Chapter 23
Infectious Diseases and Cancer: HPV

Helen Trottier and Eduardo L. Franco

23.1 Introduction

Many types of cancer are etiologically linked to infections. Historically, it has been a challenge to prove the causal link between an infectious agent and a given type of cancer; different sets of causal criteria have been applied according to the methodological approach used to study the putative association (Franco et al. 2004). Yet, epidemiologic and molecular evidence to date unequivocally demonstrate causal links between viruses, bacteria, and protozoan and metazoan parasites, and many forms of cancer. The main infectious agents that are known to cause cancer in humans are the human papillomavirus (HPV), hepatitis B and C viruses, Epstein–Barr virus (EBV), human T cell lymphotropic virus I, human immunodeficiency virus (HIV), human herpes virus 8 (HHV-8), *Helicobacter pylori*, Schistosomes, and liver flukes (genus *Opistorchis*). Altogether, it has been estimated that these agents cause 17.8% of incident cancers worldwide (12.1%, 5.6%, and 0.1% for viral, bacterial, and parasitic infections, respectively) including as much as 5.2% for HPV alone (Parkin 2006).

HPV infection is recognized today as the necessary causal factor of all cervical cancer cases in the world and of a substantial proportion of many other anogenital neoplasms. HPV has also been implicated in the genesis of several other cancers, such as head and neck cancer, non-melanoma skin malignancies and other cancers. In this chapter, we provide an overview of the types of cancer in which HPV infection has been etiologically implicated or is suspected to play a causal role.

H. Trottier (✉)
Division of Cancer Epidemiology, Departments of Oncology and Epidemiology and Biostatistics, McGill University, Montreal, Canada
e-mail: helen.trottier@mcgill.ca

A. Krämer et al. (eds.), *Modern Infectious Disease Epidemiology*,
Statistics for Biology and Health, DOI 10.1007/978-0-387-93835-6_23,

23.2 HPV Biology

23.2.1 HPV Structure

HPVs belong to the Papillomaviridae family. They have a double-stranded circular DNA genome of around 8,000 base pairs (5 million MW) with six early genes (E1, E2, E4–E7) and two late genes (L1 and L2, the capsid proteins) that are all located on the same circular DNA structure (Fig. 23.1). Over 100 HPV genotypes have been identified based on the isolation of complete genomes (de Villiers et al. 2004) and have a similar genomic organization. The L1 protein is highly conserved among all HPV types and is thus used for taxonomical purposes. A new HPV isolate is recognized as a new genotype (type for short) if the complete genome has been cloned and the nucleotide sequence of the L1 gene differs by more than 10% from the type with which it has greatest homology in DNA sequence. Differences of less than 10% but more than 2% characterize a new subtype, and of less than 2% they define a new molecular variant. Viral DNA is detectable as free-form episomes in the nucleus of the infected cell and/or as integrated sequences into the host chromosomes. In general, HPV-associated cancer arises from the integration of the viral genome into a host cell chromosome which causes disruption of cellular genes and overexpression of viral oncogenes, although there is some evidence that integration may not be a requirement for cell transformation and neoplastic development (Cullen et al. 1991; Pirami et al. 1997).

