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Vaccination against Human Papilloma Virus (HPV): Epidemiological Evidence of HPV in Non-genital Cancers

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Abstract Recently, the vaccine against human papillomavirus (HPV) was introduced in the national vaccination programmes of several countries worldwide. The established association between HPV and the progression of cervical neoplasia provides evidence of the expected protection of the vaccine against cervical cancer. During the last two decades several studies have also examined the possible involvement of HPV in non-genital cancers and have proposed the presence of HPV in oesophageal, laryngeal, oropharyngeal, lung, urothelial, breast and colon cancers. The possible involvement of HPV in these types of cancer would necessitate the introduction of the vaccine in both boys and girls. However, the role of HPV in the pathogenesis of these types of cancer has yet to be proven. Moreover, the controversial evidence of the possible impact of the vaccination against HPV in the prevention of non-genital cancers needs to be further evaluated. In this review, we present an overview of the existing epidemiological evidence regarding the detection of HPV in non-genital cancers.

Keywords HPV · Non-genital cancer · Oesophageal · Laryngeal · Oropharyngeal · Lung · Urothelial · Breast · Colon · Vaccination · Childhood

Introduction

Human papillomaviruses (HPVs) are small double-stranded DNA viruses that comprise a heterogeneous family, which consists of more than 130 different HPV types [1, 2]. Different HPV types have been detected in the anogenital tract, urethra, skin, larynx, tracheo-bronchial and oral mucosa and can cause a wide range of infections, including common warts, genital warts, recurrent respiratory papillomatosis, low-grade and high-grade squamous intraepithelial lesions (SILs), anal cancer, vaginal cancer and cervical cancer. Based on their association with cervical cancer, HPV types are classified as 'high-risk' or 'low-risk'. 'High-risk' HPV types have been implicated in the development of intraepithelial lesions (SILs) and HPV progression to cervical cancer [1, 3]. To date, fifteen different HPV types have been classified as 'high-risk' and these include HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 [4, 5]. 'Low-risk' HPVs have been associated with benign warts of oral and urogenital epithelium in adults as well as children and they are only rarely found in malignant tumours. Different HPV types vary in tissue distribution, oncogenic potential and association with anatomically and histologically distinct diseases.

It is generally accepted that HPV E6 and E7 function as the dominant oncoproteins of 'high-risk' HPVs by altering the function of critical cellular proteins [6]. Expression of the E6 and E7 proteins, as a consequence of viral integration is paramount to the establishment and maintenance of the tumorigenic state. E6 and E7 target important cellular growth regulatory circuits including the p53 and retinoblastoma tumour suppressor protein Rb, respectively. HPV E6 has been shown to interact with and enhance the degradation of p53 by the ubiquitin pathway, which plays an important role in cell cycle control and apoptosis in response to DNA damage, while HPV E7 disables the function of the retinoblastoma tumour suppressor protein Rb. It has been shown that both HPV E6 and E7 interact with the host cell targeting a plethora of key host cellular proteins that are involved in apoptosis and malignant cellular transformation [7].

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Molecular detection of HPV DNA is the gold standard for identification of HPV in tissue and exfoliated cell samples using several assays [8]. These assays include non-amplified hybridization assays, such as Southern transfer hybridization (STH), dot blot hybridization and in situ hybridization, signal amplified hybridization assays, such as hybrid capture assays and target amplification assays, such as polymerase chain reaction. Different methods can present different sensitivities and specificities. Accurate molecular diagnosis of HPV infection relies on the detection of viral DNA. Polymerase chain reaction (PCR) is the most widely used method and is both extremely sensitive and specific.

During the last two decades several studies have examined the possible involvement of HPV in non-genital cancers and have investigated the presence of HPV in oesophageal, laryngeal, tonsillar, lung, urothelial, breast and colorectal cancers. Although the role of HPV has been proven only in the pathogenesis of cervical cancer, the presence of HPV in other cancers can provide further evidence for the importance of HPV vaccination in their prevention. The wide availability of HPV for cervical cancer prevention indicates that the HPV vaccination may also affect the rates of other cancers potentially associated with HPV. The possible involvement of HPV in non-genital types of cancer would necessitate the introduction of the vaccine in both boys and girls. In this review, we present an overview of the existing evidence regarding the detection of HPV in non-genital cancers.

We searched MEDLINE, EMBASE, and Google Scholar to identify studies published in English between January 1990 and January 2009. We used the following keywords: *HPV and lung, HPV and oesophageal, HPV and laryngeal, HPV and tonsillar, HPV and urothelial, HPV and breast, HPV and colon, HPV and non-genital cancer*. We reviewed all abstracts to identify articles that assessed the prevalence of HPV in samples of different types of cancer. To ensure the complete capture of all relevant studies, we cross-referenced articles from the bibliography of the selected articles. After reviewing each article, we selected studies that used the polymerase chain reaction (PCR) technique, in situ hybridization, Southern blot hybridization, immunohistochemistry or genotyping to identify the presence of HPV. We excluded case reports and studies that did not provide a denominator or studies of benign lesions. Overall, we reviewed 398 studies and identified 176 original studies, 55 involving oesophagial samples, 9 laryngeal, 18 tonsillar, 28 lung, 41 uroepithelial samples, 18 breast and 7 studies with colon samples.

HPV and Oesophageal Cancer

Oesophageal cancer is a leading cause of cancer death, especially in developing countries [8, 9]. Oesophageal carcinogenesis is a complex multistep process with a multifactorial etiology. Environmental factors, such as alcohol and smoking, appear to play a decisive role in esophageal carcinogenesis. Furthermore, oesophageal squamous cell carcinoma demonstrates a wide regional variation in incidence and causal associations. The first reports suggesting an involvement of HPV in the development of both benign and malignant squamous cell tumours of the oesophagus date back to 1982 [9, 10]. Since then several studies have been conducted assessing the presence of HPV in oesophageal carcinoma.

In our review, we analysed 55 studies [11–65] published from 1990 to 2009. As shown in Table 1, out of the analysed oesophageal carcinomas, HPV detection rates ranged from 0% to 88.2% depending on different methods and geographical variances. In 28 studies HPV detection rates were less than 20%, in 11 studies 20–40%, while in 14 studies HPV was detected in more than 40% of the analysed samples.

