Review

Detection of Human Papillomavirus in Lung Cancer: Systematic Review and Meta-analysis

KARI SYRJÄNEN[1,2]

[1]*Department of Oncology and Radiotherapy, Turku University Hospital, Turku, Finland;*
[2]*Barretos Cancer Hospital, Teaching and Research Institute, Barretos, SP, Brazil*

Abstract. *Background: Since the first reports (in 1979) suggesting an etiological role for human papillomavirus (HPV) in bronchial squamous cell carcinoma, literature reporting HPV detection in lung cancer has expanded rapidly, but a comprehensive meta-analysis has yet to be published. We performed a systematic review and formal meta-analysis of the literature reporting on HPV detection in lung cancer. Materials and Methods: MEDLINE and Current Contents were searched through April 2012. The effect size was calculated as event rates and their 95% Confidence intervals (CI), with homogeneity testing using Cochran's Q and I^2 statistics. Meta-regression was used to test the impact of study-level co-variates (HPV detection method, geographical origin of study, cancer histology) on effect size, and potential publication bias was estimated using funnel plot symmetry (Begg and Mazumdar rank correlation, Egger's regression, and Duval and Tweedie's trim and fill method). Results: One hundred studies were eligible, covering 7,381 lung cancer cases from different geographical regions. Altogether, 1,653 (22.4%) samples tested HPV-positive; effect size was 0.348 (95% CI=0.333-0.363; fixed-effects model), and 0.220 (95% CI=0.18-0.259; random effects model). There was significant heterogeneity between the studies stratified by HPV detection technique, but the random effects in between-strata comparison was not significant (p=0.193). When stratified by i) different geographical regions, and ii) different histological types, the between-strata comparison was significant (p=0.0001). However, in meta-regression, HPV detection method (p=0.473), geographical origin (p=0.298) and histological type (p=0.589) were not significant study-level co-variates. No evidence for significant publication bias was found in funnel plot symmetry testing. In sensitivity analysis, all meta-analytic results seemed robust to all one-by-one study removals. Conclusion: These meta-analytic results imply that the reported variability in HPV detection rates in lung cancer is better explained by geographical study origin and histological types of cancer than by the HPV detection method itself. In formal meta-regression, however, none of these three factors were significant study-level co-variates accounting for the heterogeneity of the summary effect size estimates, i.e. HPV prevalence in lung cancer.*

Correspondence to: Professor Kari Syrjänen, MD, Ph.D, FIAC, Department of Oncology and Radiotherapy, Turku University Hospital, Savitehtaankatu 1, FIN-20521 Turku, Finland. Tel: +358 23131834, Fax: +358 23132809, e-mail: kari.syrjanen@tyks.fi

Key Words: Bronchus, lung, HPV, squamous cell carcinoma, adenocarcinoma, meta-analysis, meta-regression, study heterogeneity, publication bias, detection method, geographic region, review.

Lung cancer remains by far the leading cause of global cancer morbidity and mortality, with over 1.6 million new cases annually and almost 1.4 million deaths worldwide (both genders included) (1). Epidemiological and experimental data suggest that cigarette smoke, as well as occupational or environmental exposure to radon and asbestos, are the prime etiological agents of this malignancy. Other causal factors implicated include certain metals (chromium, arsenic, cadmium, silica and nickel), air pollution, coal smoke, hormones, previous lung disease, dietary factors, and genetic susceptibility (2, 3). It is well known, however, that i) fewer than 20% of smokers ever develop lung cancer, ii) a sizeable subset (25%) of lung carcinomas develop among never-smokers, and iii) lung cancer is a major course of death (300,000 cases) among never-smokers (2, 3). This indicates that factors other than cigarette smoking must exist among the causative agents of this disease (2, 4-7).

It was suggested over 30 years ago that human papillomavirus (HPV) could be one of these unknown causal agents of lung cancer among non-smokers and even in smokers, acting synergistically with cigarette smoke (8-10). This ground-breaking hypothesis was based on original observations of morphological similarities between a subset

of bronchial squamous cell carcinomas (SCCs) and the clinical manifestations of HPV in the female genital tract, characterized a few years earlier (11-14).

Following these primary reports, an interest in HPV and lung cancer increased steadily until the early 2000s when the published literature was subjected to the first systematic reviews (15, 16). By that time, 2,468 lung cancer samples had been analyzed in 44 separate studies, of which 536 (21.7%) were shown to test positively for HPV. Since then, the speed of appearance of new studies has substantially increased, but for some obscure reason, the first two meta-analyses (17, 18) published in 2009 only identified a few additional studies that were not included in the author's review of 2002 (16). HPV prevalence in the included studies had increased to 24.5%, and both reviews emphasized a major heterogeneity between the published studies. Importantly, not only HPV DNA but also active transcription of the virus has been convincingly demonstrated in lung cancer by detecting the expression of HPV oncogens E6 and E7 by reverse transcriptase PCR (RT-PCR) (19-24).

Although the role of HPV in lung carcinogenesis has been repeatedly reviewed in book chapters (15, 25) and other monographs (16), the first meta-analyses for this rapidly expanding literature were published only in 2009 (17, 18). This co-incides with the fact that since the licensing of the first prophylactic HPV vaccines (Cervarix®, Gardasil®), interest in global disease burden due to the vaccine HPV types (HPV6, 11, 16, 18) has increased tremendously (26, 27), particularly for non-genital types of cancer potentially preventable using existing and future (second generation) HPV vaccines (28, 29).

Given the fact that since the appearance of these two meta-analyses (17, 18), more than 25 new large studies have been published (increasing the number of cases by almost three-fold), it was felt necessary to update the accumulated evidence by conducting a systematic review and formal meta-analysis covering this comprehensive literature, without any restrictions concerning HPV detection method, geographical origin of the study, and histological type of lung cancer.

Materials and Methods

Data extraction. Eligible studies were identified by searching MEDLINE (via PubMed), Current Contents, and reference lists from eligible original articles, book chapters and other reviews until April 2012. No language or date-of-publication limitations were imposed. The search terms included papillomavirus, HPV, condyloma, papilloma, bronchus, lung, cancer, carcinoma, lung cancer, and bronchial carcinoma. All publications appearing in peer-reviewed journals were considered eligible, irrespective of which method (see later) was used for HPV detection in human lung cancer, provided that the report included exact numbers of analyzed cases and of those testing/interpreted as being HPV-positive, making calculation of the event rates *i.e.* HPV prevalence and their 95% confidence intervals (95% CI) possible.

With the used search terms, altogether, 950 abstracts were derived from the databases, covering the years 1954 through 2012. For the present meta-analysis, a total of 110 original studies were deemed eligible, fulfilling the criteria defined above. At this stage, all studies reporting normal bronchial samples, benign squamous cell metaplasia (SQM), and benign squamous cell papillomas (SCP) were included, following the practice of recent reviews (15, 16, 25). The formal meta-analysis, however, was focused on lung cancer, where the different histological types: adenocarcinoma (AC), squamous cell carcinoma (SCC), adeno-squamous carcinoma (ASC), large cell carcinoma (LCC), small cell carcinoma (SmCC), as well as SQM and SCP were entered as subgroups within the study.

From the summaries (where available) and/or body texts of each eligible study, the following key information was extracted: HPV detection method, geographical region where the samples were derived from, HPV genotypes analyzed and detected, total number of cases analyzed, number testing (or otherwise interpreted) as being HPV-positive, percentage of HPV-positivity, authors, and publication year. In anecdotal instances, the authors were contacted for clarification of their missing data.

Statistical analyses. A specific software package Comprehensive Meta Analysis™ (Version 2.2.064, July 27, 2011; Biostat Inc., Englewood, NJ, USA), was used to perform the meta-analysis. The data input in the software includes all the above items taken from the 110 original studies. The software calculates the event rates (logit event rates, SE and variance) based on the events and sample size data. To assess overall heterogeneity in the event rates between the different studies, Cochran's Q (two-sided) homogeneity *p*-value as well as I^2 statistics (for percentage of variation) were used (30). To explore the eventual publication bias, funnel plots were drawn by plotting the logit event rates by their precision (1/SE) (31). Funnel plots were evaluated for asymmetry using the following statistics: i) Begg and Mazumdar rank correlation (32), ii) Egger's test of the intercept (regression) (33), and iii) the Duval and Tweedie's trim and fill method (34), which imputes results that are hypothetically missing due to the publication bias. Funnel plot asymmetry analyses were also stratified by the histological type of cancer, HPV detection method, and geographical region of the studies.

To assess the variation in the event rates *i.e.* HPV prevalence due to the differences between the individual studies, the key study characteristics were evaluated using stratified random-effects meta-analysis and restricted maximum likelihood meta-regression. Stratified meta-analysis allows descriptive comparison of the summary event rates across the different categories of specified study characteristics, *e.g.* cancer histology and HPV detection method. Restricted maximum likelihood meta-regression formally compares these differences in event rates across the selected study-level covariates and estimates the among-study variance (35). Given the inherent differences in analytical sensitivities between the different HPV detection methods: histology, immunohistochemistry (IHC), Southern blot hybridization (SB), filter *in situ* hybridization (FISH), *in situ* hybridization (ISH), and polymerase chain reaction (PCR), meta-analysis were performed across these strata. Similarly, to distinguish true study-specific effects from random variation, all analyses were also stratified by the geographical regions of their origin because of the reported major differences in HPV prevalence between the distinct geographic regions (17, 18, 24, 36, 37).

Together with cancer histology (AC, SCC, ASC, LCC, SmCC, AnCC), HPV detection method and geographical study origin were also tested as study-level co-variates in meta-regression.

Finally, sensitivity analysis was performed to assess the influence of each individual study on the strength and stability of the meta-analytic results. Sensitivity analysis runs the analysis k (n=109) times, each time removing one study to show that study's impact on the combined effect size. The sensitivity of the results to these one-by-one study removals was evaluated by descriptively comparing the homogeneity *p*-value, funnel plots, and Begg and Egger's one-sided *p*-values, as well as the magnitude and precision of the random-effects summary event rates (point estimates).

