Solitary bronchial squamous cell papilloma – another human papillomavirus (HPV)-associated benign tumor: systematic review and meta-analysis

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Aim of the study: To perform a systematic review and formal meta-analysis of the literature reporting on HPV detection in bronchial squamous cell papillomas (SCP).

Material and methods: The literature was searched up to June 2012. The effect size was calculated as event rate (95% CI), with homogeneity testing using Cochran's Q and I^2 statistics. Meta-regression was used to test the impact of study-level covariates (HPV detection method, geographic origin) on effect size, and potential publication bias was estimated using funnel plot symmetry.

Results: Fifteen studies were eligible, covering 89 bronchial SCPs from different geographic regions. Altogether, 38 (42.7%) cases tested HPV-positive; effect size 0.422 (95% CI: 0.311–0.542; fixed effects model), and 0.495 (95% CI: 0.316–0.675; random effects model). In meta-analysis stratified by i) HPV detection technique and ii) geographic study origin, the between-study heterogeneity was not significant for either; p = = 0.348, and p = 0.792, respectively. In maximum likelihood meta-regression, HPV detection method (p = 0.150) and geographic origin of the study (p = 0.164) were not significant study-level covariates. Some evidence for publication bias was found only among *in situ* hybridization (ISH)-based studies and among studies from Europe, but with a negligible effect on summary effect size estimates. In sensitivity analysis, the meta-analytic results were robust to all one-by-one study removals.

Conclusions: In formal meta-regression, the variability in HPV detection rates reported in bronchial SCPs is not explained by the HPV detection method or geographic origin of the study.

Key words: bronchial papilloma, solitary, squamous cell, HPV, meta-analysis, meta-regression, study heterogeneity, publication bias, detection method.

Contemp Oncol (Pozn) 2013; 17 (5): 427–434
DOI: 10.5114/wo.2013.38565

Introduction

The first reports on solitary bronchial squamous cell papilloma (SCP) appeared in 1954, when three authors provided descriptions of this new entity [1–3]. It was soon recognized that bronchial SCP can also appear as multiple lesions called (tracheo)bronchial papillomatosis [4, 5]. Until the mid 1980s solitary bronchial SCP was regarded as an extreme rarity [5, 6]. When first reviewed in 1985, Maxwell *et al*. could collect only 11 such cases in the English literature [7]. As emphasized before [8], however, this number is a clear underestimate, because in addition to the cases included in their review [5–7, 9–13], a large number of bronchial SCPs had been reported, but mostly in non-English literature [14–53]. Interestingly, this same trend seems to continue in more recent reports [54–75]. According to our best estimates, the total number of bronchial SCPs (and papillomatosis) reported by now reaches several hundred cases [8].

Bronchial SCP must be considered a rare disease, and no estimates are available on their incidence rates [8]. There are two peculiar features in the clinical history of these lesions: i) a tendency to spread to multiple sites within the bronchial tree [4, 10, 14, 19, 25, 30, 32, 34, 43, 47, 48, 52, 63, 75], and ii) a substantial potential for malignant transformation [2, 8, 11, 27, 39, 40, 50, 51, 57, 58, 66, 71]. These two characteristics strongly implicate an infectious etiology of bronchial SCPs. Indeed, their clinical behavior closely resembles that of recurrent respiratory papillomatosis (RRP) [8], and natural history of sinonasal papillomas.

While the etiologic role of human papillomavirus (HPV) in RRP is well established [8], the possible involvement of this virus in sinonasal papillomas was first suggested by us in 1983 [76], based on detection of HPV antigen expression in a single papilloma. This was soon confirmed by demonstration of HPV DNA in a series of cases [77], and HPV involvement in sinonasal papillomas is well established at present [78].

The first clue on possible HPV involvement in bronchial SCPs was provided by two cytological reports from 1975 and 1979, when Roglic *et al*. [79] and Rubel *et al*. [80], respectively, described characteristic cytopathic changes of HPV (i.e., koilocytosis) in the sputum samples, thus emphasizing their similarity to genital HPV lesions (condyloma). This coincides with the observations of us, who in 1979 were the first to describe similar evidence in malignant bronchial squamous cell neoplasia [81, 82]. However, it took almost a decade until Trillo and Guha (in 1988) first demonstrated HPV antigens and identified

HPV particles in two bronchial SCPs [83]. The interest in bronchial SCP as a potential HPV-associated benign tumor increased slowly throughout the 1990s [8]. When first reviewed in 2002, the literature reporting HPV detection in bronchial SCPs included 9 studies covering 61 SCP cases, of which 29 (47.5%) tested HPV-positive [84].