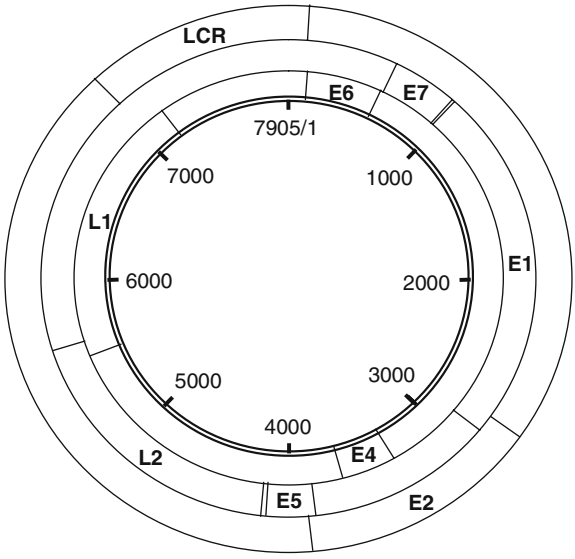

Fig. 23.1 The Papillomavirus genome

23.2.2 Classification of HPVs and Carcinogenicity

The more than 100 HPV types that have been catalogued so far (De Villiers et al. 2004) are classified according to their tissue tropism (mucosal or cutaneous) and oncogenic potential. Table 23.1 shows the general properties of HPVs in terms of tissue tropism, carcinogenic potential, and associated diseases. About 40 types infect the epithelial lining of the anogenital tract and other mucosal areas of the body. Infection with low-oncogenic risk HPVs (LR-HPV), such as HPV-6 and 11, can cause benign lesions of the anogenital areas known as *Condylomata acuminata* (genital warts), as well as a large proportion of low-grade squamous intraepithelial lesions (LSIL) of the cervix. LR-HPV infections are responsible for substantial morbidity and incur high costs associated with the treatment of clinically relevant lesions. Perinatal transmission of HPV is also possible and can cause in rare instances recurrent respiratory papillomatosis in infants and young children (Amstrong et al. 2000). Among the mucosal HPVs, some 13–18 types have been

Table 23.1 Classification of HPV genotypes and diseases associated with them. Adapted from: de Villiers et al. (2004)

Genus	Tissue tropism	HPV types		Diseases
Alpha	Mucosal and cutaneous	High-oncogenic risk:	16,18,31,33,35,39, 45,51,52,56,58,59, 66,68,73,82	Intraepithelial neoplasia/cervical, other anogenital cancers and head and neck cancer
		Low-oncogenic risk	6,11,42,44,51,53, 83	Condylomata acuminata/intraepithelial neoplasia /mucosal lesions
			32,42	Benign lesion (oral or genital)
			3,10,28,29,78	Cause more frequently cutaneous than mucosal lesions
			61,72,81,83,84,62, 86,87,89	Benign mucosal lesion
			2, 27, 57	Common skin warts
			13,26,30,34,54,71, 74,53,67,69,70,85, 90,PcPV	Mucosal lesion
			7,40,43,91	Mucosal and cutaneous lesions
Beta	Cutaneous	5,8,9,12,14,15,17,19,20,21,22, 23,25,36,37,38,47,80 49,75,76		Commonly associated with epidermodysplasia verruciformis (mostly benign lesion)
Gamma	Cutaneous	4,48,50,60,65		Cutaneous lesion
Mu	Cutaneous	1		Plantar wart
Nu	Cutaneous	63		Plantar wart

identified as probable or definite high-oncogenic risk (HR-HPV) according to their frequency of association with cervical cancer and other anogenital cancers. Since the 1990s, several classifications have been made according to the research development (reviewed in Trottier and Franco 2006). The latest classification published by the World Health Organization's International Agency for Research on Cancer (IARC) referred HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 55, 56, 58, 66 as HR-HPVs (IARC 2007). This new classification included also HPV type 6 and 11 as possibly carcinogenic.

Many HPV types can also infect the dry skin, causing verrucous lesions, more commonly known as warts. In addition to the above-mentioned carcinogenic types that belong to the alpha genus, the IARC (2007) has classified HPV-5 and 8 (genus beta) as carcinogenic. Epidermodysplasia verruciformis (EV) can occur among hosts with genetic defects in their ability to control the cutaneous proliferation of HPVs. HPV infections in EV patients are more likely to undergo malignant transformation than other warty lesions in normal individuals, although oncogenic transformation of an epithelial HPV infection is very rare.

23.3 HPV and Human Cancer

Extensive research in the last 20 years has contributed to today's recognition of HPV infection as the main etiologic agent of cervical cancer and other anogenital neoplasms, and a leading cause of death from cancer worldwide. It is now widely accepted that HR-HPV infections are a necessary, but not sufficient, cause of virtually all cases of cervical cancer worldwide and are a likely cause of a substantial proportion of other anogenital, upper aero-digestive tract, and non-melanoma skin cancers. HPV has also been suspected to play a role in several other human tumors.

23.3.1 Cervical Cancer

Cervical cancer is the second most common malignant neoplasm affecting women worldwide, after breast cancer. In 2002, 4,93,000 new cases were diagnosed in the world from which 83% occurred in developing countries (Ferlay et al. 2004; Pisani et al. 1999). This translates into a high mortality rate with an estimated 1,90,000 deaths from cervical cancer worldwide every year, with over 75% of them in developing countries, where mortality from this disease is the highest among deaths caused by neoplasms (Pisani et al. 1999). The highest-risk areas for cervical cancer are in Southern and Eastern Africa, Melanesia, the Caribbean, and Central and South America, with average incidence rates well above 30 per 1,00,000 women per year (Parkin et al. 2005). In the United States there are approximately 12,800 new cases of invasive cervical cancer and 4,600 deaths due to this disease each year (Ries et al. 2000). Overall annual cervical cancer prevention and

treatment costs in the United States were estimated at $3.4 billion, with expenditures for routine screening of $2.1 billion, impact of false-positive Papanicolaou test results at $300 million, management and treatment of CIN 1 of $150 million, CIN 2/3 of $450 million, and invasive cancer of $350 million (Insinga et al. 2004; 2004).