Results

Eligible studies. Using the specified selection criteria, a total of 110 studies were considered eligible for the present analysis (8-10, 19-24, 36, 37, 38-136), comprising 7,381 lung cancer cases analyzed by different HPV detection methods. In addition, these same studies included 82 cases of SCP, and 57 samples of SQM, as well as 483 samples of normal bronchial biopsies analysed concomitantly with the cancer samples. Both case reports and larger series are included, comprising up to 399 samples analyzed by PCR (24) and 166 lung carcinomas examined by ISH (37) (Table I). The methods used to evaluate HPV involvement include the following: light microscopic morphology (8-10), IHC (21, 39, 102), FISH (40, 49), HC2 (87), SB (38, 41, 50), ISH (37, 42, 44-48, 50-53, 56, 57, 93, 94, 98, 107, 117, 119, 131, 135), and PCR (19, 24, 54, 55, 58-86, 88-92, 95-97, 99-101, 103-106, 108-116, 118, 120-130, 132-134). Based on the available data on geographical regions with different HPV prevalence in lung cancer (17, 18, 24, 36, 37), the studies were categorized into the following regions of origin: China and Taiwan, Other Asia, South America, Australia, Europe, and North America. When all studies reporting only benign lesions were omitted, 100 studies remained that report on HPV detection in lung cancer (any histological type). These 100 studies comprise the target of this meta-analysis. Of all 7,381 lung cancer cases analyzed, 1,653 (22.4%) tested HPV-positive.

Analytical results.

Point estimates of event rates. In the entire set of 100 studies, the crude HPV-positivity rate (1,653/7,381) translates to event rates (*i.e.* effect size, HPV prevalence) of 0.348 (95% CI=0.333-0.363) using the fixed-effects model, and 0.220 (95% CI=0.180-0.259) using the random effects model. Table II depicts the meta-analysis of the 100 included studies, stratified by HPV detection technique. The random effects model results in lower point estimates than the fixed effects model. Irrespective of the HPV detection method, there is significant heterogeneity between the studies as measured by Cochran's Q and I^2 homogeneity statistics, with p=0.0001 (except for biopsy and FISH studies, p=0.235 and p=0.064, respectively). The same applies to the overall comparison within strata (p=0.0001), but not for comparison between the strata (random effects model, p=0.193; fixed effects model, p=0.054). The percentage of variation (I^2) is lowest (30.8%) for biopsy-based studies, and highest (92.7%) for IHC-based studies. Using the random effects model, studies based on biopsy alone give the highest point estimates of HPV prevalence (0.327, *i.e.* 32.7%), followed by SB- (27.3%), PCR- (22.0%) and ISH-based studies (20.9%).

All 100 studies were also subjected to meta-analysis stratified by the geographical origin of the study (Table III). There is significant heterogeneity (p=0.0001) between the studies from different geographical regions, except for Australia (p=0.123), with the percentage of variation from 57.9% (Australia) to 90.5% (Other Asia). There is three-fold higher effect size derived from studies carried out in China and Taiwan (HPV prevalence 37.7%) as compared with those from USA/Canada (12.5%), and the difference is more than two-fold as compared with the European studies (16.9%). Both the fixed effects and random effects models result in highly significant *p*-values for homogeneity (0.0001) both in the within-strata and between-strata summary comparisons, indicating substantial heterogeneity between studies from the same geographical region as well as between the different geographical regions, respectively.

The 100 studies were also subjected to meta-analysis stratified by the histological type (Table IV). There is significant heterogeneity between the studies analyzing AC, SCC and ASC, but not between the studies assessing HPV in LCC and SmCC (p=0.135 and p=0.574, respectively). The percentage of variation ranged from 36.8% (LCC) to 89.9% (SCC). With the random effects model, the point estimates for effect size are highest for SCC (HPV prevalence 25.1%), followed by LCC (20.3%), ASC (18.5%) and AC (15.1%). Both the fixed effects and random effects models result in highly significant *p*-values for homogeneity, both in the within-strata and between-strata summary comparisons, indicating substantial heterogeneity between the studies analyzing the same histological type of lung cancer (p=0.0001), and somewhat less between studies assessing different histological types (p=0.019).

Meta-regression. These stratified meta-analyses were followed by formal meta-regression to confirm the impact of the study-level co-variates (namely HPV detection methods, geographical origin, histological type) on the summary effect size. In Table V, all methods except SB (p=0.140) resulted in point estimates that were significantly different from the reference. Due to the large number of studies, the seemingly small effect size difference (–0.071) between ISH and PCR methods was also statistically significant (p=0.0001). However, the HPV detection method was not a significant study-level co-variate (p=0.473 for slope, *i.e.* regression

Table I. *Studies reporting on HPV detection in lung cancer and benign* squamous cell lesions.*

Detection method	Histological type	Area or country	HPV types detected	HPV positive		Authors and year	Number of references
				Number/ total	%		
HB	SCC	Finland	–	1/1	100	Syrjänen 1979	8
HB	SCC	Finland	–	36/104	34.6	Syrjänen 1980	9
HB	SCC	Finland	-	67/220	30.4	Syrjänen 1980	10
SB	SCC	Germany	-	0/9	0.0	Stremlau *et al*. 1985	38
SB	LCC		-	0/7	0.0		
SB	ASC		-	0/2	0.0		
SB	AnSCC		16	1/5	20.0		
IHC	SCC	USA	-	1/1	100	Helmuth *et al*. 1987	39
FISH	SCC	USA	16	1/20	5.0	Ostrow *et al*. 1987	40
SB	SCC	USA	6/11	1/1	100	Byrne *et al*. 1987	41
ISH	SCC	Finland	16/18	5/99	5.1	Syrjänen *et al*. 1987	42
EM	SCP	Canada	-	1/1	100	Trillo *et al*. 1988	43
ISH	SCC	Finland	6, 16	9/131	6.9	Syrjänen *et al*. 1989	44
ISH	SCP	USA	6/11	1/1	100	Kerley *et al*. 1989	45
ISH	SCP	UK	16	1/15	6.7	Carey *et al*. 1990	46
ISH	SQM	France	6	1/10	10.0	Bejui-Thivolet *et al*. 1990a	47
ISH	SCC		6, 6/11, 18	6/33	18.2		
ISH	SCC	France	11	1/1	100	Bejui-Thivolet *et al*. 1990	48
FISH	SCC	Australia	16/18	2/5	40.0	Kulski *et al*. 1990	49
ISH	SCP	Austria	6/11	6/6	100	Popper *et al*. 1992	50
ISH	SCC		16/18	5/5	100		
SB	SCC	Switzerland	11	1/1	100	Guillou *et al*. 1991	51
ISH	SCC	USA	6	1/1	100	DiLorenzo *et al*. 1992	52
ISH	SCC	USA	6/11, 16/18	6/20	30.0	Yousem *et al*. 1992	53
ISH	SCP		6/11	2/2	100		
ISH	LCC		31/33/35	1/6	16.7		
ISH	ASC			0/28	0.		
ISH	SQM		6/11, 16/18	2/17	11.8		
PCR	SCC	Japan	16	3/29	10.3	Ogura *et al*. 1993	54
PCR	SCC	China	6, 11, 16, 18	7/49	14.3	Xing *et al*. 1993	55
ISH	SCP	USA	6/11	1/1	100	Katial *et al*. 1994	56
ISH	SCC	China	6, 11, 16	5/7	71.4	Liu *et al*. 1994	57
PCR	SCP	Austria	6, 11, 16, 18	11/31	55.0	Popper *et al*. 1994	58
PCR	SCC		16, 18, 31, 33, 35	10/12	83.3		
PCR	SCC	Germany		0/85	0.0	Shamanin *et al*. 1994	59
PCR	LCC	Japan		0/7	0.0	Szabo *et al*. 1994	60
PCR	SCC			0/40	0.0		
PCR, ISH	SCC	China	6, 11, 16, 18	8/49	16,3	Xing *et al*. 1994	61
PCR	SCC	UK	11, 16, other types	6/66	9.0	Al-Ghamdi *et al*. 1995	62
PCR,SB,DB	SCC	Japan	18	1/10	10.0	Kinoshita *et al*. 1995	63
PCR,SB,DB	AC		18	2/26	7.7		
PCR, DB	SCC	China	16, 16/18, 18	16/50	32.0	Li *et al*. 1995	64
PCR, ISH	ASC	Finland	6, 11, 16, 18	8/22	36.4	Nuorva *et al*. 1995	65
PCR,DB	SCC	China	16,18, 16/18	14/29	48.3	Qingquan *et al*. 1995	66
PCR,DB	AC		16	2/16	12.5		
PCR,DB	ASC			0/5	0.0		
PCR	SCC	Japan	18	1/8	12.5	Sagawa *et al*. 1995	67
PCR	SCC	France	6/11, 16	2/18	11.1	Thomas *et al*. 1995	68
PCR	SCC	China		4/34	11.8	Zhang *et al*. 1995	69
PCR	LCC	China	16	9/9	100	Da *et al*. 1996	70
PCR	SCC		16	8/16	50.0		
PCR	AC		16	5/12	42.0		
PCR	AC	France	6/11, 18	¼	25.0	Thomas *et al*. 1996	71
PCR	LCC		-	0/2	0.0		
PCR	SCC		6/11	2/18	11.1		

