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REVIEW – CANCER RESEARCH

Human papillomavirus and lung cancer: an overview and a meta-analysis

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Abstract

Purpose This review is devoted to assessing the prevalence of human papillomavirus (HPV) in lung cancer (LC) in the world. HPV is recognized as the etiological factor of cervical cancer, however, there is widespread evidence that this virus is detected not only in gynecological carcinomas, but also in tumors of other organs, in particular the upper respiratory tract and digestive tract.

Materials and methods A search was conducted to a depth of 29 years in the PubMed, Web of Science, Scopus, databases. The review includes 95 articles.

Results Of all the analyzed studies (9195 patients), 12 works showed a complete absence of HPV in the biological material in patients with LC. The absence of a virus among lung cancer patients has been established for Canada, the Netherlands and Singapore. The highest average percent of occurrence of this virus is shown for such countries as: Brazil, Korea, Greece and Taiwan (more than 40%). But the highest percentage of HPV occurrence by region is observed in Latin America (33.5%), followed by the Asian countries (31%), in European countries the frequency is 18%. Interestingly, the highest occurrence of high oncogenic types (16 and 18) is observed in Asia (40.3%), then in Latin America (33.6%), Europe (25.6%) and North America (15.4%). Low-oncogenic types (6 and 11) are also predominantly observed in Asia (39.9%), while in Europe and North America 30% and 12.8%, respectively. A meta-analysis of the prevalence of HPV was conducted using Comprehensive Meta-Analysis 3.0. Program, which included 26 studies, the results of which revealed: the prevalence of HPV infection in tumor lung tissue was compared with normal lung tissue OR (95% CI) = 5.38 (3.21–9.00) $p < 0.0001$, significance was also found for Chinese studies OR = 6.3, 95% CI 3.42–11.53, $p < 0.0001$, I2 = 71.8% and for nine studies in Europe OR = 6.3, 95% CI 1.8–22.18, $p = 0.004$, I2 = 51.0%. However, given the fact that the frequency of occurrence of HPV in lung tumor tissue varies greatly, a question may arise about the real role of HPV in LC carcinogenesis, which makes further research relevant and promising.

Keywords Lung cancer · Human papillomavirus · HPV · Meta-analysis · Overview · Case–control study

Introduction

Lung cancer (LC) is the most common malignant neoplasm in the world population. It is the most frequent cancer and the leading cause of cancer death (Ferlay et al. 2015). It should be noted that LC has a strong relationship with various environmental factors (Pira et al. 2005). Chemical compounds associated with industrial processes and adverse environmental conditions play a main role in the etiology of lung cancer.

There is a large list of carcinogenic effects which affect on cells transformation from normal lung epithelium to malignant. However, their contribution to the development of lung cancer is no more than 10–20%. The vast majority of cases of lung cancer (80–90%), especially squamous type, are due to smoking. The risk of developing lung cancer largely depends on the age of the beginning of smoking, the duration of smoking and quantities of cigarettes smoked per day. The risk of lung cancer in smokers associated with exposure to these factors is higher than in non-smokers (Yang et al. 2013).

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Other risk factors include exposure to radon indoors, occupational factors, dietary patterns, carcinogens resulting from the burning of solid fuels. The results of molecular epidemiological studies show a possible causal relationship between the polymorphism of regulate the metabolism of carcinogenic substances genes, the cell cycle and other key processes of carcinogenesis, and the risk of lung cancer development (Mukeria and Zaridze 2010). The international multicenter study of LC has shown that the association with the risk of LC was most pronounced for the two SNPs (rs1051730, rs8034191). Furthermore, several genes (acetylcholine nicotine receptor genes—*CHRNA5, CHRNA3, CHRNB4*) that interact with nicotine can be activated and lead to the initiation of carcinogenesis (Hung et al. 2008). Also there is a hypermethylation of promoters of various genes responsible for cell cycle control, proliferation, apoptosis, cell adhesion, and DNA repair in lung cancer (Herceg and Vaissière 2011). These genes include: *p16INK4a, RASSF1A, APC, RARβ, CDH1, CDH13, DAPK, FHIT* and *MGMT* (Toyooka et al. 2011). Moreover, the frequency of methylation of the promoters of these genes in non-small cell lung cancer varies on average from 12 to 95% (Langevin et al. 2015). The two recent meta-analyses have shown that miRNAs, in particular, miR-196a and miR-200b, are strongly overexpressed in lung cancer (Guan et al. 2012; Vosa et al. 2013). HPV has been recognized as the etiological factor of cervical cancer. HPV-16 and HPV-18 are the types most commonly linked with cancer (zur Hausen 2008). However, the studies have shown that this virus is detected not only in gynecological carcinomas, but also in tumors of other organs, in particular, the upper respiratory tract and digestive tract (Klein et al. 2009).

Nowadays, it has been established that the frequency of occurrence of HPV in various pathologies of the cervix, including cervical cancer (CC), up to 90% (Johnson et al. 2012). Currently the question about effect of the HPV on the prognosis of cancer pathologies had studied. Integration of HPV into the cell genome in oropharynx cancer is recognized as one of the main factors of the development dysplasia and tumor epithelial transformation. Moreover, the integration of HPV into the cell genome is the main component of viral carcinogenesis (Fakhry et al. 2008). In addition, interesting cases of the presence of HPV were shown with such localization as breast cancer (Ibragimova et al. 2018c). It is important to note that the presence of a virus in a tumor with adverse prognostic factors in a patient with an HPV-positive tumor is associated with more than 8 years of relapse-free survival. Integration of HPV into the genome is one of the main factors for the development of severe dysplasia and tumor transformation of the cervical epithelium. The maximum frequency of the integrated forms of the virus is identified specifically for cervical cancer (Liu et al. 2016b; Ibragimova et al. 2016).

At the moment, the question of the mechanisms of carcinogenesis of lung cancer has not been studied enough. The question of the importance of HPV for the development of lung cancer remains open. Currently, only a few papers focus on the study of the impact of human papillomavirus (HPV) of high-risk on the development of lung cancer. This review presents many works on the infection of a lung tumor, analyzes the relationship between the frequency of infection and some indicators, such as histotype, geographical location, localization, etc. Ways of infection, possible molecular mechanisms of malignant transformation involving HPV and the significance of infection for the survival of patients with X-ray lung cancer are discussed.

HPV infection of tumor lung tissue

It was suggested by Syrjänen (1979) that HPV might be associated with the development of lung cancer (Syrjänen 1979). Virus DNA has been identified in serum, plasma and peripheral blood mononuclear cells in lung cancer, and also in healthy people (Chiou et al. 2003). It can be assumed that blood circulation plays an important role in the transmission of HPV inside the body. In addition HPV infects the cells of the basal layer of the skin or mucous membrane. When the proliferation of infected cells occurs, virus particles are released to the cell surface and infect surrounding tissues (Zur Hausen 2002). The process of basal cell hyperplasia is induced in the squamous epithelium of the lungs in these cells expressing the Ki67, p53 and bcl-2 genes, then metaplasias, which can transform into different subtypes of lung cancer. On the other hand, small cell lung cancer, originating from neuroendocrine cells that are targets of HPV, has very low HPV infection (Syrjänen et al. 2012).