23.3.1.1 Causal Role of HPV in Cervical Cancer

Cervical cancer was early hypothesized as related to sexual activity; since nuns did not develop this neoplasm whereas prostitutes had an increased risk. Moreover, sexual behavior variables were recognized as key risk factors, such as age at first sexual coitus, number of sexual partners, etc. (Harris et al. 1980; Brock et al. 1989; Cuzick et al. 1990; Parazzini et al. 1992; Munoz et al. 1993; De vet et al. 1994; Kjellberg et al. 1999). Over the years, many sexually transmitted microbes such as herpes simplex virus (HSV-2), syphylis, gonorrhea, or either *Chlamydia trachomatis* have been suspected as etiologic agents of cervical cancer. However, with the international multidisciplinary effort that began more than 25 years ago, there was a gradual realization that not only most cervical carcinomas harbored HPV DNA but also that cervical HPV infection was common in women without cervical abnormalities, with prevalences in the 10–40% range (Franco et al. 1991).

Many investigations examined the nature of the relationship between HPV and cervical cancer. In addition to the Hill's criteria (strength of the association, consistency, biologic gradient, temporality, coherence, biologic plausibility, experimental evidence, etc.), sets of other useful guidelines for causal attributions involving infectious agents have been proposed (Evans 1976; Evans et al. 1990; Fredricks et al. 1998). These causal criteria take into account the knowledge about the timing, specificity, and level of immune response against putative viruses, or the advances in nucleic acid detection methodology as used in modern molecular epidemiologic investigations (Franco et al. 2004). All those criteria help establishing that infection with HR-HPV types is the central causal factor in cervical cancer (Bosch et al. 2002; Franco et al. 1999; IARC 1995; Schiffman and Brinton 1995; Schiffman and Kjaer 2003; Herrero 1996; Holly 1996; Walboomers and Meijerr 1997; Walboomers et al. 1999; Clifford et al. 2003; Muñoz et al. 2003). The relative risk for the relation between HPV and cervical cancer is the strongest ever observed between an etiologic agent and a human cancer. For example, the relative risk between tobacco and lung cancer is estimated between 7 and 15 (IARC 1986), whereas the relative risk between HPV-16 and squamous cell cervical cancer estimated from the pool of IARC case–control studies is 435 (Muñoz et al. 2003). Although only a small proportion of HPV-infected women develop cervical cancer, it is now well known that virtually 100% of cervical cancers are caused by HR-HPV (Walboomers et al. 1999). The association is supported by strong epidemiological evidence and the detection of HPV DNA in up to 99.7% of cervical cancers from all geographic areas (Schiffman et al. 1993; Bosch et al. 1995; Walboomers et al. 1999; Munoz et al. 2003). HPV-16 is the

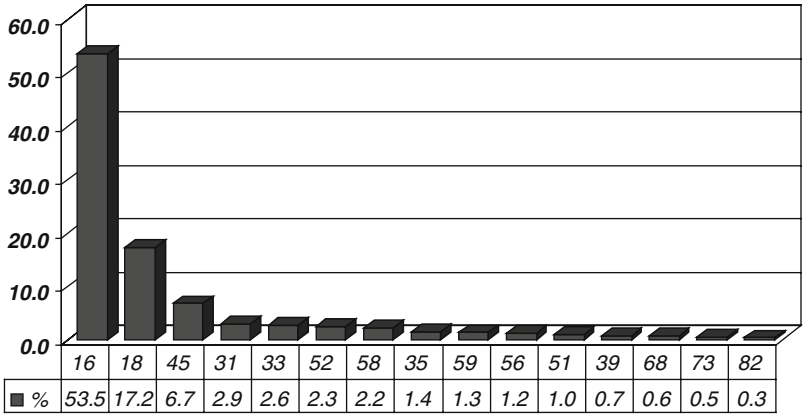

Fig. 23.2 Distribution of type-specific HPV in cervical tumor specimens. Adapted from: Munoz et al., IJC 2004

most prevalent type causing approximately 54% of cervical cancers worldwide, followed by HPV-18 which is associated with approximately 17% of cervical cancers (Fig. 23.2). In combination, HPV types 16 and 18 are the most important in terms of the attributable risk they pose causing altogether about 70–75% of all cervical cancers (Muñoz et al. 2004). The remaining tumors have been shown to contain DNA from other HR types such as HPV-45, HPV-31, and HPV-33 (Clifford et al. 2003).