Table I. *continued*

Table I. *continued*

Detection method	Histological type	Area or country	HPV types detected	HPV positive		Authors and year	Number of references
				Number/ total	%		
PCR	SmCC		16	1/6	16.7		
PCR,ISH	SCC	Japan	6/11, 16/18, 18	41/73	56.2	Hirayasu *et al*. 1996	72
PCR	AC	Greece	16	8/41	19.5	Noutsou *et al*. 1996	73
PCR	SCC		16	4/41	9.8		
PCR	LCC		11	2/10	20.0		
PCR	ASC		-	0/7	0.0		
PCR,ISH	SCC	Finland	6,6/11, 16, 18	19/28	67.8	Soini *et al*. 1996	74
PCR,ISH	AC		6, 11, 16, 18	8/12	75.0		
PCR,ISH	ASC		-	0/3	0.0		
PCR,ISH	SCC	Germany		0/32	0.0	Welt *et al*. 1997	75
PCR,ISH	ASC			0/6	0.0		
PCR,ISH	SCC	China	16, 18	16/50	32.0	Hu *et al*. 1997	76
PCR,ISH	SCC	USA	18	2/34	5.9	Bohlmeyer *et al*. 1998	77
PCR,ISH	SCP	USA	6, 11, 16, 18	5/14	35.7	Flieder *et al*. 1998	78
PCR,SB	SCC	Greece	6/11, 16/18	32/52	61.5	Papadopoulou *et al*. 1998	79
PCR,ISH	ASC	Japan	16/18	18/23	78.2	Tsuhako *et al*. 1998	80
PCR	SmCC	USA	-	0/35	0.0	Wistuba *et al*. 1998	81
PCR	SCC	China		13/50	26.0	Yang *et al*. 1998	82
PCR	SQM			11/30	36.7		
PCR	Normal			3/30	10.0		
PCR,ISH	SCC	Greece	-	0/31	0.0	Gorgoulis *et al*. 1999	83
PCR,ISH	AC		-	0/32	0.0		
PCR,ISH	LCC		-	0/5	0.0		
PCR	SCC	Norway	16/18	1/1	100	Hennig *et al*. 1999	84
PCR,EM	AC	Japan	16/18	1/285	0.4	Hiroshima *et al*. 1999	85
PCR	SCP	Japan	11	1/1	100	Kawaguchi *et al*. 1999	86
HC2	SCC	France	HR-HPV	5/185	2.7	Clavel *et al*. 2000	87
PCR,ISH	SCP	Japan	6, 16	1/1	100	Harada *et al*. 2000	88
PCR,ISH	SCC	Japan	16, 18	25/44	56.8	Iwamasa *et al*. 2000	89
PCR,ISH	SCC	Japan	6, 11, 16, 18	77/157	49.0	Miyagi *et al*. 2000	90
PCR	SCC	China	16, 18	50/110	45.5	Niyaz *et al*. 2000	91
PCR,ISH	SCC	China	16, 18	77/141	54.6	Cheng *et al*. 2001	92
ISH	SCC	Turkey	6/11, 16/18	3/26	11.5	Kaya *et al*. 2001	93
ISH	SCC	Poland	16/18	1/22	4.5	Miasko *et al*. 2001	94
ISH	AC		6/11, 16/18	2/13	15.4		
ISH	LCC		-	1/5	20.0		
PCR,ISH	SCC	Japan		29/59	49.1	Miyagi *et al*. 2001	95
PCR,ISH	AC			12/62	19.4		
PCR	SCC	Greece	16, 18	2/54	3.7	Papadakis *et al*. 2002	96
PCR	SCC	Australia	-	0/10	0.0	Plunkett *et al*. 2003	97
ISH	SCC	Canada	16	4/10	40.0	Aaron *et al*. 2004	98
PCR,ISH	SCC	China	6, 11	54/141	38.3	Cheng *et al*. 2004.	99
PCR	SCC	China	11	1/1	100	Xu *et al*. 2004	100
PCR	SCC	Turkey	16	2/40	5.0	Zafer *et al*. 2004	101
IHC	SCC	France	-	0/122	0.0	Brouchet *et al*. 2005	102
Linear blot	SCC	France	HR	4/218	1.9	Coissard *et al*. 2005	103
PCR	SCC	India	18	2/40	5.0	Jain *et al*. 2005	104
PCR	SCC	China	16, 18	91/166	54.8	Wu *et al*. 2005	105
PCR	SCC	Colombia	16, 18, 33	9 /14	64.3	Castillo *et al*. 2006	106
PCR	AC	Mexico	16	1/13	7.7		
PCR	SmCC	Peru	-	0/9	0.0		
PCR, E6,E7	SCC	Italy	16, 18, 31	8/38	21.1	Ciotti *et al*. 2006	19
ISH	SCC	China	16, 18	19 /73	26.0	Fei *et al*. 2006	107
ISH	Normal		16, 18	1/34	2.8		
PCR	SCC	China	16, 18	30/57	52.6	Wang et al. 2006	108

Table I. *continued*

Table I. *continued*

Detection method	Histological type	Area or country	HPV types detected	HPV positive		Authors and year	Number of references
				Number/ total	%		
PCR	SCC	USA	16	1/1	100	Zhao *et al*. 2006	109
PCR,SB	SCC	Chile	16	17/37	45.9	Aguayo *et al*. 2007	110
PCR,SB	AC		16	3/32	9.3		
PCR	SmCC	USA	-	0/22	0.0	Carlson *et al*. 2007	111
PCR,E6, IHC	SCC	Taiwan	16, 18	82/122	67.2	Cheng *et al*. 2007	112
PCR,E6,E7	SCC	Italy	16, 31, 6/53, 16/18	10/78	12.8	Giuliani *et al*. 2007	20
PCR,E6,E7	SCC	Italy	16	5/6	83.3	Giuliani *et al*. 2007	22
PCR	SCC	Iran	16, 18	33/129	25.6	Nadji *et al*. 2007	113
PCR	Normal		16, 18	8/90	8.9		
PCR	SCC	S. Korea	16, 18, 33	40/59	67.8	Park *et al*. 2007	114
PCR	AC			20/53	37.8		
PCR	SCC	Turkey	16, 18	1/65	1.6	Buyru *et al*. 2008	115
PCR	SCC	China	16, 18	112/215	52.1	Wang *et al*. 2008	116
PCR	AC		16, 18	26/98	26.5		
PCR	Normal		16, 18	4/96	4.2		
IHC, E6,E7	SCC	Taiwan	16, 18	11/88	12.5	Hsu *et al*. 2009	21
IHC	AC		16, 18	63/129	48.9		
ISH	AC	Singapore	16, 18	0/110	0.0	Lim *et al*. 2009	117
PCR	SCC	Germany	16, 18	9 /21	42.9	Weichert *et al*. 2009	118
ISH	SCC	China	16, 18	32/44	72.7	Xu *et al*. 2009	119
InnoLipa/PCR	SCC	China	16, 18	37/72	51.4	Yu *et al*. 2009	120
InnoLipa	AD		16, 18	6/37	16.2		
InnoLipa	Normal		6, 16, 18	16/71	22.5		
PCR	SCC	Pakistan, papua, New Guinea	16	8/18	44.4	Aguayo *et al*. 2010	121
PCR	AC		-	0/38	0.0		
PCR	SmCC		-	0/4	0.0		
InnoLipa	AC	Japan		9/30	30.0	Baba *et al*. 2010	122
InnoLipa	SCC			2/27	7.0		
PCR	SCC	Croatia	16, 18, 33	3/84	3.6	Branica *et al*. 2010	123
PCR	AC	Japan	16, 18, 33	0/297	0.0	Iwakawa *et al*. 2010	124
PCR	AC	USA	11, 16	5/30	16.7	Joh *et al*. 2010	125
PCR,E7	SCC	Greece	16	14/23	60.8	Krikelis *et al*. 2010	23
PCR	SCC	China	16, 18	19/45	42.2	Wang *et al*. 2010	126
PCR	SCC	China	16	18/104	17.3	Zhang *et al*. 2010	127
PCR	SCC	Italy	16, 18, 31	15/89	16.4	Carpagnano *et al*. 2011	128
PCR,ISH	SCC	Japan, Korea	16, 18	11/176	6.3	Goto *et al*. 2011	129
PCR,ISH	AC	Taiwan	16, 18	12/128	9.4		
PCR	SCC	Pakistan		3/30	10.0	Halimi *et al*. 2011	130
ISH	SCP	Japan	-	0/1	0.0	Inamura *et al*. 2011	131
PCR, E6,E7	SCC	USA	16, 18	2/399	0.6	Koshiol *et al*. 2011	24
PCR	SCP/SCC	USA	-	0/1	0.0	Lagana *et al*. 2011	132
PCR	Normal	Greece	16, 18, 31	6/71	8.4	Mammas *et al*. 2011	133
PCR	SCC	France	11	1/1	100	Saumet *et al*. 2011	134
PCR	SCC	China	16, 18	64/107	59.8	Yu *et al*. 2011	36
PCR	AC		16, 18	11/63	17.5		
PCR	Normal		16, 18	21/91	23.1		
ISH	SCC	USA	-	0/166	0.0	Bishop *et al*. 2012	37
ISH	SCC	USA	16, 18	0/7	0.0	Doxtader *et al*. 2012	135
PCR	SCC	Finland	6, 16	4/77	5.2	Syrjänen *et al*. 2012	136

EM, Electron microscopy; FISH, filter in situ hybridization; HB, histological biopsy; HC2, Hybrid Capture 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; PCR, polymerase chain reaction; SB, Southern blot hybridization; AC, adenocarcinoma; AnSCC, anaplastic carcinoma; ASC, adenosquamous carcinoma; LCC, large cell carcinoma; SmCC, small cell carcinoma; SCP, squamous cell papilloma; SCC, squamous cell carcinoma; SQM, squamous cell metaplasia; *Benign lesions were omitted from the formal meta-analysis.

Table II. *Meta-analysis of the 100 lung cancer* studies stratified by the HPV detection method.*

Detection method	No. of studies	Events	Sample size	Point estimates of event rates				**Homogeneity (Cochran's Q)	**I^2	**Homogeneity (*p*-value)
				Fixed effects model		Random effects model				
				Point estimate	95%CI	Point estimate	95%CI			
Biopsy	3	105	326	0.321	0.273-0.374	0.327	0.259-0.404	2.893	30.858	0.235
FISH	2	3	25	0.178	0.054-0.452	0.164	0.016-0.742	3.418	70.744	0.064
HC2***	1	5	185							
IHC	3	76	341	0.373	0.336-0.445	0.203	0.043-0.591	41.041	92.690	0.0001
ISH	17	144	882	0.292	0.248-0.341	0.209	0.115-0.351	154.209	87.031	0.0001
PCR	71	1.315	5.595	0.361	0.344-0.378	0.220	0.181-0.266	863.780	88.539	0.0001
SB	3	5	27	0.262	0.102-0.524	0.273	0.074-0.638	9.108	45.101	0.105
Summary	100	1.653	7.381	0.348	0.333-0.363	0.232	0.201-0.266	1128.039	87.944	0.0001
Total within (FE)								1074.448		0.0001
Total between (FE)								10.893		0.054
Total between (RE)								7.388		0.193

DB, Dot blot hybridization; FISH, filter *in situ* hybridization; HC2, Hybrid Capture 2 assay; IHC, immunohistochemistry for HPV antigens; ISH, *in situ* hybridization; PCR, polymerase chain reaction; SB, Southern blot hybridization; FE, fixed effects; RE, random effects; *All benign lesions as subgroups within study are omitted; **only calculated for fixed effects model; ***only one study, meta-analysis redundant (omitted from summary effect analysis).

Table III. *Meta-analysis of the 100 lung cancer* studies stratified by their geographical origin.*

Region	No. of studies	Events	Sample size	Point estimates of event rates				**Homogeneity (Cochran's Q)	**I^2	**Homogeneity (*p*-value)
				Fixed effects model		Random effects model				
				Point estimate	95%CI	Point estimate	95%CI			
China/Taiwan	24	911	2.190	0.443	0.412-0.457	0.377	0.314-0.443	240.760	87.124	0.0001
Other Asia	19	350	1.962	0.335	0.305-0.367	0.172	0.110-0.259	275.260	90.554	0.0001
South America	2	30	105	0.361	0.258-0.477	0.237	0.079-0.528	19.742	79.739	0.001
Australia	2	2	15	0.239	0.065-0.588	0.185	0.017-0.742	2.378	57.951	0.123
Europe	39	331	2.324	0.222	0.200-0.246	0.169	0.120-0.232	340.441	84.138	0.0001
North America	14	29	785	0.133	0.090-0.191	0.125	0.049-0.287	71.011	78.876	0.0001
Summary	100	1.653	7.381	0.348	0.333-0.363	0.265	0.228-0.306	1128.039	87.944	0.0001
Total within (FE)								922.578		0.0001
Total between (FE)								162.764		0.0001
Total between (RE)								27.776		0.0001

FE, fixed effects; RE, random effects; *All benign lesions as subgroups within study are omitted; **only calculated for fixed effects model.

coefficient β1 or effect parameter). The same was true when only the studies using ISH (n=17) or PCR (n=71) were included in this meta-regression (p=0.984 for slope).

