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Chapter

Human Papillomavirus Infection and Lung Cancer

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Abstract

Lung cancer continues to be the most common neoplasia and represents the leading cause of cancer-related death in the world. Nonetheless, contrary to expected projections, the decrease in incidence expected by decrease in tobacco exposure has been partially halted due to an increasing amount of lung cancer cases in nonsmokers, particularly in female patients. This led to the development of new hypotheses in terms of lung cancer etiology, including the involvement of oncogenic viruses such as the human papillomavirus (HPV). HPV role in the pathophysiology of lung cancer, including adenocarcinoma and squamous cell carcinoma, is currently under research. Exposure to HPV, and the resulting infection, can occur in several possible ways, including sexual transmission and airborne fomites. Main pathogenic occurrences include alterations in inhibition of p53 and retinoblastoma. This chapter presents the current evidence as to the role of HPV in the development of lung cancer, methods to establish HPV infection, and also explores the role of predisposing factors, as well as immunological and inflammatory factors in nonsmokers. Additionally, the role of other molecular factors, such as EGFR, interleukins 6 and 10, and others, is discussed. Finally, future perspectives in this new paradigm of lung cancer in nonsmokers are broadly reviewed.

Keywords: HPV, lung cancer, inflamation, immunogenicity, viral DNA

1. Introduction

Lung cancer is the most common cancer in the world. In 2012, 1.8 million new cases were diagnosed and 1.6 million people died as a consequence of this disease [1]. It is one of the top 10 leading causes of death worldwide [2]. About 90% of lung cancer cases in men and 75% in women in the United States and Europe are caused by tobacco smoke [3, 4]. An important proportion of lung cancer cases presents in non-smokers, as shown in several reports. In the Caucasian population, the rate of non-small cell lung cancer (NSCLC) in non-smokers is 10% for men and 20% for women, while for Asian populations the rate reached 30–40% [5, 6]. In the United States, the overall lung cancer incidence rates and mortality have been declining for the past two decades, and the reduction in both of these parameters has been more prominent in men than in women, a trend that likely reflects the decrease in smoking rates in the

male population [7]. Interestingly, in developed countries, lung cancer incidence has been gradually increasing for non-smokers [8–10]. In Asian countries, the situation is similar; lung cancer incidence and mortality have been increasing despite the implementation of successful anti-smoking campaigns [11, 12].

Among the histologic subtypes of NSCLC, squamous cell lung cancer (SCC) is more common in men (44% cases in men vs. 25% in women) and adenocarcinoma (ADC) is more common in women (28% cases in men and 42% in women). SCC and small cell lung cancers (SCLC) are more closely associated with smoking, in contrast to ADC that is most commonly found in non-smokers [13]. In fact, the calculated histological distribution of lung cancer among smokers and non-smokers in 17 different studies has shown that 53% of the cases in smokers and 19% in non-smokers are SCC while 62% in non-smokers and 18% in smokers are ADC [14]. Furthermore, ADC in non-smokers appears to have a less complex histology with a higher presence of targetable driver mutations, particularly *EGFR*, *Her2* as well as *ALK* and *ROS* translocations [15, 16].