Recent studies have shown that the presence of HPV associated with the risk of developing lung cancer. (Hasegawa et al. 2014; Zhai et al. 2015). Data for 2015 show that HPV infection in lung tissue is associated with the risk of developing lung cancer (odds ratio (OR) 5.67, 95% CI 3.09–10.40, $p < 0.001$). The prevalence of HPV type 16 was 19.8% and 3.37%, in tumor and normal tissue. A similar result is shown for HPV type 18: 18.59% in tumor tissue and 5.24% in normal. In addition, HPV 16 and 18 types were observed mainly in squamous LC compared to adenocarcinoma (HPV 16/18 types was 45.18% and 22.78% cases) (Zhai et al. 2015). Other authors noted that infection was more often found was found at adenocarcinoma (55.6%) than at squamous cell carcinoma (35.6%) (Chiou et al. 2003).

Different studies have shown a significant variation of the HPV infection of a lung tumor. Table 1 presents data on the frequency of virus occurrence, which depends on the number of patients examined. These vary widely: from the total absence of virus in the tissue to more than 75%. In the vast majority of cases the study of HPV in tissue (58 of 86

Table 1 The frequency of the presence of HPV high-risk in patients with a diagnosis of lung cancer

Author, year	Country	Sample type	Method	HPV type	HPV type positive	Cases (*n*/*N*), (*n* %)	Controls (*n*/N), (*n* %)	*p* level	Histologic type		
									Ad.	SCC	Other types
North America											
Yanagawa et al. (2013)	Canada	FFPE	PCR	16	–	0/331 (0)	–	–	0/204 (0)	0/127 (0)	–
Yousem et al. (1992)	USA	FFPE	IHC	6, 11, 16, 18, 31, 33, 35	6, 11, 16, 18, 31, 33, 35	7/79 (8.9)	–	–	0/12 (0)	6/20 (30)	1/47 (2.1)
Shimizu et al. (1994)	USA	Cell lines	PCR	–	–	0/166 (0)	–	–	–	–	–
Bohlmeyer et al. (1998)	USA	FFPE	PCR	6, 11, 16, 18, 31, 33	18	2/34 (5.9)	–	–	–	2/34 (5.9)	–
Wistuba et al. (1998)	USA	FFPE	PCR, Sequencing	16, 18, 31, 33	–	0/11 (0)	–	–	–	–	–
Joh et al. (2010)	USA	FF	PCR, Sequencing	11, 16	11, 16	5/30 (16.7)	5/22 (22.7)	0.725	5/18 (27.5)	0/7 (0)	0/5 (0)
Pillai et al. (2013)	USA	FFPE	PCR	6, 16, 18, 39, 53,	16, 18	32/208 (15.4)	–	–	–	–	–
Mehra et al. (2013)	USA	FFPE	PCR	6, 16, 18, 35, 52, 53, 44, 68, 39, 74, 82,	16, 18, 35, 52, 53	4/36 (11.1)	–	–	2/11 (18.2)	2/2 (100)	0/23 (0)
Colombara et al. (2015)	USA	Serum	LBMA	6, 11, 16, 18, 31, 33, 52, 58	16, 18	4/200 (2)	15/200 (7.5)	**0.016**	–	–	–
Robinson et al. (2016)	USA	FFPE	PCR, Microarray	6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 70, 73, 74	16, 18, 39, 44, 51, 52, 68	15/57 (26.3)	1/10 (10)	0.43	5/17 (29.4)	9/30 (30)	1/10 (10)
Europe											
Al-Ghamdi et al. (1995)	United Kingdom	FFPE	PCR, Sequencing	6, 7, 11, 16, 18	11	3/40 (7.5)	3/26 (11.5)	0.676	0/2 (0)	2/21 (9.5)	1/18 (5.6)
Stremlau et al. (1985)	Germany	FF	DNA hybridization	1, 2, 4, 8, 9, 10, 11, 13, 16, 18	16	1/24 (4.2)	–	–	–	0/9 (0)	1/15 (6.7)

Table 1 (continued)

Author, year	Country	Sample type	Method	HPV type	HPV type positive	Cases (*n*/*N*), (*n* %)	Controls (*n*/N), (*n* %)	*p* level	Histologic type		
									Ad.	SCC	Other types
Shamanin et al. (1994)	Germany	FF	PCR	1–4, 5b, 6–19, 25–27, 30–35, 35H, 39–42, 45, 47, 49, 51–53, 56–58, 63, 65	–	0/85 (0)	–	–	–	–	–
Welt et al. (1997)	Germany	FFPE	PCR, IHC	6, 11, 16, 18	–	0/38 (0)	–	–	0/6 (0)	0/32 (0)	–
Papadopoulou et al. (1998)	Greece	FFPE, FF	PCR	6, 11, 18	6, 11, 16, 18	32/52 (61.5)	0/26 (0)	**4.76e−8**	–	32/52 (61.5)	–
Gorgoulis et al. (1999)	Greece	FFPE, FF	PCR	6, 11, 16, 18, 31, 33, 35	6, 16, 18, 33	20/68 (29.4)	–	–	19/37 (51.4)	1/31 (3.2)	–
Krikelis et al. (2010)	Greece	FF	PCR	16	16	26/26 (100)	11/16 (68.8)	0.254	16/16 (100)	10/10 (100)	–
Sarchianaki et al. (2014)	Greece	FFPE	PCR	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82, 26, 53, 66, 6, 11, 40, 42, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 81, 83, 84, IS39, CP6108	6, 11, 16, 18, 31, 33, 59	19/100 (19)	0/16 (0)		12/50 (24)	4/39 (10.3)	3/11 (27.3)
Ciotti et al. (2006)	Italy	FF	PCR, Sequencing	16, 18, 31	16, 18, 31	8/38 (21.1)	0/38 (0)	0.07	5/15 (33.3)	3/16 (18.8)	0/7 (0)
Giuliani et al. (2007)	Italy	FFPE, FF	PCR, Sequencing	6, 16, 18, 31, 53,	6, 16, 18, 31, 53,	10/78 (15.4)	0/50 (0)	**0.013**	10/27 (37)	0/33 (0)	0/18 (0)
Carpagnano et al. (2011)	Italy	FFPE, FF	PCR, Sequencing	16, 18, 30, 31, 33, 45, 35/68, 39/56, 58/52, 59/51, 6/11	16, 30, 31, 39	12/89 (13.5)	0/68 (0)	**0.001**	8/37 (21.6)	4/36 (11.1)	0/16 (0)
Koshiol et al. (2011)	Italy	FFPE	PCR	16, 18	–	0/399 (0)	–	–	0/246 (0)	0/137 (0)	0/67 (0)
Gatta et al. (2012)	Italy	FFPE	PCR	16, 18, 33, 35, 52, 58	16	2/50 (4)	1/23 (4.3)	1.00	–	2/50 (4)	–

Table 1 (continued)