Table VI gives the results of a similar meta-regression examining the impact of geographical origin as the study-level co-variate of the effect size. The effect size difference of 0.178 between the high-incidence regions (HIR: China and Taiwan, Other Asia, South America) and low-incidence regions (LIR: Australia, Europe, North America) was highly significant (p=0.0001). In meta-regression, geographical origin of the study had a significant impact on the effect size (p=0.020 for slope) only when used as dichotomized (HIR/LIR) variable, but not when all individual regions were included as separate categories (p=0.298).

Table IV. *Meta-analysis of the 100 lung cancer* studies stratified by the histological type of carcinoma.*

Histological type	No. of studies	Events	Sample size	Point estimates of event rates				**Homogeneity (Cochran's Q)	**I^2	**Homogeneity (*p*-value)
				Fixed effects model		Random effects model				
				Point estimate	95%CI	Point estimate	95%CI			
AC	23	197	1.561	0.254	0.223-0.287	0.151	0.098-0.224	136.473	83.880	0.0001
SCC	92	1.415	5.592	0.369	0.352-0.385	0.251	0.206-0.302	901.393	89.905	0.0001
AnSCC***	1	1	5							
ASC	8	26	96	0.397	0.271-0.538	0.185	0.056-0.467	25.862	72.933	0.001
LCC	8	13	51	0.202	0.099-0.369	0.203	0.079-0.431	11.077	36.805	0.135
SmCC	5 (137)	1	76	0.057	0.018-0.165	0.057	0.018-0.165	2.905	0.000	0.574
Summary	100	1.653	7.381	0.348	0.333-0.363	0.215	0.181-0.253	1128.039	87.944	0.0001
Total within (FE)								1077.709		0.0001
Total Between (FE)								49.870		0.0001
Total Between (RE)								11.837		0.019

AC, adenocarcinoma; AnSCC, anaplastic carcinoma; ASC, adenosquamous carcinoma; LCC, large cell carcinoma; SmCC, small cell carcinoma; SCC, squamous cell carcinoma; FE, fixed effects; RE, random effects; *All benign lesions as subgroups within study are omitted. **only calculated for fixed effects model; ***Only one study, meta-analysis redundant (omitted from summary effect analysis).

A similar meta-regression was carried out using the histological type as the study-level co-variate (Table VII). Using AC as the reference, the effect size differences from the other histological types are all significant (p=0.003 to p=0.0001). In meta-regression, however, the histological type had no significant impact on the effect size (p=0.589) when all histological categories were included. When only AC and SCC categories were included, histological type is a significant study-level co-variate associated with HPV prevalence (p=0.035).

Publication bias. Potential publication bias was assessed by funnel plot asymmetry statistics, separately for the three major study characteristics. There was practically no evidence for publication bias among studies using different HPV detection methods (Begg p>0.05, Egger's p>0.05), except for PCR-based studies (Egger's p=0.0001). However, Duval and Tweedie's trim and fill method imputed no hypothetically missing studies, and thus had no effect on the adjusted point estimates for effect size. As to the studies stratified by geographical region, Begg and Egger's p-values did suggest some funnel plot asymmetry for studies from Other Asia (Begg p=0.012) and Europe (Egger's p=0.038). Duval and Tweedie's trim and fill method did not impute any hypothetically missing studies for these two regions, however, leaving the effect size estimates unchanged. Finally, both Begg and Egger's p-values suggested some funnel plot asymmetry for studies on AC (n=23) (p=0.013 and p=0.003, respectively), but again Duval and Tweedie's trim and fill method led to no adjustments in the effect size estimates for the AC studies. The same was true for the SCC studies (n=92) and ASC studies (n=8), despite Egger's p=0.0004, and p=0.014, respectively.

Sensitivity analysis. Sensitivity analysis was performed to assess the influence of each individual study on the strength and stability of meta-analytic results. Meta-analytic results seemed robust to all (n=99) one-by-one study removals, with no change in the magnitude and precision of the fixed effects and random effects summary event rates.

Discussion

Since the first evidence in 1979 suggesting that HPV might be involved in etiology of at least a subset of lung carcinomas (8-10), this topic has become a subject of increasing interest, with widely expanded literature (15-24). To date, only two meta-analyses have been published (17, 18), and unfortunately, both have an incomplete coverage of the literature. The meta-analysis presented here is based on a systematic review, updating all the literature published since the author's own review of 2002 (16). Importantly, no restrictions were made according to the method used for HPV detection, even if some of the early DNA techniques are obsolete today, to validate by formal meta-analysis the frequently presented concept that the wide variation in HPV prevalence in lung cancer is mainly due to the different

Table V. *Effect of HPV detection method on the effect size in maximum likelihood meta-regression.*

Study-level co-variates	No. of studies (homogeneity *p*-value)**	Effect size*		Difference in effect size estimates		
HPV detection method:		Point estimate***	95% CI	Difference in point estimates	95% CI	*p*-value
Biopsy	3 (0.235)	0.327	0.259-0.404	1.000		
FISH	2 (0.064)	0.164	0.016-0.742	0.202	0.064-0.339	0.035
pHC2#	1					
IHC	3 (0.0001)	0.203	0.043-0.591	0.099	0.031-0.166	0.004
ISH	17 (0.0001)	0.209	0.115-0.351	0.146	0.089-0.203	0.0001
PCR	71 (0.0001)	0.220	0.181-0.266	0.087	0.035-0.138	0.0001
SB	3 (0.0001)	0.273	0.074-0.638	0.136	–0.018-0.291	0.140
Meta-regression for all	Slope: –0.090 (95% CI=–0.339-0.157) (p=0.473): Intercept: –0.701 (95% CI=–2.372-0.968) (p=0.410)					
ISH	17 (0.0001)	0.209	0.115-0.351	1.000		
PCR	71 (0.0001)	0.220	0.181-0.266	–0.071	–0.098-(–0.044)	0.0001
Meta-regression (ISH/PCR)	Slope: –0.008 (95% CI=–0.798-0.782) (p=0.984): Intercept: -1.282 (95% CI=–6.696-4.130) (p=0.642)					

CI, Confidence interval; FISH, filter *in situ* hybridization; HC2, Hybrid Capture 2 assay; IHC, immunohistochemistry for HPV antigens; ISH, *in situ* hybridization; PCR, polymerase chain reaction; SB, Southern blot hybridization; Slope, effect parameter=regression coefficient β_1; Intercept =coefficient β_0; *Random effects model; **Cochran's Q; ***HPV prevalence; #only one study, omitted from calculations.

Table VI. *Effect of geographic origin of the study on the effect size in maximum likelihood meta-regression.*

Study-level co-variates	No. of studies (homogeneity *p*-value)**	Effect size*		Difference in effect size estimates		
Geographic origin of study:		Point estimate***	95% CI	Difference in point estimates	95% CI	*p*-value
China and Taiwan	24 (0.0001)	0.377	0.314-0.443	1.000		
Other Asia	19 (0.0001)	0.172	0.110-0.259	0.237	0.210-0.264	0.0001
South America	2 (0.001)	0.237	0.079-0.528	0.130	0.041-0.219	0.008
Australia	2 (0.123)	0.185	0.017-0.742	0.282	0.109-0.455	0.027
Europe	39 (0.0001)	0.169	0.120-0.232	0.273	0.248-0.298	0.0001
North America	14 (0.0001)	0.125	0.049-0.287	0.379	0.354-0.403	0.0001
Meta-regression for all	Slope: 0.110 (95% CI=–0.096-0.319) (p=0.298); Intercept: –1.679 (95% CI=–2.440-(–0.918) p=0.0002					
HIR	45 (0.0001)	0.294	0.243-0.350	1.000		
LIR	55 (0.0001)	0.167	0.124-0.221	0.178	0.160-0.196	0.0001
Meta-regression (HIR/LIR)	Slope: –0.625 (95% CI=–1.153-(–0.096) (p=0.020); Intercept: –0.362 (95% CI=–1.196-0.471) (p=0.394)					

Slope, effect parameter=regression coefficient β_1; Intercept=coefficient β_0; HIR, high-incidence region; LIR, low-incidence region; *Random effects model; **Cochran's Q; ***HPV prevalence rate.

detection techniques (16-18, 24, 36, 37). The other study-level co-variates with potential impact on the effect size considered in this meta-analysis are the geographical origin of the study and the histological type of lung cancer, also listed as potential causes of variation in HPV prevalence.