The differences in epidemiology, genetic profile, and survival outcomes of lung cancer in non-smokers have made it clear that this malignancy is a separate entity from lung cancer in smokers [17]. Over the last decades, the investigation of the preventable risk factors associated with lung cancer in non-smokers has gained much attention. Of interest, human papillomavirus (HPV) has been reported in
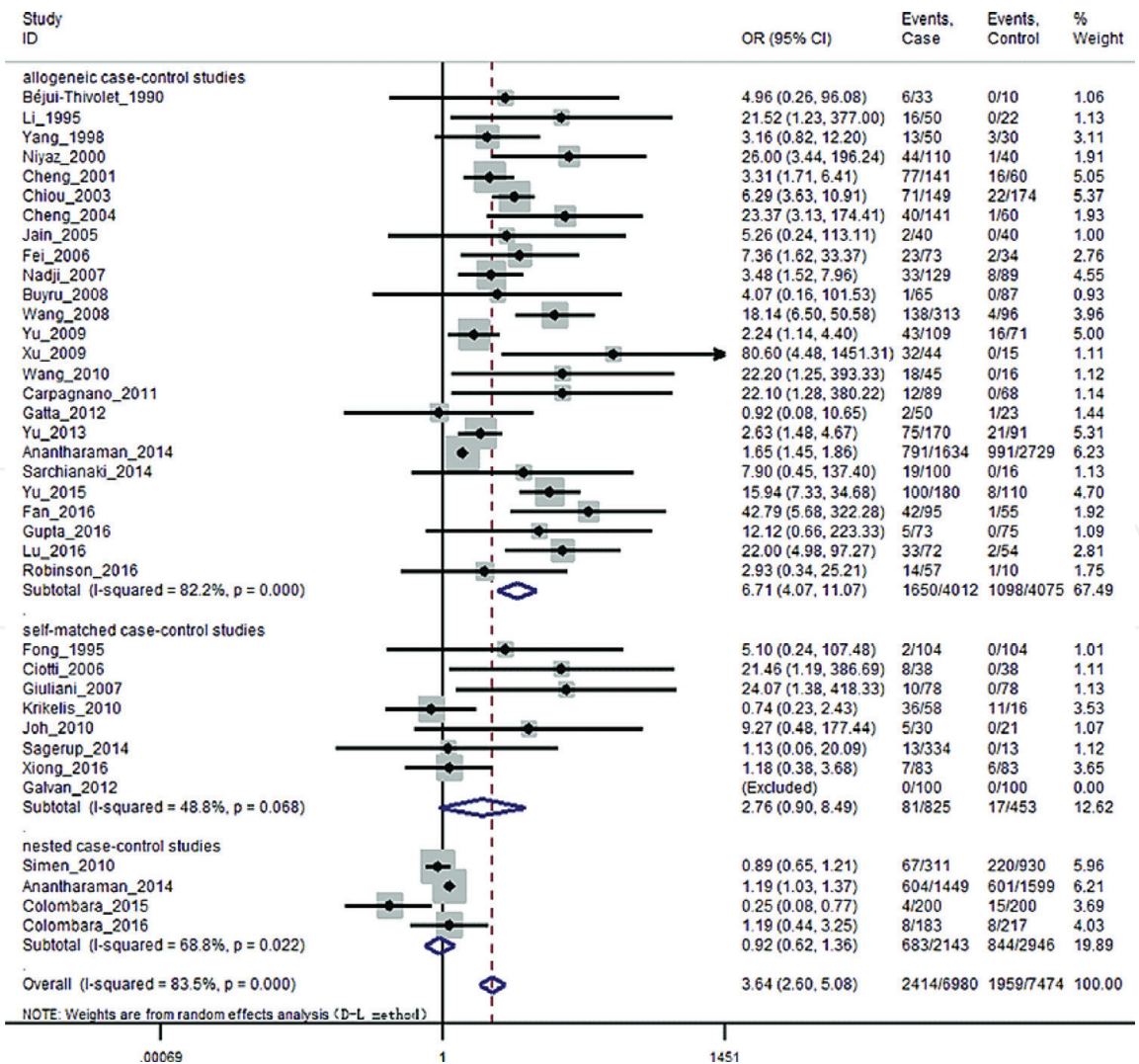

Figure 1.
Forest plot of random effects model stratified by study design. Individual study OR and grouped ORs sub (reproduced with authorization from Ref. [24].

lung cancer tissues from Western and Eastern countries, being types 18 and 16 the most common pathogenic species [18–21]. Likewise, recent studies have demonstrated a significantly increased risk of acquiring lung cancer in non-smokers who are exposed to HPV infection (OR 5.32; 95% CI 1.75–16.17) [22, 23]. **Figure 1** depicts a meta-analysis of recent studies evaluating the association between HPV infection and lung cancer.

Importantly, the public health impact of these recent findings has been recently explored, since vaccination against HPV could represent an efficacious measure to prevent lung cancer. Additionally, the timely detection of HPV in the respiratory tract could warrant a method for early diagnosis of lung cancer, particularly in the non-smoker population [25, 26].

2. Immune and inflammation markers in lung cancer among never smokers

Multiple studies have shown an increased incidence of non-smoker lung cancer in females [3, 9, 10, 27–30]. After analyzing a cohort of 975 patients in Singapore, Yano et al. identified that non-smoker lung cancer patients presented at a younger age and with an earlier stage at diagnosis than their smoker counterparts [10]. The most important risk factors for lung cancer in non-smokers are second-hand smoke, indoor air pollution, occupational exposures, genetic susceptibility, family history, estrogen levels, HPV infection, and pre-existing respiratory diseases [15].

Respiratory diseases elicit a deleterious chronic inflammatory response in lung tissue, which in turn causes an increased rate of cell division leading to an augmented risk of DNA damage [31]. Additionally, inflammation stimulates anti-apoptotic signal activation and angiogenesis further promoting tumorigenesis [32, 33]. Previous studies have also suggested an important role for lung diseases in the development of lung cancer, even when not associated with tobacco use. In 2012, Brenner et al. carried out an extensive analysis from 17 studies and identified that a history of emphysema, pneumonia, and tuberculosis elevated the risk for lung cancer development among non-smokers [34]. Likewise, other case-control studies across various populations have concluded that a history of respiratory diseases, including chronic obstructive pulmonary disease (COPD), asthma, pneumonia, and tuberculosis, would increase the risk of developing lung cancer [35–40]. A systematic review demonstrated that pre-existing tuberculosis increased lung cancer risk in non-smokers (RR 1.78, 95% CI 1.42–2.23); interestingly, the increased risk was only associated with ADC histology, while SCC and SCLC showed no association [41].

