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Chapter 1: HPV in the etiology of human cancer

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Abstract

The causal role of human papillomavirus (HPV) in all cancers of the uterine cervix has been firmly established biologically and epidemiologically. Most cancers of the vagina and anus are likewise caused by HPV, as are a fraction of cancers of the vulva, penis, and oropharynx. HPV-16 and -18 account for about 70% of cancers of the cervix, vagina, and anus and for about 30–40% of cancers of the vulva, penis, and oropharynx. Other cancers causally linked to HPV are non-melanoma skin cancer and cancer of the conjunctiva.

Although HPV is a necessary cause of cervical cancer, it is not a sufficient cause. Thus, other cofactors are necessary for progression from cervical HPV infection to cancer. Long-term use of hormonal contraceptives, high parity, tobacco smoking, and co-infection with HIV have been identified as established cofactors; co-infection with *Chlamydia trachomatis* (CT) and herpes simplex virus type-2 (HSV-2), immunosuppression, and certain dietary deficiencies are other probable cofactors. Genetic and immunological host factors and viral factors other than type, such as variants of type, viral load and viral integration, are likely to be important but have not been clearly identified.

Keywords: HPV; Cancer; Epidemiology; Etiology

1. Mechanisms of HPV carcinogenesis

Human papillomavirus particles consist of 8000 base-pair (bp) long circular DNA molecules wrapped into a protein shell that is composed of two molecules (L1 and L2). The genome has the coding capacity for these two proteins and at least six so-called early proteins (E1, E2, E4–E7) that are necessary for the replication of the viral DNA and for the assembly of newly produced virus particles within the infected cells. Both sets of genes are separated by an upstream regulatory region (URR) of about 1000 bp that does not code for proteins but contains cis-elements required for regulation of gene expression, replication of the genome, and its packaging into virus particles (Fig. 1).

Papillomaviruses are perfectly adapted to their natural host tissue, the differentiating epithelial cell of skin or mucosae, and exploit the cellular machinery for their own purposes [1]. The cycle is initiated when infectious particles reach the basal layer of the epithelium, where they bind to and enter into cells, through small breaks. It has been suggested that for maintenance of the infection, the virus has to infect an epithelial stem cell [2]. The replication cycle within the epithelium can be divided into two parts. First, the viral genome is replicated to a copy number of about 100 and maintained for varying periods of time at this low copy number within the initially infected, but still replicating, competent cells. The viral proteins E1 and E2 are essential for this basal DNA replication. One can speculate that during viral persistence, the immune system keeps the infection in this state [2]. Second, once the basal cells are pushed to the suprabasal compartment, they lose their ability to divide and instead initiate the terminal differentiation program. Papillomaviruses replicate in

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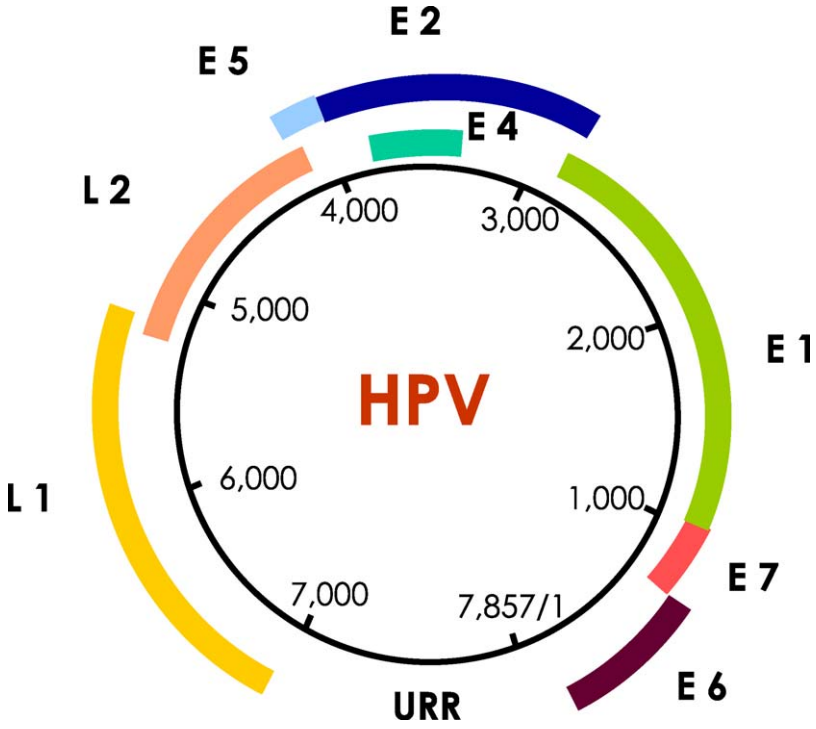

Fig. 1. Schematic presentation of the HPV genome showing the arrangement of the early E or nonstructural genes, the capsid genes (L1 and L2) and the upstream regulatory region (URR).

this compartment, and for their release into the environment, take advantage of the disintegration of the epithelial cells that occurs as a consequence of their natural turn-over at the superficial layers (Fig. 2).