Assessing the heterogeneity in meta-analysis is crucial because the presence or absence of true heterogeneity (*i.e.* between-study variability) directly affects the statistical model that should be used to analyze the database (30, 137-139). The usual way of assessing whether true heterogeneity

Table VII. *Effect of histological type of lung cancer the effect size in maximum likelihood meta-regression.*

Study-level co-variates	No. of studies (homogeneity *p*-value)**	Effect size*		Difference in effect size estimates		
Histological type of cancer:		Point estimate***	95% CI	Difference in point estimates	95% CI	*p*-value
AC	23 (0.0001)	0.151	0.098-0.224	1.000		
SCC	92 (0.0001)	0.251	0.206-0.302	–0.134	–0.154-(-0.114)	0.0001
AnSCC#	1					
ASC	8 (0.001)	0.185	0.056-0.467	–0.144	–0.235-(-0.054)	0.0001
LCC	8 (0.135)	0.203	0.979-0.431	–0.128	–0.249-(-0.008)	0.007
SmCC	5 (0.574)	0.057	0.018-0.165	0.113	0.082-0.143	0.003
Meta-regression for all	Slope: –0.070 (95% CI=–0.328-0.186) (*p*=0.589): Intercept: –1.152 (95% CI=–1.770-(–0.535) (*p*=0.0002)					
AC	23 (0.0001)	0.151	0.098-0.224	1.000		
SCC	92 (0.0001)	0.251	0.206-0.302	–0.134	–0.098-(-0.044)	0.0001
Meta-regression (AC/SCC)	Slope: 0.781 (95%CI 0.052-1.510 (*p*=0.035): Intercept: –2.655 (95%CI –3.999-(-1.310) (*p*=0.0001)					

AC, adenocarcinoma; AnSCC, anaplastic carcinoma; ASC, adenosquamous carcinoma; LCC, large cell carcinoma; SmCC, small cell carcinoma; SCC, squamous cell carcinoma; Slope, effect parameter=regression coefficient β_1; Intercept=coefficient β_0; *Random effects model; **Cochran's Q; ***HPV prevalence; #only one study, omitted from calculations.

exists has been the Q test, originally introduced by Cochran (140). Non-significant homogeneity *p*-values in the Q test indicate that the homogeneity hypothesis should not be rejected, and justifies the adoption of a fixed effects model, assuming that the estimated effect sizes only differ by sampling error (137). In contrast, significant *p*-values in the Q test imply true heterogeneity, warranting the use of a random effects model that includes both within- and between-study variability. The Q statistic has the shortcoming in that it has a poor power to detect true heterogeneity in meta-analyses including a small number of studies, but excessive power to detect even insignificant variability when large number of studies are available (30, 137-140). Furthermore, the Q statistic does not indicate the magnitude of true heterogeneity, only its statistical significance (137). To overcome these shortcomings, Higgins et al. (141) recently proposed three indices for assessing the heterogeneity in meta-analysis: the H^2, R^2, and I^2 indices. Of the three, the I^2 index measures the extent of true heterogeneity, interpreted as the percentage of the total between-study variability of the effect sizes. The I^2 index values 25, 50 and 75 indicate a low, medium, and high degree of heterogeneity, respectively (137, 141). One of the major advantages of the I^2 index is that the indices obtained from meta-analyses with different numbers of studies and different effect metrics are directly comparable (141).

Given the above considerations, there is little doubt that marked heterogeneity exists between the studies within all HPV detection method categories (Table II), as indicated by the significant *p*-values for homogeneity ($p=0.0001$) for the Q test among most of the method categories, despite a markedly variable number of studies in each category (n=1 up n=71). This is also concordant with the values of the I^2 index, indicating that the percentage of the total variability within each method category is very high (up to 93.2%). This marked heterogeneity justifies the adoption of the random effects model to analyze the summary statistics for within- and between-strata heterogeneity (137-139). Using the random effects model, the most important conclusion from the data in Table II is that there is no true heterogeneity between the studies using different HPV detection techniques, as indicated by the non-significant *p*-value for homogeneity ($p=0.193$ for the random effects and $p=0.054$ for the fixed effects model) for the between-study comparison. In other words, we can revisit the concept raised in several recent reviews (15-18, 24), suggesting that the differences in HPV prevalence reported in the lung cancer literature would be explained by the different HPV detection techniques. In this meta-analysis, however, there are no formal grounds to reject the between-studies homogeneity hypothesis, thus precluding the role of HPV detection methods as being the main explanatory factor for the highly variable prevalence of HPV in lung cancer.

An alternative view suggests that this variable HPV prevalence in lung cancer is related to the different geographical regions of the study origin (15-18, 24, 36, 37). This has provoked a hypothesis that HPV plays a different role in lung cancer in the LIRs and in the HIRs (17, 18, 21,

24, 57, 112, 122, 123, 129). To validate this concept, we performed our meta-analyses stratified by the geographical origin of studies (Table III). Both the Q test and the I^2 index demonstrate a marked heterogeneity between the published studies within all distinct geographical regions, irrespective of the number of studies included in each stratum. Using the above rationale, we adopted the random effects model to interpret the summary statistics for the between-strata heterogeneity. The highly significant summary *p*-value for homogeneity of the between-strata comparison leads to rejection of the homogeneity hypothesis. This implies that the major variation in HPV prevalence reported in the published literature is explained by the geographical origin of the studies; HPV prevalence is significantly higher in China and Taiwan, Other Asia and South America, as compared with the LIRs (Europe, Australia, North America) (15-18, 24, 36, 37).

The third potential source of variation in HPV prevalence is the histological type of lung cancer analyzed in different studies. To date, data on HPV detection has been provided for several histological types, most frequently in SCC and AC, but also of ASC, LCC and even SmCC (five studies) (Table IV). Major heterogeneity was found between studies of AC, SCC, and ASC, but not between those assessing LCC and SmCC. Using the random effects model to interpret the summary results, both the within-strata and between-strata comparisons are significant (p=0.0001 and p=0.019, respectively), confirming the substantial heterogeneity i) between the studies analyzing the same histological type of lung cancer, and (somewhat less) ii) between the studies assessing the different histological types. Thus, another source of variation in HPV prevalence seems to be the histological type of lung cancer, of which SCC and AC are the two clinically most important types.

In addition to these stratified meta-analyses that allow a descriptive comparison of the summary event rates across the different study characteristics, here meta-regression was also performed to formally compare these differences in summary effect sizes (35). In meta-regression with the HPV detection method as the co-variate, the regression coefficient for the effect parameter ($\beta 1$, or slope) is not statistically significant (p=0.473). The same is true when the geographical origin of the study (p=0.298) and histological type of lung cancer (p=0.589) are tested for their impact as study-level co-variates. These data imply that despite the marked heterogeneity observed for these three study characteristics in stratified meta-analysis, no formal confirmation was obtained in meta-regression to indicate that any of the three are significant study-level co-variates accounting for the heterogeneity of the summary effect size estimates (*i.e.* HPV prevalence) of the lung cancer studies. Significant regression coefficients in meta-regression were only obtained, if the geographical study origin was used as a dichotomized variable (HIR/LIR) (p=0.020), and if the histological type variable only included the two most important categories, AC and SCC (p=0.035). Including only ISH and PCR studies in the HPV detection method variable does not make the regression coefficient significant, however (p=0.984). Thus, unlike in another HPV-associated type of cancer, esophageal squamous cell cancer (ESCC), where the highly variable HPV prevalence in different geographical origin of the study seems to indicate a different etiology in LIRs and HIRs (142), no similar conclusions can be drawn from lung cancer on the basis of the present meta-analysis.

However, as determined from the results of the stratified meta-analysis, the reported heterogeneity of HPV prevalence is attributed more to the geographical origin of the study and the histological type of lung cancer than to the HPV detection method itself. Considering only the studies based on ISH and PCR (representing the bulk of all studies; 88/100), it is obvious that the summary effect size is almost identical (20.9% and 22.0%, respectively). On the other hand, almost three-fold differences in effect size exist between the HIRs (*e.g.* China=0.377) and LIRs (*e.g.* North America=0.125), and similarly, even larger differences between the summary effect size of SCC (0.251) and SmCC (0.057).

Taken together, in the absence of any documented publication bias, and because of the robustness of all of our meta-analytic results in sensitivity analysis, it can be concluded that the reported wide variability in HPV detection rates in lung cancer is not mainly due to the HPV detection technique used, but is better explained by the geographical origin of the study and the histological type of lung cancer. Since this is not formally confirmed by the meta-regression, however, it seems premature to conclude that lung cancer has a different etiology in different geographical regions (2,4-7, 15-18, 21, 24, 57, 112, 122, 123, 129). Similarly, failure to control for the smoking history and gender of the patients in the present meta-analysis precludes any speculations on the possible different pathogenesis of lung cancer among smokers and non-smokers, as well as between the two genders (2, 4-7, 99, 136, 143-145). Prospective cohort studies are urgently needed to better evaluate the impact of HPV in the pathogenesis of lung cancer, as related to the other known risk factors.

References

1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr last accessed April 19, 2012.

2 Thun MJ, Henley SJ and Calle EE: Tobacco use and cancer: an epidemiologic perspective for geneticists. Oncogene *21*: 7307-7325, 2002.

3 Sun S, Schiller JH and Gazdar AF: Lung cancer in never smokers- a different disease. Nat Rev Cancer *7*: 778-790, 2007.

4 Brownson R C, Alavanja MC, Caporaso N, Simoes EJ and Chang JC: Epidemiology and prevention of lung cancer in non-smokers. Epidemiol Rev *20*: 218-236, 1998.

5 Subramanian J and Govindan R: Lung cancer in never smokers: a review. J Clin Oncol *25*: 561-570, 2007.

6 Bilello KS, Murin S and Matthay RA: Epidemiology, etiology, and prevention of lung cancer. Clin Chest Med *23*: 1-25, 2002.

7 Patel JD: Lung cancer: A biologically different disease in women? Women Health *5*: 685-691, 2009.

8 Syrjänen KJ: Condylomatous changes in neoplastic bronchial epithelium. Report of a case. Respiration *38*: 299-304, 1979.

9 Syrjänen KJ: Epithelial lesions suggestive of a condylomatous origin found closely associated with invasive bronchial squamous cell carcinomas. Respiration *40*: 150-160, 1980.

10 Syrjänen KJ: Bronchial squamous cell carcinomas associated with epithelial changes identical to condylomatous lesions of the uterine cervix. Lung *158*: 131-142, 1980.

11 Meisels A and Fortin R: Condylomatous lesions of the cervix and vagina. I. Cytologic patterns. Acta Cytol *20*: 505-509, 1976.

12 Purola E and Savia E: Cytology of gynaecologic condyloma acuminata. Acta Cytol *21*: 26-31, 1977.

13 Syrjänen KJ: Histological and cytological evidence of a condylomatous lesion in association with an invasive carcinoma of uterine cervix. Arch Geschwulstforsch *49*: 436-443, 1979.

14 Syrjänen KJ: Morphologic survey of the condylomatous lesions in dysplastic and neoplastic epithelium of the uterine cervix. Arch Gynaecol *227*: 153-161, 1979.

15 Syrjänen K: HPV infections in the respiratory tract. Chapter 16. In: Papillomavirus Infections in Human Pathology. Syrjänen K and Syrjänen S: (eds.). J. Wiley & Sons, New York, pp. 355-378, 2000.

16 Syrjänen KJ: HPV infections and lung cancer. J Clin Pathol *55*: 885-891, 2002.

17 Klein F, Kotb WFM and Petersen I: Incidence of human papilloma virus in lung cancer. Lung Cancer *65*: 13-18, 2009.

18 Srinivasan M, Taioli E and Ragin CC: Human papillomavirus type 16 and 18 in primary lung cancers – a meta-analysis. Carcinogenesis *30*: 1722-1728, 2009.

19 Ciotti M, Giuliani L, Ambrogi V, Ronci C, Benedetto A, Mineo TC, Syrjänen K and Favalli C: Detection and expression of human papillomavirus oncogenes in non-small cell lung cancer. Oncol Rep *16*: 183-189, 2006.

