positive for chlamydia in their blood or cervical mucus are more likely to develop cervical cancer. Several studies indicate that Chlamydia bacteria can increase the susceptibility to HPV in cervical cancer by promoting the growth of lesions. The proliferation and survival of HPV in the cervix is associated with an elevated susceptibility to cervical cancer [7].

Family history of cervical cancer

An inherited predisposition to cervical cancer cannot be altered. There are instances where cervical cancer tends to run in families. If any of your maternal or sororal relatives have cervical cancer, your risk of having the condition is elevated. A small number of cases of this hereditary tendency have led some researchers to speculate that some women are more prone to HPV infection than others due to genetic anomaliesFurthermore, women with a family history of the condition may be more likely to develop any of the other non-genetic risk factors discussed previously in this section [7]. It is mostly unclear whether genetic processes lead to HSIL and invasive cervical cancer. Previous research has looked into the possibility of a genetic component to cervical cancer since, while, signs of familial clustering have been present for over 60 years. Evidence from the Swedish cancer registry suggests that diseases tend to cluster in families, as there is strong evidence of a high FRR [42][43]. According to these research, RR of cervical cancer in female offspring and siblings ranged from 1.5 to 2.3. There is a high degree of inherited predisposition for breast cancer, and this risk is comparable to that. On the other hand, there are a lot of heritable factors that may work in tandem with HPV infection, there has been a scarcity of documented instances involving large families affected by cervical cancer. This indicates that there is a low occurrence of high-penetrance germline mutations in cervical cancer. HPV infection is widely regarded as a significant contributor to cervical cancer, a specific type of human neoplasia that is known to have just one established cause [44].

Multiple pregnancies

Pregnancy increases a woman's susceptibility to acquiring cervical cancer. One of the reasons behind this is that engaging in sexual activity heightens the likelihood of acquiring HPV infections. Research indicates that pregnant women may have an elevated susceptibility to HPV infection and the advancement of cancer due to hormonal fluctuations. Pregnant women may exhibit heightened vulnerability to HPV infection and cancer progression due to their compromised immune systems [7].

Numerous epidemiological studies have revealed solid evidence of a link between parity, or the number of births a woman has had, and the prevalence of cervical cancer. These investigations delve into the complex interplay of biological and behavioral factors that contribute to cervical carcinogenesis. The link between parity and cervical cancer risk could be linked to a variety of processes, including hormonal changes during pregnancy and childbirth, which can impact the cervix's cellular environment. Additionally, the number of sexual partners and sexual behaviors, often influenced by reproductive experiences, may contribute to the observed link. Furthermore, the impact of immune system modulation during pregnancy and childbirth on the body's ability to suppress HPV infections, a well-established precursor to cervical cancer, is a subject of exploration [45][46][47].

Cervical cancer and full-term pregnancies have been linked in the past. Some hypothesized that this was due to the fact that blood levels of the reproductive hormones estrogen and progesterone naturally increase during pregnancy, reaching a peak in the last weeks of the gestation. During pregnancy, the transformation zone, which is formed by the intersection of the columnar and squamous epithelium, undergoes modifications. These changes could be caused by hormonal changes. As the pregnancy progresses, the transition zone squamous metaplasia increases, reaching its highest point in the third trimester. Other research suggests that the increased detection of cervical abnormalities in pregnant women is caused by endocervical migration, which may explain why there is a link between multiple

pregnancies and cervical cancer. Cervical injuries from vaginal birth have also been proposed as a possible reason for the favorable relationship between cervical cancer and having children. Cervical cancer does not exhibit a correlation with cesarean sections, in contrast to conventional wisdom. This finding provides support for the idea that complications after a vaginal delivery could increase the likelihood of cervical cancer [48].