The detection of HPV 16 in tumour samples is more frequent compared to HPV 18 [18, 22–24, 40, 61, 65] or other types including HPV 33 and 13 [20] and 'low-risk' HPVs including HPV 11 [33]. In the study by Chang et al, HPV 16 or 18 were present in one out of three HPV-positive samples, while 60.2% of the HPV-positive lesions contained DNA sequences other than HPV types 6, 11, 16, 18, 30 and 53 [46]. In contrast to other studies, the study by Matsha et al [41] showed that HPV 11 and 39 were detected more frequently than HPV 16, suggesting a possible role of HPV types other than 16 and 18 in the pathogenesis of oesophageal cancer.

'High-risk' HPV types 16 and 18 were detected more frequently in cancerous tissues, followed by paracancerous tissues and normal mucosa [39]. Different p53 codon 72 polymorphisms were noted as 'high-risk' factors in HPV-associated oesophageal cancers [19, 31, 38]. P53 overexpression is frequently detected and involved in the carcinogenesis of oesophageal cancer [49, 60]. Loss of function of the wild-type p53 tumour suppressor gene product by binding to E6 oncoproteins of 'high-risk' HPVs is considered an important event in tumour development [42]. HPV infection appears unlikely to be a significant factor in the etiology of Barrett's oesophagus, a premalignant condition which may give rise to oesophageal adenocarcinoma [13]. Koilocytosis, an epithelial change consistent with HPV infection, has been found in 37.5–80% of the esophageal squamous cell tumors with HPV DNA [55, 65]. Integrated 'high-risk' HPV DNA within the host chromosome has also been demonstrated in patients with oesophageal cancers [64, 66]. Real-time PCR analysis suggested the presence of an integrated form of HPV DNA in the HPV 16-positive samples, but its viral load was estimated to be only less than 1–2 copies per cell [18].

HPV infection has been correlated with a response to neoadjuvant therapy and better prognosis in patients with

Table 1 Detection of HPV in oesophageal cancer

Reference	Country	Diagnosis	Number of samples	Number of HPV-positive samples
PCR, In situ hybridization				
Bohn et al. 2008 [11]	USA	Oesophageal squamous papilloma	16	14 (87.5%)
Chang et al. 2000 [43]	China	Oesophageal squamous carcinoma	103	6 (5.8%)
Miller et al. 1997 [55]	USA	Oesophageal squamous carcinoma	22	10 (45.5%)
PCR, Southern blot hybridization				
Bognar et al. 2008 [14]	Hungary	Oesophageal carcinoma	26	6 (23.1%)
Shuyama et al. 2007 [18]	Japan	Oesophageal squamous carcinoma	59	19 (32.2%)
Castillo et al. 2006 [22]	Colombia	Oesophageal squamous carcinoma	47	16 (34%)
Castillo et al. 2006 [22]	Chile	Oesophageal squamous carcinoma	26	5 (19.2%)
He et al. 1997 [53]	China	Oesophageal squamous carcinoma	152	32 (21.1%)
Mizobuchi et al. 1997 [57]	Japan	Oesophageal squamous carcinoma	41	3 (7.3%)
Morgan et al. 1997 [58]	UK	Oesophageal squamous carcinoma	17	0 (0%)
Shibagaki et al. 1995 [62]	Japan	Oesophageal squamous carcinoma	72	15 (20.8%)
Chen et al. 1994 [65]	USA	Oesophageal squamous carcinoma	40	24 (60%)
PCR, Immunochemistry				
Acevedo-Nuno et al. 2004 [32]	Mexico	Oesophageal squamous carcinoma	17	15 (88.2%)
Acevedo-Nuno et al. 2004 [32]		Barrett's oesophagus	28	27 (96.4%)
PCR				
van Zeeburg et al. 2008 [12]	Netherlands	Oesophageal squamous carcinoma	2	0 (0%)
Rai et al. 2008 [13]	UK	Barrett's oesophagus	73	1 (1.4%)
Koh et al. 2008 [15]	South Korea	Oesophageal squamous carcinoma	110	0 (0%)
Matsha et al. 2007 [17]	South Africa	Oesophageal squamous carcinoma	114	51 (44.7%)
Pantelis et al. 2007 [19]	Germany	Oesophageal squamous carcinoma	53	9 (17%)
Far et al. 2007 [20]	Iran	Oesophageal squamous carcinoma	140	33 (23.6%)
Souto et al. 2006 [23]	Brazil	Oesophageal squamous carcinoma	165	26 (15.8%)
Dreilich et al. 2006 [24]	Sweden	Oesophageal squamous carcinoma	100	16 (16%)
Lyronis et al. 2005 [26]	Greece	Oesophageal squamous carcinoma	30	17 (56.7%)
White et al. 2005 [27]	Kenya	Oesophageal squamous carcinoma	29	0 (0%)
Farhadi et al. 2005 [28]	Iran	Oesophageal squamous carcinoma	38	14 (36.8%)
Bahnassy et al. 2005 [29]	Egypt	Oesophageal squamous carcinoma	50	27 (54%)
Katiyar et al. 2005 [30]	India	Oesophageal squamous carcinoma	101	25 (24.8%)
Lu et al. 2004 [31]	China	Oesophageal squamous carcinoma	104	55 (52.9%
de Villiers et al. 2004 [33]	Germany	Oesophageal squamous carcinoma	21	14 (66.7%)
Kamath et al. 2000 [35]	USA	Oesophageal carcinoma	46	1 (2.2%)
Awerkiew et al. 2003 [36]	Germany	Oesophageal carcinoma	37	0 (0%)
Li et al. 2002 [38]	China	Oesophageal carcinoma	62	39 (62.9%)
Shen et al. 2002 [39]	China	Oesophageal carcinoma	176	115 (65.3%)
Hasegawa et al. 2002 [40]	Japan	Oesophageal squamous carcinoma	48	20 (41.7%)
Matsha et al. 2002 [41]	South Africa	Oesophageal squamous carcinoma	50	23 (46%)
Astori et al. 2001 [42]	Italy	Oesophageal carcinoma	17	8 (47.1%)
Lambot et al. 2000 [44]	Belgium	Oesophageal squamous carcinoma	21	1 (4.8%)
Talamini et al. 2000 [45]	Italy	Oesophageal squamous carcinoma	45	0 (0%)
de Villiers et al. 1999 [47]	China	Oesophageal carcinoma	117	20 (17.1%)
Lavergne et al. 1999 [48]	China	Oesophageal carcinoma	29	10 (34.5%)
Lavergne et al. 1999 [48]	South Africa	Oesophageal carcinoma	34	9 (26.5%)
Khurshid et al. 1998 [50]	Japan	Oesophageal carcinoma	27	17 (63%)
Kok et al. 1997 [52]	Netherlands	Oesophageal carcinoma	63	0 (0%)
Lam et al. 1997 [54]	Hong Kong	Oesophageal squamous carcinoma	75	6 (8%)