With the widespread implementation of prophylactic HPV vaccines, it has become increasingly important to estimate the total disease burden (in addition to genital lesions) potentially preventable by the current and new generation HPV vaccines [85, 86]. To cast further light on the controversial role of HPV in bronchial SCP, it was felt appropriate to conduct a systematic review and formal meta-analysis, covering all the published literature without any restrictions to the HPV detection methods or geographic origin of the study.

Material and methods

Data abstraction

We identified eligible studies by searching MEDLINE (via PubMed) and reference lists from original articles, book chapters and other reviews until June 2012. No language or date-of-publication limitations were imposed. The search terms included: papillomavirus, HPV, papilloma, solitary, squamous cell, bronchus, bronchial, papillomatosis, malignant transformation. We considered all publications appearing in peer-reviewed journals eligible, irrespective of which method (see later) was used for HPV detection, provided that the report included exact numbers of analyzed cases and those testing HPV-positive, necessary for calculation of the event rates (= HPV prevalence) and their 95% confidence intervals (95% CI).

Altogether, > 400 abstracts were derived from the database, covering the years 1954 to 2012. For the present meta-analysis, a total of 15 original studies were determined eligible, all including cases of bronchial papillomas analyzed for HPV detection. Because they were included in a recent meta-analysis, all studies reporting only bronchial carcinomas were excluded from this meta-analysis.

From the summaries and/or body texts of each eligible study, we abstracted the following information: HPV detection method, geographic region of the study, HPV genotypes analyzed and/or detected, total number of cases analyzed, number testing HPV-positive, per cent HPV-positivity, authors, and publication year. Only the studies reporting HPV in solitary bronchial papillomas or cases of bronchial papillomatosis were included, whereas all studies describing tracheobronchial spread of RRP and/or their malignant conversion were excluded.

Statistical analyses

The specific software Comprehensive Meta Analysis™ (Version 2.2.064; Biostat Inc., Englewood, NJ, USA) was used to perform the meta-analysis. 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 [87]. To evaluate the possible publication bias, funnel plots were drawn by plotting the logit event rates by their precision (1/SE) [88]. Funnel plots were evaluated for asymmetry using the following statistics: i) Begg and Mazumdar rank correlation [89], ii) Egger's test of the intercept (regression) [90], and iii) Duval and Tweedie's "trim and fill" method [91], which imputes the results that are hypothetically missing due to the publication bias.

To assess the variation in the event rates (i.e., HPV prevalence) due to the differences between the individual studies, we evaluated the study characteristics 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. Restricted maximum likelihood meta-regression formally compares these differences in event rates across the selected study-level covariates and estimates the among-study variance [92]. Given the inherent differences in analytical sensitivities between the different HPV detection methods – immunohistochemistry (IHC), *in situ* hybridization (ISH), and polymerase chain reaction (PCR) – meta-analyses were performed across these strata. Similarly, to distinguish true study-specific effects from random variation, all analyses were also stratified by the geographic regions of their origin, blamed as one of the reasons for variability in HPV prevalence [8, 45]. HPV detection method and geographic study origin were also tested as study-level covariates in formal meta-regression.

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 = 14) 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 magnitude and precision of the random-effects summary event rates (point estimates).

Results

Eligible studies

A total of 15 studies were considered eligible for the present analysis [58, 70, 74, 83, 93–103], comprising 89 bronchial SCPs analyzed by different HPV detection methods. Included are both case reports and larger series, comprising up to 31 cases analyzed by PCR [98] and 15 papillomas examined by ISH [94] (Table 1). The methods used to evaluate the HPV involvement include the following: IHC [83], ISH [58, 70, 74, 93–97, 102], and PCR [98–101, 103]. Based on the available data on geographic regions with different HPV prevalence, the studies were categorized into the following regions of origin: Other Asia (China excluded), Europe, and North America. These 15 studies comprise the target of this meta-analysis. Of all analyzed 89 bronchial SCPs, 38 (42.7%) tested HPV-positive.

Analytical results

Point estimates of event rates

The crude HPV-positivity (38/89) translates to event rates (i.e., effect size, summary HPV prevalence) of 0.422 (95%

Table 1. Studies reporting on HPV detection in solitary bronchial squamous cell papillomas