The critical molecules in the process of virus replication are the viral proteins E6 and E7, which interact with a number of cellular proteins. In experimental systems these interactions have been shown to induce proliferation and eventually immortalization and malignant transformation of cells [3]. There are differences between the E6/E7 proteins of high-risk and low-risk HPV types, but these are often of a quantitative rather than a qualitative nature [4]. The best characterized interactions are with the proteins pRB and p53, which are central molecules in cell cycle control, and remarkably, are mutated in many human cancers. Binding of E7 to pRB activates the E2F transcription factor, which triggers the expression of proteins necessary for DNA replication [3]. Unscheduled S-phase would normally lead to apoptosis by the action of p53; however, in HPV-infected cells, this process is counteracted by the viral E6 protein, which targets p53 for proteolytic degradation [5]. As a consequence, the dependence on cell cycle control is abolished and normal keratinocyte differentiation is retarded [2] (Fig. 2). The outstanding ability of HPV-16 to persist and induce progression towards malignancy may be explained by a particularity at this stage of its life cycle. As an aberration of virus infection, constant activity of the viral proteins E6 and E7 leads to increasing genomic instability, accumulation of oncogene mutations, further loss of cell-growth control, and ultimately cancer [6]. During tumor progression, the viral genomes often integrate into the host chromosome, which results in a constant level of E6/E7 proteins via stabilization of the mRNA, by the influence of modified chromatin structures or by loss of negative regulation of transcription mediated by the viral E2 protein [7].

Over 100 HPV types have been characterized molecularly and about 40 types are able to infect the genital tract. Phylogenetically, the genital HPVs belong to the alpha genus and those associated with cutaneous epidermodysplasia verruciformis to the beta genus. Clusters of lower order are known as species; they are closely related phylogenetically and have similar biological properties.

2. Epidemiological evidence for the causal link between HPV and cervical cancer

2.1. Case series

The largest series of cases of invasive cervical cancer investigated with a standard protocol has been assembled by the International Agency for Research on Cancer (IARC). About 1000 women with histologically verified invasive cervical cancer were recruited from 22 countries around the world. Frozen biopsies from the tumors were analyzed in a central laboratory for the detection of HPV-DNA, using strict control for the presence of malignant cells in sections adjacent to the sections used for PCR-based assays. After reanalysis