Table 1 (continued)

Reference	Country	Diagnosis	Number of samples	Number of HPV-positive samples
Saegusa et al. 1997 [56]	Japan	Oesophageal carcinoma	103	0 (0%)
Turner et al. 1997 [59]	USA	Oesophageal squamous carcinoma	51	1 (2%)
Suzuk et al. 1996 [61]	China	Oesophageal squamous carcinoma	110	4 (3.6%)
Smits et al. 1995 [63]	The Netherlands	Oesophageal squamous carcinoma	61	0 (0%)
Genotyping				
Lu et al. 2008 [16]	China	Oesophageal squamous carcinoma	67	20 (29.9%)
Immunochemistry				
Qi et al. 2006 [21]	China	Oesophageal squamous carcinoma	60	11 (18.3%)
Immunochemistry, in situ hybridization				
Zhou et al. 2003 [37]	China	Oesophageal carcinoma	48	31 (64.6%)
Hybrid Capture II				
Gao et al. 2006 [25]	China	Oesophageal squamous carcinoma	4	0 (0%)
Weston et al. 2003 [34]	Brazil	Oesophageal squamous carcinoma	40	1(2.5%)
In situ hybridization				
Chang et al. 2000 [46]	China	Oesophageal squamous carcinoma	700	118 (16.9%)
Takahashi et al. 1998 [49]	Japan	Oesophageal squamous carcinoma	123	37 (30.1%)
Chang et al. 1997 [60]	China	Oesophageal squamous carcinoma	36	3 (8.3%)
Cooper et al. 1995 [64]	South Africa	Oesophageal carcinoma	48	25 (52.1%)
Southern blot hybridization				
Morgan et al. 1997 [51]	UK	Oesophageal squamous carcinoma	22	0 (0%)

oesophageal cancer [14]. However, other investigators have shown that HPV 16 infection has no significant effect on survival and does not improve survival after treatment (radiotherapy or chemotherapy) [24]. No correlation was found between HPV in esophageal squamous cell carcinoma tissues and in grade 1–3 esophageal squamous cell carcinoma cells [67]. In the study by Lyronis et al conducted at the University of Crete, no statistically significant correlation was found between the HPV status of the tumour samples and clinical parameters including gender, age of the patients, tobacco or alcohol use, differentiation grade of the lesions and stage of the disease [26].

HPV and Laryngeal Cancer

The pathogenesis of larynx oncogenesis is complex and controlled by various etiological factors, including heavy tobacco smoking, chewing snuff and excessive alcohol consumption [68]. Data concerning the involvement of HPV in laryngeal cancers are controversial. Different researchers [69–77] have identified HPV DNA in biopsy samples of laryngeal carcinoma at a rate ranging from 3.3 to 50% (Table 2). In only 2 studies analysed in our review were HPV detection rates less than 20%, in 4 studies 20–40%, while in 3 studies HPV was detected in more than 40% of the analysed samples, suggesting that the role of HPV infection is important during the multistage process of neoplastic transformation of the larynx.

Different HPV types, including 16, 18, 33, 26, 31, 39, 6, 11 and 52 have been detected in laryngeal carcinomas [69, 70, 78]. Among 'high-risk' HPVs, HPV 16 has been detected more frequently than HPV 18 or 33 [70]. The detection rate of 'low-risk' HPV 6 has been found to be lower than that of HPV 16 or 18 [75]. Extensive koilocytes, an indication of HPV infection, can be observed by histological examination in papillomas and carcinoma [68]. HPV DNA has been detected more frequently in laryngeal carcinomas than in normal mucosa [69, 73], but less frequently compared to laryngeal leukoplakia [73].

'Low-risk' HPV 6 and 11 are frequently found in recurrent laryngeal papillomatosis (RRP), the most frequent benign tumour of the larynx in childhood [79]. HPV 11 has been proposed as an aggressive virus that plays a significant role in the development of laryngeal cancer in patients with a history of RRP [78]. Reidy et al [78] examined patients with a history of RRP that progressed to laryngeal cancer. These authors noted that HPV 11, but not HPV 6, 16, or 18, was found in all of the laryngeal cancers in the studied patients. Integration of the viral genome of HPV 11 DNA was also revealed. However, other investigators have proposed that the malignant transformation of laryngeal papillomas without demonstrable HPV DNA is more common and these patients require a more frequent follow-up [80].

