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Human Papillomavirus Infection and Primary Prevention

Diploma thesis

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Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature.

In Prague on April 28th, 2010 Tamara Al-Talib, BSc.

Summary

Human papillomavirus (HPV) infection is the most common sexually transmitted disease, and more than 80% of the population are infected at some point in their life.[19] More than 100 different types of HPV have been isolated and more than 40 of these types infect the anogenital tracts and other mucosal areas. Most individuals with HPV infections are asymptomatic and resolve within 2 years.[18]

HPV infection has now been established as a primary cause of cervical cancer as well as increasing evidence of its role in other anogenital cancers (anus, vulva, vagina and penis) and head and neck cancers.

Throughout this diploma thesis, I have concentrated on the United Kingdom using data collected from The World Health Organisation (WHO), where currently, estimates indicate that every year within the United Kingdom, 3181 women are diagnosed with cervical cancer and 1529 die from the disease. About 8.9% of women in the general population are estimated to harbour cervical HPV infection at a given time, and 79.1% of invasive cervical cancers are associated with HPVs 16 or 18.[23]

Thus, we can now affirm that cervical cancer is the final result of a viral infection and, as such, vaccination is a strategy to consider in the primary prevention of cancers and other diseases caused by HPVs.[2]

HPV vaccines that prevent against HPV 6, 11, 16 and 18 infections are now available and have the potential to reduce the incidence of cervical and other anogenital cancers.[23] The current trials regarding prevention and treatment of HPV infections with vaccines are promising, however, the true value can only be seen after several decades.[19]

Contents

1. Introduction

Human papillomavirus (HPV) are well established as one of the most common sexually transmitted infections[11], with more than 80% of the world population infected at one point in time in their life.[19]

One of the most important discoveries in the etiologic investigation of cancer over these last 25 years has been the demonstration that cervical cancer is caused by the persistent infection by certain genotypes of the Human Papillomavirus (HPV).[2]

More than 100 different HPV types have been described, about 30 of which infect the anogenital system and at least 15 of which are oncogenic.[11] HPV is a very common infection, though the majority of individuals infected by the virus eliminate evidence of it without ever developing any clinical symptoms,[1] some types can cause warts, while very few HPV infected individuals as stated above, can lead to most invasive cervical cancers and their associated pre-cancerous lesions.[1,20] Virtually all squamous cell carcinomas and the overwhelming majority of adenocarcinomas of the cervix are HPV positive.[19]

There is also increasing evidence of HPV being an important factor in other anogenital cancers (anus, vulva, vagina and penis) as well as head and neck cancers. HPV types 16 and 18 are responsible for about 70% of all cervical cancer cases worldwide,[21] and associated with 500,000 new cases of cervical cancer and 250,000 cervical cancer deaths worldwide each year.[16]

The United Kingdom has a population of 25.51 million women ages 15 years and older who are at risk of developing cervical cancer and estimates indicate that every year 3181 women are diagnosed with cervical cancer and 1529 die from the disease. Cervical cancer ranks as

the 11th most frequent cancer among women in United Kingdom, and the 2nd most frequent cancer among women between 15 and 44 years of age. About 8.9% of women in the general population are estimated to harbour cervical HPV infection at a given time, and 79.1% of invasive cervical cancers are attributed to HPVs 16 or 18.[23]

The increase in studies related to HPV as well as the refinement of techniques of clinical diagnosis has opened newer options to improve screening programmes including HPV DNA assays in conjunction with the older and well known Papanicolau smear test and other cytological examinations.[2] HPV vaccines that prevent against HPV 16 and 18 infection as well as others are now available and have the potential to reduce the incidence of cervical and other anogenital cancers.[23]

I chose the theme of my diploma thesis, HPV infections and primary prevention based on its evolving investigations and the importance of its prevention in hopefully reducing the burden of its clinical outcomes including cervical cancer. This review will summarized HPV infections and their role in carcinogenesis as well as the several preventive methods available in the hopes of reducing its incidence.

2. The Human Papillomavirus

The human papillomavirus (HPV) is a member of the Papillomaviridae family of viruses that is capable of infecting humans. They are small, nonenveloped, icosahedral capsid viruses with double stranded DNA genomes as shown in figure 1. The virus encode proteins that promote cell growth which facilitates lytic viral replication in a tolerant cell type however, it may also oncogenically transform a cell that is not tolerant.[15]

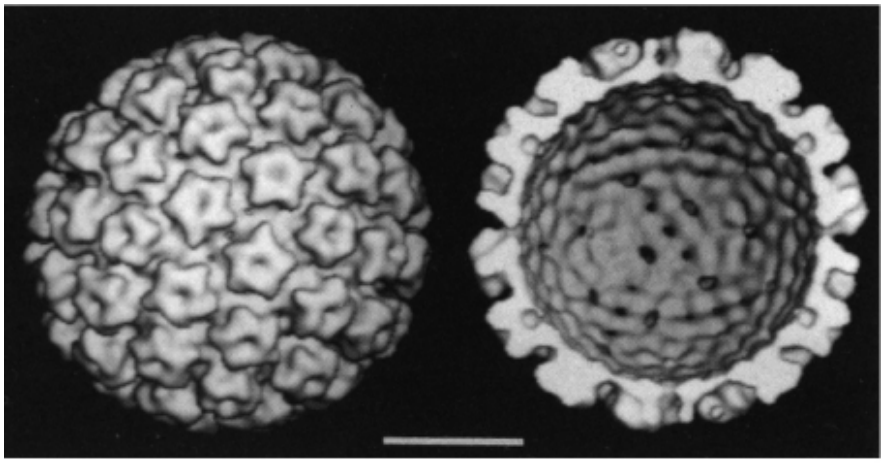

Figure 1: Computer reconstruction of cryoelectron micrographs of (human papillomavirus [HPV]). *Left,* View of the surface of HPV shows 72 capsomeres arranged in an icosadeltahedron. All the capsomeres (pentons and hexons) appear to form a regular five-point-star shape. *Right,* Computer cross-section of the capsid shows the interaction of the capsomeres and channels in the capsid.[15]