Author, year	Country	Sample type	Method	HPV type	HPV type positive	Cases (*n*/*N*), (*n* %)	Controls (*n*/N), (*n* %)	*p* level	Histologic type		
									Ad.	SCC	Other types
Galvan et al. (2012)	Italy, United Kingdom	FF	PCR	16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, 82, 85, 6, 11, 40, 42, 43, 44, 54, 61, 62, 71, 72, 81, 83, 84, 89	–	0/100 (0)	0/100 (0)	1.00	0/72 (0)	0/20 (0)	0/8 (0)
van Boerdonk et al. (2013)	Netherlands	FFPE	PCR	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 6, 11, 26, 34, 40, 42, 43, 44, 53, 54, 55, 57, 61, 70, 71, 72, 73, 81, 82, 82, 83, 84	–	0/223 (0)	–	–	0/101 (0)	0/93 (0)	0/122 (0)
Hennig et al. (1999b)	Norway	FFPE	PCR, IHC	6, 11,16, 18	6, 11,16, 18	37/75 (49.3)	–	–	13/26 (50)	11/23 (47.8)	13/26 (50)
Hennig et al. (1999a)	Norway	FFPE	PCR, IHC	11,16, 18	16	1/2 (50)	–	–	–	–	–
Sagerup et al. (2014)	Norway	FF	PCR	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 6, 11	16, 33, 66	13/334 (3.9)	0/13 (0)	1.00	11/198 (5.6)	1/84 (1.2)	1/52 (1.9)
Miasko et al. (2001)	Poland	FFPE, FF	PCR, Sequencing	6, 11, 16, 18, 31, 33	6, 11, 16, 18, 31, 33, 35	5/40 (12.5)	–	–	2/13 (15.4)	1/22 (4.5)	1/5 (20)
Kaya et al. (2001)	Turkey	FFPE	IHC	6, 11, 16, 18, 31, 33	6, 11, 16, 18	3/26 (11.5)	–	–	–	3/26 (11.5)	–
Zafer et al. (2004)	Turkey	FF	PCR	16, 18	18	2/40 (5)	–	–	0/13 (0)	2/25 (8)	0/2 (0)
Buyru et al. (2008)	Turkey	Blood	PCR	16, 18	16, 18	1/65 (1.5)	0/87 (0)	0.427	1/21 (4.8)	0/25 (0)	0/14 (0)
Syrjänen et al. (1989)	Finland	FFPE	IHC	6, 11, 16, 18, 30.	6, 16	12/131 (9.2)	–	–	–	12/131 (9.2)	–

Table 1 (continued)

Author, year	Country	Sample type	Method	HPV type	HPV type positive	Cases (*n*/*N*), (*n* %)	Controls (*n*/N), (*n* %)	*p* level	Histologic type		
									Ad.	SCC	Other types
Nuorva et al. (1995)	Finland	FFPE	PCR	6, 11, 16, 18, 31, 33	6, 11, 16, 31, 33	17/22 (77.3)	–	–	–	–	–
Soini et al. (1996)	Finland	FFPE	PCR, IHC	6, 11, 16, 18, 31, 33	6, 11, 16, 18, 31, 33	13/43 (30.2)	–	–	4/12 (33.3)	9/28 (32.1)	0/3 (0)
Simen–Kapeu et al. (2010)	Finland	Serum	ELISA	16, 18	16, 18	67/311 (21.5)	220/930 (23.7)	1.00	–	–	–
Syrjänen et al. (2012)	Finland	FFPE	PCR	6, 16	6, 16	4/77 (5.2)		–	1/42 (2.4)	3/31 (3.1)	0/11 (0)
Bejui–Thivolet et al. (1990)	France	FFPE	IHC	6, 11, 16, 18	11	6/33 (18.2)	0/10 (0)	0.308	–	6/33 (18.2)	–
Thomas et al. (1995)	France	FFPE	IHC	6, 11, 16, 18, 31, 33, 35	6, 11, 16, 18	5/31 (16.1)	–	–	1/4 (25)	2/18 (11.1)	2/9 (22.2)
Thomas et al. (1996)	France	FF	IHC	6, 11, 16, 18	6, 11, 16, 18	5/31 (16.1)	–	–	1/4 (25)	2/18 (11.1)	2/9 (22.2)
Clavel et al. (2000)	France	FF	PCR	6, 11, 42, 43, 44, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	16, 33, 31	5/185 (2.7)	–	–	2/60 (3.3)	2/101 (2)	1/24 (4.2)
Brouchet et al. (2005)	France	FFPE	IHC	16, 18, 31, 33, 51	–	0/122 (0)	–	–	0/31 (0)	0/40 (0)	0/51 (0)
Coissard et al. (2005)	France	FF	PCR	16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 7, 68, 70, 73, 82	16	3/218 (1.4)	–	–	0/80 (0)	1/126 (0.8)	2/12 (16.7)
Vrabec Branica et al. (2010)	Croatia	Bronchial aspirate	PCR	16, 18, 33	16, 18, 33	3/84 (3.6)	–	–	1/14 (7.1)	1/38 (2.6)	1/32 (3.1)
Ananthara-man et al. (2014)	Central Europe (Meta-analysis)	Blood	BMSM	6, 11, 16, 18, 31	11, 16, 51, 58	791/1634 (60.6)	991/2729 (36.3)	–	–/375	–/685	–/574
Australia											
Kulski et al. (1990)	Australia	FFPE	IHC	6, 11, 16, 18	6, 11, 16, 18	2/5 (40)	–	–	–	–	–

Table 1 (continued)

Author, year	Country	Sample type	Method	HPV type	HPV type positive	Cases (*n*/*N*), (*n* %)	Controls (*n*/N), (*n* %)	*p* level	Histologic type		
									Ad.	SCC	Other types
Fong et al. (1995)	Australia	FFPE	PCR	6, 11, 16, 18, 31, 33, 52b, 58	16	2/104 (1.9)	0/104 (0)	0.497	0/46 (0)	2/43 (4.7)	0/19 (0)
Asia											
Jain et al. (2005)	India	FF	PCR	16, 18	18	2/40 (5)	0/40 (0)	0.493	0/9 (0)	2/21 (9.5)	0/10 (0)
Gupta et al. (2016)	India	FF	PCR	16, 18, 31, 33, 45,	16, 18, 45,	5/73 (6.8)	0/75 (0)	**0.027**	0/22 (0)	4/36 (11.1)	1/15 (6.7)
Nadji et al. (2007)	Iran	FFPE	Sequencing	6, 11, 26, 31, 16, 18	16, 18	33/141 (23.4)	8/90 (8.9)	**0.007**	3/16 (18.8)	24/104 (23.1)	6/21 (28.6)
Xing et al. (1993)	China	FFPE	PCR	6, 11, 16	6, 11, 16	7/49 (14.3)	–	–	–	7/49 (14.3)	–
Liu et al. (1994)	China	FFPE	PCR, IHC	11, 16	11, 16	7/49 (14.3)	–	–	–	7/49 (14.3)	–
Xing et al. (1994)	China	FF	PCR	6, 11, 16	6, 11, 16	7/49 (14.3)	–	–	–	7/49 (14.3)	–
Li et al.(1995)	China	FFPE, FF	PCR	16, 18	16, 18	16/50 (32)	–	–	2/22 (9.1)	13/27 (48.1)	1/1 (100)
Zhang et al. (1995)	China	FF	PCR	–	–	4/34 (11.8)	–	–	0/10 (0)	4/12 (33.3)	0/12 (0)
Da et al. (1996)	China	FF	PCR, IHC	–	–	22/40 (55)	–	–	5/12 (41.7)	8/16 (50)	9/12 (75)
Yang et al. (1998)	China	FFPE	PCR	6, 11,16, 31, 33	6, 11,16	13/50 (26)	3/30 (10)	0.094	–	13/50 (26)	–
Niyaz et al. (2000)	China	FF	PCR, IHC	16, 18	16, 18	44/110 (40)	1/40 (2.5)	**2.52e−5**	–	–	–
Fei et al. (2006)	China	FFPE	IHC	16, 18	16, 18	23/73 (31.5)	2/34 (5.9)	**0.005**	10/33 (30.3)	13/40 (32.5)	–
Wang et al. (2008)	China	FF	PCR	16, 18	16, 18	138/313 (44.1)	4/96 (4.2)	**1.10e−12**	112/215 (5.1)	26/98 (26.5)	–
Yu et al. (2009)	China	FFPE	PCR	6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 70, 73, 74	6, 16, 18	43/109 (39.4)	16/71 (22.5)	**0.022**	6/37 (16.2)	37/72 (51.4)	–
Xu et al. (2009)	China	FFPE	IHC	16, 18	16, 18	32/44 (72.7)	0/15 (0)	**4.35e–7**	–	32/44 (72.7)	–