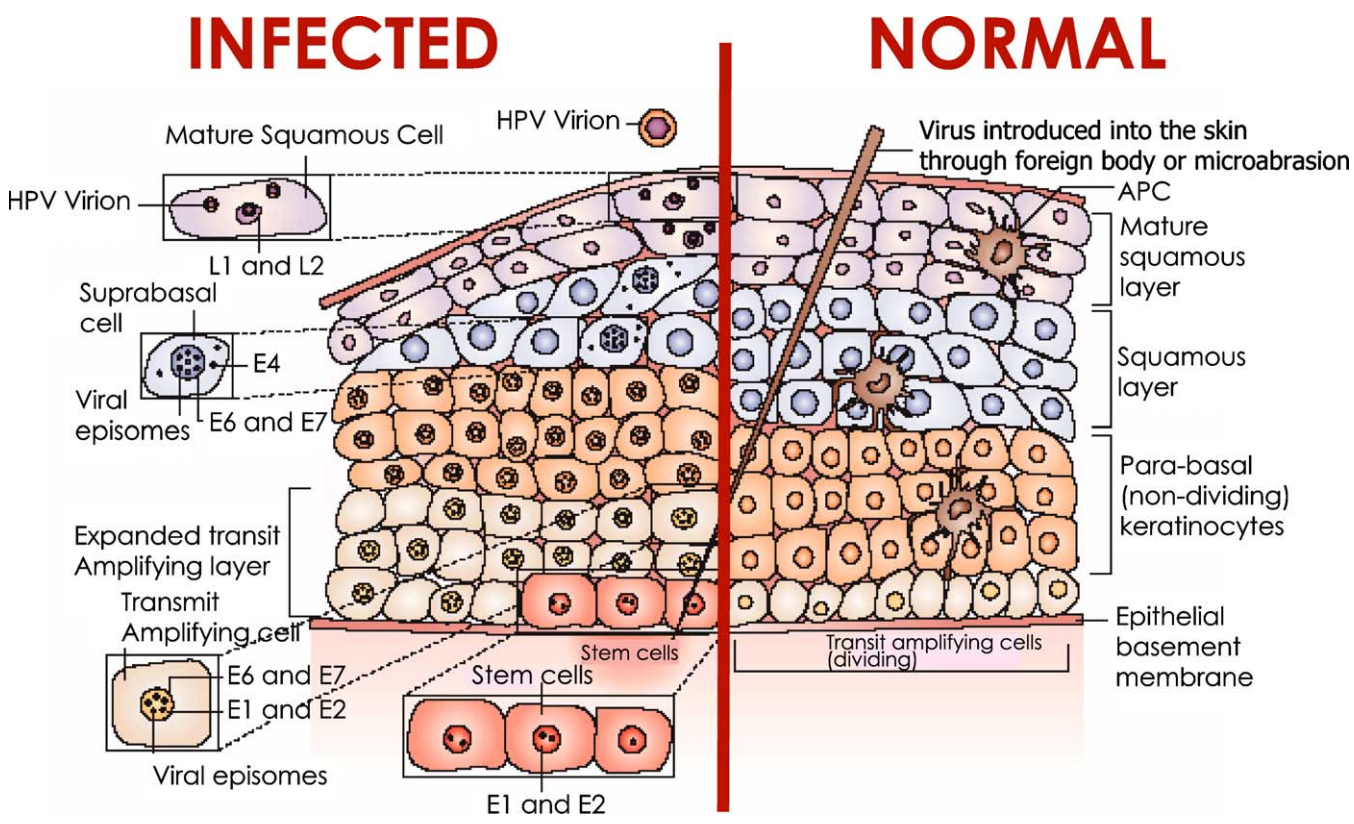

Fig. 2. The location in the squamous epithelium of the main stages of the papillomavirus life cycle. Cervical stratified squamous epithelial cell architecture and the expression of HPV proteins after infection. Daughter cells of epithelial stem cells divide along the basement membrane and then mature vertically through the epithelium without further division (right side). After the introduction of HPV into the stem cells in the basal layer of the epithelium, expression of viral non-structural proteins occurs. Under the regulation of these proteins, the dividing-cell population expands vertically and epithelial cell differentiation is delayed and is less complete. Viral proteins are expressed sequentially with differentiation, as shown, and mature virions are produced only in the most superficial layers of the epithelium. Intraepithelial antigen-presenting cells (APCs) are depleted in the HPV-infected epithelium. Reprinted from Macmillan Publishers Ltd: Nature Reviews Immunology 2004; 4(1) 46–54.

of the initially HPV-negative cases, HPV-DNA was detected in 99.7% of the tumors, leading to the conclusion that HPV is a necessary cause of cervical cancer [8,9]. The distribution of HPV types in cervical cancer has been published in a pooled analysis of about 3000 cases from the IARC studies [10] and in a meta-analysis of about 10,000 cases [11]. The eight most common HPV types detected in both series, in descending order of frequency, were HPV-16, -18, -45, -31, -33, -52, -58, and -35, and these are responsible for about 90% of all cervical cancers worldwide (see Section 3).

2.2. Case-control studies

In 1995, the IARC monograph working group concluded that there was sufficient evidence for the carcinogenicity of HPV-16 and -18 and limited evidence for the carcinogenicity of HPV-31 and -33. [12] Since then, at least 10 case-control studies with histological diagnosis of cancer and with HPV-DNA detected by PCR-based methods have been completed that estimate the risk of cancer to additional HPV types. The largest report corresponds to the pooled analysis of 11 case-control studies of invasive cervical cancer conducted by the IARC in 11 countries [13,14]. In this update, we included two additional studies from Algeria and India. The pooled data include about 2500 women with cervical cancer and about 2500 control women without cervical cancer. The main advantage of these studies is the use of a common study protocol and of well-validated PCR assays for the detection of 33 HPV types that were carried out in a central laboratory.

Figs. 3 and 4 summarize the prevalence of HPV-DNA among cases and controls and the corresponding adjusted odds ratios for squamous-cell carcinoma (SCC) and for adenocarcinoma (ADC)/adenosquamous carcinoma (ADSC) of the cervix, respectively [13,14]. HPV-16 and -18 were the two most common types in both histological types, but the fraction of SCCs attributable to HPV-16 and -18 was 70% while that for ADC was 86% [10,14].

Fig. 5 summarizes the odds ratios for invasive cervical cancer, for SCC and ADC, associated with the 15 most common HPV types; their magnitude range from 3.6 for HPV-6 to 573 for HPV-33 [13].

2.3. Cohort studies

Only studies using CIN-2, CIN-3, or invasive cervical cancer as endpoints and HPV-DNA detected by PCR-based assays will be considered here.