Table 2 Detection of HPV in laryngeal cancer

Reference	Country	Diagnosis	Number of samples	Number of HPV-positive samples
PCR, In situ hybridization				
Baumann et al. 2009 [69]	USA	Laryngeal squamous carcinoma	38	6 (15.8%)
PCR				
Szladek et al. 2005 [71]	Hungary	Laryngeal carcinoma	25	8 (32%)
Almadori et al. 2001 [72]	Italy	Laryngeal squamous carcinoma	42	15 (35.7%)
Azzimonti et al. 2004 [95]	Italy	Laryngeal squamous carcinoma	25	14 (56%)
Smith et al. 2000 [73]	USA	Laryngeal carcinoma	44	11 (25%)
Lindeberg et al. 1999 [74]	Denmark	Laryngeal carcinoma	30	1 (3.3%)
Clayman et al. 1994 [76]	USA	Laryngeal carcinoma	65	30 (46.2%)
El-Mofty et al. 2003 [97]	USA	Laryngeal carcinoma	7	2 (28.6%)
Genotyping				
Wang et al. 1991 [77]	Taiyuan	Laryngeal carcinoma	6	3 (50%)
In situ hybridization				
Cerovac et al. 1996 [75]	Croatia	Laryngeal carcinoma	26	11 (42.3%)
Immunochemistry, genotyping				
Morshed et al. 2008 [70]	Poland	Laryngeal squamous carcinoma	93	33 (35.5%)

A positive correlation has been found in the HPV detection rates according to the grade G1, G2 and G3 [75]. Detection of HPV has been significantly related to decreased survival, independent of disease stage [76]. HPV co-infection with genogroup 1 TT virus has been proposed to be associated with poor clinical outcome in laryngeal cancer [71]. However, other investigators have failed to demonstrate that HPV infection influences survival rates as an independent prognostic factor in patients with laryngeal cancer [70].

HPV and Oropharyngeal Cancer

Tonsillar cancer is the most common oropharyngeal carcinoma. The etiology of tonsillar carcinoma is multifactorial, with smoking and alcohol consumption being significant factors in tonsillar cancer. By the end of 2002, 432 cases of tonsillar carcinoma had been analyzed for the presence of HPV DNA, with an overall detection rate of 51% as reviewed by Syrjanen in 2004 [81].

In our review of 18 studies [82–99], HPV detection rates ranged from 12.6% to 90.9% (Table 3). In only 1 study, analysed in our review, was the HPV detection rate less than 20%, in 34 studies 20–40%, in 2 studies 20–30%, while in 15 studies HPV was detected in more than 40% of the analysed samples. HPV detection rates were significantly higher in tonsillar cancers than in other head and neck tumours [94]. Moreover, among head and neck cancers, the viral load of HPV DNA was higher in tonsillar cancers, with the median copy numbers of HPV DNA in tonsillar specimens being approximately 80,000 times higher than that in non-tonsillar cases [100]. It has been suggested that tonsillar localization is considered as a hot spot for viral transformation [94].

During the last decades, an increase in the incidence of tonsillar cancer was reported by several researchers [82, 101], and it has been suggested that this increase is due to an increased proportion of HPV in these tumours [102]. In Sweden, the proportion of HPV-positive cancers significantly increased from 1970 to 2007, with the incidence rate of HPV-positive tumours almost doubling each decade between 1970 and 2007, with a concomitant decline of HPV-negative tumours [82]. In the study by Ryerson et al [101], the annual incidence rates of potentially HPV-associated tonsillar cancer in the US increased significantly from 1998 through 2003, whereas the incidence rates of cancer at the comparison sites generally decreased. Similar results were published by Romanitan et al [83] in Greek patients with tonsillar cancer during the years 1986–2007.

Compared to other HPV types such as 18, 33, 35, 6 and 58, HPV 16 has proven to be the dominant HPV type in tonsillar carcinoma [82, 83, 86, 92, 93, 96]. HPV 16 DNA integration was noted in 41% and 48% of tonsillar cancer samples studied by Hafkam et al [84] and by Koskinen et al [100], respectively. Moreover, it was proposed that HPV 16 DNA plays an important role in tonsillar carcinogenesis [92, 100, 103]. Interestingly, the presence of HPV has been correlated with low tobacco and alcohol consumption, indicating its possible role as an independent causative factor in tonsillar carcinogenesis [84, 87, 98]. HPV positivity has been correlated with female gender [89, 90] and young age [89, 96]. In the study by Hafkamp et al [84], the presence of HPV was correlated with poor differentiation grade, small tumor size, presence of a local metastasis

Table 3 Detection of HPV in oropharyngeal cancer

Reference	Country	Diagnosis	Number of samples	Number of HPV-positive samples
PCR, In situ hybridization				
Chien et al. 2008 [90]	Taiwan	Tonsillar squamous carcinoma	111	14 (12.6%)
Mellin Dahlstrand et al. 2005 [91]	Sweden	Tonsillar carcinoma	51	25 (49%)
PCR				
Nasman et al. 2009 [82]	Sweden	Tonsillar squamous carcinoma	98	83 (84.7%)
Romanitan et al. 2008 [83]	Greece	Tonsillar carcinoma	28	12 (42.9%)
Charfi et al. 2008 [87]	France	Tonsillar squamous carcinoma	52	32 (61.5%)
Pintos et al. 2008 [88]	Canada	Tonsillar carcinoma	21	9 (42.9%)
Li et al. 2007 [89]	Hong Kong	Tonsillar carcinoma	31	9 (29%)
Hoffmann et al. 2005 [93]	Germany	Tonsillar carcinoma	9	8 (88.9%)
Venuti et al. 2004 [94]	Italy	Tonsillar carcinoma	8	6 (75%)
Azzimonti et al. 2004 [95]	Italy	Tonsillar squamous carcinoma	9	5 (55.6%)
Li et al. 2004 [96]	Australia	Tonsillar squamous carcinoma	50	21 (42%)
El-Mofty et al. 2003 [97]	USA	Tonsillar carcinoma	11	10 (90.9%)
Mellin et al. 2003 [99]	Sweden	Tonsillar carcinoma	66	30 (45.5%)
In situ hybridization				
Hafkamp et al. 2008 [84]	Netherlands	Tonsillar carcinoma	81	33 (40.7%)
Kuo et al. 2008 [85]	Taiwan	Tonsillar carcinoma	92	40 (43.5%)
Westra et al. 2008 [86]	USA	Tonsillar squamous carcinoma	21	12 (57.1%)
Hafkamp et al. 2003 [98]	Netherlands	Tonsillar carcinoma	12	8 (66.7%)
Begume et al. 2005 [92]	USA	Oropharyngeal carcinoma	45	37 (82.2%)