Table 1 (continued)

Author, year	Country	Sample type	Method	HPV type	HPV type positive	Cases (*n*/*N*), (*n* %)	Controls (*n*/N), (*n* %)	*p* level	Histologic type		
									Ad.	SCC	Other types
Wang et al. (2010)	China	FF	PCR	16, 18	16, 18	18/45 (40)	0/16 (0)	**0.002**	–	18/45 (40)	–
Yu et al. (2013)	China	FFPE	PCR	16, 18	16, 18	75/170 (44.1)	21/91 (23.1)	**0.027**	11/63 (17.5)	64/107 (59.8)	–
Yu et al. (2015)	China	FF	PCR	16, 18	16, 18	100/180 (55.6)	8/110 (7.3)	**1.23e−16**	15/56 (26.8)	45/88 (51.1)	7/36 (19.4)
Colombara et al. (2016)	China	Serum	LBMA	6, 11, 16, 18, 31, 33, 52, 58	6, 11, 16, 18, 31, 33, 52, 58	8/183 (4.4)	2/217 (0.9)	**0.048**	3/31 (9.7)	5/72 (6.9)	0/80 (0)
Xiong et al. (2016)	China	FF	PCR	16, 18	16, 18	7/83 (8.4)	6/83 (7.2)	1.00	–	–	–
Fan et al. (2016)	China	Pleural effusion	IHC	16	16	42/95 (44.2)	1/55 (1.8)	**2.09e−8**	41/92 (44.6)	1/3 (33.3)	–
Lu et al. (2016)	China	FF	PCR	16, 18	16, 18	33/72 (45.8)	2/54 (3.7)	**2.10e−7**	10/24 (41.7)	23/48 (47.9)	–
Park et al. (2007)	Korea	FF	PCR	16, 18, 33	16, 18	51/112 (45.5)	–	–	29/53 (54.7)	31/53 (58.5)	1/6 (16.7)
Lim et al. (2009)	Singapore	FFPE	IHC	16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 66	–	0/110 (0)	–	–	0/110 (0)	–	–
Cheng et al. (2001)	Taiwan	FFPE	PCR, IHC	16, 18	16, 18	77/141 (54.6)	16/60 (26.1)	**3.41e−4**	46/83 (55.4)	31/58 (53.4)	–
Chiou et al. (2003)	Taiwan	Blood	PCR	16, 18	16, 18	71/149 (47.7)	22/174 (12.6)	**2.75e−12**	50/90 (55.6)	21/59 (35.6)	–
Cheng et al. (2004)	Taiwan	FF	PCR, IHC	6, 11	6, 11	40/141 (28.4)	1/60 (1.7)	**1.72e−5**	23/83 (27.7)	17/58 (29.3)	–
Lin et al. (2005)	Taiwan	FF	PCR, IHC	16, 18	16, 18	29/57 (50.9)	–	–	–/29	–/28	–
Wu et al. (2005)	Taiwan	FF	PCR, IHC	16, 18	16, 18	91/166 (54.8)	–	–	–/95	–/71	–
Wang et al. (2006)	Taiwan	FFPE	PCR, IHC	16, 18	16, 18	85/153 (55.5)	–	–	–/89	–/64	–
Wang et al. (2014)	Taiwan	FFPE	PCR	16, 18	16, 18	74/210 (35.2)	–	–	74/210 (35.2)	–	–
Ogura et al. (1993)	Japan	FF	PCR, Sequencing	16, 18	16, 18	16/121 (13.2)	–	–	–	16/121 (13.2)	–
Szabó et al. (1994)	Japan	FFPE	PCR, IHC	6, 11, 18, 31, 33, 52b, 58	–	0/47 (0)	–	–	–	0/40 (0)	0/7 (0)

Table 1 (continued)

Author, year	Country	Sample type	Method	HPV type	HPV type positive	Cases (*n*/*N*), (*n* %)	Controls (*n*/N), (*n* %)	*p* level	Histologic type		
									Ad.	SCC	Other types
Kinoshita et al. (1995)	Japan	FF	PCR	16, 18, 33	18	3/36 (8.3)	–	–	2/26 (7.7)	1/10 (10.0)	–
Sagawa et al. (1995)	Japan	FFPE	PCR, Sequencing	16, 18, 33	16, 18, 33	1/8 (12.5)	–	–	–	1/8 (12.5)	–
Hirayasu et al. (1996)	Japan	FFPE	PCR	6, 16, 18	6, 16, 18	43/94 (45.7)	–	–	–	–	–
Tsuhako et al. (1998)	Japan	FFPE	PCR	6, 11, 16, 18	6, 11, 16, 18	18/23 (78.3)	–	–	13/16 (81.3)	2/2 (100)	3/5 (60)
Hiroshima et al. (1999)	Japan	FFPE	PCR	16, 18, 33	16	1/22 (4.5)	–	–	1/22 (4.5)	–	–
Miyagi et al. (2000)	Japan	FF	PCR	6, 11,16, 18	6, 11,16, 18	876/1109 (79)	–	–	–	876/1109 (79)	–
Miyagi et al. (2001)	Japan	FFPE	PCR, IHC	6, 11, 16, 18	6, 16, 18	41/121 (33.9)	–	–	12/62 (19.4)	29/59 (49.2)	–
Baba et al. (2010)	Japan	FFPE	PCR	6, 16, 18, 33	16	11/57 (19.3)	–	–	9/30 (30)	2/27 (7.4)	–
Iwakawa et al. (2010)	Japan	FF	PCR	16, 18, 33	–	0/275 (0)	–	–	0/275 (0)	–	–
Kato et al. (2012)	Japan	FFPE	Microarray	16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, 82, 85, 6, 11, 40, 42, 43, 44, 54, 61, 62, 71, 72, 81, 83, 84, 89	16, 58	7/42 (16.7)	–	–	4/26 (15.4)	2/12 (16.7)	1/4 (25)
Goto et al. (2011)	Japan, Korea, Singapore	FFPE	PCR	6, 11, 16, 18	16, 18	16/304 (5.3)	–	–	8/128 (6.3)	8/176 (4.5)	–
Latin America											
Falcone et al. (2017)	Argentina	FFPE, FF	PCR, IHC	16, 18	16, 18	10/40 (25)	–	–	–	10/40 (25)	–
de Oliveira et al. (2018)	Brazil	FF	PCR, IHC	16, 18	16, 18	33/63 (52.4)	–	–	11/20 (55)	13/25 (52)	9/18 (50)
Castillo et al. (2006)	Mexico, Colombia, Peru	FFPE	PCR	16, 18, 33	16, 18	10/36 (27.8)	–	–	3/13 (23.1)	4/14 (28.6)	3/9 (33.3)

Table 1 (continued)

Author, year	Country	Sample type	Method	HPV type	HPV type positive	Cases (*n*/*N*), (*n* %)	Controls (*n*/N), (*n* %)	*p* level	Histologic type		
									Ad.	SCC	Other types
Aguayo et al. (2007)	Chile	FFPE	PCR	6, 16, 18, 31, 45	6, 16, 18, 31	20/69 (29)	–	–	3/32 (9.4)	17/37 (45.9)	–

Statistically significant differences between the frequency of occurrence of HPV in tumor and normal tissue are given in bold (p-value - Fisher's exact test)

FFPE formalin-fixed paraffin-embedded, *FF* fresh-frozen, *PCR* polymerase chain reaction, *IHC* immunohistochemistry, *LBMA* multiplex hybridization to liquid bead microarray, *BMSM* bead-based multiplex serology method, *ELISA* enzyme-linked immunosorbent assay, *Ad* adenocarcinoma, *SCC* squamous cell carcinoma

studies) indicated 16 and 18 types of HPV (Table 1), which today are recognized as the leaders in the incidence of cervical cancer (Ibragimova et al. 2018a). Of the 95 studies in 12 studies (13%), the absence of HPV in lung tumor tissue was shown of HPV in lung tumor tissue.