Due to the association between respiratory diseases and lung cancer among non-smokers, inflammatory pathways and markers have been the focus of much interest in recent years and hence have been widely studied. A case-control study nested within three prospective cohort studies carried out in Australia and Sweden identified a higher lung cancer risk for participants who had elevated concentrations of interleukin (IL)-6 and IL-8. These associations were stronger for former smokers (smoking cessation at least 10 years before study was performed) than for current smokers, both for IL-6 and IL-8; however, these associations were not observed in never-smoker patients [42]. Other inflammatory markers have been found to be significantly associated with lung cancer risk. In a previous case-control study within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial (PLCO), 11 markers of importance were identified. Interestingly, nine of these markers were significantly associated with lung cancer among non-smokers, which

included the epithelial neutrophil-activating peptide 78 (ENA-78/CXCL5) and IL-7, and also associated with lung cancer overall, and others not associated with lung cancer overall, which included human granulocyte chemotactic protein-2 (GCP2/CXCL6), granulocyte colony stimulating factor (G-CSF), IL-6, macrophage inflammatory protein 1B, 2 and 4 (MIP-1B/CCL4, MCP-2/CCL8, MCP-4/CCL13), and stromal cell derived factor-1 (SDF-1 A-B/CXCL12) [43]. Two years later, the PLCO trial was nested to its replication in a case-control study. Both of the nested case-control trials demonstrated that circulating levels of C-reactive protein (CRP), serum amyloid A (SAA), soluble tumor necrosis factor receptor 2 (sTNFRII), and monokine induced by gamma interferon (CXCL9/MIG) were associated with lung cancer risk [43, 44]. These associations were limited to smokers, and the study was considered to be underpowered to evaluate associations among non-smokers [44]. Finally, a nested case-control study carried out within the Shanghai Women's Health Study evaluated 61 inflammatory markers among non-smoker Chinese women. Nine markers were statistically significantly associated with lung cancer: soluble IL-6 receptor (sIL6R) and chemokine ligand 2/monocyte chemotactic protein 2 (CCL2/MCP-1) were associated with an increased risk of lung cancer, while IL-21, chemokine (C-X3-C motif) ligand 1/fractalkine (CX3CL1/fractalkine), soluble vascular endothelial growth factor receptor 2 (sVEGFR2) and sTNFRII and CRP were associated with a decreased risk. Interestingly sIL-6R was associated with an increased lung cancer risk even 7.5 years prior to diagnosis. The results of this study further support our current knowledge in terms of the role of inflammation and immune response on the development of lung cancer among the female non-smoker population.

3. HPV transmission in lung cancer

Since the respiratory tract is composed of two different epitheliums, it contains various squamous columnar junctions (SCJ). In the bronchi, the SCJ may occur naturally or most commonly as squamous metaplasia (SQM) secondary to cigarette smoking [45]. The SQM process initiates with the activation and posterior hyperproliferation of the SQM quiescent basal cells present in the pseudostratified epithelium. As a consequence, the epithelial cells begin to show a squamous cell differentiation, given by the expression of squamous epithelial cytokeratins and cell adhesion molecule SQM1. Finally, cells express involucrin, a protein which indicates that the cells are in a terminal differentiation stage [46–52]. The biochemical and metabolic changes that SQM induces make the bronchial epithelium susceptible to HPV infection. Hence, the multiple foci of SQM in the bronchi are analogous to the transformation zone of the uterine cervix, as both work as the point of entry for HPV [53, 54].