2.1. Classification of HPV

Originally, papillomaviruses where classified together with polyomaviruses in a family called *Papovaviridae* because the viruses shared many similar features. However, many studies revealed many differences; thus, papillomavirus were later designated by the International Committee on the Taxonomy of Viruses as a separate family, the *Papillomaviridae*.[8]

Each papillomavirus is specific to the species it infects, hence, there are a few hundred types of papillomavirus and because of its strong association with cervical cancer, efforts have been focused on sequencing the HPV types based on DNA sequence homology.[8] At least over 100 types have been identified and classified.[15]

Phylogenetic organization of papillomaviruses has arisen from sequencing papillomavirus genomes (see figure 2), though they are more largely classified according to the species they infect and the sites or disease with which they may be associated[8]; into cutaneous HPV and mucosal HPV. [15] (see table 2)

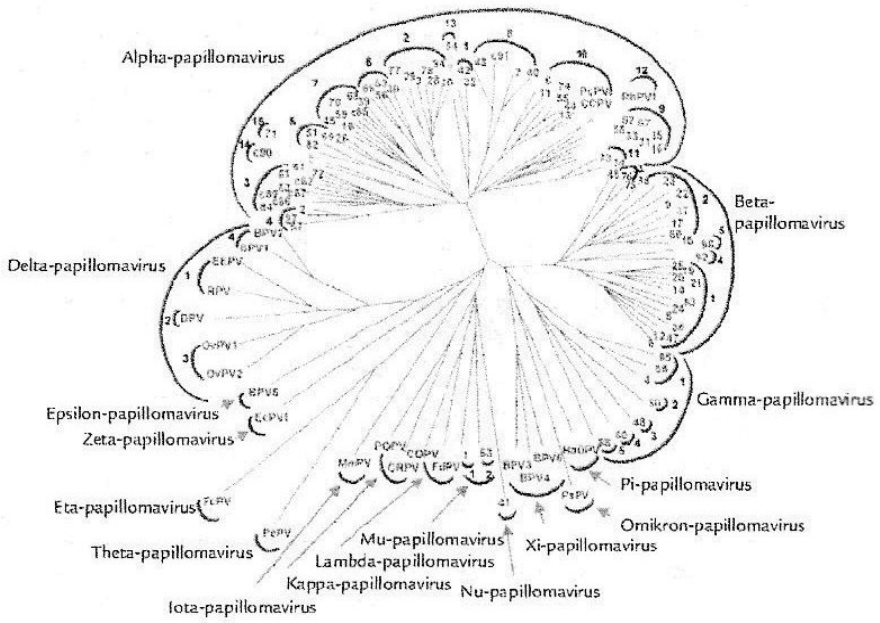

Figure 2: Phylogeny of papillomaviruses. Using the L1 open reading frame sequences to classify papillomaviruses and generate a phylogenetic tree. At the end of each branch is the papillomavirus type, at the end of the first set of semicircular groupings is the species and the end of the second set of larger semicircular groupings is the papillomavirus genus. Most HPV types are in the alpha-papillomavirus genus, as well as beta, gamma and mu genera. The c-number refers to potential HPV types.[8]

A further classification system is based on their association with cervical cancer, dividing the HPV types into undetermined risk, low-risk, probable high-risk and high-risk groups.[19] (see table 3)

2.2. Structure and Replication

As stated above, HPVs are small, nonenveloped, icosahedral capsid viruses with double stranded DNA genomes. The icosahedral capsid is 50 to 55nm in diameter and consists of two structural proteins. The genome of HPV is circular and has approximately 8000 base pairs.[15]

Replication is controlled by the host's transcriptional machinery, determined by skin of mucosal epithelial differentiation. It gains access through breaks in the skin into the basal cell layer where the early genes of the virus stimulates cell growth.[15]

As the basal cells differentiate and mature, the HPV genome is replicated with the exploitation of the host cell's DNA machinery to synthesize the structural proteins needed for viral assembly. Infected epithelial cells out grow non-infected cells, and causes thickening of the basal and prickle cell layer giving rise to dysplasia, warts, or tumours. The entire process eventually results in the release of new virus particles (virus-laden koilocytes) to the epithelial surface.[16] Using the maturation of the skin cell, the virus continues through the skin layers and eventually shed with the dead cells of the upper layer.[15] The shedding of koilocytes serves as the vector of HPV transmission, with each koilocyte containing approximately 50---100 virions.[16] (See figure 3 below).

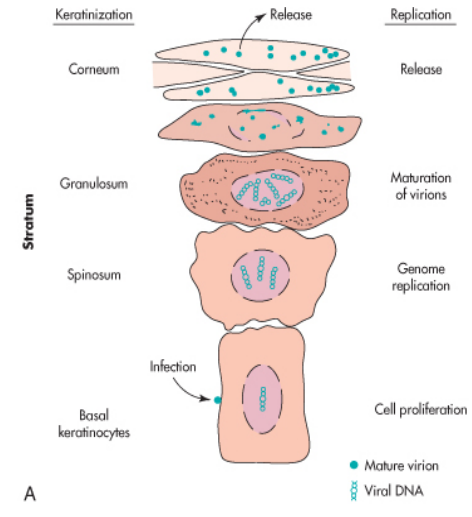

Figure 3: Comparison of normal skin and a papilloma. HPV infection promotes the outgrowth of the basal layer, increasing the number of prickle cells. These changes cause the skin to thicken and promote hyperkeratosis, thereby causing epithelial spikes to form (papillomatosis). Virus is produced in the granular cells close to the final keratin layer.[15]

2.3. Pathogenesis

Papillomaviruses induce epithelial proliferation by infecting and replicating in the squamous epithelium of the forming warts and mucous membranes forming genital, oral and conjunctival papillomas. The HPV types are very tissue specific, thus, can form various disease presentations.[15] (See table 2)