Except high-risk HPV were considered 6 and 11 types of HPV in some cases which are currently recognized as low risk and the often found at papillomatosis of various localization (Ibragimova et al. 2018b), and of the head and neck cancer regions (Bychkov et al. 2016). Infection with HPV type 6 was detected in tumors in 66 of 89 studies (74%). For 11 types of 43 studies in the lungs, it was found in 21 studies (Table 1). Thus, studies have already been conducted to study the infection of HPV in a lung tumor with a high and low oncogenic profile.

In many studies, HPV DNA has been found in lung tumor tissue, but also some authors indicate the presence of various types of virus in peripheral blood and bronchial aspirates (Carpagnano et al. 2011; Chiou et al. 2003; Vrabec Branica et al. 2010).

Taking stock of the results (Table 1), which had different histological types of LC, the highest percentage of HPV detection in lung tumor tissue is observed in squamous cell carcinoma than in adenocarcinoma (25.8% and 21.1% cases). In the study of other biopsy specimens (blood, serum, and others; 9 works, Table 1) the frequency of occurrence of HPV at adenocarcinoma is higher (24.4%) than at squamous cell carcinoma (15.7%).

In all studies examined (Table 1), 12 works have shown a complete absence of HPV in the biological material in patients with LC.

The prevalence of HPV by country is shown in Fig. 1. The absence of a virus among lung cancer patients has been established for Canada, the Netherlands and Singapore. The highest average percent of occurrence of this virus is shown for such countries as: Brazil, Korea, Greece and Taiwan (more than 40%). It should be noted that the highest percentage of occurrence of HPV is observed in Latin America (33.5%), followed by the Asian region (31%), in European countries the frequency is 18% (Fig. 2). The highest incidence of high oncogenic types (16 and 18) is observed in Asia (40.3%), then in Latin America (33.6%), Europe (25.6%) and North America (15.4%). Low-oncogenic types (6 and 11) are also mainly observed in Asia (39.9%), while in Europe and North America 30% and 12.8% cases.

The prevalence of HPV infection in lung tumor tissue: a meta-analysis

A systematic search was conducted using search terms to identify all relevant and acceptable research. 30 studies were included in the meta-analysis, for which paraffin blocks and frozen tissue (FFPE, FF) were used as the test samples.

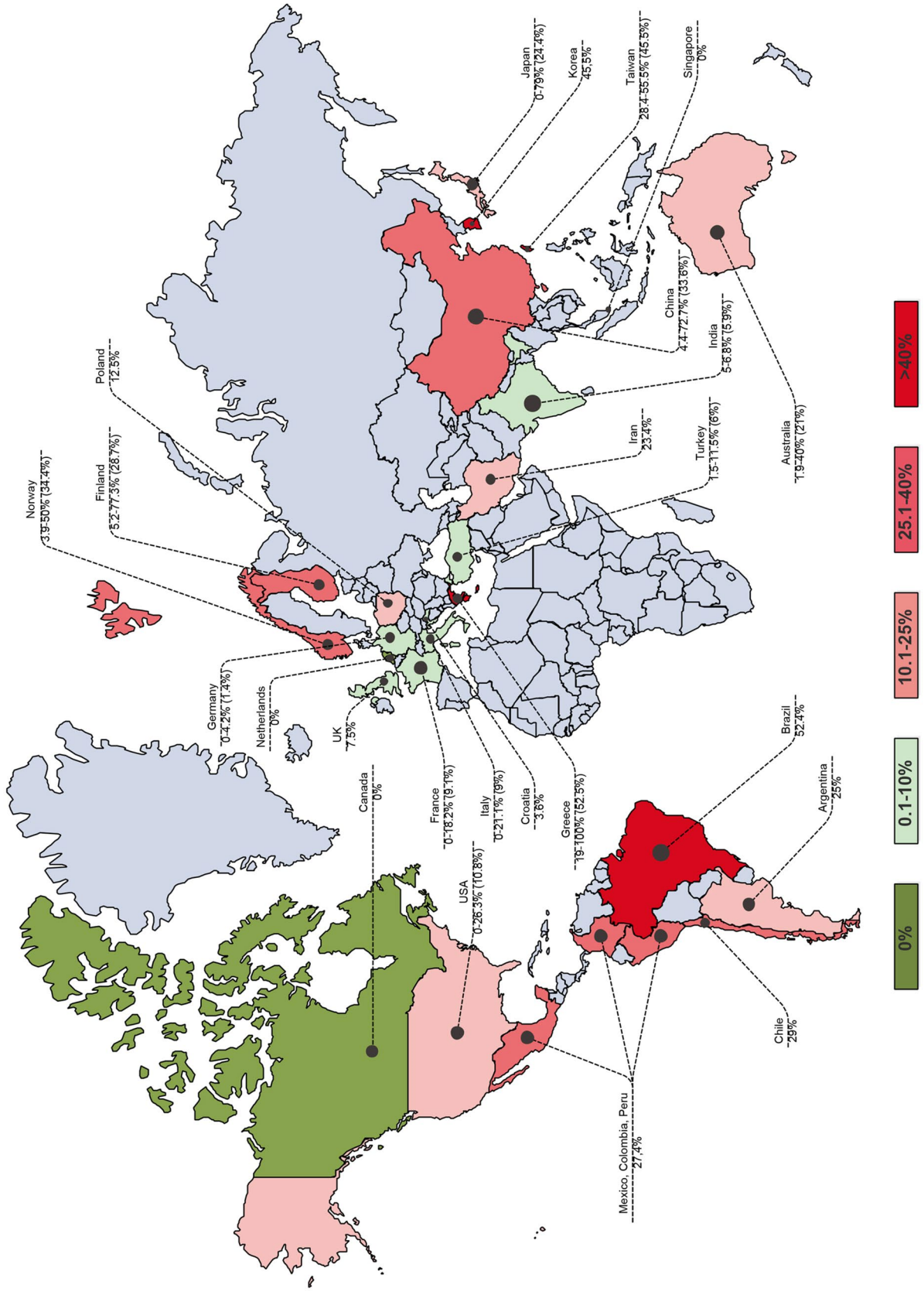

Fig. 1 The frequency of HPV detection in patients diagnosed with LC in the world (by country). Note: country color is an indicator of HPV availability (%). For each country the limit (in %) of HPV detection is prescribed, depending on the work of various authors and the average value of the frequency of occurrence of HPV (different types)