To date, there are three hypotheses regarding HPV infection and transmission into the pulmonary tissue [24, 55]. The first one states that the HPV infection occurs in the reproductive system (male or female) and then hematogenously transmitted to the lung tissue. A study reports that approximately 80% of female HPV-positive lung cancer patients also have cervical intraepithelial neoplasia [56]. Peripheral blood cells (B cells, dendritic cells, NK cells, and neutrophils) on healthy men have been shown to be infected by high- and low-risk HPV [57]. Furthermore, Bodaghi et al. identified HPV types 16 and 18 on peripheral blood from healthy transfusion donors [58]. Since the lung is a highly vascularized tissue, this makes it susceptible to capture the virus and eventually develop the tumor. More evidence to support this hypothesis is the high prevalence of HPV DNA in peripheral blood samples
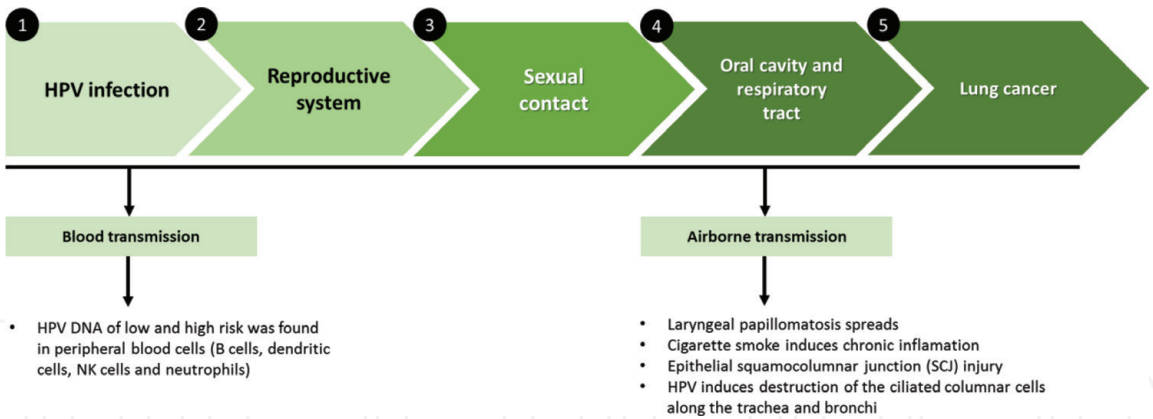
Figure 2.
Possible transmission pathways of HPV infection.

seen in NSCLC patients [25]. These findings have led some authors to suggest that these peripheral blood cells can be a viral reservoir for the infection of other organs and even contribute to viral spread in a sexual contact-independent manner [55]. Another hypothesis refers to oral-genital HPV infection that causes transmission through the throat into the lung. HPV infection may be propagated either through oral-oral contact or genital to oral contact. A survey that followed 222 men and their female patterns showed an infection rate in men of 7.2% with the majority of their female partners having either cervical or oral HPV infection. And finally, a third hypothesis is that HPV may be transmitted as an airborne disease. Carpagnano et al. reported the presence of HPV DNA in exhaled breath condensate of lung cancer patients, hence proposing that HPV transmission can occur through inhalation [59]. These hypotheses are summarized in **Figure 2**.

4. Possible molecular mechanisms of HPV-induced lung carcinogenesis

HPV initially interacts with cellular receptors and infects the basal lamina, transferring its viral genomes to the nucleus [60]. These events are followed by an initial phase of genome amplification and afterwards by a steady maintenance of the viral episome at low copy number [61, 62], particularly around 200 copies per cell, based on the study of episomal cell lines derived from cervical lesions [63]. The replication process requires the hijacking of the of the Retinoblastoma family of proteins (RB, p108 and p130), which regulate cell proliferation, as well as the inhibition of p53, which disrupts apoptosis [64]. The carcinogenic potential comes from the presence of the genes E6 and E7 in the HPV genome, especially in serotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. The E6 protein is composed of roughly 150 amino acids and has the ability to interact with many targets due to its structure containing two zinc fingers built by two pairs of CXX motifs [65]. The main target of this protein is p53. After binding with E3 ubiquitin ligase UBE3A/E6AP (E6-associated protein), the E6/E6AP complex marks p53 for proteasome-dependent degradation. E6 is also involved in other steps of oncogenesis including guarantying survival of the infected cells and offering evasion of the infected cells from the immune system. This protein has in turn the ability to stimulate interleukin-10 (IL10) expression, a cytokine responsible for immunomodulation and anti-inflammatory effects. Among its effects, IL10 has the ability to induce autocrine and paracrine immunologic tolerance due to activation of T helper 2 and T regulatory lymphocytes, inhibition of pro-inflammatory cytokines, and downregulation of the MHC classes I and II, arresting DC maturation