and a decreased regional recurrence rate. However, other investigators [94] have shown that HPV status is not related to age, gender, tumour stage or grade, and use of alcohol and/or tobacco. Interestingly, patients with HPV-positive tonsillar tumours have a better overall and disease-specific survival, than HPV-negative patients. Patients with HPV-positive tonsillar cancer have been shown to have a lower risk of relapse and longer survival compared to patients with HPV-negative tonsillar cancer [84, 89, 90, 102]. Five-year disease-specific survival was found to be higher in HPV 16-positive patients compared to HPV-negative patients [87]. Similar results have been demonstrated by reasearchers who analysed the role of p16, a significant biomarker of HPV infection, in the prognosis of patients with oropharyngeal cancer [84, 85, 91]. Recently, overexpression of p16 was related to a significant better prognosis in patients with oropharyngeal squamous cell carcinoma treated by either radiotherapy or primary surgery [104]. The correlation between HPV viral load and recurrence, disease-free survival, and overall survival has also been demonstrated [105]. HPV-positive patients with the highest viral HPV loads had improved overall and disease-free survival. Recurrences of squamous cell carcinoma were significantly less likely to occur with an increasing viral load.

An interesting issue that has been examined by several researchers is the possible mode of HPV transmission in the oropharyngeal cavity in childhood or adulthood [106]. Although HPV infection is considered as a sexually transmitted infection, other non-sexual modes of HPV transmission have also been implicated [107]. These modes include casual physical contact and perinatal vertical transmission. The virus infects primarily epithelial cells through abrasion of the skin or the mucosa, where it can exist as a long-term latent infection that can reactivate or persist. Although in the majority of individuals HPV infection remains transient and asymptomatic and in most cases HPV infection resolves within 2 years, HPV infection can persist for several years. Further research will evaluate the impact of HPV transmission during childhood in the oropharyngeal carcinogenesis in adulthood.

HPV and Lung Cancer

Squamous cell carcinoma and adenocarcinoma of the lung are leading causes of cancer-related death in Western countries. Interestingly, over the past three decades, the incidence of lung adenocarcinoma has increased worldwide [108]. Several factors have been implicated in their etiology, including cigarette smoking, environmental pollution, asbestos and genetic factors [108]. The presence of HPV DNA in lung cancer has been excessively studied, and in the review by Syrjanen in 2002 [109] comprising 2,468 lung carcinomas, the mean incidence of HPV was 21.7%.

In our review of 28 studies [110–137], HPV was detected in 0–78.3% carcinomas, with a rate of less than 20% reported in 15 studies (Table 4).

HPV detection rates have been considerably higher in lung cancer samples compared to the non-cancer controls with benign lesions or normal lung histology [110, 112, 122]. The risk of lung squamous cell carcinomas has been 3.5 times higher for HPV-positive compared to HPV-negative patients [110]. HPV DNA has been more frequently detected in squamous cell carcinoma than in adenocarcinomas [110, 113]. The presence of HPV in both squamous lung carcinoma and adenocarcinoma samples has been reported worldwide. However, a considerable heterogeneity between different countries and regions has been demonstrated by several researchers [110, 111, 119, 122]. The average reported frequencies in the US and Western European countries have been lower compared to the rates reported in Asian lung cancer samples [119]. Different rates

Table 4 Detection of HPV in lung cancer

Reference	Country	Diagnosis	Number of samples	Number of HPV-positive samples
PCR, In situ hybridization				
Soini et al. 1996 [131]	Finland	Lung carcinoma	43	13 (30.2%)
Miyagi et al. 2001 [124]	Japan	Lung squamous carcinoma	59	29 (49.2%)
Miyagi et al. 2001 [124]	Japan	Lung adenocarcinoma	62	12 (19.4%)
Cheng et al. 2001 [126]	China	Lung carcinoma	141	77 (54.6%)
Gorgoulis et al. 1999 [127]	Greece	Non-small cell lung carcinoma	68	0 (0%)
Tsuhako et al. 1998 [128]	China	Lung adenocarcinoma	23	18 (78.3%)
PCR, Southern blot hybridization				
Castillo et al. 2006 [111]	Colombia, Mexico, Peru	Lung carcinoma	36	10 (27.8%)
Aguayo et al. 2007 [113]	Chile	Lung carcinoma	69	20 (29%)
Bohlmeyer et al. 1998 [130]	USA	Lung squamous carcinoma	34	2 (5.9%)
Papadopoulou et al. 1998 [129]	Greece	Lung squamous carcinoma	52	32 (61.5%)
Kinoshita et al. 1995 [134]	Japan	Lung squamous carcinoma	10	1 (10%)
Kinoshita et al. 1995 [134]	Japan	Lung adenocarcinoma	22	2 (9.1%)
PCR				
Yu et al. 2006 [110]	China	Lung squamous carcinoma	72	37 (51.4%)
Yu et al. 2006 [110]	China	Lung adenocarcinoma	37	6 (16.2%)
Wang et al. 2008 [112]	China	Non-small cell lung carcinoma	313	138 (44.1%)
Park et al. 2007 [115]	Korea	Non-small cell lung carcinoma	112	60 (53.6%)
Nadji et al. 2007 [116]	Iran	Lung carcinoma	129	33 (25.6%)
Ciotti et al. 2006 [117]	Italy	Non-small cell lung carcinoma	38	8 (21.1%)
Jain et al. 2005 [118]	India	Lung carcinoma	40	2 (5%)
Zafer et al. 2004 [121]	Turkey	Non-small cell lung carcinoma	40	2 (5%)
Miasko et al. 2001 [123]	Poland	Lung carcinoma	40	4 (10%)
Thomas et al. 1995 [132]	France	Lung squamous carcinoma	18	2 (11.1%)
Thomas et al. 1995 [132]	France	Lung adenocarcinoma	4	1 (25%)
Li et al. 1995 [133]	China	Lung carcinoma	50	16 (32%)
Szabo et al. 1994 [135]	Japan	Lung squamous carcinoma	40	0 (0%)
In situ hybridization				
Fei et al. 2006 [122]	China	Non-small cell lung carcinoma	73	19 (26%)
Kaya et al. 2001 [125]	Turkey	Lung carcinoma	26	3 (11.5%)
Yousem et al. 1992 [136]	USA	Lung carcinoma	26	7 (26.9%)
Bejui-Thivolet et al. 1990 [137]	France	Lung squamous carcinoma	33	6 (18.2%)
Immunochemistry, In situ hybridization				
Brouchet et al. 2005 [120]	France	Lung carcinoma	122	0 (0%)
Roche line blot assay				
Coissard et al. 2005 [119]	France	Lung carcinoma	218	4 (1.8%)

have also been reported in different regions of the same country [122] and in the same ethnic populations in different countries [110].