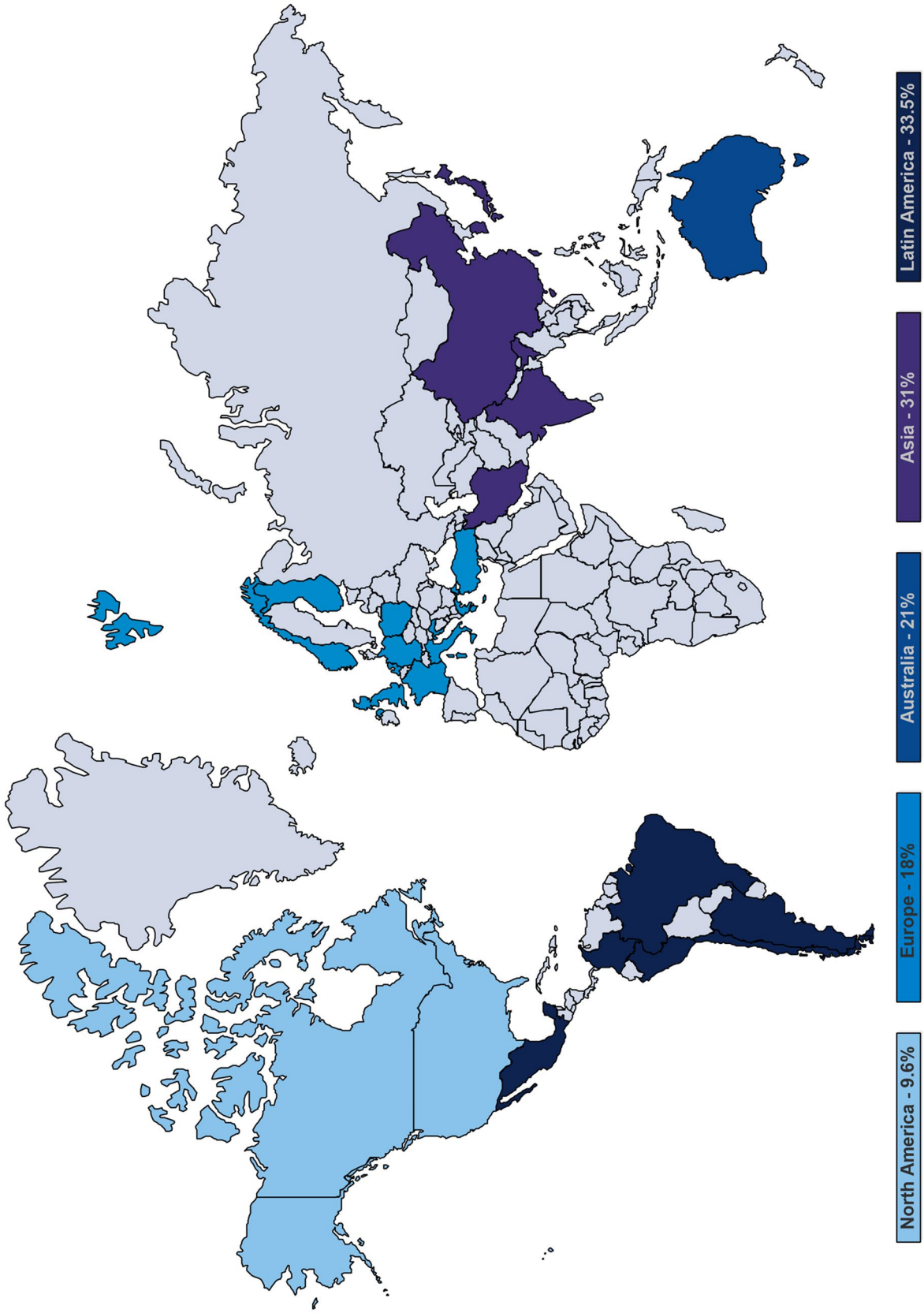

Fig. 2 The frequency of HPV detection in patients diagnosed with LC in the world (by region). Note: Country color is an indicator of HPV availability (%).The average frequency of HPV occurrence (different types) was determined for each region

Each study contained a control group (Table 1). Among these studies, 16 were conducted in Asia (Cheng et al. 2001, 2004; Fei et al. 2006; Gupta et al. 2016; Jain et al. 2005; Lu et al. 2016; Nadji et al. 2007; Niyaz et al. 2000; Wang et al. 2008, 2010; Xiong et al. 2016; Xu et al. 2009; Yang et al. 1998; Yu et al. 2009, 2013, 2015); two in the USA (Joh et al. 2010; Robinson et al. 2016), одна в Австралии (Fong et al. 1995), the other were held in Europe (Al-Ghamdi et al. 1995; Bejui-Thivolet et al. 1990; Carpagnano et al. 2011; Ciotti et al. 2006; Galvan et al. 2012; Gatta et al. 2012; Giuliani et al. 2007; Krikelis et al. 2010; Papadopoulou et al. 1998; Sagerup et al. 2014; Sarchianaki et al. 2014). In addition, 26 studies used PCR, while three used in situ hybridization (ISH) (Bejui-Thivolet et al. 1990; Fei et al. 2006; Xu et al. 2009) and one used sequencing (Nadji et al. 2007). For homogeneity of the sample, the analysis included studies that used the polymerase chain reaction as a method for assessing the infection of HPV. Histological subtypes of lung cancer include squamous cell carcinoma, adenocarcinoma, small cell lung cancer, undifferentiated carcinoma, and bronchoalveolar carcinoma. Sample sizes from 26 suitable studies ranged from 42 (cases/controls: 26/16) (Joh et al. 2010) to 409 subjects (cases/controls: 313/96) (Wang et al. 2008). Thus, 3963 subjects (cases/controls: 2625/1338) were registered to study the relationship between HPV and the risk of developing lung cancer.

According to the results of the meta-analysis, a low but statistically significant level of prevalence of HPV infection in tumor lung tissue was established compared with normal lung tissue (Fig. 3a) (OR (95% CI) = 5.38 (3.21–9.00) $p < 0.0001$). The heterogeneity index of the I2 sample was 63% and the Cochrane Q test (p value < 0.0001, with the required level $p > 0.1$), therefore a random model was used. In addition, significance was also found individually for Chinese studies (OR 6.3, 95% CI 3.42–11.53, $p < 0.0001$, I2 = 71.8%) (Fig. 3b) and nine studies in Europe (OR = 6.3, 95% CI 1.8–22.18, $p = 0.004$, I2 = 51.0%) (Fig. 3c).

We also assessed the risk of developing LC with HPV in various histological types. HPV was significantly associated with cancer risk in adenocarcinoma (OR 5.37, 95% CI 2.46–11.73, $p < 0.0001$, I2 = 74.6%); as with SCC (OR 5.84, 95% CI 3.71–9.19, $p < 0.0001$, I2 = 39.02%).

To evaluate the effect of one single study on the overall risk of LC, sensitivity analyses were performed by sequential omission of individual studies and the recalculating of pooled ORs and 95% CIs were performed. The potential influence of publication bias was assessed by visual inspection using Begg's funnel plot and assessed statistically using Egger's linear regression test.

Although the funnel plot shows some asymmetry (Fig. 4), Begg's test suggested no significant publication bias existed in this meta-analysis ($p = 0.279$). However, the result of Egger's test was not significant ($p = 0.08$). Furthermore, the limited number of studies ($n = 7$) indicated a potential publication bias.

Molecular mechanism of HPV infection leading to lung cancer

HPV is a double-stranded epitheliotropic DNA virus (Psyrri et al. 2011). There are more than 150 types of this virus transmitted through the skin and/or with sexual contact (Bernard et al. 2010). Currently, there are three main hypotheses of the pathogenesis of HPV in the lungs: 1—transmission through the bloodstream from cervical lesions to the lungs, microcracks; 2—unprotected oral sex; 3—infection through inhaled air. Iwamasa et al. (2000) showed that 80% of women with lung cancer have cervical interepithelial neoplasia. Another study showed that the incidence of HPV infection in men is 7.2%, the majority of infected men had female partners who had either oral or genital HPV infection (Dahlstrom et al. 2014). The third hypothesis was confirmed by a study conducted by Carpagnano et al. (2011). He reported about the attendance of human papillomavirus DNA in exhaled breath condensate samples from patients with lung cancer.