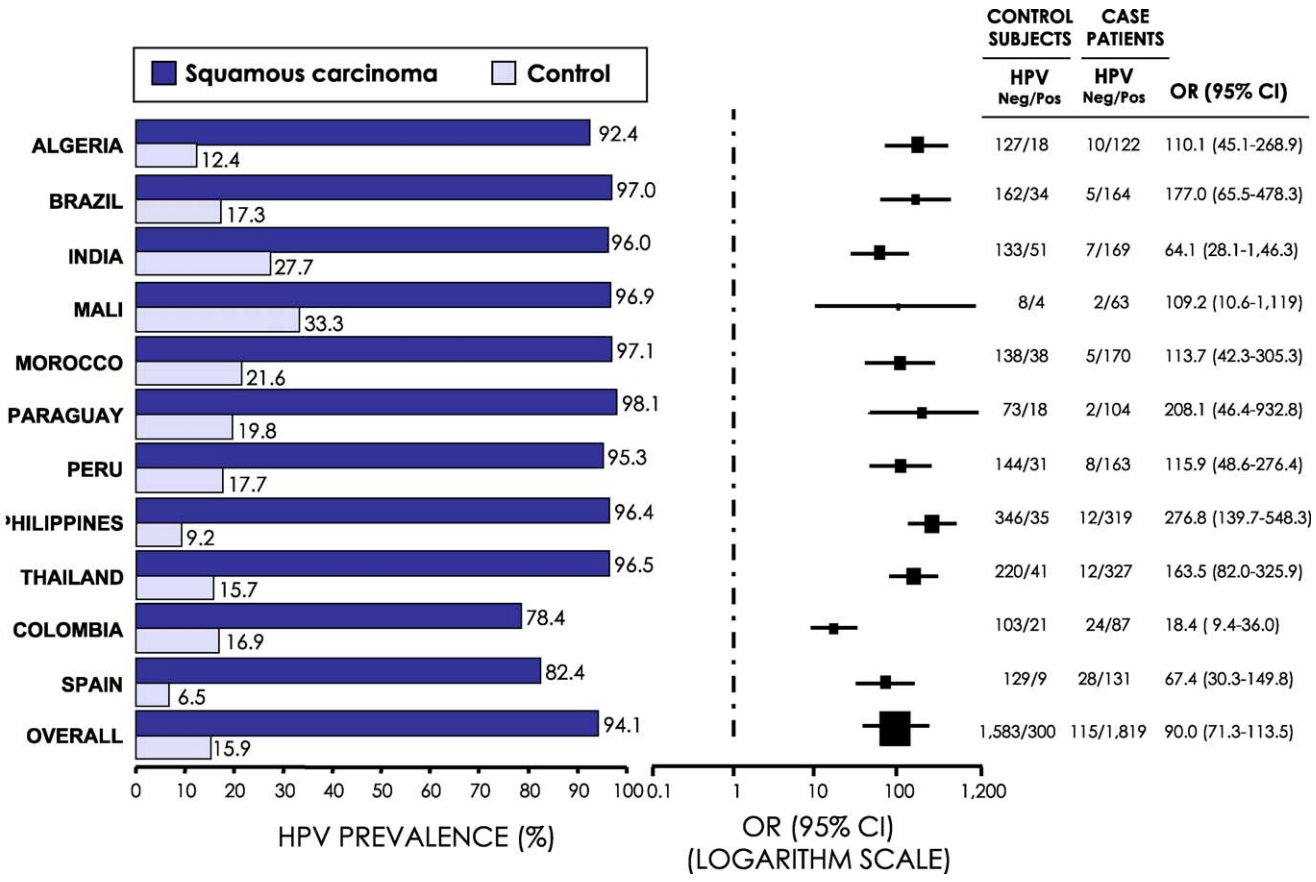

Fig. 3. Left panel: prevalence of HPV-DNA by country among women with squamous cell carcinoma (SCC) and among control women. Right panel: odds ratios (OR) for cervical SCC with 95% confidence intervals (CI). ORs are adjusted by center and age. Adapted and expanded from [13].

Several prospective studies have shown that women who are HPV-DNA-positive at baseline have a higher risk of developing CIN-3 or invasive cervical cancer during the follow-up than HPV-DNA-negative women. However, many of these early studies did not assess HPV type-specific carcinogenicity [15]. Furthermore, results from these studies are sometimes difficult to interpret and compare because the HPV-type detected in the cervical smears may not be the same HPV type detected in the subsequent CIN-2/3 lesions or cervical cancer.

Few studies have evaluated the HPV type-specific risk of developing CIN-2/3 and they have consistently reported an increased risk for CIN-2/3 linked to the baseline detection of HPV-16. A few of them have reported increased risks associated with the presence of HPV-18 and of HPV types related phylogenetically to HPV-16 and HPV-18 [15,16]. In some of these studies, CIN-2/3 developed within 2 years of HPV-DNA detection, thus indicating that, contrary to the theory that prolonged HPV infection is necessary for progression to CIN-2/3, these precancerous lesions can be an early manifestation of HPV infection, at least in young women [15,17].

Several nested case-control studies have examined the archival smears of women with invasive cervical cancer and of control women. In all of them, a higher prevalence of HPV-16 DNA was detected in the smears and diagnostic biopsies of women who subsequently developed cervical cancer than in smears from control women without cervical cancer. The risk of types other than HPV-16 was difficult to assess [15].

Table 1 summarizes the phylogenetic and epidemiological classification of anogenital HPV types [13,18]. The recent IARC monograph concluded that there was sufficient evidence in humans for the carcinogenicity of HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, and -66 in the cervix [15]. HPV types 26, 68, 73, and 82 were found to be associated with cervical cancer in some case-control studies, but were rarely found in case series and there are no prospective studies of enough size or follow-up length to assess their risk [15]. However, since the odds ratios for HPV types 26, 53, 68, 73, and 82 are of similar magnitude to that of HPV-66, and are based on less than 10 cases of cervical cancer, we consider that it is arbitrary to classify HPV-66 as carcinogenic and not HPV-26, -53, -68, -73, and -82. We therefore propose that these six HPV types should also be considered as probably carcinogenic (Table 2). In summary, strong epidemiological evidence allows us to conclude that certain