Method/histological type		HPV positive					
Detection method*	Histological type	Area or country	HPV types detected	Number/ total	%	Authors and year	Ref. No
IHC, EM	SCP	Canada	–	2/2	100	Trillo *et al*. 1988	[83]
ISH	SCP	USA	6/11	1/1	100	Kerley *et al*. 1989	[93]
ISH	SCP	France	11	1/1	100	Bejui-Thivolet *et al*. 1990	[58]
ISH	SCP	UK	16	1/15	6.7	Carey *et al*. 1990	[94]
ISH	SCP	Austria	6/11	6/6	100	Popper *et al*. 1992	[95]
ISH	SCP	USA	6/11	2/2	100	Yousem *et al*. 1992	[96]
ISH	SCP	USA	6/11	1/1	100	Katial *et al*. 1994	[97]
PCR, ISH	SCP	Austria	6, 11, 16, 18	11/31	35.5	Popper *et al*. 1994	[98]
PCR, ISH	SCP	USA	6, 11, 16, 18	5/14	35.7	Flieder *et al*. 1998	[99]
PCR	SCP	Japan	11	1/1	100	Kawaguchi *et al*. 1999	[100]
PCR, ISH	SCP	Japan	6, 16	1/1	100	Harada *et al*. 2000	[101]
ISH	SCP	France	–	0/1	0.0	Paganin *et al*. 2009	[70]
ISH, PCR	SCP	Japan	–	0/1	0.0	Inamura *et al*. 2011	[102]
PCR	SCP	USA	–	0/1	0.0	Lagana *et al*. 2011	[103]
ISH	SCP	USA	–	1/3	33.3	Lang *et al*. 2011	[74]

**Method listed first was used as the HPV detection method in meta-analysis database, EM – electron microscopy, IHC – immunohistochemistry, ISH – in situ hybridization, PCR – polymerase chain reaction, SCP – squamous cell papilloma*

CI: 0.311–0.542), using the fixed effects (FE) model, and 0.495 (95% CI: 0.316–0.675), using the random effects (RE) model (Fig. 1). Table 2 depicts the meta-analytic results of those 15 studies, stratified by the HPV detection technique. There is significant heterogeneity only between the studies ($n = 9$) using ISH, as measured by Cochran's Q statistic, with $p = 0.038$. This heterogeneity becomes of borderline significance in comparison within strata ($p = 0.056$), and disappears in comparison between strata (random effects model, $p = 0.348$). The percentage of variation (I^2) is higher (50.9%) for ISH-based studies than among PCR studies (7.0%). Using the RE model, studies based on ISH give higher point estimates of HPV prevalence (0.534, i.e. 53.4%), as compared with PCR studies (39.1%).

Model	Study name	Subgroup within study	Method	Year	Statistics for each study						Event rate and 95% CI
					event rate	lower limit	upper limit	*Z*-value	*p*-value	total	
	Trillo *et al*.	SCP	IHC	1988	0.833	0.194	0.990	1.039	0.299	2/2	
	Kerley *et al*.	SCP	ISH	1989	0.833	0.194	0.990	1.039	0.299	2/2	
	Carey *et al*.	SCP	ISH	1990	0.067	0.009	0.352	–2.550	0.011	1/15	
	Bejui-Thivolet *et al*.	SCP	ISH	1990b	0.833	0.194	0.990	1.039	0.299	2/2	
	Popper *et al*.	SCP	ISH	1992	0.929	0.423	0.996	1.748	0.081	6/6	
	Yousemat *et al*.	SCP	ISH	1992	0.833	0.194	0.990	1.039	0.299	2/2	
	Popper *et al*.	SCP	PCR	1994	0.355	0.209	0.534	–1.593	0.111	11/31	
	Katial *et al*.	SCP	ISH	1994	0.833	0.194	0.990	1.039	0.299	2/2	
	Flieder *et al*.	SCP	PCR	1998	0.357	0.157	0.624	–1.054	0.292	5/14	
	Kawaguchi *et al*.	SCP	PCR	1999	0.833	0.194	0.990	1.039	0.299	2/2	
	Harada *et al*.	SCP	PCR	2000	0.833	0.194	0.990	1.039	0.299	2/2	
	Paganin *et al*.	SCP	ISH	2009	0.167	0.010	0.806	–1.039	0.299	0/2	
	Inamura *et al*.	SCP	ISH	2011	0.167	0.010	0.806	–1.039	0.299	0/2	
	Lagana *et al*.	SCP	PCR	2011	0.167	0.010	0.806	–1.039	0.299	0/2	
	Lang *et al*.	SCP	ISH	2011	0.333	0.043	0.846	–0.566	0.571	1/3	
Random					0.495	0.316	0.675	–0.054	0.957	38/89	

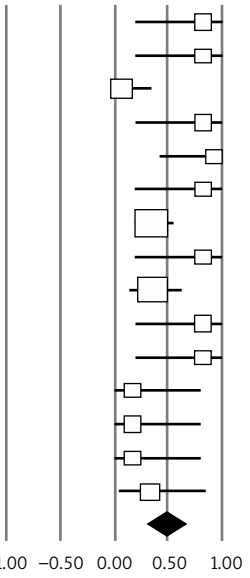

Fig. 1. Forest plot of the 15 studies reporting on HPV detection in bronchial SCPs