and downregulating intercellular adhesion molecules and co-stimulating mediators. Additionally, IL10 has been shown to promote early E6 and E7 expression, consolidating a vicious cycle [66]. Other interleukins such as IL6 have been shown to be both a stimulator and an inhibitor of cell proliferation, depending on the cell line exposed. Through a complex process in which E6 causes STAT3 activation and IL6 expression, the cancer-associated fibroblast cells, present in the tumor microenvironment, suffer from IL6-induced and p16-mediated senescence. This phenomenon of adjacent cell dysfunction has been shown to promote neoplastic growth due to paracrine stimulation, chronic inflammation, and loss of oncolytic countermeasures [67]. Furthermore, IL6 has the ability to induce antiapoptotic Mcl-1 expression in HPV-infected lung cancer cells [68]. Mcl-1, member of the BCL-2 gene family is responsible, together with the Bcl-2 protein, for the apoptotic response of the mitochondria. Mcl-1 inhibits apoptosis by capturing BH3 and thus inhibiting Bax/Bcl-xl translocation, crucial steps in propagating an apoptotic signal in the cell [69]. Similarly, Bcl-2 offers a comparable Bax translocation inhibition, thus offering a strong antiapoptotic signal [70]. All in all, E6-activated and Il6-mediated BCL2 family modulation seems to be responsible for contributing to apoptosis inhibition and immortalization of HPV-infected cells. Other mechanisms of E6-induced immortalization include the expression of cIAP2, which is considered to be a very potent antiapoptotic factor in these cells by being the upstream inhibitor of caspase 3 activity. This hypothesis was validated in a study of induction of apoptosis in HeLa cells transfected with E6 and E7 proteins by knockdown of this molecule. E6 in turn causes the binding of p52 to NF-κB leading to an upregulation in the expression of cIAP [71, 72]. Additionally, this molecule lays as a downstream step in EGFR signaling, and its expression has also been strongly correlated with the presence of *EGFR* mutations [73]. One possible hypothesis to explain this phenomenon relates to the E6 inhibition of p53. Inactivation of this protein in turn leads to the loss of function in the MMR pathway, especially in MLH1 and MSH2, thus causing an increase in reactive oxygen species, which also strongly correlates with exon 19 *EGFR* mutations in lung cancer [74]. Finally, matrix metalloproteinases (MMP) seem to be also influenced by E6 interactions. These enzymes are responsible for degradation of the extracellular matrix, process required for cell migration and development of metastasis. MT1-MMP, MMP-2, and MMP-9 are the main members of this family that were upregulated by the expression of this oncogene [75], possibly by the induction of microRNAs [76].

E7, on the other hand, is responsible for binding and degrading pRb, p105, p107, and p130, especially in the upper epithelial layers. Additionally, E7 causes genome instability by deregulating the centrosome cycle [60]. Additionally, occurs the induction of the aryl hydrocarbon receptor signaling, a transcription factor involved in proliferation, differentiation, and apoptosis. Members of this family and inhibitors of cyclin-dependent kinases p16 and p21 have been proven to bind to E7 increasing pRb phosphorylation and promoting furthermore cell cycle deregulation [77]. Other activities can also be impaired by E7, such as epigenetic cell function. This molecule has the capacity to displace histone deacetylases, specially HDAC 1, 4, and 7 blocking their binding sites to the HIF-1α promoter regions and leading to an upregulation of its expression. This, in turn, is considered a key step in angiogenesis and thus strongly contributes to tumor growth [78].

5. HPV gene expression and detection in lung tissue

The relation between HPV and lung cancer was postulated since the decade of the 1970s. In 1975, Roglic et al., followed by Rubel and Reynolds in 1979, observed

koilocytosis, a classical pattern in HPV infection, in sputum samples from benign bronchial lesions [79, 80]. Simultaneously, Syrjanen described that the epithelial changes seen in bronchial carcinoma closely resembled HPV-induced genital lesions [81]. Afterwards, several epidemiological data, particularly in non-smoking lung cancer patients, firmly established the relationship between HPV infection and development of lung cancer.

Although several studies showed the presence of oncogenic HPV in lung cancer tissue, demonstrating a causal role is necessary. Taking into account that integration of HPV DNA within the host is the critical point for oncogenic transformation, demonstration of the HPV DNA presence in lung cancer DNA cells is the main goal.

Cheng et al. demonstrated that HPV DNA was integrated into lung cancer DNA cells but not in the adjacent non-tumor cells and also demonstrated that HPV (+) lung cancer patients were predominantly non-smoking females, suggesting a role of HPV infection in the development of lung cancer in non-smokers (OR 10.12, CI 95%: 3.88–26.38 for non-smoking females), and it was one of the first proofs of concept of this causative role [82]. In this study, HPV DNA of high-risk serotypes 16 and 18 was determined by nested PCR and *in situ* hybridization (ISH). Taking this under consideration, PCR is an ideal method for determining HPV-Host DNA integration. The presence of HPV infection can be assessed through different methods, including the use of lung tissue samples (Frozen, Fresh or Formalin fixed and paraffin embedded tissue) but also serological samples (using techniques such as Bead-based multiplex serology method or Multiplex liquid bead microarray antibody assay) [24]. However, one must consider that serologic analysis is usually limited by the low amount of HPV circulating in the bloodstream and also by the low sensitivity and specificity of serological detection techniques; therefore, lung tissue is usually better accepted. In a previous meta-analysis, Xiong et al. [24] evaluated the association between HPV and lung cancer in over 6000 lung cancer patients and 24,000 HPV-exposed individuals. The results showed an association between lung cancer and HPV (OR 3.64; 95% CI: 2.60–5.08), with most studies (75% [28/37]) using polymerase chain reaction (PCR) analysis in lung cancer tissue for HPV detection. The sensitivity and false-positive rate of PCR is higher than with other methods, including *in situ* hybridization, Southern blot, dot blot, and sequencing [83, 84].