23.3.1.2 Natural History of Cervical Cancer

The natural history of cervical cancer is represented by acquisition of HPV, development of a persistent HPV infection with HR types, and cervical neoplastic development (Fig. 23.3). Cervical neoplastic development is a slow process of disruption of the normal maturation of the transformation zone epithelium of the uterine cervix near its squamo-columnar junction (Franco and Ferenczy 2002). This process of abnormal changes is initially limited to the cervical epithelium. These preinvasive lesions known as dysplasia or as squamous intraepithelial lesion (SIL) can be discovered through cytological examination using the Papanicolaou technique and confirmed by colposcopic examination and biopsy as cervical intraepithelial neoplasia (CIN). They are invariably asymptomatic and if left untreated, the low-grade lesions may eventually extend to the full thickness of the cervical epithelium (cervical carcinoma in situ (CIS)) and traverse the lining formed by the basement membrane to become invasive. This process may take a decade or longer but will eventually occur in a substantial proportion of CIS patients.

Although HPV infection is the central cause of cervical cancer, only a small percentage of women who are infected go on to develop cervical cancer or its precursors. In fact, HPV alone is not a sufficient cause and much work has been devoted to determining why certain HPV-positive women develop cervical cancer while

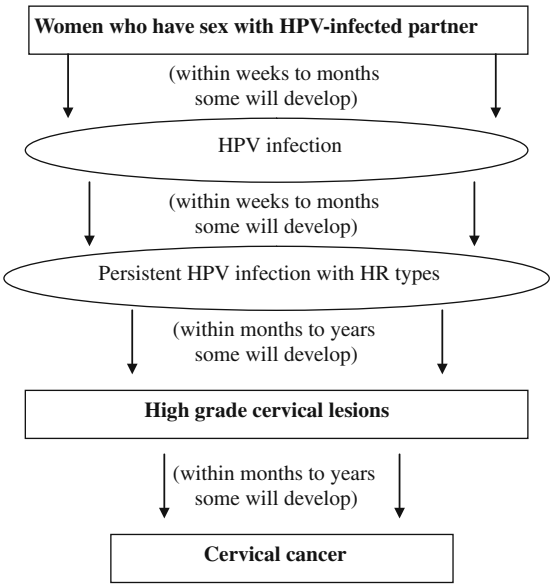

Fig. 23.3 Cervical cancer carcinogenesis. Source: Franco and Ferenczy 2002

others do not. The multifactorial model of cervical cancer etiology shows an interplay of various cofactors in the relation between persistent HPV, the main etiologic agent, and cervical cancer (Spence et al. 2005). Smoking, high parity, long-term use of oral contraceptive, coinfections, and immunosuppression have been found to increase risk of cervical cancer (Spence et al. 2005; Richardson et al. 2003; Winer et al. 2003; Koutsky 1997; Moscicki et al. 2001; Sellors et al. 2003; Baseman and Koutsky, 2005; Giuliano et al. 2002; Rousseau et al. 2000; Aral and Holmes 1999; Kahn et al. 2002; Manhart and Koutsky 2002; Stone et al. 1999). Results about condom are inconsistent; the majority showing that condom is not protective while other have shown that consistent condom use by their partners appears to reduce the risk of cervical lesions (Manhart and Koutsky 2002; Winer et al. 2006). Others factors such as genetic polymorphisms in the human leukocyte antigen (HLA) system, p53 polymorphism, nutrition, insulin-like growth factors (IGFs), and viral factors (molecular variants of HPV-16 and 18 and high viral load) have been associated with cervical cancer (Schaffer et al. 2007; Wang and Hildesheim 2003; Maciag et al. 2002; Garcia-Closas et al. 2005; Giuliano et al. 2003; Sichero et al. 2007; Schlecht et al. 2003).