The warts develops as a result of virus stimulation of cell growth and thickening of the basal and prickle layers (stratum spinosum), as well as stratum granulosum and can take 3-4 months to develop. The infection remains local and generally regresses spontaneously probably through actions of the innate and cell-mediated immune systems which may initiate an inflammatory response causing activation of a protective cytolytic response.[15]

However, in some patients who are persistently infected by the virus, the HPV genome can become integrated into the DNA of the host cells and interfering with normal control of cell growth, leading to precancerous and subsequent cancerous changes.[16] Thus it is important to state the oncogenic potential of HPV which has been extensively studied.[15]

3. Natural History of HPV

3.1. HPV transmission

HPV transmission almost exclusively occurs following skin to skin contact with an infected partner.[16] Overall, HPV infection is acquired via 3 main pathways: by direct contact through small breaks in the skin or mucosa; during sexual intercourse, or; while an infant is passing through an infected birth canal.[15]

To date, there is little evidence to suggest that HPV can be transmitted by nonsexual routes (that is, environmental transmission).[16] However, some studies state that HPV resists inactivation and can be transmitted on surfaces of countertops, furniture, bathroom floors and towels. Asymptomatic shedding may promote transmission.[15]

Having sexual contact is the main source of HPV infection. It is estimated that for every three people who have sex with a HPV-positive person, two will develop an infection within the next few months. In the majority of cases (75%), the infection will be asymptomatic.[19] It should be noted that sexual intercourse is not strictly necessary and the virus can also be transmitted during sexual foreplay including fingers.[16]

As stated in the pathogenesis above, HPV is exclusively an intraepithelial pathogen and can only replicate in stratified squamous epithelium. Therefore, as a result of micro abrasions or tears that can occur during sexual activity, HPV penetrates and infects the basal keratinocytes of the epithelium, where it may persist in a latent state.[16]

Although genital HPV types are sometimes transmitted perinatally from mother to child during birth, the appearance of genital HPV-related diseases in newborns is rare. Perinatal transmission of HPV types 6 and 11 can result in the development of the rare, juvenile-onset

recurrent respiratory papillomatosis (JORRP). Although JORRP rates are substantially higher if a woman presents with HPV related genital warts at the time of giving birth, the risk of JORRP in such cases is still less than 1%.[20]

3.2. Risk factors for infection

HPV infection leads to an imbalance between cell proliferation and apoptosis. However, it is likely that several cofactors are necessary for progression to invasive cervical cancer[19] (See table 1 below). These cofactors can either act by stimulation of the persistence of HPV infections or by stimulation of progression to an invasive cancer.[19]

Cofactors affecting persistence and progression can be divided into three groups and several of them described in more detail below:

Cofactors		
Environmental factors	**Host-related factors**	**Viral factors**
Sexually transmitted disease (STDs) Smoking Oral contraceptives Parity Diet	Endogenous hormones Immune response Genetic susceptibility traits	HPV type and variant Viral load Viral integration

HLA, human leukocyte antigen; HPV, human papillomavirus.

Table 1: Cofactors related to risk of HPV infections.[19]

3.2.1. Environmental factors

Number of sex partners and STDs

The most consistent risk factor for HPV infection is increased number of sex partners.[1] More than 100 years ago, it was noticed that nuns had no risk and prostitutes had an increased risk for development of cervical cancer. Over time, the suspected linkage between sexual behaviour and the development of precancerous lesions and cervical cancer was confirmed.[19]

Several studies of women and men have shown strong relationships between lifetime number of sex partners and genital HPV acquisition. One study showed that a shorter time interval between meeting a new partner and engaging in sexual intercourse also increases risk of HPV infection in women. Another study of HPV infection among adolescent women found that a mean increase of greater than 1.5 years in the age of the male partner relative to the age of the woman conferred a two-fold increase in risk of HPV DNA detection in the woman probably attributable to the relationship between increasing age of the male partner and a higher number of sexual partners.[1]

Infection with sexually transmitted diseases enhances the risk of cervical carcinogenesis, but this is also associated with sexual behaviour in general. Infection with Chlamydia trachomatis has also been suggested as a possible contributor to the oncogenic effect on HPV as well as HIV-infected women, who are also at higher risk for cervical HPV detection, infection with high-oncogenic-risk types of HPV, persistent HPV infection, cervical cytological abnormalities and CIN.[19]

Smoking

HPV infection has been positively related with current as well as past smoking, although one study had conflicting results, finding that past smokers had a lower prevalence of HPV infection than women who had never smoked. Another study investigating the relationship between smoking and oncogenic HPV infection found no association between number of cigarettes smoked per day and presence of HPV DNA, and most other studies investigating the relationship between smoking and HPV infection have failed to detect an association.[1]

Oral contraceptives

The relationship between oral contraceptive use and HPV infection is difficult to evaluate due to its association between oral contraceptive use and sexual activity.[1] One study found that, after adjusting for variables such as age and lifetime number of sex partners, oral contraceptive use exhibited a borderline association with HPV 16 and HPV 18 seropositivity. Other studies have reported an association between oral contraceptive use and HPV DNA positivity after adjusting for variables such as number of sex partners, but most studies have found no association.[1]

Diet

There appears to be a relationship between food intake and cervical carcinogenesis, although study results are sometimes conflicting. Folate, carotenoids, vitamin C, vitamin E and retinols have been investigated extensively as potential modifiers of cervical dysplasia and cancer risk.[19]

One of the most recent studies found that a high intake of foods rich in vitamin A, particularly high retinol foods, is associated with a reduced risk of in-situ disease and less strongly with a reduced risk of invasive compared with in-situ disease. Some studies suggest that circulating vitamin B12 concentrations may be protective against HPV persistence, as well as thiamine and riboflavin, probably due to their effect on DNA methylation. Carotenoids, tocopherols and ascorbic acid are potent anti-oxidants, thus potentially preventing DNA damage.[19]