Molecular mechanisms of infection and pathogenesis of lung cancer have been described in many studies. They all indicate the activation of HPV proteins E6 and E7, which are involved in regulating the expression of such target genes and their proteins as p53, pRb, HIF-1α, EGFR, VEGF, IL-6, IL-10, Bcl-2, Mcl-1, cIAP-2, FHIT, hTERT, HER-2, ALK, ROS1, AhR, etc. These target genes are involved in the proliferation of lung cells, the development of blood vessels, and the immortalization of cells through various signaling pathways (de Freitas et al. 2016; Liu et al. 2016a).

After the viral DNA integration into the cell, E6 and E7 proteins are expressed, which play a fundamental role in carcinogenesis. E6 inhibits the process of interaction between the p53 complex (tumor protein p53) and DDX3 (dead-box helicase 3), which leads to subsequent inactivation of p21 (Wu et al. 2014). Thus, the release of the cyclin A/CDK2 complex (cyclin A/cyclin-dependent kinase 2), which participates in the phosphorylation of pRb (RB transcriptional corepressor 1) destroys its active form. The protein encoded by this gene is a negative regulator of the cell cycle during cell proliferation and differentiation. Also, this gene stabilizes constitutive heterochromatin to maintain the overall structure of chromatin. The active hypophosphorylated form of the protein associates to the transcription factor E2F1. As a result of the phosphorylation this gene, the release of E2F factor occurs, dysregulation of the cell cycle, transition from G1 to S-phase, and subsequent uncontrolled cell proliferation (Fig. 5).

Protein E7 of human papillomavirus interacting with pRb causes dissociation of the complex HDAC/pRb/E2F