HPV infection has been detected in smoking and non-smoking patients with lung squamous cell carcinoma or adenocarcinoma [112]. Although smoking has been more frequently noted in heavy smokers than in patients with a low daily cigarette consumption and non-smokers [122, 127], other investigators [115] have not found any correlation between HPV and smoking status. There has been no correlation between HPV infection and gender, age, stage, grade, and lymph node status of the carcinomas [115, 122, 125, 127].

Different 'high-risk' types such as HPV 16, 18, 31 and 33 as well as the 'low-risk' types HPV 6 and 11 have been found; the latter mainly in association with squamous cell carcinomas. Among squamous cell lung carcinomas and adenocarcinomas, 'high-risk' HPV 16 and 18 have been detected more frequently compared to other 'high-risk' HPVs and the 'low-risk' HPV 6 and 11 [116, 129, 136]. Although HPV 16 has been detected more frequently than HPV 18 in both squamous cell carcinomas and adenocarcinomas [111, 113, 115, 117, 133], HPV 18 predominance has been demonstrated by other researchers [118, 130, 134] in both squamous cell carcinomas and adenocarcinomas. The higher prevalence of HPV 33 infections in Korean lung cancer patients compared to other Asian and Western countries [115] has not been confirmed in the US and Western European countries.

It has been shown that HPV 16 and 18 DNA have been uniformly located in lung tumor cells, but not in the adjacent non-tumor cells [126]. In the study by Miyagi et al [124], extremely large numbers of Langerhans cells were demonstrated in the tumour nests in the HPV-infected adenocarcinoma and squamous cell carcinoma cases. In contrast, in the non-HPV-infected adenocarcinomas and squamous cell carcinomas, only a few Langerhans cells were observed. Koilocytosis has also been described in HPV-infected cells of the squamous carcinomas [136].

The viral load of HPV has been low in most of the samples with lung cancer [113]. Expression of E6 and E7 has been confirmed in HPV-positive lung cancer cases [114, 134] and has been related to p53 inactivation and the transcriptional activation of human telomerase reverse transcriptase (hTERT) [138–142]. It has been demonstrated that the expression of HPV-16/18 E6 oncoprotein in stage I non-small cell lung cancer had a higher 5-year cumulative survival rate compared with patients who did not express both oncoproteins [140]. Abnormal p53 protein accumulation by point mutation has also been proposed to play an important role in the development of lung carcinomas and, in some cases, HPV may contribute to it by binding and inactivating the p53 protein [131]. P53 codon 72 polymorphisms have also been detected in patients with lung cancer compared to healthy individuals [118, 141, 142]. However, no significant correlation was noted between different p53 polymorphisms and clinical stage or prognosis [118].

HPV and Urothelial Cancer

Urinary bladder carcinoma is a common urological malignancy, that remains an important cause of oncological morbidity and mortality. Known etiological agents include smoking, alcohol use and exposure to certain industrial chemical compounds, although the origin of the majority of cases remains unknown. Several studies have examined the possible correlation between different bacterial or viral infections with the development of bladder carcinoma [143]. It has been suggested that chronic infection with Schistosoma haematobium is etiologically related to the occurence of bladder carcinoma. Other investigators have linked the development of urinary infection, urinary stones and indwelling catheters with bladder cancer [143]. The possibility that HPV infection is also related to the development of bladder carcinoma has also been investigated but no definite conclusions have been drawn. In the review by Lopez-Beltran et al [144] published in 1997, the incidence of 'high-risk' HPV DNA ranged from 2.5% to 81%. Similarly, in the meta-analysis of 239 cases by Wiwanitkit et al [145], the overall HPV DNA-positive rates for the patients and healthy control subjects were 25.5% (61/239) and 11.5% (6/52).

In the 41 studies recruited in our review (Table 5), HPV detection rates ranged from 0 to 81.3% [146–186]. In 21 studies detection rates were less than 20%, with rates ranging from 0% to 5% in 16 of them. In these studies, HPV was not correlated with urothelial carcinogenesis and did not appear to play a role in the development of the studied malignant renal tumors. These results agree with the finding by Helal et al [149] who have demonstrated schistosomiasis-associated urothelial cancers more frequently compared to HPV-associated tumours. However, in 7 studies, HPV was detected in more than 40% of the analysed samples. To a great extent the discrepancies reported in different studies on the association of HPV to bladder cancer can be attributed to the large variability in the sensitivity of HPV DNA detection, depending on sample fixation, DNA preparation and amplification conditions. Moreover, the low HPV viral load observed in bladder tumours [176] can lead to more false negative results compared to other cancer types.

'High-risk' HPV 16 and 18 have been detected with significantly higher rates in bladder cancer than cystitis cases, non-neoplastic urinary samples or normal samples