3.2.2. Host related factors

The endocrine system is likely to play an important role in the process of cervical carcinogenesis. Oestrogen is a possible cofactor to the oncogenic effect of HPV. High levels of oestrogen during

puberty are considered to be a major influence in the metaplastic changes in the cervical transformation zone during that period. Oestrogen apparently reduces susceptibility to primary HPV infection, but in the event of persistent HPV infection, sex steroid hormones (oestrogen and/or progesterone) are associated with progression to cervical cancer.[19]

The importance of the immune system in the infection, progression and persistence of HPV is clear. Both the humoral and cellular immune responses play an important role in cervical carcinogenesis. Although cellular immunity is essential for the elimination of HPV, the mechanisms involved is still poorly understood.[19] There is an association between human leukocyte antigens and the prevalence of cervical carcinogenesis. There is, for example, a negative association between DRB1*13 and cervical cancer, and a positive association for specific DRB1-DQB1 haplotype combinations.[19]

3.2.3. Viral factors

Viral factors play a major role in the oncogenic potential. As stated above, HPV can be divided into high-risk, intermediate-risk and low-risk and undetermined risk types. Some viral types (e.g. HPV 16, HPV 52) show different variants with different oncogenic potentials.[19]

The amount of virus present in the cervix (viral load) plays an important role in the possible progression towards dysplasia. This was first described for HPV 16 and more recently for other types. The viral load may be predictive of the future risk of developing high-grade dysplasia or carcinoma, even in patients with negative smears.[19]

4. HPV Infections

HPV infection of the genital tract is as stated above, now recognized as a common sexually transmitted disease. Infection is usually asymptomatic but may result in slight itching. As discussed above, HPV can be distinguished further as cutaneous HPV or mucosal HPV, on the basis of the susceptible tissue. Within the mucosal HPV, there is a high risk group associated with cervical cancer. Viruses in similar groups frequently cause similar types of warts.[15]

These clinical syndromes along with their associated papillomaviruses are summarized in table 2 and discussed in further detail below.

Syndrome	HPV Types	
	Common	Uncommon
Cutaneous Syndromes		
Skin warts		
Plantar wart	1	2, 4
Common wart	2, 4	1, 7, 26, 29
Flat wart	3, 10	27, 28, 41
Epidermodysplasia verruciformis	5, 8, 17, 20, 36	9, 12, 14, 15, 19, 21-25, 38, 46
Mucosal Syndromes		
Benign head and neck tumours		
Laryngeal papilloma	6, 11	-
Oral papilloma	6, 11	2, 16
Conjunctival papilloma	11	-
Anogenital warts		
Condyloma acuminatum	6, 11	1, 2, 10, 16, 30, 44, 45

Table 2: Clinical Syndromes Associated with Papillomaviruses[15]

4.1 Cutaneous Syndromes

Skin warts: As sumarized above, the cutaneous syndromes consist of skin warts. A wart is a self-limited, benign proliferation of skin that regresses with time. Most people with HPV infection have the common types of the HPV virus (HPV-1 through HPV-4), which usually effect the hands and feet,[15] but can also occur in other areas, such as the elbows or knees.[20]

Common, plantar, and flat warts are most common in children and young adults with an incubation period as long as to 4 months after the infection. The appearance of the wart (dome shaped, flat, or plantar) depends on the HPV type and the infected site.[15]

4.2 Mucosal Syndromes

Benign head and neck tumors: Single oral papillomas are the most benign epithelial tumors of the oral cavity. They are pedunculated with a rough and papillary appearing surface. They can occur in people of any age group and usually are solitary. Laryngeal papillomas are commonly associated with HPV-6 and HPV-11 and are the most common benign epithelial tumors of the larynx. They occur in young children and middle-aged adults and although benig, can be lifethreatening in children due to obstruction of the airway. Rarely, papillomas may be found further down in the trachea and into the bronchi.[15]

Anogenital warts: Genital warts (condylomata acuminata) occur almost exclusively on the squamous epithelium of the external genitalia and perianal areas. Approximately 90% are caused by HPV-6 and HPV-11. Genital warts may appear like soft, flesh-colored warts that are flat, raised, and sometimes cauliflower shaped. The warts can appear within weeks or months of sexual contact with an infected person.[15]

HPV types that tend to cause genital warts are not those that cause cervical cancer. However, since an individual can be infected with multiple types of HPV, the presence of warts does not rule out the possibility of a high-risk HPV type also being present.[20]

4.3 HPV and Cervical cancer

Cervical cancer is still one of the leading cancers worldwide, although there is differences between developed and developing countries. In developed countries there is a continuous decline in incidence and mortality, whereas in developing countries, there is a more stable or even increasing pattern, likely due to the lack of screening and infectious risk factors than to ethnic differences.[19]

Cervical cancer is thought to develop through persistent infection with HPV causing a continuum of progressive cellular changes, progressing to precancerous lesions such as mild (cervical intraepithelial neoplasia [CIN I]) to moderate neoplasia (CIN II) to severe neoplasia or carcinoma in situ (CIN III) with 40% to 70% of the mild lesions spontaneously regressing.[15,20] However, when untreated, about one third of women with CIN II/III will develop cervical cancer over the next 10 years.[9]

The many different HPV types is a well establised factor that partially explains differential cancer risk. Based on their association with cervical cancer, they are divided into undetermined risk, low-risk, probable high-risk and high-risk groups.[19]

15 HPV types have been classified as high-risk for development of cervical cancer, 3 have been classified as probable high-risk, 12 as low-risk and 3 are considered to have undetermined risk[1] (See table 3 below).