20 Giuliani L, Favalli C, Syrjanen K and Ciotti M: Human papillomavirus infections in lung cancer. Detection of E6 and E7 transcripts and review of the literature. Anticancer Res *27*: 2697-2704, 2007.

21 Hsu NY, Cheng YW, Chan IP, Ho HC, Chen CY, Hsu CP, Lin MH and Chou MC: Association between expression of human papillomavirus 16/18 E6 oncoprotein and survival in patients with stage I non-small cell lung cancer. Oncol Rep *21*: 81-87, 2009.

22 Giuliani L, Jaxmar T, Casadio C, Gariglio M, Manna A, D'Antonio D, Syrjanen K, Favalli C and Ciotti M: Detection of oncogenic viruses SV40, BKV, JCV, HCMV, HPV and p53 codon 72 polymorphism in lung carcinoma. Lung Cancer *57*: 273-281, 2007.

23 Krikelis D, Tzimagiorgis G, Georgiou E, Destouni C, Agorastos T, Haitoglou C and Kouidou S: Frequent presence of incomplete HPV16 E7 ORFs in lung carcinomas: memories of viral infection. J Clin Virol *49*: 169-174, 2010.

24 Koshiol J, Rotunno M, Gillison ML, Van Doorn LJ, Chaturvedi AK, Tarantini L, Song H, Quint WG, Struijk L, Goldstein AM, Hildesheim A, Taylor PR, Wacholder S, Bertazzi PA, Landi MT and Caporaso NE: Assessment of human papillomavirus in lung tumor tissue. J Natl Cancer Inst *103*: 501-507, 2011.

25 Syrjänen KJ, Chang F and Syrjänen SM: HPV infections in etiology of benign and malignant sinonasal, bronchial and oesophageal squamous cell lesions. *In*: 4th International Multidisciplinary Congress EUROGIN 2000. Monsonego J: (ed.). Monduzzi Editore, Bologna, pp. 169-179, 2000.

26 Syrjänen KJ: Annual disease burden due to human papillomavirus (HPV) 6 and 11 infections in Finland. Scand J Infect Dis Suppl *107*: 3-32, 2009.

27 Syrjänen KJ: Annual disease burden due to human papillomavirus (HPV) 16 and 18 infections in Finland. Scand J Infect Dis Suppl *108*: 2-32, 2009.

28 Mammas IN, Sourvinos G, Zaravinos A and Spandidos DA: Vaccination against human papilloma virus (HPV): Epidemiological evidence of HPV in non-genital cancers. Pathol Oncol Res *17*: 103-119, 2011.

29 Stanley M: Prospects for new human papillomavirus vaccines. Curr Opin Infect Dis *23*: 70-75, 2010.

30 Hardy RJ and Thompson SG: Detecting and describing heterogeneity in meta-analysis. Stat Med *17*: 841-856, 1998.

31 Sterne JA, Gavaghan D and Egger M: Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol *53*: 1119-1129, 2000.

32 Begg CB and Mazumdar M: Operating characteristics of a rank correlation test for publication bias. Biometrics *50*: 1088-1101, 1994.

33 Egger M, Davey SG, Schneider M and Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ *315*: 629-634, 1997.

34 Duval S and Tweedie R: Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics *56*: 455-463, 2000.

35 Thompson SG and Sharp SJ: Explaining heterogeneity in meta-analysis: a comparison of methods. Stat Med *18*: 2693-2708, 1999.

36 Yu Y, Yang A, Hu S, Zhang J and Yan H: Significance of human papillomavirus 16/18 infection in association with p53 mutation in lung carcinomas. Clin Respir J 2011. doi: 10.1111/j.1752-699X.2011.00277.x.

37 Bishop JA, Ogawa T, Chang X, Illei PB, Gabrielson E, Pai SI and Westra WH: HPV analysis in distinguishing second primary tumors from lung metastases in patients with head and neck squamous cell carcinoma. Am J Surg Pathol *36*: 142-148, 2012.

38 Stremlau A, Gissmann L, Ikenberg H, Stark M, Bannasch P and zur Hausen H: Human papillomavirus type 16 related DNA in an anaplastic carcinoma of the lung. Cancer *55*: 1737-1740, 1985.

39 Helmuth RA and Strate RW: Squamous carcinoma of the lung in a nonirradiated, nonsmoking patient with juvenile laryngotracheal papillomatosis. Am J Surg Pathol *11*: 643-650, 1987.

40 Ostrow RS, Manias DA, Fong WJ, Zachow KR and Faras AJ: A survey of human cancers for human papillomavirus DNA by filter hybridization. Cancer *59*: 429-434, 1987.

41 Byrne JC, Tsao MS, Fraser RS and Howley PM: Human papillomavirus-11 DNA in a patient with chronic laryngotracheobronchial papillomatosis and metastatic squamous-cell carcinoma of the lung. N Engl J Med *317*: 873-878, 1987.

42 Syrjänen KJ and Syrjänen SM: Human papillomavirus DNA in bronchial squamous cell carcinomas. Lancet 1: 168-169, 1987.

43 Trillo A and Guha A: Solitary condylomatous papilloma of the bronchus. Arch Pathol Lab Med *112*: 731-733, 1988.

44 Syrjänen K, Syrjänen S, Kellokoski J, Kärjä J and Mäntyjärvi R: Human papillomavirus (HPV) type 6 and 16 DNA sequences in bronchial squamous cell carcinomas demonstrated by *in situ* DNA hybridization. Lung *167*: 33-42, 1989.

45 Kerley SW, Buchon-Zalles C, Moran J and Fishback JL: Chronic cavitary respiratory papillomatosis. Arch Pathol Lab Med *113*: 1166-1169, 1989.

46 Carey FA, Salter DM, Kerr KM and Lamb D: An investigation into the role of human papillomavirus in endobronchial papillary squamous tumours. Respir Med *84*: 445-447, 1990.

47 Bejui-Thivolet F, Liagre N, Chignol MC, Chardonnet Y and Patricot LM: Detection of human papillomavirus DNA in squamous bronchial metaplasia and squamous cell carcinomas of the lung by *in situ* hybridization using biotinylated probes in paraffin-embedded specimens. Hum Pathol *21*: 111-116, 1990.

48 Bejui-Thivolet F, Chardonnet Y and Patricot LM: Human papillomavirus type 11 DNA in papillary squamous cell lung carcinoma. Virchows Arch A Pathol Anat Histopathol *417*: 457-461, 1990.

49 Kulski JK, Demeter T, Mutavdzic S, Sterrett GF, Mitchell KM and Pixley EC: Survey of histologic specimens of human cancer for human papillomavirus types 6/11/16/18 by filter *in situ* hybridization. Am J Clin Pathol *94*: 566-570, 1990.

50 Popper HH, Wirnsberger G, Juttner-Smolle FM, Pongratz MG and Sommersgutter M: The predictive value of human papilloma virus (HPV) typing in the prognosis of bronchial squamous cell papillomas. Histopathology *21*: 323-330, 1992.

51 Guillou L, Sahli R, Chaubert P, Monnier P, Cuttat JF and Costa J: Squamous cell carcinoma of the lung in a nonsmoking, nonirradiated patient with juvenile laryngotracheal papillomatosis. Evidence of human papillomavirus-11 DNA in both carcinoma and papillomas. Am J Surg Pathol *15*: 891-898, 1991.

52 DiLorenzo TP, Tamsen A, Abramson AL and Steinberg BM: Human papillomavirus type 6a DNA in the lung carcinoma of a patient with recurrent laryngeal papillomatosis is characterized by a partial duplication. J Gen Virol *73*: 423-427, 1992.

53 Yousem SA, Ohori NP and Sonmez-Alpan E: Occurrence of human papillomavirus DNA in primary lung neoplasms. Cancer *69*: 693-697, 1992.

54 Ogura H, Watanabe S, Fukushima K, Masuda Y, Fujiwara T and Yabe Y: Human papillomavirus DNA in squamous cell carcinomas of the respiratory and upper digestive tracts. Jpn J Clin Oncol *23*: 221-225, 1993.

55 Xing LQ, Liu HR and Si JY: Detection of human papillomavirus DNA in squamous cell carcinomas of the lung by multiple polymerase chain reaction. Zhonghua Jie He He Hu Xi Za Zhi *16*: 275-277, 1993. Article in Chinese.

56 Katial RK, Ranlett R and Whitlock WL: Human papilloma virus associated with solitary squamous papilloma complicated by bronchiectasis and bronchial stenosis. Chest *106*: 1887-1889, 1994.

57 Liu HR, Xing LQ and Si JY: A study of human papillary virus infection by *in situ* hybridization and histopathology in squamous cell carcinoma of the lung. Chung Hua Ping Li Hsueh Tsa Chih *23*: 299-301, 1994. Article I Chinese.

58 Popper HH, el-Shabrawi Y, Wockel W, Hofler G, Kenner L, Juttner-Smolle FM and Pongratz MG: Prognostic importance of human papilloma virus typing in squamous cell papilloma of the bronchus: comparison of *in situ* hybridization and the polymerase chain reaction. Hum Pathol *25*: 1191-1197, 1994.

59 Shamanin V, Delius H and de Villiers EM: Development of a broad spectrum PCR assay for papillomaviruses and its application in screening lung cancer biopsies. J Gen Virol *75*: 1149-1156, 1994.

60 Szabo I, Sepp R, Nakamoto K, Maeda M, Sakamoto H and Uda H: Human papillomavirus not found in squamous and large cell lung carcinomas by polymerase chain reaction. Cancer *73*: 2740-2744, 1994.

61 Xing LQ, Liu HR and Si JY: Analysis of the characteristics of human papilloma virus infection in 85 neoplasms of the respiratory system in adult patients. Zhonghua Zhong Liu Za Zhi *16*: 424-427, 1994. Article in Chinese.

62 Al-Ghamdi AA, Sanders CM, Keefe M, Coggon D and Maitland NJ: Human papillomavirus DNA and TP53 mutations in lung cancers from butchers. Br J Cancer *72*: 293-297, 1995.

63 Kinoshita I, aka-Akita H, Shindoh M, Fujino M, Akie K, Kato M, Fujinaga K and Kawakami Y: Human papillomavirus type 18 DNA and E6-E7 mRNA are detected in squamous cell carcinoma and adenocarcinoma of the lung. Br J Cancer *71*: 344-349, 1995.

64 Li Q, Hu K, Pan X, Cao Z, Yang J and Hu S: Detection of human papillomavirus types 16, 18 DNA related sequences in bronchogenic carcinoma by polymerase chain reaction. Chin Med J (Engl) *108*: 610-614, 1995.