Table 5 Detection of HPV in urothelial cancer

Reference	Country	Diagnosis	Number of samples	Number of HPV-positive samples
PCR, Southern blot hybridization				
Aynaud et al. 1998 [163]	France	Bladder carcinoma	57	0 (0%)
LaRue et al. 1995 [176]	Canada	Bladder carcinoma	71	28 (39.4%)
Knowles, 1992 [185]	UK	Bladder carcinoma	109	0 (0%)
Anwar et al. 1992 [182]	Japan	Bladder carcinoma	48	39 (81.3%)
PCR, In situ hybridization				
Gopalkrishna et al. 1995 [172]	India	Bladder carcinoma	10	2 (20%)
Sano et al. 1995 [173]	Japan	Bladder carcinoma	93	0 (0%)
Lopez-Beltran et al. 1995 [174]	Spain	Bladder carcinoma	76	7 (9.2%)
Agliano et al. 1994 [179]	Italy	Bladeer carcinoma	46	23 (50%)
PCR, Immunochemistry				
Youshya et al. 2005 [151]	UK	Bladder carcinoma	78	47 (60.3%)
PCR				
Aggarwal et al. 2009 [146]	India	Bladder carcinoma	33	14 (42.4%)
Badawi et al. 2008 [147]	Egypt	Bladder carcinoma	20	9 (45%)
Barghi et al. 2005 [150]	Iran	Bladder carcinoma	59	21 (35.6%)
Khaled et al. 2003 [152]	Egypt	Bladder carcinoma	99	48 (48.5%)
Fioriti et al. 2003 [153]	Italy	Bladder carcinoma	32	0 (0%)
Soulitzis et al. 2002 [154]	Greece	Bladder carcinoma	50	6 (12%)
Sur et al. 2001 [157]	South Africa	Bladder carcinoma	91	1 (1.1%)
Simoneau et al. 1999 [158]	Canada	Bladder carcinoma	187	16 (8.6%)
Mvula et al. 1996 [167]	Japan	Bladder carcinoma	36	1 (2.8%)
Tenti et al. 1996 [168]	Italy	Bladder carcinoma	79	26 (32.9%)
Lopez-Beltran et al. 1996 [169]	Spain	Bladder carcinoma	76	7 (9.2%)
Tekin et al. 1999 [160]	Turkey	Bladder carcinoma	42	2 (4.8%)
Gazzaniga et al. 1998 [161]	Italy	Bladder carcinoma	35	11 (31.4%)
Chan et al. 1997 [162]	Hong Kong	Bladder carcinoma	20	6 (30%)
Kim et al. 1995 [171]	Korea	Bladder carcinoma	23	8 (34.8%)
Noel et al. 1994 [177]	Belgium	Bladder carcinoma	75	2 (2.7%)
Maloney et al. 1994 [178]	USA	Bladder carcinoma	42	1 (2.4%)
Saltzstein et al. 1993 [181]	USA	Bladder carcinoma	33	0 (0%)
Chetsanga et al. 1992 [184]	Sweden	Bladder carcinoma	44	1 (2.3%)
In situ hybridization				
Helal et al. 2006 [149]	Egypt	Bladder carcinoma	114	1 (0.9%)
Khaled et al. 2001 [155]	Egypt	Bladder carcinom	50	23 (46%)
Westenend et al. 2001 [156]	Netherlands	Bladder carcinoma	16	0 (0%)
De Gaetani et al. 1999 [159]	Italy	Bladder carcinoma	43	17 (39.5%)
Lu et al. 1997 [164]	UK	Bladder carcinoma	31	0 (0%)
Smetana et al. 1995 [170]	Israel	Bladder carcinoma	110	24 (21.8%)
Kamel et al. 1995 [175]	Finland	Bladder carcinoma	47	27 (57.4%)
Furihata et al. 1993 [180]	Japan	Bladder carcinoma	90	28 (31.1%)
Bryant et al. 1991 [186]	UK	Bladder carcinoma	100	12 (12%)
Southern blot hybridization				
Boucher et al. 1996 [165]	UK	Bladder carcinoma	55	0 (0%)
Shibutani et al. 1992 [183]	USA	Bladder carcinoma	20	4 (20%)
Immunochemistry, In situ hybridization				
Lopez-Beltran et al. 1996 [166]	Spain	Bladder carcinoma	76	25 (32.9%)
Hodges et al. 2006 [148]	USA	Renal carcinoma	62	0 (0%)

[147, 176, 179, 182]. Similarly, multiple HPV infections were significantly higher in carcinoma than in normal tissues [182]. These results suggest that 'high-risk' HPV 16 and 18 carries a risk for the development of malignancy in the urinary tract. HPV positivity has been found more frequently in squamous than in transitional cell carcinoma [155]. Among patients with transitional cell carcinoma, HPV 16 [147] and 18 [150, 162] have been the most frequently detected HPV types, indicating that 'high-risk' HPVs play a causative role in transitional cell carcinoma of bladder. The overall and 'high-risk' HPV infections in neoplastic specimens were distributed almost equally in male and female patients [180]. Several studies have shown geographical differences [155].

Koilocytosis has been shown to be a good morphological marker for HPV DNA in the urothelium [166], with a positive predictive value of 84.6% [146]. In the study by Khled et al [152], p53 mutations were detected in bladder carcinoma samples and a significant correlation was found between p53 mutations and the pathological stage. Similar results were published by Soulitzis et al [154], showing that p53 polymorphisms are implicated in bladder carcinogenesis and that individuals harboring the Arg/Arg genotype have an increased risk of developing bladder cancer. In the study by Kim et al [171], p53 mutations were shown to play a significant role in the development of bladder carcinoma.

The presence of HPV infection has been correlated with the stage and grade of bladder carcinoma [159, 168]. In the study by LaRue et al [176], the presence of HPV was correlated with grade but not stage of the tumours. Pathological grade was found to be an independent factor in bladder cancer survival [169]. The presence of HPV infection was also related with outcome on follow-up and survival [159, 180]. However, data on the possible relationship between HPV detection and prognosis remain limited.

HPV and Breast Cancer

Breast cancer is one of the major health problems in developed countries, occupying first place in mortality in women. It is well known that the etiology of human breast cancer is affected by several hereditary as well as environmental risk factors. The idea that a different viruses, including Epstein-Barr virus EBV, the human equivalent of murine mammary tumour virus MMTV and HPV, could cause breast cancer has been investigated for quite some time, even though the mode of HPV transmission to the breast has not yet been explained.

In 15 out of 18 studies included in our review, researchers have supported the presence of HPV in breast carcinoma samples [187–201]. Detection rates of HPV DNA using the polymerase chain reaction technique range from 0% to 74% [187–204]. HPV DNA has been detected in a higher frequency in breast carcinoma samples compares to benign or normal samples [187, 193, 199]. HPV DNA viral load in breast carcinoma cases has been estimated to be lowed compared to cervical cancer cases [188]. HPV 16 has been detected more frequently compared to HPV 18 [187, 188, 199]. However, other researchers have identified HPV 33 [189, 193, 201] or HPV 11, followed by HPV 6 [197], as the most prevalent HPV types in breast carcinoma. Southern blot analysis has showed that HPV DNA in breast carcinoma samples was largely episomal [200]. Recently, real-time PCR analysis has also demonstrated the presence of integrated form of viral DNA in HPV 16-positive breast carcinoma samples [188] (Table 6).