Risk Classification	HPV types
High-risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
Probable high-risk	26, 53, 66
Low risk	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108
Undetermined risk	34, 57, 83

Table 3: Classification of HPV types by cervical oncogenicity[1]

High-risk HPV types 16, 18, 31, and 45 and, rarely, by other types of HPV account for more than 95% of all cases of cervical cancer, with the most common member being HPV 16, accounting for more than 60% of all cervical cancers.[15,19] Invasive cervical cancer can be divide in two major histological types; squamous cell cancinoma (SCC) and adenocarcinoma. In terms of percentages, 80-85% of cases are SCC, 10% are adenocarcinmoas orginating from the columnar epithelium, and 3% are adenosquamous carcinoma and other rare tumors.[19] Adenocarcinomas have a worse prognosis and are increasing in proportion as the screening programmes prevent propotionally more SCC.[9]

In addition to cervical cancer, high risk HPV is also associated with approximately 50% or more of vaginal, vulvar, and penile carcinomas; 85% of anal carcinomas; and 10 % of cancers of the larynx and aerodigestive tract.[16] (See figure 4 below).

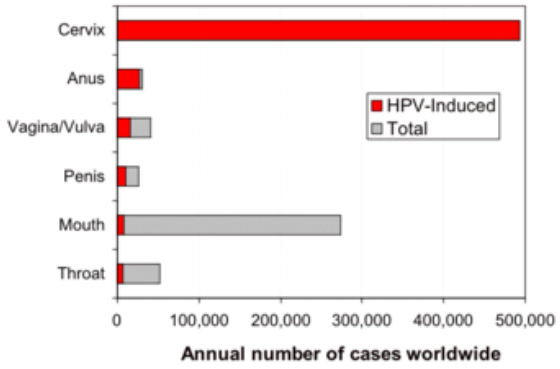

Figure 4: HPV-induced cancers.[20]

5. Epidemiology of HPV infections

Presently, HPV is possibly the most diagnosed sexually transmitted infection in the world, with certain HPV types common among sexually active people.[18]

5.1. Prevalence

HPV prevalence is the proportion of subjects infected by the human papillomavirus (HPV) according to a DNA assay at a specific point in time.[22]

Estimates of the population prevalence of HPV infection among women around the world range from 6%-21%.[21] (See table 4) The wide variation in estimates can be largely explained by several factors including the range of age differences within the population and the sensitivity of the DNA assay used.[1] Overall, these DNA assays, combined with measurements of type-specific antibodies against HPV capsid antigens, have shown that over 50% of sexually active women have been infected by one or more genital HPV types at some point in time.[1]

Age group	HPV prevalence (%)	
	UK and Northern Ireland	World
All ages	**8.9**	**11.4**
<25	22.5	20.8
25-34	13.7	13.5
35-44	7.5	7.9
45-54	5.7	6.2
55+	5.6	6.8

Table 4: HPV prevalence of women with normal cervical cytology comparing data from The United Kingdom of Great Britain and Northern Ireland and the world[21, 23]

HPV causes virtually 100% of cases of cervical cancer, and an underestimation of HPV prevalence in cervical cancer is most likely due to the limitations of study methodologies.[23]

The prevalence of HPV increases with severity of the lesion. Worldwide, HPV-16 and 18, the two vaccine-preventable types contribute to over 70% of all cervical cancer cases, between 41% and 67% of high-grade cervical lesions and 16-32% of low-grade cervical lesions. After HPV-16/18, the six most common HPV types are the same in all world regions, namely 31, 33, 35, 45, 52 and 58; these account for an additional 20% of cervical cancers worldwide.[23] The prevalence of type-specific HPV infections among HPV-infected population is shown in table 5.

Ranking	HPV type	Number of women tested	HPV prevalence	95% confidence interval
1st	16	218339	2.7	(2.7-2.8)
2nd	31	208818	1.1	(1.1-1.2)
3rd	18	215093	1.1	(1.0-1.1)
4th	52	193577	1.0	(0.9-1.0)
5th	51	191886	0.8	(0.8-0.9)
6th	58	196908	0.7	(0.7-0.7)
7th	56	192557	0.6	(0.6-0.7)
8th	39	191492	0.6	(0.6-0.7)
9th	45	194232	0.6	(0.5-0.6)
10th	33	207376	0.5	(0.5-0.6)

Table 5: World Prevalence of Top 10 HPV type distribution of women with normal cervical cytology.[21]

5.1.1 Age

The prevalence of HPV infection is highest among young women and appears to decrease with increasing age,[1, 23] as shown in table 4 and figure 5 below.

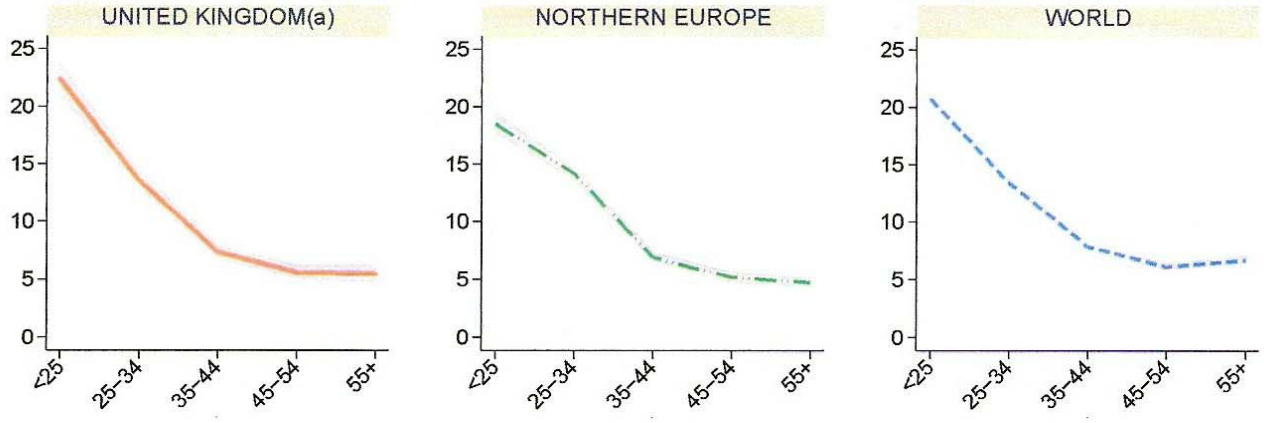

Figure 5: Crude age-specific HPV prevalence (%) in women with normal cytology in United Kingdom compared to Northern Europe and the World.[23]