5.1 HPV detection and genotyping

In brief, DNA is extracted from lung cancer tissue and then different PCR methods can be used. One of the most common PCR methods used for HPV detection and genotyping is INNO-LiPA Genotyping Extra assay (Innogenetics N.V., Ghent, Belgium) [84]. This assay can detect 18 high-risk types using a reverse hybridization line probe (16, 18, 26, 31, 33, 35, 39, 45, 51–53, 56, 58, 59, 66, 68, 73, 82), 7 low-risk types (6, 11, 40, 43, 44, 54, 70), and some additional types (69, 71, 74). The assay also includes negative and positive controls (HPV6), as well as an internal control (HLA-DPB1 gene), to confirm DNA quality and the absence of PCR inhibitors. The results of trials conducted using each technique are summarized in **Table 1**.

In conclusion, the association between HPV infection and lung cancer should demonstrate the integration between HPV DNA and lung tumor cells DNA. The method usually performed for this assessment is PCR, and different techniques for genotyping have been used, mainly methodologies that include detection of high-risk serotypes but also low risk serotypes.

Author, year	Country	Method	HPV types	Sample type	Cases (n/N)	Controls (n/N)
Béjui-Thivolet, 1990	France	ISH	6, 11, 16, 18	Tissue	6/33	0/10
Li, 1995	China	PCR, DB	16, 18	Tissue	16/50	0/22
Fong, 1995	Australia	PCR	6, 11, 16, 18, 31, 33, 52b, 58	Tissue	2/104	0/104
Yang, 1998	China	PCR	6/11, 16, 31/33	Tissue	13/50	3/30
Niyaz, 2000	China	PCR	16, 18	Tissue	44/110	1/40
Cheng, 2001	China	PCR, ISH	16, 18	Tissue	77/141	16/60
Chiou, 2003	China	PCR	16, 18	Blood	71/149	22/174
Cheng, 2004	China	PCR, ISH	6, 11	Tissue	40/141	1/60
Jain, 2005	India	PCR	16, 18	Tissue (case) Blood (control)	2/40	0/40
Ciotti, 2006	Italy	PCR, sequencing	16, 18, 31	Tissue	8/38	0/38
Fei, 2006	China	ISH	16, 18	Tissue	23/73	2/34
Giuliani, 2007	Italy	PCR, reverse blot hybridization, sequencing	—	Tissue	10/78	0/78
Nadji, 2007	Iran	PCR, sequencing	—	Tissue	33/129	8/89
Buyru, 2008	Turkey	PCR, SB	16, 18	Blood	1/65	0/87
Wang, 2008	China	PCR, ISH, IHC	16, 18	Tissue	138/313	4/96
Yu, 2009	China	PCR	25 types	Tissue	43/109	16/71
Xu, 2009	China	ISH	16/18	Tissue	32/44	0/15
Krikelis, 2010	Greece	PCR	16	Tissue, BW	36/58	11/16
Wang, 2010	China	PCR	16, 18	Tissue	18/45	0/16
Joh, 2010	USA	PCR, sequencing	—	Tissue	5/30	0/21
Carpagnano, 2011	Italy	PCR, sequencing, INFINITI HPV-QUAD assay	16, 18, 30, 31, 33, 45, 35/68, 39/56, 58/52, 59/51, 6/11	Tissue, BW, EBC	12/89	0/68
Galvan, 2012	Italy, UK	PCR, DB	35 types	Tissue	0/100	0/100
Gatta, 2012	Italy	PCR	16, 18, 33, 35, 52, 58	Tissue	2/50	1/23