23.3.2 Other Anogenital Cancers

HPV has also been implicated in the development of malignancies of other anogenital sites including anus, vagina, vulva, and penis. Unlike the situation for cervical cancer, in which 100% of cancers are caused by HPV, cancers of other anogenital

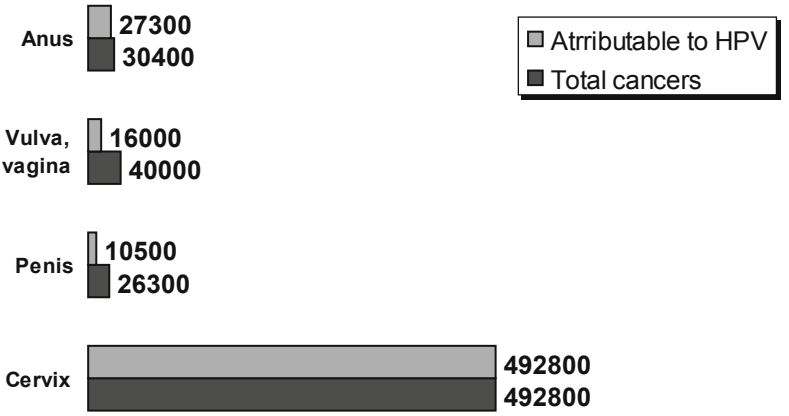

Fig. 23.4 Total number of annual incident cancers in the world and total attributable to HPV. Adapted from Parkin 2006

sites show lower risk attributions for HPV. It is estimated that 85–95% of anal cancers, 60–65% of vaginal cancers, 20–50% of vulvar cancers, and 40–50% of penile cancers are attributed to HPV (Fig. 23.4) (Parkin 2006).

23.3.2.1 Anal Cancer

Anal cancer is relatively rare although there has been a considerable increase in the incidence over the last 25 years among both men (160%) and women (78%) (Melbye et al. 1994; Frisch et al. 1993; Johnson et al. 2004). This increase was especially pronounced among homosexual men, particularly those who are HIV positive. Such subpopulations as homosexuals, HIV-positive persons, transplant recipients, and women with cervical squamous intraepithelial lesions are at a higher risk than the general population (Palefsky 2000a; Ryan et al. 2000).

Historically, anal cancer was believed to develop as a result of chronic irritation resulting from benign conditions (e.g., hemorrhoids, fissures) and was also associated with inflammatory bowel disease (Ryan et al. 2000). These factors notwithstanding, a substantial proportion of anal cancer are unequivocally linked to HPV (Welton et al. 2004). The proportion of anal cancers due to HPV is around 90% (Palefsky et al. 1991; Frisch et al. 1997; Daling et al. 2004). Similar to cervical cancer, HPVs 16 and 18 are the most common types present in anal carcinoma specimens. The model of anal cancer pathogenesis is very similar to that of cervical cancer: HPV infection is associated with the development of precursor lesions (SILs), which can be low grade (LSIL) or high grade (HSIL) and progression of anal SIL to invasive anal cancer is influenced by other cofactors. In men, homosexual behavior is the strongest risk factor for anal cancer (Daling et al. 1987). Immunosuppression is also an important risk factor. The incidence of anal cancer in men who have sex with men (MSM) is doubled with HIV positivity (Palefsky et al.

2000b). In heterosexual men, syphilis, lifetime number of sexual partners, being unmarried, anogenital warts, anal fissures, or hemorrhoids are risk factors (Holly et al. 1989; Frisch et al. 1997). In women, anogenital warts, cervical squamous intraepithelial lesions, C. *trachomatis* and HSV-2 infections, gonorrhea, hemorrhoids, anal intercourse, lifetime number of sexual partners, partners with history of venereal disease, smoking, and anal fissures are risk factors for anal cancer (Daling et al. 1987; Holly et al. 1989; Frisch et al. 1997).

23.3.2.2 Vaginal Cancer

Cancer of the vagina is extremely rare with an average incidence rate of approximately 1 case per 1,00,000 women per year worldwide (Parkin et al. 1997). In the United States, little more than 2,000 new cases occurred and 800 died from vaginal cancer in 2006 (Ries et al. 2006). HPV seems to play a central role in the causal pathway, being found in the majority of cases (Daling et al. 2002; Ikenberg et al. 1990). HPV DNA is detected in 64–91% of vaginal cancers and 82–100% of their precursor lesions (vaginal intraepithelial lesions of grade 3) and HPV-16 appear to be the most prevalent type (Munoz et al. 2006). The model of vaginal cancer pathogenesis is very similar to that of cervical cancer and is highly associated with sexual behaviors (Daling et al. 2002). In addition, women with primary vaginal carcinoma are more likely to have been previously diagnosed with an anogenital tumor, particularly of the cervix (Daling et al. 2002).