Most HPV infections occur after initiation of sexual activity and are transient. Therefore, women over age 30 who are HPV positive include those with new infections as well as those who are persistent carriers.[1]

Although, most studies show a decrease in HPV prevalence with age, many studies on the other hand have shown a peak prevalence of HPV infection in women below age 25, a decrease among women aged 35-54 and a second peak after age 55. This second peak could be attributed to a cohort effect of higher cervical cancer rates in women born during the 1920s who first became sexually active during or after the Second World War or to reactivation of latent virus.[1, 9] This difference can be seen in figure 6 below.

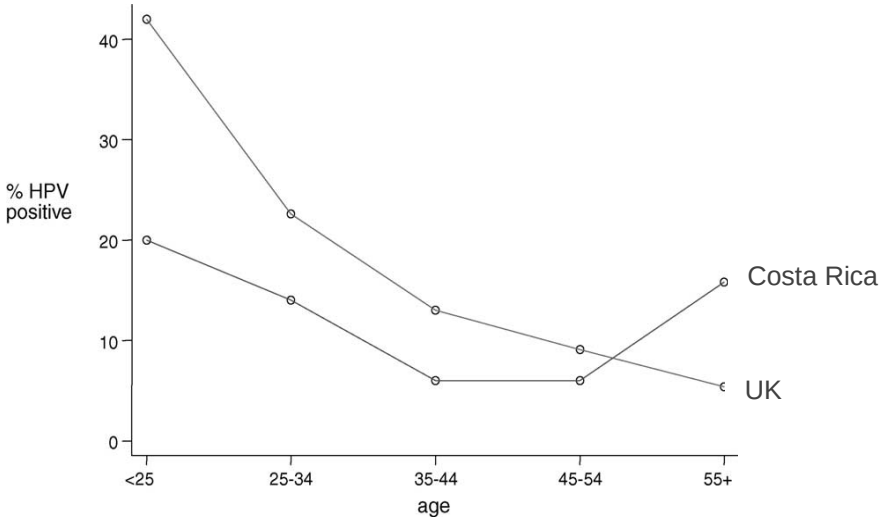

Figure 6: Age-specific prevalence of HPV in a routine screening population in the UK and in rural Costa Rica.[1]

5.1.2 Men

HPV infection in the genital tract has been detected in up to 73% of healthy men.[23] Therefore, HPV infection also appears to be very common in men as in women, however less is known about the natural history of genital HPV infection and associated lesions in males as it has not been studied as extensively as HPV infections in women.[1, 6] Like other sexually transmitted diseases, HPV may be transmitted more readily from men to women than from women to men.[23] The ongoing HPV in Men (HIM) study provides the most current data on HPV infection and lesion development in males.[6]

HPV prevalence in men appears to vary widely country to country (ranging from 1 to 60% HPV prevalence).[23] However, it is difficult to compare the studies made as different methods where used in obtaining genital sampling from men amongst the different countries.[1]

5.2 Incidence

Incidence is the number of new cases that occurs during a given period of time in a specified population. It can be expressed as an absolute number of cases per year or as a rate per 100,000 persons per year.[22]

Acquisition of HPV is very common, especially among sexually active young adults, and the incidence of infection with oncogenic HPV types appears to be higher than the incidence of infection with non-oncogenic types.[1] The cumulative incidence of HPV infection among women aged 15-19 in England was found to be 44% over a 3 year period and increase to 60% at 5 years.[1]

Cervical cancer is the second most common cancer among women worldwide, with an estimated 493,000 new cases and 274,000 deaths in 2002. About 83% of the cases occur in developing countries, representing 15% of female cancers. Worldwide, mortality rates of cervical cancer are substantially lower than incidence with a ratio of mortality to incidence to 55%.[21, 23] (See table 6 below). The incidence of cervical carcinoma falling in the UK, largely due to the success of screening programmes.[9]

Indicator	United Kingdom	Northern Europe	World
Crude incidence rate[1]	10.5	11.7	16.0
Age-standardized incidence rate[1]	8.3	9.0	16.2
Cumulative risk (%) ages 0-64 years[1]	0.6	0.6	1.3
Standardized incidence ratio (SIR)[1]	46.0	51.0	100.0
Annual number of new cancer cases	3181	5647	493243

Standardized rates have been estimated using the direct method and the World population as the reference.
1 Rates per 100,000 women per year.

Table 6: Incidence of cervical cancer in United Kingdom, Northern Europe and the World.[21, 23]

6. Burden of HPV infection

As stated above, HPV infections are associated with a wide spectrum of disease. Most patients with cervical HPV infection are typically never seen in gynaecology practice because the HPV infections do not lead to any detectable cytological abnormalities and clear spontaneously or because there is no access to care.[16] An important subset of these patients subsequently progress to low- or high-grade cervical dysplasia (30 million and 10 million cases, respectively), and eventually cervical cancer (0.5 million cases).[16]

It is important to note that a clinically important segment of the overall burden of HPV disease is associated with non-oncogenic HPV 6 and 11. These two HPV types are not only associated with low grade cervical lesions and anogenital warts but also cutaneous lesions, and respiratory papillomatosis. In addition, the clinical consequences of HPV 6 and 11 infections tend to become manifest more rapidly compared with high-risk HPV types. Genital warts are almost exclusively caused by HPV 6 and 11, are extremely contagious, and result in a high level of emotional distress and anxiety.[16]