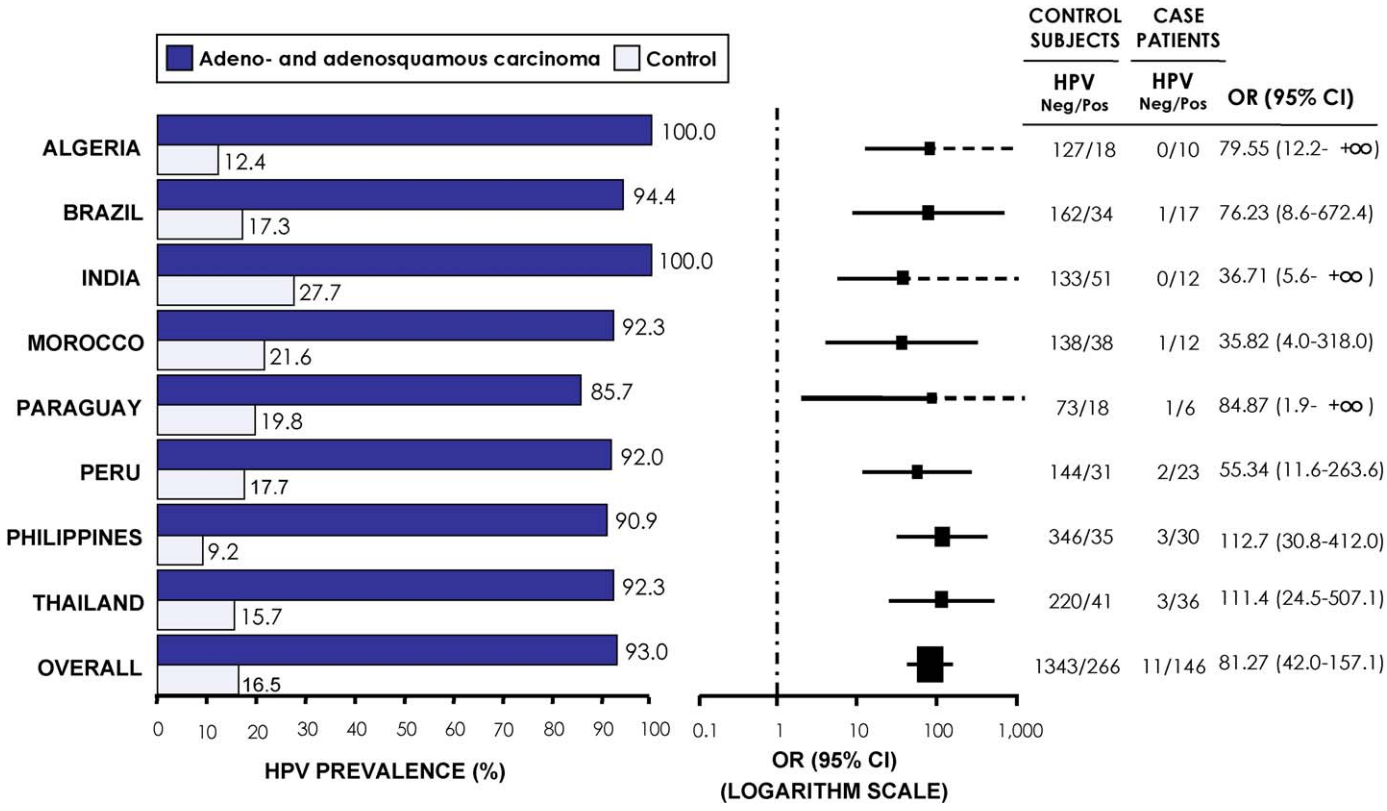

Fig. 4. Left panel: prevalence of HPV DNA by country among women with cervical adenocarcinoma (ADC) and among control women. Right panel: odds ratios (OR) for cervical ADC with 95% confidence interval (CI). ORs are adjusted by age group, years of schooling, age at first sexual intercourse, and number of pap smears before 12 months before enrollment. Adapted from [14].

HPV types are the central and necessary cause of cervical cancer [19].

3. The role of HPV in anogenital cancers others than cervical cancer

The number of studies on the role of HPV in other genital cancers is limited, and in most, the search for HPV-DNA has been done for a few HPV types and in fixed tissue.

The available epidemiological studies indicate that cancers of the vagina and of the anus resemble cancer of the cervix with respect to the role of HPV. In both, HPV-DNA is detected in the great majority of tumors and their precursor lesions. Between 64 and 91% of vaginal cancers and 82 and 100% of VAIN-3 lesions are HPV-DNA positive. In anal cancers, HPV-DNA is detected in 88–94%.

Cancers of the vulva and of the penis have been associated to HPV. The tumors diagnosed in young individuals are usually of histological types called basaloid or warty; the majority (60–90%) are positive for HPV and their pre-neoplastic lesions are also strongly associated with HPV. In older subjects, the tumors are usually keratinizing SCCs and are rarely (less than 10%) associated with HPV.

In all HPV-positive anogenital cancers, HPV-16 is by far the most common HPV type detected, followed by HPV-18, -31, and -33. The recent IARC monograph concluded that there was sufficient evidence for the carcinogenicity of HPV-16 in the vulva, penis (basaloid and warty tumors), vagina, and anus; limited evidence for the carcinogenicity of HPV-18 in the vulva, penis (basaloid and warty tumors), vagina, and anus; and limited evidence for the carcinogenicity of HPV-6 and -11 in the vulva, penis, and anus (verrucous carcinomas) [15].

4. The role of HPV in non-anogenital cancers

4.1. Evidence linking HPV to head and neck squamous-cell carcinoma (HNSCC)

Over the past 15 years evidence implicating HPV as an important carcinogenic agent in a subset of HNSCCs (cancers of the oral cavity, pharynx, and larynx) has been accumulating.