23.3.2.3 Vulvar Cancer

Invasive squamous cell carcinoma of the vulva is relatively rare; it accounts for slightly less than 5% of all female tract malignancies but the incidence of vulvar cancer has increased over the past 30 years, especially in younger women (Judson et al. 2006). In the United States, it was estimated that there were 3,740 new cases and 880 deaths from vulvar cancer in 2006 (Ries et al. 2006). Approximately 60% of vulvar cancers contain HPV DNA. HPV-16 is the most frequently observed type in these tumors (Hampl et al. 2006; IARC 2007). However, there seems to be two distinct risk factor profiles for vulvar cancer that are age dependent (Fig. 23.5). Keratinizing squamous cell carcinomas mostly affect older women and are rarely associated with HPV infection (less than 10%). On the other hand, warty or basaloid carcinomas are more often diagnosed in young women and constitute a HPV-related subgroup of tumors (60–90% are positive for HPV) (Al-Ghamdi et al. 2002; Munoz et al. 2006). These HPV-positive tumors have seem to have become more frequent in recent decades (Hørding et al. 1994) and tend to have the same risk profile as other anogenital cancers, i.e., association with high-risk sexual behaviors.

23.3.2.4 Penile Cancer

Squamous cell carcinoma (SCC) of the penis is a relatively rare disease in developed countries in Europe and North America, where incidence rates vary between 0.3 and

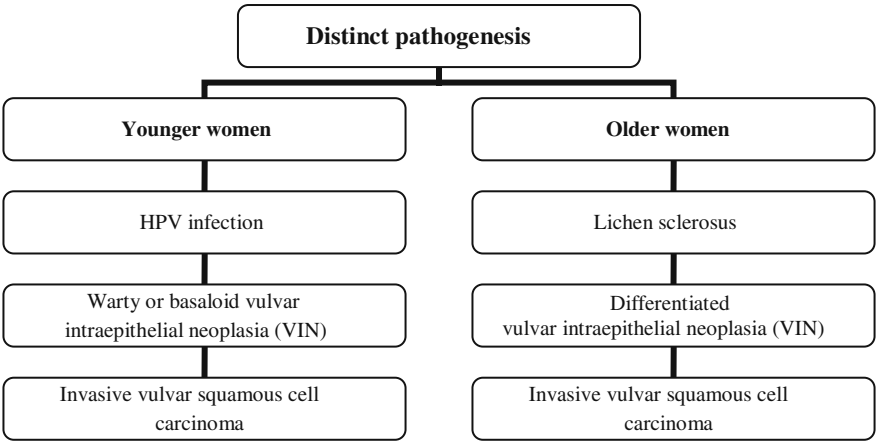

Fig. 23.5 Pathogenesis of vulvar invasive squamous cell carcinoma in young versus old women

1 cases per 1,00,000 men-years. Incidence is higher in parts of Africa (Uganda), Asia, and South America (Brazil and Colombia) where it may reach four cases per 1,00,000 men-years (Parkin et al. 2002; Malek et al. 1993). The etiology of penile cancer also appears to be multifactorial, with a history of smoking, phymosis, poor hygiene, history of genital warts, large number of lifetime sexual partners, and lack of circumcision during childhood being commonly associated with this neoplasm (Dillner et al. 2000; Heideman et al. 2007; Rubin et al. 2001; Maden et al. 1993; Hellberg et al. 1987). Interestingly, wives of men who have been diagnosed with penile cancer are at higher risk of cervical neoplasia (Spence et al. 2005). The exact etiologic mechanisms that lead to the development of penile cancer are largely unknown although HPV has been associated with this neoplasm (Parkin 2006). Similarly to vulvar cancer, basaloid or warty penile carcinomas show the highest HPV prevalence (up to 100%) (Cubilla et al. 2000; Cubilla et al. 1998; Rubin et al. 2001). Keratinizing penile SCCs, which represent more than 95% of penile cancer diagnosed in Europe and the United States generally showed a lower HPV prevalence (approximately 30–40%) (Heideman et al. 2007; Ferreux et al. 2003; Rubin et al. 2001). HPV-16 is also the most prevalent type detected in HPV-related penile cancer (Rubin et al. 2001; Maden et al. 1993; Heideman et al. 2007).