There is a substantial economic burden associated with sexually transmitted diseases. For example, in the United Kingdom, over 2000 cervical cancer cases a year cost the National Health Service (NHS) about £35 million a year; routine vaccinations of 370, 000 girls as well as catch-up vaccinations of 2,700,000 girls cost the NHS an approximate total of £570 million a year. Significant costs were also associated with the screening and treatment of cervical cancer. 3.5 million women are screened per year in the United Kingdom and cost the National Health Service approximately £150 million.[25]

7. Primary prevention of HPV

7.1 Abstinence, be faithful, use condoms

HPV infections associated with anogenital cancers are sexually transmitted, thus, effort focusing on prevention of HPV infection can and should mirror those of other STDs.[1]

In the late 1980s and 1990s in Uganda, the 'ABC' approach, an acronym that stands for Abstain, Be faithful, use Condoms was found to be successful for HIV prevention.[1] Some aspects of the epidemiology of HPV suggest that the ABC approach might have some success in preventing HPV infection. By definition, abstaining from sexual activity would prevent most HPV infections, just as it would prevent acquisition of other sexually transmitted diseases. Given the strong association between increasing number of sex partners and HPV infection, being faithful to one partner would likely decrease the prevalence and incidence of HPV infection. The possible effects of promoting condom use in HPV prevention are less clear. Though condoms appear to protect against genital warts, CIN2, CIN3 and invasive cervical cancer, one study revealed that there is no consistent evidence that condom use reduces the risk of acquiring a HPV infection.[1]

In addition, male circumcisions have shown a significant protective effect against HPV transmission and may offer an alternative preventative strategy.[23]

7.2 Screening programmes

It is established that well-organised cervical screening programmes or widespread good quality cytology can prevent up to 80% of these cancers and overall reduce cervical cancer incidence and mortality.[23]

HPV-induced changes in the cervical epithelium can be detected by cytology using a microscopic examination of exfoliated cells, which is also known as a Papanicolaou (Pap) smear.[24] These should be performed on all women from the age of 25 years, or after first intercourse if later, and then repeated every 3 years until the age of 49. Between 50 and 64 years of age smears are performed 5-yearly, and from the age of 65 years only those who have not been screened since age 50 nor have recent abnormal tests are screened.[9] (See table 7 below).

Indicator Value	Value
Screening ages (years)	25-64; 20-65
Screening interval (years) or frequency of screens	Every 3 years for ages 25-49; Every 5 years for ages 50-64; Every 3 years for ages 20-39; Every 5 years for ages 40-65
Life time number of recommended smears	12
Smear taker	General Practitioner or general practice nurses

Variable screening ages and screening intervals or frequency of screens depend on different guidelines followed in the country.

Table 7: Main characteristics of cervical cancer screening in United Kingdom.[23]

Pap smears have reduced the incidence and fatalities of cervical cancer in the developed world, but there are still a large percentage of cervical cancer worldwide. Cervical cancer has substantial mortality in areas with poor resources and worldwide, there are 490,000 cases and 270,000 deaths with 80 to 85 percent of cervical cancer deaths occur in the developing world.[23]

A cervical examination also detects warts and other abnormal growths which can be visualized with a speculum and microscope (coloposcopy). After washing the growths with 5% acetic acid, they become visible as white patches of skin, suggesting a precancerous lesion.[9]

In spite of the success of cervical cancer screening, Pap cytology screening is yet to be effectively implemented or has failed to reduce cervical cancer rates to an appreciable extend. Screening appears to benefit only a small fraction of women although a much larger percentage endure the inconvenience of the Pap test in order to avoid cervical cancer.[24]

There is now convincing evidence that suggests testing for oncogenic HPV is more sensitive and has a higher negative predictive value for moderate to severe precancerous lesions (CIN II/III) compared to Pap smears and visual inspection. The sensitivity of HPV DNA testing is so high that few cancers and precancerous lesions are missed.[14] A lower costing HPV DNA test suitable for low resource settings may become available soon, potentially making high-sensitivity screening feasible where it currently does not exist in Africa, Asia and Latin America.[20]

7.3 HPV Vaccinations

The discovery of Human Papillomavirus (HPV) infection as the main cause of genital warts, cervical cancer and other HPV-related cancers and provide a great opportunity for cervical cancer prevention through vaccination. HPV 16 and 18 cause 70% of cervical cancers worldwide. Thus a prophylactic vaccine to prevent HPV related precancerous lesions and cancers would save lives; reduce the need for costly medical procedures and substantial benefits to individual women and communities throughout the world.[13]

Based on the induction of neutralizing antibodies by non infectious Virus Like Particles (VLP) of capsid proteins, HPV vaccines have consistently induced high titre of neutralizing antibodies with

minimal side effects and induce more than 90% protection from persistent HPV 16-18 infection and HPV 16 and 18 associated high-grade Cervical Intraepithelial Neoplasia (CIN) in proof of concept efficacy trials. The level of protection from death due to cervical cancer has been suggested to exceed 95%.[14]

Currently, two HPV vaccines are widely marketed internationally, a quadrivalent vaccine *(Gardasil)* first licensed in 2006 for HPV types 6, 11, 16 and 18; and a bivalent vaccine *(Cervarix)*, which was first licensed in 2007, for HPV types 16 and 18. Using recombinant technology, both are prepared from purified proteins that form HPV type-specific empty shells or virus-like particles (VLPs). Neither vaccine contains live biological products or viral DNA, so they are non-infectious (see table 8). HPV vaccines are designed for prophylactic use only; they do not clear existing HPV infection or treat HPV-related disease. The mechanisms by which these vaccines induce protection have not been fully defined but seem to involve both cellular immunity and neutralizing immunoglobulin G antibodies.[24]