The most recent systematic review included 5,046 HNSCC specimens from 60 studies that employed PCR-based methods to detect and genotype HPV-DNA [20]. The estimated summary prevalence of HPV-DNA was 25.9%, although this was significantly higher in oropharyngeal SCCs (35.6%; range 11–100%) than in oral (23.5%; range 4–80%) or laryngeal SCCs (24.0%; range 0–100%). HPV-

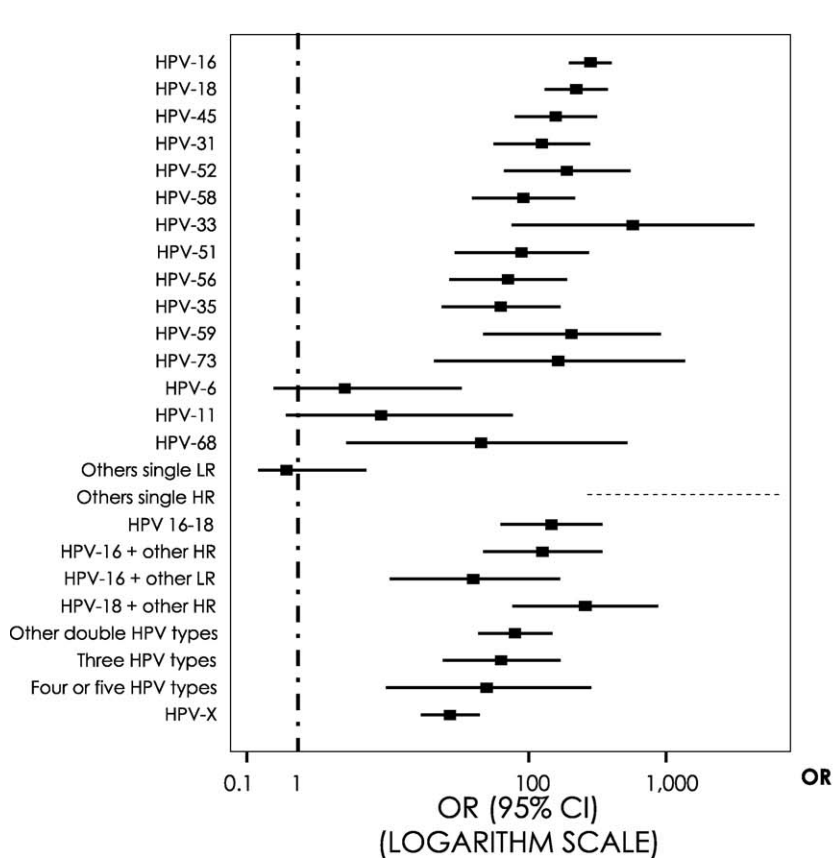

Fig. 5. Type-specific odds ratios (OR) and 95% confidence intervals (CI) for cervical carcinoma (squamous cell and adenocarcinoma). Subjects with HPV-DNA-negative results were used as the reference category. ORs are adjusted by country and age-group. HR: high-risk; LR: low-risk. HPV type X denotes undetermined type (i.e., specimens that were positive with the GP5+/6+ system but that did not hybridize with any of the 33 type-specific probes). Adapted and expanded from [13].

16 accounted for a larger majority of HPV-positive oropharyngeal SCCs (86.7%) than HPV-positive oral (68.2%) and laryngeal SCCs (69.2%). HPV-18 was the second most frequent type detected: 2.8% in oropharyngeal, 34.1% in oral, and 17% in laryngeal SCCs. Other oncogenic HPVs were rarely detected in HNSCC.

Results from several case-control studies, including a large multicentric case-control study conducted by the IARC [21], have consistently identified positive and statistically significant associations between markers of HPV (DNA and/or serology) and HNSCC risk, thereby pointing to a likely role of HPV in cancers of the oropharynx, tonsil, and to a lesser extent, the oral cavity and larynx [15]. As in genital cancers, HPV-16 is also the most common type in these tumors.

The 2005 IARC evaluation on the carcinogenicity of HPV in humans concluded that there is sufficient evidence for the carcinogenicity of HPV-16 in the oral cavity and in the oropharynx, limited evidence for HPV-18 in the oral cavity, inadequate evidence for other HPV types in the oral cavity and in the oropharynx, limited evidence for HPV-6, -11, -16, and -18 in the larynx, and inadequate evidence for the carcinogenicity of HPV in the esophagus [15].

4.2. Evidence linking HPV to cancer of the skin

Apart from genital types, the HPV family includes many cutaneous types that belong to the so-called epidermodysplasia verruciformis (EV)-HPV types. These types are potentially involved in the development of non-melanoma skin cancer (NMSC), which includes SCC and basal cell carcinoma. HPV-DNA has been identified in a substantial proportion (30–50%) of NMSCs in immunocompetent populations; this proportion increases up to 90% in immunosuppressed organ transplant recipients [22].

The 2005 IARC evaluation of the carcinogenicity of HPV in humans concluded that there is sufficient evidence for EV-associated HPVs in squamous-cell skin cancer among EV patients, limited evidence for EV-associated HPVs in squamous-cell cancer in the general population, and sufficient evidence for HPV in periungual squamous-cell skin carcinomas [15].