23.3.3 Head and Neck Cancer

In 2000, head and neck cancer (cancers of the oral cavity, pharynx, and larynx) was ranked as the eighth leading cause of cancer death worldwide with an average incidence rate of 8.8 and 5.1 per 1,00,000 males and females per year, respectively (Shibuya et al. 2002). There is an extensive variation in head and neck squamous cell carcinoma (HNSCC) incidence by both sex and geographic region (Parkin et al. 2002). In North America, the incidence rates are 5.0 and 2.6 per 1,00,000 males

and females per year, respectively; whereas in Europe the equivalent rates are 8.6 and 2.7, respectively (Shibuya et al. 2002). However, the results of many studies suggest that head and neck cancer, particularly oral tongue cancer, is increasing in young adults internationally (Macfarlane et al. 1992; Shiboski et al. 2000; Schantz and Yu 2002).

The main risk factors are tobacco and alcohol but it has been proposed that HPV also play a role in a subset of head and neck squamous cell carcinomas. The association is strongest in the oropharynx, particularly in the tonsil (Klussmann et al. 2003a; Venuti et al. 2004; Tran et al. 2007; Dahlstrand et al. 2004; Gillison 2004; Klussmann et al. 2003b; El-Mofty and Lu 2003; Klussmann et al. 2001; Mork et al. 2001; D'Souza et al. 2007). Sexual activity (high numbers of sexual partners, younger age of first sexual intercourse, the practice of oral sex, and a history of genital warts) has been associated with an increased risk of oropharyngeal cancer (Kreimer et al. 2004; Garrote et al. 2001; Maden et al. 1992). Also, husbands of women who had cervical cancer are more likely to have tonsillar and other upper aerodigestive cancers (Hemminki et al. 2000).

Evidence supports the idea that HNSCC is a multifactorial disease with at least two distinct pathogenesis models, one model implicating smoking and alcohol consumption, and the other driven by HPV (Ragin et al. 2007). The overall prevalence of HPV in head and neck cancer is 26% (Kreimer et al. 2005). For oropharyngeal, oral, and laryngeal SCCs considered separately, the prevalence of HPV is 36, 23, and 24%, respectively (Kreimer et al. 2005). Higher proportions are seen for tonsillar carcinomas, where 51% are found to be HPV DNA positive (Syrjanen 2005). HPV-16 and HPV-18 are the most prevalent types detected in HNSCC (Munoz et al. 2006) whereas HPV-6 and 11 are strongly associated with the development of respiratory papillomas (Kashima et al. 1992; Silverberg et al. 2003).

23.3.4 Non-melanoma Skin Cancer

Non-melanoma skin cancer (NMSC), which includes squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) have also been linked to HPV. However, the types implicated among these types of cancers are different than the types implicated in the anogenital and head and neck cancer. The HPV family includes many cutaneous types (the most important clinically being EV-associated HPVs) which are involved, particularly HPV-5 and HPV-8, in the development of NMSC. About 30–50% of NMSC of immunocompetent individuals contain HPV DNA and this proportion increases to up to 90% among immunosuppressed organ transplant recipients (Pfister 2003; Munoz et al. 2006). It is clear that UV light is the primary etiological agent in NMSC, but it is now becoming clear that HPV may act as co-carcinogen with UV radiation or immunosuppression (Munoz et al. 2006).

23.3.5 Squamous Cell Carcinoma of the Conjunctiva

Squamous cell carcinoma of the conjunctiva is a rare tumor of the eye (Gichuhi and Irlam 2007; McKelvie et al. 2002). However, in Africa it is becoming more

common, more aggressive, and more likely to affect young persons (Ateenyi-Agaba 1995). This pattern seems to be related to the coexistence of the HIV/AIDS pandemic, high HPV exposure, and solar radiation in the region. So far the causes of the disease are not adequately understood. There have been a number of investigations that have studied the impact of several factors, including solar exposure (Newton 1996) and HPV. The presence of HPV is strongly correlated with the occurrence of conjunctival papilloma (Sjo et al. 2007) and HPV has been detected in 35–100% of SCC of the conjunctiva (McDonnell et al. 1992; Tabrizi et al. 1997; Scott et al. 2002; Moubayed et al. 2004; Ateenyi-Agaba et al. 2004; Nakamura et al. 1997). However, since some studies failed to detect HPV in SCC of conjunctiva (Eng et al. 2002; Palazzi et al. 2000), the IARC has concluded that there is limited evidence for the carcinogenicity of HPV in this ocular site (IARC 2007).