Author, year	Country	Method	HPV types	Sample type	Cases (n/N)	Controls (n/N)
Yu, 2013	China	PCR, reverse blot hybridization, SB	25 types	Tissue	75/170	21/91
Anantharaman, 2014	7 European countries	BMSM	6, 11, 16, 18, 31	Blood	791/1634	991/2729
Sagerup, 2014	Norway	PCR	15 types	Tissue	13/334	0/13
Sarchianaki, 2014	Greece	PCR, genotyping	37 types	Tissue	19/100	0/16
Yu, 2015	China	PCR	L1, 16, 18	Tissue	100/180	8/110
Fan, 2016	China	ICC	16	Pe	42/95	1/55
Gupta, 2016	India	PCR	16, 18, 31, 33, 45	FNAC, tissue	5/73	0/75
Lu, 2016	China	PCR	16, 18	Tissue	33/72	2/54
Robinson, 2016	USA	Microarray, oncovirus panel, genotyping PCR	28 types	Tissue	15/57	1/10
Xiong, 2016	China	PCR, reverse blot hybridization	21 types	Tissue	7/83	6/83
Simen, 2010	Finland	ELISA	16, 18	Serum	67/311	220/930
Anantharaman, 2014	10 European countries	BMSM	6, 11, 16, 18, 31	Blood	604/1449	601/1599
Colombara, 2015	USA	LBMA	6, 11, 16, 18, 31, 33, 52, 58	Serum	4/200	15/200
Colombara, 2016	China	LBMA	6, 11, 16, 18, 31, 33, 52, 58	Serum	8/183	8/2

Table 1.
Summary of reported trials conducted using each HPV detection and genotyping technique.

6. HPV in lung cancer clinical information and perspective

There are at least three postulated ways for HPV virus to reach the tracheobronchial tract and cause epithelial transformation and malignancy: (1) cervical to lung transmission, (2) from an infected reproductive system to the mouth, throat, and finally lungs, and (3) airborne transmission. All of these have been supported by solid epidemiological data [56, 59, 85, 86]. Once HPV reaches the tracheobronchial epithelium, several molecular and cytological changes can occur as consequence of proteins E6 and E7 from HPV. These oncogene proteins can regulate expression of

several target genes and proteins, which derives in promoted lung cell proliferation, angiogenesis, and cell immortalization. Among the genes and proteins affected are p53, pRb, HIF-1α, VEGF, IL-6, IL-10, Mcl-1, Bcl-2, cIAP-2, EGFR, FHIT, hTERT, HER-2, ALK, ROS1, and AhR [55, 87–90]. Evidence which supports the association between HPV infection and lung cancer continues to grow, but debate will likely continue due to heterogeneous methodologies for HPV detection in lung tissue. At least eight systematic reviews and meta-analysis have consistently found that HPV infection is a risk factor for lung cancer [22–24, 84, 91–94]. One of them included longitudinal studies: a nested case-control and a cohort study with high causality [24]. According to subgroup analyses from several trials, the HPV infection constitutes a risk for lung cancer, especially in non-smokers, similar to the findings in head and neck cancers, females and Asian race [22, 24, 82]. Additionally considering HPV affinity to squamous cells, HPV infection constitutes a risk for squamous cell lung cancer; however, other histologic subtypes including ADC and SCLC have also been related to HPV infection [23, 24, 94].