65 Nuorva K, Soini Y, Kamel D, Pöllänen R, Bloigu R, Vähäkangas K and Pääkkö P: p53 protein accumulation and the presence of human papillomavirus DNA in bronchiolo-alveolar carcinoma correlate with poor prognosis. Int J Cancer *64*: 424-429, 1995.

66 Qingquan L, Xianguang P, Zuoyan C, Jiong Y and Suping H: Detection of human papillomavirus types 16, 18 DNA related sequences in bronchogenic carcinoma by polymerase chain reaction. Chin Med J (Engl) *108*: 610-614, 1995.

67 Sagawa M, Saito Y, Endo C, Sato M, Usuda K, Kanma K, Takahashi S, Chin E, Sakurada A and Aikawa K: Detection of human papillomavirus type 16, 18 and 33 DNA in stage I (pT1N0M0) squamous cell carcinoma of the lung by polymerase chain reaction. Kyobu Geka *48*: 360-362, 1995.

68 Thomas P, De L, X, Garbe L, Douagui H and Kleisbauer JP: Detection of human papillomavirus DNA in primary lung carcinoma by nested polymerase chain reaction. Cell Mol Biol *41*: 1093-1097, 1995.

69 Zhang X, Zhu Y and Li L: Point mutation of p53 and detection of human papillomavirus DNA in bronchogenic carcinoma. Chung Hua Nei Ko Tsa Chih *34*: 673-675, 1995. Article in Chinese.

70 Da J, Chen L and Hu Y: Human papillomavirus infection and p53 gene mutation in primary lung cancer. Chung Hua Chung Liu Tsa Chih *18*: 27-29, 1996. Article in Chinese.

71 Thomas P, DeLamballerie X, Garbe L, Castelnau O and Kleisbauer JP: Detection of human papillomavirus by polymerase chain reaction in primary lung carcinoma. Bull Cancer *83*: 842-846, 1996.

72 Hirayasu T, Iwamasa T, Kamada Y, Koyanagi Y, Usuda H and Genka K: Human papillomavirus DNA in squamous cell carcinoma of the lung. J Clin Pathol *49*: 810-817, 1996.

73 Noutsou A, Koffa M, Ergazaki M, Siafakas NM and Spandidos DA: Detection of human papilloma virus (HPV) and K-RAS mutations in human lung carcinomas. Int J Oncol *8*: 1089-1093, 1996.

74 Soini Y, Nuorva K, Kamel D, Pöllänen R, Vähäkangas K, Lehto VP and Pääkkö P: Presence of human papillomavirus DNA and abnormal *p53* protein accumulation in lung carcinoma. Thorax *51*: 887-893, 1996.

75 Welt A, Hummel M, Niedobitek G and Stein H: Human papillomavirus infection is not associated with bronchial carcinoma: evaluation by *in situ* hybridization and the polymerase chain reaction. J Pathol *181*: 276-280, 1997.

76 Hu K, Li Q, Yang J and Hu S: Detection of human papillomavirus types 16 and 18 DNA-related sequences in bronchogenic carcinoma. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi *11*: 147-149, 1997. Article in Chinese.

77 Bohlmeyer T, Le TN, Shroyer AL, Markham N and Shroyer KR: Detection of human papillomavirus in squamous cell carcinomas of the lung by polymerase chain reaction. Am J Respir Cell Mol Biol *18*: 265-269, 1998.

78 Flieder DB, Koss MN, Nicholson A, Sesterhenn IA, Petras RE and Travis WD: Solitary pulmonary papillomas in adults: a clinicopathologic and *in situ* hybridization study of 14 cases combined with 27 cases in the literature. Am J Surg Pathol *22*: 1328-1342, 1998.

79 Papadopoulou K, Labropoulou V, Davaris P, Mavromara P and Tsimara-Papastamatiou H: Detection of human papillomaviruses in squamous cell carcinomas of the lung. Virchows Arch *433*: 49-54, 1998.

80 Tsuhako K, Nakazato I, Hirayasu T, Sunakawa H and Iwamasa T: Human papillomavirus DNA in adenosquamous carcinoma of the lung. J Clin Pathol *51*: 741-749, 1998.

81 Wistuba II, Behrens C, Milchgrub S, Virmani AK, Jagirdar J, Thomas B, Ioachim HL, Litzky LA, Brambilla EM, Minna JD and Gazdar AF: Comparison of molecular changes in lung cancers in HIV-positive and HIV-indeterminate subjects. JAMA *279*: 1554-1559, 1998.

82 Yang Y, Dong D, Peng L, Ling J, Xiao Y and Zhuang H: A study on the relationship between HPV infection and the oncogenesis of primary squamous carcinoma of the lung. Zhongguo Fei Ai Za Zhi *1*: 35-36, 1998. Article in Chinese.

83 Gorgoulis VG, Zacharatos P, Kotsinas A, Kyroudi A, Rassidakis AN, Ikonomopoulos JA, Barbatis C, Herrington CS and Kittas C: Human papilloma virus (HPV) is possibly involved in laryngeal but not in lung carcinogenesis. Hum Pathol *30*: 274-283, 1999.

84 Hennig EM, Suo Z, Karlsen F, Holm R, Thoresen S and Nesland JM: HPV 16 in multiple neoplastic lesions in women with CIN III. J Exp Clin Cancer Res *18*: 369-377, 1999.

85 Hiroshima K, Toyozaki T, Iyoda A, Ohwada H, Kado S, Shirasawa H and Fujisawa T: Ultrastructural study of intranuclear inclusion bodies of pulmonary adenocarcinoma. Ultrastruct Pathol *23*: 383-389, 1999.

86 Kawaguchi T, Matumura A, Iuchi K, Yamamoto S, Inoue Y, Sunami T, Naka N, Okishio K, Ueno K, Atagi S, Ogawara M, Hosoe S and Kawahara M: Solitary squamous papilloma of the bronchus associated with human papilloma virus type 11. Intern Med *38*: 817-819, 1999.

87 Clavel CE, Nawrocki B, Bosseaux B, Poitevin G, Putaud IC, Mangeonjean CC, Monteau M and Birembaut PL: Detection of human papillomavirus DNA in bronchopulmonary carcinomas by hybrid capture II: a study of 185 tumors. Cancer *88*: 1347-1352, 2000.

88 Harada H, Miura K, Tsutsui Y, Mineta H, Urano M, Abe M, Kuroda M and Kasahara M: Solitary squamous cell papilloma of the lung in a 40-year-old woman with recurrent laryngeal papillomatosis. Pathol Int *50*: 431-439, 2000.

89 Iwamasa T, Miyagi J, Tsuhako K, Kinjo T, Kamada Y, Hirayasu T and Genka K: Prognostic implication of human papillomavirus infection in squamous cell carcinoma of the lung. Pathol Res Pract *196*: 209-218, 2000.

90 Miyagi J, Tsuhako K, Kinjo T, Iwamasa T and Hirayasu T: Recent striking changes in histological differentiation and rate of human papillomavirus infection in squamous cell carcinoma of the lung in Okinawa, a subtropical island in southern Japan. J Clin Pathol *53*: 676-684, 2000.

91 Niyaz H, Zhao C and Li Y: Detection and significance of HPV16, 18 infection, P53 overexpression and telomerase activity in patients with lung cancer. Zhonghua Jie He He Hu Xi Za Zhi *23*: 679-682, 2000. Article in Chinese.

92 Cheng YW, Chiou HL, Sheu GT, Hsieh LL, Chen JT, Chen CY, Su JM and Lee H: The association of human papillomavirus 16/18 infection with lung cancer among nonsmoking Taiwanese women. Cancer Res *61*: 2799-2803, 2001.

93 Kaya H, Kotiloglu E, Inanli S, Ekicioglu G, Bozkurt SU, Tutkun A and Kullu S: Prevalence of human papillomavirus (HPV) DNA in larynx and lung carcinomas. Pathologica *93*: 531-534, 2001.

94 Miasko A, Niklinska W, Niklinski J, Chyczewska E, Naumnik W and Chyczewski L: Detection of human papillomavirus in non-small cell lung carcinoma by polymerase chain reaction. Folia Histochem Cytobiol *39*: 127-128, 2001.

95 Miyagi J, Kinjo T, Tsuhako K, Higa M, Iwamasa T, Kamada Y and Hirayasu T: Extremely high Langerhans cell infiltration contributes to the favourable prognosis of HPV-infected squamous cell carcinoma and adenocarcinoma of the lung. Histopathology *38*: 355-367, 2001.

96 Papadakis ED, Soulitzis N and Spandidos DA: Association of p53 codon 72 polymorphism with advanced lung cancer: the Arg allele is preferentially retained in tumours arising in Arg/Pro germline heterozygotes. Br J Cancer *87*: 1013-1018, 2002.

97 Plunkett M, Brestovac B, Thompson J, Sterrett G, Filion P, Smith D and Frost F: The value of HPV DNA typing in the distinction between adenocarcinoma of endocervical and endometrial origin. Pathology *35*: 397-401, 2003.

98 Aaron S, Wong E, Tyrrell D, Duggan M, Vallieres E, Jewell L, Romanowski B and Doe PJ: Interferon treatment of multiple pulmonary malignancies associated with papilloma virus. Can Respir J *11*: 443-446, 2004.

99 Cheng YW, Chiou HL, Chen JT, Chou MC, Lin TS, Lai WW, Chen CY, Tsai YY and Lee H: Gender difference in human papillomarvirus infection for non-small cell lung cancer in Taiwan. Lung Cancer *46*: 165-170, 2004.

100 Xu H, Lu DW, El-Mofty SK and Wang HL: Metachronous squamous cell carcinomas evolving from independent oropharyngeal and pulmonary squamous papillomas: association with human papillomavirus 11 and lack of aberrant p53, Rb, and p16 protein expression. Hum Pathol *35*: 1419-1422, 2004.

101 Zafer E, Ergun MA, Alver G, Sahin FI, Yavuzer S and Ekmekci A: Detection and typing of human papillomavirus in non-small cell lung cancer. Respiration *71*: 88-90, 2004.

102 Brouchet L, Valmary S, Dahan M, Didier A, Galateau-Salle F, Brousset P and Degano B: Detection of oncogenic virus genomes and gene products in lung carcinoma. Br J Cancer *92*: 743-746, 2005.

103 Coissard CJ, Besson G, Polette MC, Monteau M, Birembaut PL and Clavel CE: Prevalence of human papillomaviruses in lung carcinomas: a study of 218 cases. Mod Pathol *18*: 1606-1609, 2005.