It has been proposed that breast cancer patients harboring 'high-risk' HPV DNA sequences in their tumor were younger than the rest of the patients [195]. However, no correlations with histological type, tumour grade, steroid receptor status, ERB-2, p53 expression have been observed [190, 196]. The presence of HPV DNA has also not been correlated with specific prognostic predictors of disease [190, 196, 199]. HPV have been reported to be found in a significant portion of breast cancers of women with concomitant cervical intraepithelial neoplasia or cervical cancer [205, 206]. These researchers have supported that HPV DNA might be transported from the original site of infection to the breast tissue by the blood or lymph, and be involved in the development of breast neoplasia.

HPV and Colon Cancer

In spite of the limited number of studies [207–213], several researchers have detected HPV DNA in colon carcinoma samples, suggesting that HPV may be related to the pathogenesis of colon neoplasia (Table 7). HPV DNA has been detected more frequently in colorectal malignant specimens compared to matched normal tissues or non-malignant control samples [207–209, 213]. HPV 16 has been identified more frequently, although its viral load has been estimated low [207, 208]. No correlation between the presence of HPV DNA and specific prognostic predictors for the disease outcome has been observed [207], however data on the prognostic role of the presence HPV is limited. Since the relationship between HPV infection and natural course of colorectal cancer has not been fully defined further research is required to investigate the presence of HPV in colon cancer.

Conclusions

HPV is a well-known risk factor for cervical cancer development and the recently introduced HPV vaccination

Table 6 Detection of HPV in breast cancer

Reference	Country	Diagnosis	Number of samples	Number of HPV-positive samples
PCR				
De Leon et al. 2009 [187]	Mexico	Breast carcinoma	51	15 (29.4%)
Khan et al. 2008 [188]	Japan	Breast carcinoma	124	26(21%)
Akil et al. 2008 [189]	Syria	Breast carcinoma	113	96(61.1%)
Choi et al. 2007 [190]	Korea	Breast carcinoma	123	8(6.5%)
Mendizabal-Ruiz et al. 2009 [191]	Mexico	Breast carcinoma	67	3(4.4%)
De Cremoux et al. 2008 [202]	France	Breast carcinoma	50	0(0%)
Grenier et al. 2007 [192]	France	Breast carcinoma	27	2(14%)
Gumus et al. 2006 [193]	Turkey	Breast carcinoma	50	37(74%)
Lindel et al. 2007 [194]	Germany	Breast carcinoma	81	0(0%)
Kroupis et al. 2006 [195]	Greece	Breast carcinoma	107	17(15.9%)
Kan et al. 2005 [196]	Australia	Breast carcinoma	50	24(48%)
De Villiers et al. 2005 [197]	Germany	Breast carcinoma	29	20(68.9%)
Tsai et al. 2005 [198]	Taiwan	Breast carcinoma	62	8 (12.9%)
Damin et al. 2004 [199]	Brazil	Breast carcinoma	101	25 (24.8%)
Wrede et al. 1992 [203]	UK	Breast carcinoma	80	0 (0%)
PCR, Southern blot hybridization				
Liu et al. 2001 [200]	USA	Breast carcinoma	17	6 (35%)
Yu et al. 2000 [201]	China	Breast carcinoma	32	14 (43.8%)
Bratthauer et al. 1992 [204]	USA	Breast carcinoma	28	0 (0%)

of girls in clinical practice is an important step towards cervical cancer prevention. During the last decade, the established association between HPV and cervical cancer has provided a framework from which to evaluate the possible pathogenic role for the virus in cancers at non-genital sites. This would provide the required evidence supporting the hypothesis that HPV plays an etiological role in the malignant transformation of squamous epithelial cells in non-genital sites. This would also support HPV vaccination not only as a prevention tool against cervical cancer, but, also, against other non-genital types of cancer.

To date, several researchers worldwide have detected the presence of HPV in different non-genital cancer types and recognised the possible role of HPV in non-genital carcinogenesis. Epidemiological and experimental evidence partly re-inforce this possibility and suggest that HPV is involved in non-genital carcinogenesis as an important etiological factor. The precise role of HPV, if there is indeed any, in the carcinogenesis as a possible major causative agent or as a co-adjuvant factor remains to be elucidated. However, other investigators have published low detection rates of HPV in non-genital cancers. Although the results are somewhat controversial due to the marked heterogeneity in the frequencies with which HPV was detected, as well as in the methods used, the overall picture suggests involvement of HPV in the evolution of oesophageal,

Table 7 Detection of HPV in colon cancer

Reference	Country	Diagnosis	Number of samples	Number of HPV-positive samples
PCR				
Damin et al. 2007 [207]	Brazil	Colorectal adenocarcinoma	72	60 (83.3%)
Bodaghi et al. 2005 [208]	USA	Colorectal carcinoma	55	28 (51%)
Lu et al. 2003 [209]	USA	Colorectal squamous cell carcinoma	29	29 (100%)
Lee et al. 2001 [210]	Taiwan	Coloreactal carcinoma	19	16 (84%)
Shah et al. 1992 [212]	USA	Colorectal carcinoma	50	0 (0%)
PCR, Southern blot hybridization				
McGregor et al. 1993 [211]	USA	Colorectal carcinoma	38	13 (32%)
Immunochemistry				
Kirgan et al. 1990 [213]	USA	Colorectal carcinoma	30	29 (97%)

laryngeal, oropharyngeal and urothelial cancer. Nevertheless, no prospective study has examined the association between HPV infection and non-genital cancer risk thus far. Thus, the debate remains open as to whether there is any direct link between HPV infection and non-genital cancers that could necessitate HPV vaccination in boys and girls. Prospective studies with large numbers of patients and controls are therefore required to confirm this hypothesis.

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