In conclusion, while UV light is the primary etiological agent in NMSC, it is now becoming clear that EV-HPV types, in particular HPV-5 and -8, may act as co-carcinogens with UV radiation or immunosuppression in the development of NMSC. This relationship is important from a public health

Table 1
Phylogenetic and epidemiologic classification of anogenital HPV types

HPV SPECIES (alpha)	HPV GENOTYPE	RISK
9	HPV 52	High
	HPV 67	Undetermined
	HPV 33	High
	HPV 58	High
	HPV 16	High
	HPV 31	High
	HPV 35	High
11	HPV 34	Undetermined
	HPV 73	Probably high
7	HPV 59	High
	HPV 18	High
	HPV 45	High
	HPV 70	Low
	HPV 39	High
	HPV 68	Probably high
	HPV 85	Undetermined
5	HPV 26	Probably high
	HPV 69	Undetermined
	HPV 51	High
	HPV 82	Probably high
6	HPV 30	Undetermined
	HPV 53	Probably high
	HPV 56	High
	HPV 66	Probably high
10	HPV 6	Low
	HPV 11	Low
	HPV 13	Low
	HPV 74	Undetermined
	HPV 44	Low
	HPV 55	Undetermined
8	HPV 91	Undetermined
	HPV 7	Undetermined
	HPV 40	Low
	HPV 43	Low
1	HPV 32	Undetermined
	HPV 42	Low
13	HPV 54	Low
4	HPV57	Undetermined
	HPV 2a	Undetermined
	HPV 27	Undetermined
15	HPV 71	Undetermined
	HPV 90	Undetermined
3	HPV 61	Low
	HPV 72	Low
	HPV 62	Undetermined
	HPV 81	Low
	HPV 83	Undetermined
	HPV 89	Low
	HPV 84	Undetermined
	HPV 86	Undetermined
	HPV 87	Undetermined
2	HPV 28	Undetermined
	HPV 3	Undetermined
	HPV 10	Undetermined
	HPV 29	Undetermined
	HPV 77	Undetermined

Adapted from [13] and [18] including the cancer risk reclassification proposed by Muñoz et al. in this chapter.

perspective since NMSC is the most common form of malignancy among fair-skinned populations.

4.3. Evidence linking HPV to cancer of the conjunctiva

HPV-DNA has been detected in benign conditions of the conjunctiva as well as dysplasia, carcinoma *in situ*, and invasive carcinoma. HPV-16 and -18 E6 gene expression has been demonstrated in intraepithelial neoplasia of the conjunctiva [23].

Squamous-cell carcinoma of the eye conjunctiva (SCCC) is a rare tumor that has been strongly associated with exposure to solar UV radiation and immunosuppresion, particularly in those with HIV infection. A single case-control study in Uganda has reported an increased risk of conjunctival squamous-cell carcinomas among HIV-positive subjects [24].

The 2005 IARC evaluation on the carcinogenicity of HPV in humans concluded that there is limited evidence for the carcinogenicity of HPV in the conjunctiva [15].

Table 2
Epidemiological classification of HPV types

Group	HPV types
Established high-risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probably high-risk	26, 53, 66, 68, 73, 82
Established low-risk	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108

Adapted from [13]. *Established high-risk or oncogenic types*: HPV types whose high odds ratios (ORs) were based on 10 or more cervical cancer cases positive for the type being analyzed. *Probably high-risk or oncogenic types*: HPV types whose high ORs were based on nine or less cervical cancer cases positive for the type being analyzed. *Established low-risk types*: HPV types with moderately increased ORs but with the lower bound of their 95% confidence intervals lower than 1, or those HPV types that were only detected among the control women and not among women with cervical cancer.

5. The role of cofactors in the etiology of cervical cancer

Although many women get cervical HPV infections, most do not progress to cervical cancer. A number of other cofac-

tors are therefore likely to be involved in the disease process. Three groups of potential cofactors are: (1) environmental or exogenous cofactors, including hormonal contraceptives, tobacco smoking, parity, and co-infection with other sexually transmitted agents; (2) viral cofactors, such as infection by specific types, co-infection with other HPV types, HPV variants, viral load, and viral integration; (3) host cofactors, including endogenous hormones, genetic factors, and other factors related to the immune response.

The evidence for a role of oral contraceptives, parity, and tobacco smoking was recently reviewed [25] and it has been updated due to the availability of results from a series of pooled analyses of a large number of epidemiological studies. The International Collaboration of Epidemiological Studies of Cervical Cancer (ICESCC) was set up to study the effects of hormonal contraceptives and other exogenous cofactors on cervical cancer risk after taking into account the woman's number of sexual partners as a surrogate measure of the risk of HPV exposure. Individual subject data from 24 epidemiological studies were collated and combined, and included about 85% of the women with cervical cancer enrolled in published epidemiological studies [26]. The main ICESCC findings for high parity and smoking are summarized below. Results for hormonal contraceptives will be available later this year.

5.1. High parity

Results from the ICESCC indicate that the number of full-term pregnancies is associated with an increased risk of invasive cervical carcinoma after adjustment for the number of sexual partners and age at first intercourse [27]. The relative risk (RR) for invasive cervical cancer increases with number of full-term pregnancies (RR = 1.10; 95% confidence interval, CI: 1.08–1.12 for each additional pregnancy) and with decreasing age at first full-term pregnancy (RR = 1.07; 95% CI: 1.06–1.09 per year decrease). The effects of these two variables were found to be independent. The findings were similar for analyses restricted to women who tested positive for high-risk HPV-DNA. Although age at first full-term pregnancy was associated with CIN-3/carcinoma *in situ*, among parous women, there was no association with number of full-term pregnancies.

The mechanisms through which high parity is thought to increase the risk of cervical carcinoma is through the maintenance of the transformation zone on the exocervix for many years in which may facilitate exposure to HPV, although hormonal factors may also be involved.