23.4 Other Cancers in Which HPV Is Suspected to Play a Causal Role

It has been proposed that HPV may also play a role in the development of a whole range of other epithelial cancers such as malignancies of the bladder and urethra (Chrisofos et al. 2004; Youshya et al. 2005), lung (Chen et al. 2004; Giuliani et al. 2007; Coissard et al. 2005), retina (Orjuela et al. 2000; Palazzi et al. 2003), breast (de Villiers et al. 2005; Damin et al. 2004), prostate (Dennis and Dawson, 2002; Sutcliffe et al. 2007), colon (Lee et al. 2001; Pérez et al. 2005), ovary, and endometrium (Atalay et al. 2007; Konidaris et al. 2007). However, the role of the HPV in these cancers is still subject of considerable debate, as a strong proof of a causal relation is still lacking for each of them. Simply showing that HPV DNA is present in a lesion is not sufficient to demonstrate causality; contamination is a possible factor when testing specimens from these cancers. These cancers have usually more than one etiologic factor and even if it is eventually shown that HPV may be causally implicated it would probably not explain a large proportion of cases. Carefully performed molecular epidemiologic studies (using PCR as a more sensitive HPV detection method) with appropriate control groups and meticulous avoidance of sample contamination is needed to obtain unequivocal evidence for causal associations between HPV and these cancers.

23.5 Clinical Implications, HPV DNA Testing, and HPV Vaccines

HR-HPV has been definitely recognized as the main causal factor for cervical cancer. The recognition of this etiologic relationship has an enormous impact on prevention research and policy. This has led to the development of two new exciting fronts for cervical cancer prevention: HPV DNA testing for screening and HPV vaccination. Recent research on the safety and efficacy of two prophylactic vaccines

against HPV has shown nearly 100% efficacy in preventing persistent infections and development of cervical precancerous lesions caused by the vaccine-targeted HPV types (Harper et al. 2004; Harper et al. 2006; Villa et al. 2006). An important caveat is that the vaccines are prophylactic only and not therapeutic. They are efficacious only in women without evidence of genital HPV DNA at the time of vaccination. The first one to be licensed, Gardasil™ (Merck Inc.) is a quadrivalent vaccine and protects against HPV types 6, 11 (the two types that cause most anogenital warts), 16, and 18 (the two main HPV types that together cause about 75% of all cervical cancers). A bivalent Cervarix™ (GlaxoSmithKline Inc.) has also been licensed in many countries; it protects against HPVs 16 and 18. A small degree of cross-protection against other HR-HPVs may also be expected (Harper et al. 2006). HPV vaccines are certainly among the most prominent public health achievements of the decade and can serve a central role in the prevention of cervical cancer. High vaccine coverage, sustained over many decades, with a long duration of vaccine-conferred protection would have a great impact on type-specific cancer incidence. Testing for HPV DNA has also shown great promise as a screening tool with much greater sensitivity but slightly lower specificity than Pap cytology (Mayrand et al. 2007). In combination with vaccination, HPV testing has the potential to improve the overall effectiveness of cervical cancer screening, thus allowing for increased testing intervals, which would lower program costs with acceptable safety.

23.6 Conclusions

HPV is the most common sexually transmitted viral infection and has been unequivocally considered as a human carcinogen. Progress has been grounded on the recognition that HPV infection is the central, necessary cause of many neoplastic diseases. This virus is the main causal factor of all cervical cancer cases in the world and of a substantial proportion of many other anogenital neoplasms (vagina, vulva, anus, and penis). To date, it has also been etiologically linked to a non-negligible proportion of head and neck cancer (oral cavity, pharynx, and larynx) and non-melanoma skin cancer. A causal role for HPV in other malignancies such as the conjunctiva, bladder, urethra, lung, retina, breast, prostate, colon, ovarian or endometrium, is yet to be credibly established. Properly designed and conducted molecular epidemiologic studies will be necessary to provide conclusive evidence for an association between HPV and these cancers. What is clear, however, is that vaccination against HPV-16/18 can serve a central role in the prevention of cervical cancer and of a substantial proportion of anogenital, and head and neck cancers. HPV vaccination is among the most important public health achievement of this decade.

Acknowledgments Cervical cancer research activities in the Division of Cancer Epidemiology at McGill University have been funded by an endowment from the Cancer Research Society and multiple grants from the Canadian Institutes of Health Research (CIHR), National Cancer Institute

of Canada (NCIC), and US National Institutes of Health. The authors have also received salary awards from the CIHR (Distinguished Scientist to ELF), Fonds de la recherche en santé du Quebec (Chercheur National to ELF) and chercheur-boursier to HT. Supplemental unconditional financial support to the work of the division has been provided by Merck Frosst.

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