	Bivalent	**Quadrivalent**
Vaccine Type	Bivalent HPV-16 and HPV-18 VLP L1 capsid component	Quadrivalent HPV-6/11/16/18 VLP L1 capsid component
Expression System	Baculovirus	Yeast
Concentration	20µg HPV 16 20µg HPV 18 0µg	20µg HPV 6 40µg HPV11 40µg HPV16 20µg HPV18
Adjuvant	AS04: 500µg Aluminium Hydroxide 50µg MPL (3-deacylated Monophosphoryl Lipid A)	Alum: 225µg Aluminium Hydroxyphosphate Sulphate
Placebo	Aluminium Hydroxide	Aluminium Hydroxyphosphate Sulphate
Dose	0.5ml, Intramuscular	0.5ml, Intramuscular
Schedule	0, 1, 6 months	0, 2, 6 months
Age-range	15-25 years	16-23 years

Table 8: Summary of Human Papillomavirus vaccines and its strategy within the UK [25]

There are different types of programmes to implement HPV vaccination across Europe. These include Organized school based programmes, Opportunistic “on demand” programmes and Private sector provision only programmes (see figure 7). The United Kingdom HPV vaccination protocol is a school based system. [25]

Gardasil has been licensed for use in young adolescent girls (as young as 9 years in some countries) to prevent cervical precancerous lesions and cancers and anogenital warts in females. In addition, it is also licensed for prevention of vulvar and vaginal precancerosis and cancers as well as anogenital warts in females. In some countries, the vaccine is also licensed for the prevention of anogenital warts in males. Cervarix has been licensed for use in females as young as 10 years of age to prevent cervical precancerosis and cancers. Registration for indications in males has not been sought.[24]

Figure 7: HPV Vaccination programmes across Europe.[25]

HPV vaccination will reduce the number of women who require colposcopy, biopsy and cervical treatment for precancerous cervical lesions.[14] However, it should be noted that women should continue with cervical screening even after receiving the vaccine. Without continued screening, the number of cervical cancers preventable by vaccination alone is less than the number of cervical cancers prevented by regular screening alone.[20]

Both vaccines are intended to be administered to females before the onset of sexual activity. That is, before first exposure to HPV infection. Most countries that have licensed these vaccines, recommend their use in girls aged 10–14 years. Some national programmes also recommend routine or temporary catch-up vaccination of older adolescent females and young women.[24] Consideration should also be given to the vaccination of mature women given the lifetime risk of HPV infection. The decision who to vaccinate, should be taken on an individual patient basis, taking in consideration various risk factors involved in developing cervical cancer.[14]

An important question, that many studies are asking, is whether boys should be included in the HPV vaccination programme as well as girls. Gardasil is already licensed in the UK for use in boys aged 9–15 although concerns on the immunogenicity and efficacy of HPV vaccines in men are still ongoing. However, one published multi-centre study of a quadrivalent vaccine similar to Gardasil (supplied by Merck Research Laboratories), administered to 10–15 year olds (506 girls and 510 boys) showed high levels of immunogenicity (greater than 99%) to all four HPV types (6,11,16,18) in both boys and girls.[12]

Another report of HPV vaccination in males showed that Gardasil was 86% effective in preventing persistent infection and 90%

effective against external lesions such as genital warts caused by vaccine-related HPV types. These results are based on a randomized, double-blind, placebo-controlled trial involving 4065 men aged 16–26 years with a 3-year follow-up period.[24]

However, a new study published in the *British Medical Journal* stated that vaccinating boys against human papillomavirus (HPV) in addition to girls is not likely to be cost-effective and concluded that including boys in an HPV vaccination program is unlikely to provide good value for resources, compared with vaccinating girl's only.[3, 10]

7.4 Education and Awareness

Another important topic in prevention of HPV infections and their outcomes is importance of greater educational measures. The health belief model, which claims that individuals will engage in preventive health behaviour if they believe themselves at risk of contracting a condition and that the benefits of preventive actions outweigh the barriers to or costs of such actions, clearly does not work for adolescent populations. Students reported that they received most of their information from school classes and media sources, which send a clear message to health educators that they must devise programs that will help adolescents, get information about HPV infection and its consequences.[5]

Studies in the United States showed that sexually active college women lack awareness of HPV, are at considerable risk of contracting HPV, and are not practicing behaviours that would reduce the risk of HPV infection and sequelae.[5] One study summarized that, the students did not know that HPV can cause cervical cancer, neither of the preventive measures including cervical cancer screening. The usual sources that provide adolescents with health education and health care need to benefit from the rising literature about adolescent sexual behaviour to create more effective sexual health prevention messages, especially for HPV.[5]

8. Conclusion

In conclusion, over the past 10 years, significant progress has been made in the field of HPV infections and its prevention and treatment.

The discovery of HPV as a primary cause for several significant cancers, such as cervical cancer and other anogenital cancers as well as some other HPV related lesions such as genital warts has led to increasing HPV screening and diagnosis. In addition, this understanding has also made possible the development of preventive interventions such as HPV vaccines.

As described by The Joint Committee on Vaccination and Immunisation, UK strategy on HPV vaccination recommend routine vaccination of 12-13 year old girls, efficiently delivered through a school based programme. As well as a catch-up programme for girls up to the age of 18 years. Within the UK, indications in males has not been sought.

Although the development of HPV vaccination is a tremendous step in the right direction in preventing HPV related diseases, it is important to note that realistically these interventions are at least a decade away and several decades must pass before any effects will be evident.

On a positive note however, progress made has allowed us to appreciate other cofactors involved in the carcinogenesis of HPV related malignancies and thus it is plausible to state that future endeavours will focus on other cofactors, facilitating our understanding of HPV pathogenesis. And fundamentally, this can lead to better prevention, diagnosis and treatment of HPV infections.

Finally, through reviewing this topic I became aware of the lack of education and awareness that individuals had of this problem and when a

population is at high risk of infection, however lacks knowledge of its existence, as well as the symptoms and consequences associated to it, prevention is somewhat difficult. Therefore, a large part of primary prevention of HPV infections should entail greater education of the public.

9. References

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