5.2. Tobacco smoking

IARC has classified tobacco smoking as a cause of cervical cancer [28]. In the ICESCC, after adjusting for potential confounders, current smokers were found to have a significantly increased risk of SCC of the cervix compared to never smokers (RR = 1.60; 95% CI: 1.48–1.73) [26]. The risk was lower for past smokers (RR = 1.12; 95% CI: 1.01–1.25), but there was no trend in the risk estimates with time since stopping smoking (p-trend = 0.6). In current smokers, the risk increased with the number of cigarettes smoked per day (RR = 1.98; 95% CI: 1.78–2.21 for 15+ cigarettes per day versus none], but not with duration of smoking. Patterns of risk were similar when analysis was restricted to women who were positive for high-risk HPV-DNA. No association was found between smoking and ADC of the cervix (RR = 0.89; 95% CI: 0.74–1.06; and RR = 0.89; 95% CI: 0.72–1.10 for current and past smokers, respectively).

Possible mechanisms for the effect of smoking include a reduction of the immunoresponse in the cervix, effects related to the metabolism of female hormones, and direct genetic damage caused by tobacco-related carcinogens.

5.3. Hormonal contraceptives

The recent IARC monograph on hormones and cancer classed combined oral contraceptives as carcinogenic to the cervix [29]. A meta-analysis of cervical cancer and hormonal contraceptives, which included most of the same studies as the ICESCC, found that the risk of invasive cervical cancer increases with increasing duration of oral contraceptive use, such that 10 years use is associated with approximately a doubling in risk compared to never users. The limited available data suggest that this risk decreases after use of oral contraceptives has ceased, but the risk is still significantly elevated for use that ceased more than about 8 years ago [30]. A similar pattern of risk was seen in women likely/not likely to have been screened, in women who tested positive for high-risk HPV-DNA, and for CIN-3/carcinoma *in situ*. The limited available data on injectable progestagen-only contraceptives suggest that their use is probably associated with a small increase in the risk of cervical cancer.

The hypothesized mechanism through which hormonal contraceptives may act as a cofactor for cervical cancer is the estrogens or progestagens enhancing HPV gene-expression in the cervix via progesterone-receptor mechanisms, and hormone-response elements in the viral genome.

5.4. Evidence for a role of other sexually transmitted agents as cofactors in cervical carcinogenesis.

The specific role of other infectious agents in the pathogenesis of cervical cancer has been studied in many epidemiological studies. The most studied sexually transmitted infectious agents for which some evidence has been shown in relation to cervical cancer are HSV-2, CT, and HIV.

In the large IARC multi-center case-control study, HSV-2 seropositivity was associated with an increased risk of both squamous cervical cancer (odds ratio, OR = 2.2; 95% CI: 1.4–3.4) and ADC or ADSC (OR = 3.4; 95% CI: 1.5–7.7) among HPV-positive women seropositive for CT antibodies [31]. CT was also associated with a two-fold increased risk for cervical cancer (OR = 1.8; 95% CI, 1.2–2.7) in these

women [32]. It is likely that the increased cancer risk associated with HSV-2 and CT is, at least in part, the result of the inflammatory response that has been associated with the generation of free radicals and development of genetic instability [33].

Individuals with immunosuppression caused by HIV infection or organ transplantation are at increased risk of HPV-associated anogenital cancers compared with age-matched healthy individuals [34]. HIV-positive women have consistently shown to be at an increased risk of cervical SIL when compared with their HIV-negative counterparts. This association appears to be stronger for women with a low CD4 T-lymphocyte count. Women infected with both HIV and HPV are at a higher risk of SILs than women infected with either of the two viruses separately. HIV-infected men and women show higher incidence rates of anal HPV infection, AIN, and anal cancer [34]. As HIV infection is related to an immunocompromised state, these findings underscore the importance of the host's immunological cofactors in HPV carcinogenesis.

5.5. Nutritional factors

A recent systematic literature review assessing the epidemiologic evidence for the potential role of diet and nutrition on the risk of HPV persistence and cervical neoplasia has been published [35]. The review classified the scientific evidence into four levels: convincing, probable, possible, and insufficient. None of the dietary and nutritional factors evaluated were classified as having "convincing" evidence for a role in cervical carcinogenesis. The few published studies assessing the role of diet on HPV persistence have shown a "possible" protective effect of diets rich in fruits, vegetables, Vitamins C and E, beta- and alpha-carotene, lycopene, lutein/zeaxanthin, and cryptoxanthin. Evidence for a protective effect against cervical neoplasia was "probable" for folate, retinol, and Vitamin E, and "possible" for vegetables, Vitamins C and B12, alpha-carotene, beta-carotene, lycopene, lutein/zeaxanthin, and cryptoxanthin. Evidence for an increased risk of cervical neoplasia associated with high blood homocysteine was considered "probable".

The current available evidence for an association between diet, nutritional status and cervical HPV carcinogenesis is not yet convincing, even though there is some support for the hypothesis that antioxidant nutrients may play a protective role in cervical carcinogenesis [33].

Table 3 shows the most commonly studied "established" and "probable" cofactors in cervical cancer.

Table 3
Established and probable cofactors in cervical carcinogenesis

Established cofactors	Probable cofactors
Smoking	HSV-2* coinfection
Long term OC* use	*Chlamydia trachomatis* coinfection
HIV* coinfection	Immunosuppression
High parity	Diet and nutrition[a]

*HSV-2: herpes simplex virus type-2; OC: oral contraceptives; HIV: human immunodeficiency virus.

[a] Protective effect for high consumption of fruits and vegetables.

Disclosed potential conflicts of interest

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