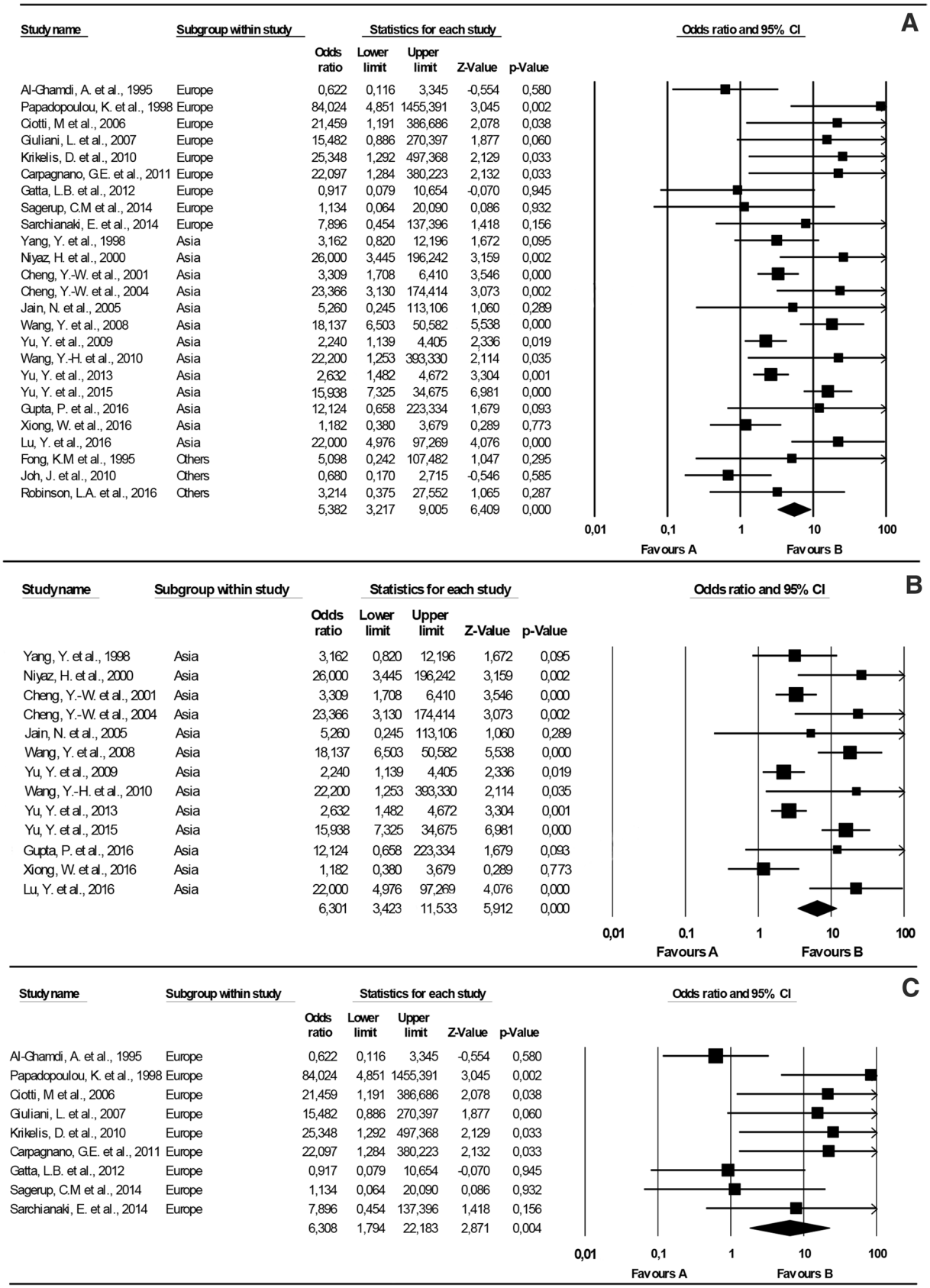

Fig. 3 Results of a meta-analysis of the infection rate of HPV lung tumor

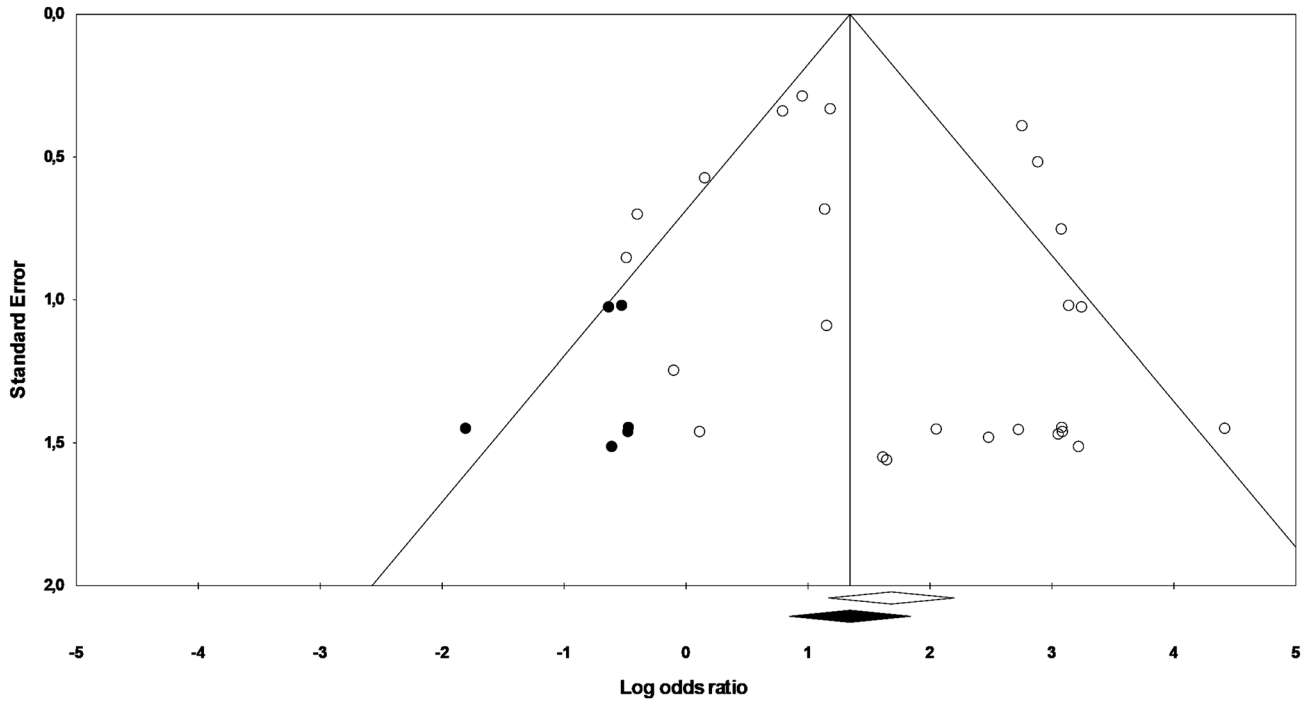

Fig. 4 Funnel plot with pseudo 95% CI of publication bias on the association between HPV infection and LC risk

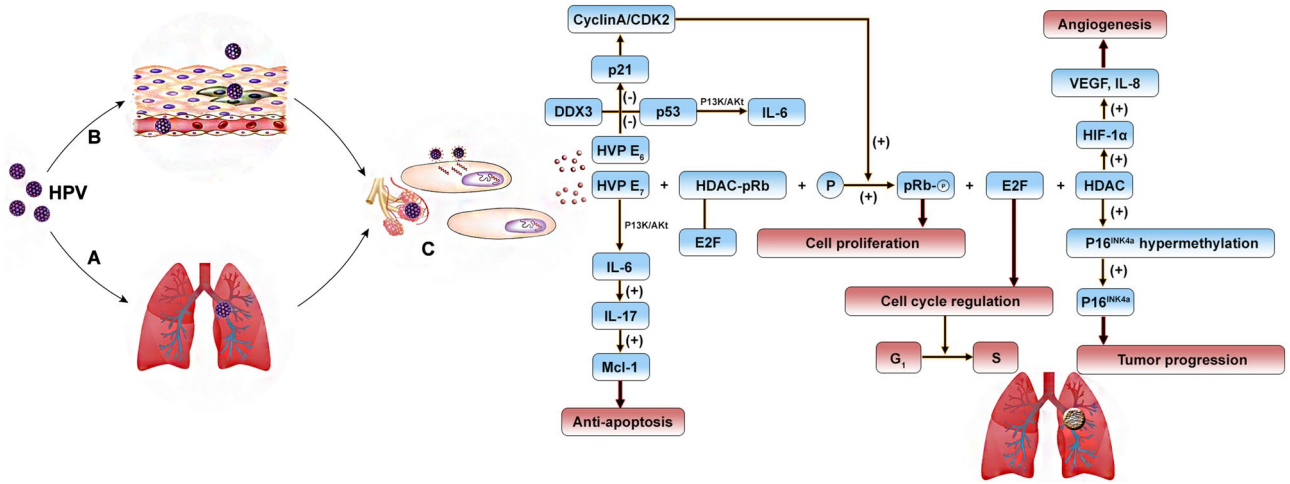

Fig. 5 Molecular mechanisms of infection and pathogenesis of lung cancer. **a**, **b** Ways of penetration of HPV DNA into the lung tissue, through inhaled air (**a**) and/or through damage to the epithelium and the bloodstream (**b**); B - HPV DNA recognition by membrane receptors and DNA integration into the host cell

(histone deacetylase/RB transcriptional corepressor 1/E2F transcription factor). As a result, HDAC participates in p16INK4 hypermethylation (cyclin-dependent kinase inhibitor 2A) and together with E2F factor inactivates tumor suppressor genes and accordingly activates cell proliferation genes, which leads to tumor progression (de Freitas et al. 2016). Also, HDAC can trigger the process of angiogenesis, by inducing VEGF and IL-8 through the HIF-1α factor. E7 expression and inhibition of p53, through the expression of E6, is involved in the regulation of the anti-apoptotic protein Mcl-1 (MCL1, BCL2 family apoptosis regulator, which increases cell survival by inhibiting apoptosis (Kozopas et al. 1993)), through PI3K/Akt- (IL-6) - (IL-17) pathway.

Physical status and viral load in lung cancer: association with survival

Our previous studies of cervical cancer have shown that both viral load and the physical status of HPV play an important role in the prognosis of the disease and the risk of malignancy. A decrease in total ($p = 0.0009$) and disease-free survival ($p = 0.02$) was shown in HPV-negative and HPV-positive cervical cancer patients. The median of relapse-free survival for HPV-negative was 20 months, the median of overall survival was 37 months. The median of relapse-free and overall survival was not achieved with 68 and 123 months of follow-up at the HPV + patients group (Ibragimova et al. 2018a).

The relationship between HPV infection and lung cancer still remains uncertain and controversial. First of all, it is connected with a small amount of research on this topic. Wang et al. (2014) showed that patients with HPV 16 and 18 types at adenocarcinoma of the lungs have higher rates of survival compared with patients without the presence of virus in the tumor (Wang et al. 2014). Ragin et al. (2014) also showed that presence of a virus in lung tumor tissue is associated with a good prognosis of the disease (Ragin et al. 2014).

One of the first studies of the value of viral load as a predictor of LC development is the work of Coissard et al. (2005). There authors showed a very low viral load: less than one copy of the virus per cell (Coissard et al. 2005; Koshiol et al. 2011). Other authors also found a very low viral load in the lung tumor tissue: 0.02 (Baba et al. 2010) and 0.003 (Kato et al. 2012) copies per cell, while in case of cervical cancer 333 copies per cell were noted. This phenomenon may be due to the "Hit-and-run" mechanism, when the virus is integrated into the cell and the viral genome is subsequently eliminated. Some authors believe that even a low viral load (1–2 copies per cell) is sufficient to trigger a carcinogenic process in the lung tissue (Aguayo et al. 2011), also that it may be caused by infection of the tumor stem cells as well as genome instability (Kato et al. 2012).

Nowadays, it is known for cervical cancer that in 90% of cases of HPV infection during a few months can be spontaneously eliminated from the body (Stanley 2010). At the same time, the possibility of the virus elimination from the host cell is determined by a combination of many factors: the physical status of the HPV DNA (episomal, integrated or mixed forms). For cervical cancer, we found that disease-free and overall survival depending on the physical status of the virus (HPV type 16). 100% relapse-free and overall survival is observed at patients with episomal HPV16 type. The median relapse-free survival of patients with mixed HPV16 was 52 months. The median overall survival was not achieved. This is higher than in HPV patients, whom the median disease-free and overall survival is 20 and 37 months. The most adverse outcome is observed in patients with an integrated form of HPV16 type. The median of relapse-free survival was 7 months and the median overall survival was 25 months (Ibragimova et al. 2018a).

In fact, large-scale studies of the physical status of HPV in lung tumor tissue have not yet been conducted.

Conclusion

Thus, the published data do not provide evidence of the involvement of human papillomavirus in the pathogenesis of lung cancer. The incidence of HPV in lung tumor tissue varies greatly, so there is an important question about the role HPV plays in LC carcinogenesis. This makes further research in this area relevant and promising.

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Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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