Long-term use of oral contraceptives (birth control pills)

The use of OCs for an extended period of time appears to raise the risk of cervical cancer. Research indicates that the longer a woman uses oral contraceptives, the higher her chance of developing cervical cancer becomes, but decreases if the pills are stopped and returns to normal within a few years. Oral contraception has both benefits and hazards, which a woman and her doctor should consider. Cervical cancer is more common in women who use specific types of birth control. An international collaborative epidemiological research of current users discovered that as the length of oral contraceptive use grew, so did the relative risk of cervical cancer. It has been suggested that oral contraceptive use for a duration of five years or longer may increase the risk of developing breast cancer by a factor of two [16]. In women who tested positive for HPV DNA, the use of oral contraceptives for five years or longer increased the risk of cervical cancer, according to a multicenter case-control study [21]. Furthermore, adenocarcinoma, a kind of cervical cancer, is more common in women who take oral contraceptive pills, according to a recent meta-analysis and systematic review [25].

Smoke

Researchers believe that tobacco use significantly increases the likelihood of cervical cancer, CIN, and the persistence of hrHPV infections [49]. Other risk factors to consider are having a weakened immune system and using hormonal contraception [49]. Various hypotheses have been put forward to explain the connection between smoking and cervical cancer, such as a direct oncogenic impact on chemical carcinogenesis or a carcinogenic effect resulting from a decrease in cell-mediated immunity [50]. The precise function of smoking in the development of cervical cancer is unknown [51].
Tobacco smoke contains carcinogens that have the potential to metastasize to other organs in addition to the lungs. These toxic compounds enter the bloodstream via the lungs and are then disseminated throughout the body. Female individuals who engage in smoking have a twofold increased likelihood compared to those who do not smoke of developing cervical cancer. Smokers' cervical mucus contains residues of tobacco. Researchers discovered that this chemical can harm the DNA of cervical cells, potentially increasing the risk of cervical cancer. In addition to lowering the immune system's capacity to fight HPV infection, smoking [52].

Economic status

Tests for human papillomavirus (HPV) and cervical cancer (Pap) may be difficult for low-income women to obtain. Because of this, screening for cervical pre-cancer and treatment for it are highly improbable [25].

A number of studies have consistently linked cervical cancer with low socioeconomic status as assessed by income, education level, and occupation. There is a common perception that cervical cancer disproportionately affects "poor, uneducated, and underserved women." [53].

Socioeconomic position does not have a direct correlation with the risk of cervical cancer. However, it does have a substantial impact on the exposure to HPV and the subsequent development of cervical cancer. While this study does not calculate this correlation, it is crucial to consult other studies that have established this connection in order to comprehend the conclusions of the current research. The assumption that a woman's income, profession, and level of education affect her decision-making abilities and her access to information constitute the basis of this connection. Cervical cancer and related preventative measures are less well known to low-income and uneducated women, which may result in insufficient screening and gynecological follow-up [54]

CONCLUSION

Basically, these results conclude that cervical cancer is a complex and multifaceted health concern, with various risk factors contributing to its significant morbidity and mortality globally. The findings underscore the importance of considering a multitude of elements in understanding and addressing the epidemiology of cervical cancer. Factors such as compromised immunity, the presence of Human Immunodeficiency Virus (HIV), specific reproductive characteristics including frequent pregnancies and early age at first pregnancy, prolonged use of contraceptives such as birth

control pills, and the incidence of sexually transmitted infections like Syphilis, HBC, HVC, and Chlamydia all play integral roles in the development of cervical cancer.

Moreover, the inclusion of lifestyle choices like smoking and socioeconomic status as additional risk factors further highlights the intricate interplay of biological, behavioral, and socio-economic factors in the pathogenesis of this disease. Recognizing and comprehensively addressing these risk factors are imperative for the development of effective prevention and intervention strategies to mitigate the impact of cervical cancer on global public health. The HPV mechanism in generating cervical cancer comprises a number of non-structural proteins such as E6 and E7 proteins, which cause apoptosis to fail and uncontrolled cell division, resulting in the creation of cancer cells. Because not everyone infected with the HPV virus develops cervical cancer, it is critical to recognize these risk factors and to educate the public, particularly women.

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