HPV serotypes 16 and 18, known as high-risk serotypes, are mainly associated with lung cancer risk, though low-risk serotypes are believed to cause benign, non-malignant, lesions [23, 24, 95]. However, this relationship has not been fully studied, and other serotypes including HPV 11 and HPV 31 have a less clear role in terms of lung cancer association. Currently available vaccines against HPV could theoretically prevent lung cancer development; however, this important issue has seldom been explored and more research is needed to draw robust conclusions. HPV status modifies treatment modalities and prognosis in head and neck cancers. Further research is necessary to determine whether lung cancer treatment should change according to HPV infection status. HPV coinfection in lung cancer favors the inclusion of E5 oncoprotein, which alters the mitogenic signaling downstream of Ras, EGFR, and PKC, as well as the constitutive activation of AP-1, which through c-jun may result in cell survival [96]. In the same way, E6 HPV protein blocks p53 activation causing an inhibition of p21 action, upregulating the expression of EGFR and inhibiting apoptosis by activating cIAP28. Additionally, the inclusion of the E7 protein leads to the downregulation of p16INK4 by hypermethylation and migration of tumor-infiltrating lymphocytes (TILs) [97]. Recently, Cheng et al. have found that HPV infection increases tumor activity via hypermethylation of the XRCC3 and XRCC5, an event that generates induced DNA [98]. In parallel, Zhang et al. proposed that inflammation related to HPV lung cancer is induced by increasing levels of HIF, VEGF and [90]. We previously reported a high HPV positivity rate in Hispanic patients suffering lung ADC; in addition, we described that presence of viral DNA leads to a better prognosis in *EGFR* and *KRAS*—mutated lung ADC and increases the expression of PDL1 [99]. Based on this information, HPV infection could modify host immune response and subsequently predict response to immunotherapy, which is currently a treatment modality in certain subgroups of lung cancer patients. Similarly, HPV infection appears to be associated with lung cancer in non-smokers, as are *EGFR* mutations; therefore, it is possible that a synergistic approach could be reached when treating the infection in *EGFR*-mutated lung cancer patients who receive targeted agents. In this regard, a previous study by Li et al. demonstrated that the presence of HPV DNA was significantly associated with *EGFR* mutations in advanced lung ADC. Interestingly, patients with both HPV infections and *EGFR* mutations have a reduced risk of progression compared to those without HPV infection or *EGFR* mutation (adjusted HR = 0.640; 95% confidence interval: 0.488–0.840; P = 0.001), suggesting a prognostic role for HPV status in this patient subgroup [73]. Another likely suitable target for therapy is MEK, a mitogenic signaling pathway protein
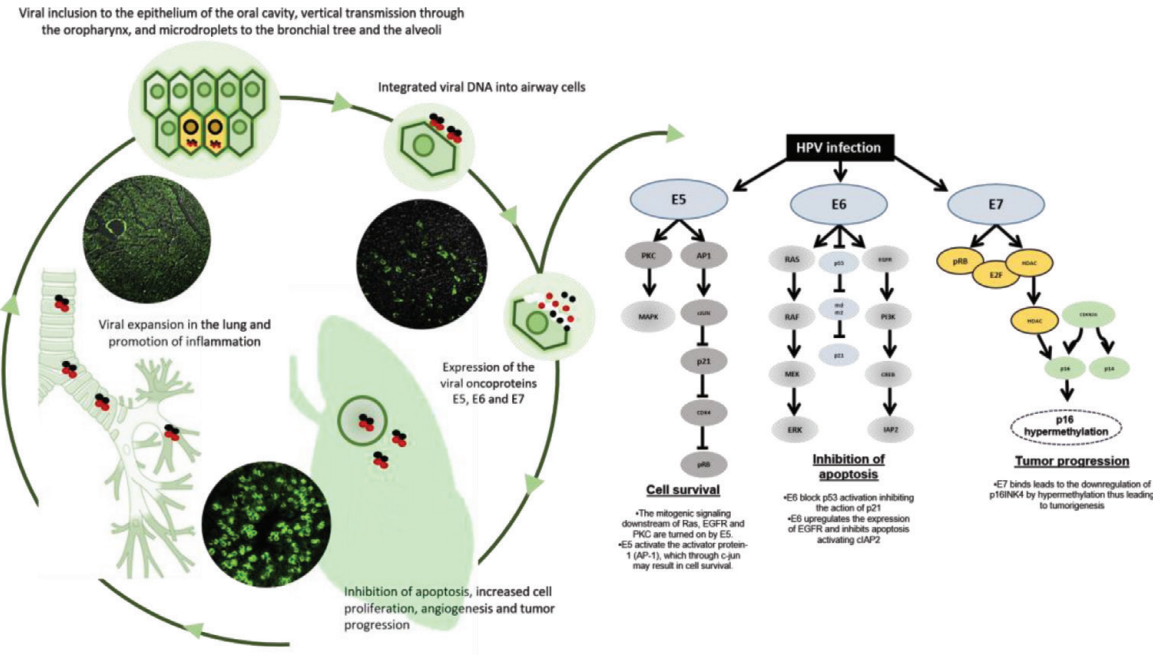
Figure 3.
Pathophysiology of HPV infection and development of lung cancer.

activated as a result of *KRAS* mutations in HPV, and some anti-MEK therapies have been tested in lung cancer [100]. Pathophysiology of infection and main molecular pathways compromised are presented in **Figure 3**.

If lung cancer patients with HPV infection need to de-escalate treatment, as in head and neck cancer patients, they requires further investigation. Some arguments are in favor of de-escalation considering, for example, the fact that lung cancer patients with HPV infection seem to have a better prognosis. Wang et al. described ADC with HPV 16/18 infections as having significantly higher survival rates compared to those that are HPV16/18 negative [101]. In a similar way, Hsu et al. reported survival benefits for stage I NSCLC patients who expressed the HPV16/18 E6 oncoprotein [102].

7. Conclusion

In conclusion, HPV infection constitutes a risk factor for lung cancer development, especially in patients infected with high-risk serotypes 16 and 18, non-smokers and females. HPV vaccination could have a potential role in the prevention of development of HPV-associated lung cancer. Furthermore, HPV status could modify some lung cancer treatment decisions; however, more information is needed to draw definitive conclusions.

8. Future perspectives

Future work in this field will likely include the validation of a screening test for HPV infection in lung cancer patients and also a strategy to follow HPV-infected individuals who might be at a higher risk of developing lung cancer. Additionally, the potential efficacy of anti-HPV vaccination for reducing the incidence of lung cancer must be adequately explored.

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