104 Jain N, Singh V, Hedau S, Kumar S, Daga MK, Dewan R, Murthy NS, Husain SA and Das BC: Infection of human papillomavirus type 18 and *p53* codon 72 polymorphism in lung cancer patients from India. Chest *128*: 3999-4007, 2005.

105 Wu MF, Cheng YW, Lai JC, Hsu MC, Chen JT, Liu WS, Chiou MC, Chen CY and Lee H: Frequent $p16^{INK4a}$ promoter hypermethylation in human papillomavirus-infected female lung cancer in Taiwan. Int J Cancer *113*: 440-445, 2005.

106 Castillo A, Aguayo F, Koriyama C, Shuyama K, Akiba S, Herrera-Goepfert R, Carrascal E, Klinge G, Sanchez J and Eizuru Y: Human papillomavirus in lung carcinomas among three Latin American countries. Oncol Rep *15*: 883-888, 2006.

107 Fei Y, Yang J, Hsieh WC, Wu JY, Wu TC, Goan YG, Lee H and Cheng YW: Different human papillomavirus 16/18 infection in Chinese non-small cell lung cancer patients living in Wuhan, China. Jpn J Clin Oncol *36*: 274-279, 2006.

108 Wang J, Cheng YW, Wu DW, Chen JT, Chen CY, Chou MC and Lee H: Frequent *FHIT* gene loss of heterozygosity in human papillomavirus-infected non-smoking female lung cancer in Taiwan. Cancer Lett *235*: 18-25, 2006.

109 Zhao M, Rasmussen S, Perry J and Kiev J: The human papillomavirus as a possible cause of squamous cell carcinoma: A case study with a review of the medical literature. Am Surg *72*: 49-50, 2006.

110 Aguayo F, Castillo A, Koriyama C, Higashi M, Itoh T, Capetillo M, Shuyama K, Corvalan A, Eizuru Y and Akiba S: Human papillomavirus-16 is integrated in lung carcinomas: a study in Chile. Br J Cancer *97*: 85-91, 2007.

111 Carlson JW, Nucci MR, Brodsky J, Crum CP and Hirsch MS: Biomarker-assisted diagnosis of ovarian, cervical and pulmonary small cell carcinomas: the role of TTF-1, WT-1 and HPV analysis. Histopathology *51*: 305-312, 2007.

112 Cheng YW, Wu MF, Wang J, Yeh KT, Goan YG, Chiou HL, Chen CY and Lee H: Human papillomavirus 16/18 E6 oncoprotein is expressed in lung cancer and related with p53 inactivation. Cancer Res *67*: 10686-10693, 2007.

113 Nadji SA, Mahmoodi M, Ziaee AA, Naghshvar F, Torabizadeh J, Yahyapour Y, Nategh R and Mokhtari-Azad T: Relationship between lung cancer and human papillomavirus in north of Iran, Mazandaran province. Cancer Lett *248*: 41-46, 2007.

114 Park MS, Chang YS, Shin JH, Kim DJ, Chung KY, Shin DH, Moon JW, Kang SM, Hahn CH, Kim YS, Chang J, Kim SK and Kim SK: The prevalence of human papillomavirus infection in Korean non-small cell lung cancer patients. Yonsei Med J *48*: 69-77, 2007.

115 Buyru N, Altinisik J, Isin M and Dalay N: *p53* codon 72 polymorphism and HPV status in lung cancer. Med Sci Monit *14*: CR493-CR497, 2008.

116 Wang Y, Wang A, Jiang R, Pan H, Huang B, Lu Y and Wu C: Human papillomavirus type 16 and 18 infection is associated with lung cancer patients from the central part of China. Oncol Rep *20*: 333-339, 2008.

117 Lim WT, Chuah KL, Leong SS, Tan EH and Toh CK: Assessment of human papillomavirus and Epstein-Barr virus in lung adenocarcinoma. Oncol Rep *21*: 971-975, 2009.

118 Weichert W, Schewe C, Denkert C, Morawietz L, Dietel M and Petersen I: Molecular HPV typing as a diagnostic tool to discriminate primary from metastatic squamous cell carcinoma of the lung. Am J Surg Pathol *33*: 513-520, 2009.

119 Xu Y, Cheng B, Pan H, Wu A and Zhang L: The Relationship between the status of human papillomavirus 16/18 infection and the expression of BCL-2 and BAX in squamous cell carcinomas of the lung. Zhongguo Fei Ai Za Zhi *12*: 849-852, 2009. Article in Chinese.

120 Yu Y, Yang A, Hu S and Yan H: Correlation of HPV-16/18 infection of human papillomavirus with lung squamous cell carcinomas in Western China. Oncol Rep *21*: 1627-1632, 2009.

121 Aguayo F, Anwar M, Koriyama C, Castillo A, Sun Q, Morewaya J, Eizuru Y and Akiba S: Human papillomavirus-16 presence and physical status in lung carcinomas from Asia. Infect Agent Cancer *5*: 20-28, 2010.

122 Baba M, Castillo A, Koriyama C, Yanagi M, Matsumoto H, Natsugoe S, Shuyama KY, Khan N, Higashi M, Itoh T, Eizuru Y, Aikou T and Akiba S: Human papillomavirus is frequently detected in gefitinib-responsive lung adenocarcinomas. Oncol Rep *23*: 1085-1092, 2010.

123 Branica BV, Smojver-Jezek S, Juros Z, Grgic S, Srpak N, Mitrecic D and Gajovic S: Detection of human papillomaviruses type 16, 18 and 33 in bronchial aspirates of lung carcinoma patients by polymerase chain reaction: a study of 84 cases in Croatia. Coll Anthropol *34*: 159-162, 2010.

124 Iwakawa R, Kohno T, Enari M, Kiyono T and Yokota J: Prevalence of human papillomavirus 16/18/33 infection and *p53* mutation in lung adenocarcinoma. Cancer Sci *101*: 1891-1896, 2010.

125 Joh J, Jenson AB, Moore GD, Rezazedeh A, Slone SP, Ghim SJ and Kloecker GH: Human papillomavirus (HPV) and Merkel cell polyomavirus (MCPyV) in non small cell lung cancer. Exp Mol Pathol *89*: 222-226, 2010.

126 Wang YH, Chen DJ, Yi TN and Liu XH: The relationship among human papilloma virus infection, survivin, and *p53* gene in lung squamous carcinoma tissue. Saudi Med J *31*: 1331-1336, 2010.

127 Zhang J, Wang T, Han M, Yang ZH, Liu LX, Chen Y, Zhang L, Hu HZ and Xi MR: Variation of human papillomavirus 16 in cervical and lung cancers in Sichuan, China. Acta Virol *54*: 247-253, 2010.

128 Carpagnano GE, Koutelou A, Natalicchio MI, Martinelli D, Ruggieri C, Di TA, Antonetti R, Carpagnano F and Foschino-Barbaro MP: HPV in exhaled breath condensate of lung cancer patients. Br J Cancer *105*: 1183-1190, 2011.

129 Goto A, Li CP, Ota S, Niki T, Ohtsuki Y, Kitajima S, Yonezawa S, Koriyama C, Akiba S, Uchima H, Lin YM, Yeh KT, Koh JS, Kim CW, Kwon KY, Nga ME and Fukayama M: Human papillomavirus infection in lung and esophageal cancers: analysis of 485 Asian cases. J Med Virol *83*: 1383-1390, 2011.

130 Halimi M and Morshedi AS: Human papillomavirus infection in lung vs. oral squamous cell carcinomas: a polymerase chain reaction study. Pak J Biol Sci *14*: 641-646, 2011.

131 Inamura K, Kumasaka T, Furuta R, Shimada K, Hiyama N, Furuhata Y, Tanaka I and Takemura T: Mixed squamous cell and glandular papilloma of the lung: A case study and literature review. Pathol Int *61*: 252-258, 2011.

132 Lagana SM, Hanna RF and Borczuk AC: Pleomorphic (spindle and squamous cell) carcinoma arising in a peripheral mixed squamous and glandular papilloma in a 70-year-old man. Arch Pathol Lab Med *135*: 1353-1356, 2011.

133 Mammas IN, Zaravinos A, Sourvinos G and Spandidos DA: Detection of human papillomavirus in bronchoalveolar lavage samples in immunocompetent children. Pediatr Infect Dis J *30*: 384-386, 2011.

134 Saumet L, Damay A, Jeziorski E, Cartier C, Rouleau C, Margueritte G, Rodiere M and Segondy M: Bronchopulmonary squamous cell carcinoma associated with HPV 11 in a 15-year-old girl with a history of severe recurrent respiratory papillomatosis: a case report. Arch Pediatr *18*: 754-757, 2011.

135 Doxtader EE and Katzenstein ALA: The relationship between p16 expression and high-risk human papillomavirus infection in squamous cell carcinomas from sites other than uterine cervix: A study of 137 cases. Hum Pathol *43*: 327-332, 2012.

136 Syrjänen K, Silvoniemi M, Salminen E, Vasankari T and Syrjänen S: Detection of human papillomavirus genotypes in bronchial cancer using sensitive multimetrix assay. Anticancer Res *32*: 625-631, 2012.

137 Huedo-Medina T, Sanchez-Meca J, Marin-Martinez F and Botella J: Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? CHIP Documents. 2006; Paper 19. http://digitalcommons.uconn.edu/chip_docs/19 Last accessed April 19, 2012.

138 Field AP: Meta-analysis of correlation coefficients: A Monte-Carlo comparison of fixed- and random-effects methods. Psychol Meth *6*: 161-180, 2001.

139 Field AP: The problems in using fixed-effects models of meta-analysis on real-world data. Understand Stat *2*: 77-96, 2003.

140 Cochran WG: The combination of estimates from different experiments. Biometrics *10*: 101-129, 1954.

141 Higgins JPT, Thompson SG, Deeks JJ and Altman DG: Measuring inconsistency in meta-analyses. Brit Med J *327*: 557-560, 2003.

142 Syrjänen KJ: Human Papillomavirus (HPV) Involvement in Esophageal Carcinogenesis. Nova Science Publishing, New York, USA, pp. 1-96, 2010.

143 Li YJ, Tsai YC, Chen YC and Christiani DC: Human papilloma virus and female lung adenocarcinoma. Semin Oncol *36*: 542-552, 2009.

144 Rezazadeh A, Laber DA, Ghim SJ, Jenson AB and Kloecker G: The role of human papilloma virus in lung cancer: a review of the evidence. Am J Med Sci *338*: 64-67, 2009.

145 Kountouri MP, Mammas IN and Spandidos DA: Human papilloma virus (HPV) in lung cancer: Unanswered questions. Lung Cancer *67*: 125-126, 2010.

Received April 18, 2012
Revised June 13, 2012
Accepted June 14, 2012