Table 2. Meta-analysis of the 15 studies* stratified by the HPV detection method

Detection method	No. of studies	Events	Sample size	Point estimates of event rates (fixed effects model)		Point estimates of event rates (random effects model)		Homogeneity (Cochran's Q)**	I-squared (I^2)**	Homogeneity (*p*-value)**
				Point estimate	95% CI	Point estimate	95% CI			
IHC	1	2	2	0.833	0.194–0.990	0.833	0.194–0.990	0.000	0.000	1.000
ISH	9	16	36	0.478	0.268–0.697	0.534	0.232–0.812	16.317	50.971	0.038
PCR	5	20	51	0.384	0.259–0.526	0.391	0.252–0.549	4.305	7.082	0.366
Summary	15	38	89	0.422	0.311–0.542	0.434	0.302–0.575	22.690	38.300	0.065
Total within (FE)								20.622		0.056
Total between (FE)								2.069		0.355
Total between (RE)								2.112		0.348

**All studies reporting only bronchial carcinomas are omitted;*
***only calculated for fixed effects model*
IHC – immunohistochemistry, ISH – in situ hybridization, PCR – polymerase chain reaction, FE – fixed effects model, RE – random effects model

When stratified by the geographic origin of the study (Table 3), there is significant heterogeneity ($p = 0.027$) only between the studies from Europe, with the percentage of variation up to 63.6%. The highest summary effect size (63.1%) is derived from studies reported from Other Asia, followed by those conducted in USA/Canada (51.7%), and Europe (41.1%). In the between-strata comparisons using the RE model, the difference in results is not significant ($p = 0.792$), indicating that the heterogeneity between the studies from different geographic regions is not statistically significant.

Meta-regression

In meta-regression testing HPV detection methods as study-level covariates (Table 4), none of the methods resulted in summary point estimates that were significantly different from the reference (IHC), including the effect size difference (0.052) between ISH and PCR methods ($p = 0.626$). The HPV detection method was not a significant study-level covariate ($p = 0.150$ for regression coefficient $\beta 1$ or effect parameter). The same was true when only the studies using ISH ($n = 9$) or PCR ($n = 5$) were included in this meta-regression ($p = 0.484$).

Using Other Asia as the reference, the effect size differences to the other geographic regions are not statistically significant ($p = 0.139$ and $p = 0.510$) (Table 5). In formal meta-regression, the geographic origin of the study did not have a significant impact on the effect size ($p = 0.164$).

Publication bias

There was little evidence for publication bias among studies based on ISH: Begg $p = 0.301$, Egger's $p = 0.019$, Duval and Tweedie's trim and fill (RE) method identified no missing studies. For studies using PCR, there was some evidence of publication bias (Begg $p = 0.231$; Egger's $p = 0.161$), but Duval and Tweedie's trim and fill (FE and RE) method imputed 1 hypothetically missing study, with a marginal effect on adjusted point estimates (from 0.391 to 0.373).

There was no evidence for publication bias among studies ($n = 3$) from Other Asia and Europe ($n = 5$). For studies

Table 3. Meta-analysis of the 15 studies* stratified by their geographic origin

Detection method	No. of studies	Events	Sample size	Point estimates of event rates (fixed effects model)		Point estimates of event rates (random effects model)		Homogeneity (Cochran's Q)**	I-squared (I^2)**	Homogeneity (*p*-value)**
				Point estimate	95% CI	Point estimate	95% CI			
Other Asia	3	4	6	0.631	0.229–0.908	0.631	0.173–0.933	2.878	30.510	0.237
Europe	5	20	56	0.356	0.226–0.513	0.411	0.127–0.770	10.989	63.601	0.027
North America	7	14	27	0.486	0.297–0.678	0.517	0.297–0.730	6.808	11.867	0.339
Summary	15	38	89	0.422	0.311–0.542	0.507	0.328–0.685	22.690	38.300	0.065
Total within (FE)								20.675		0.055
Total between (FE)								2.015		0.365
Total between (RE)								0.467		0.792

**All studies reporting only bronchial carcinomas are omitted*
***Only calculated for fixed effects model*
FE – fixed effects, RE – random effects

Table 4. Effect of HPV detection method on the effect size in maximum likelihood meta-regression

Study-level covariates HPV detection method	No. of studies (homogeneity *p*-value)**	Effect size*		Difference in effect size estimates	
		Point estimate	95% CI	Difference in point estimates	95% CI
IHC	1 (p = 1.000)	0.833	0.194–0.990	1.000	
ISH	9 (p = 0.038)	0.534	0.232–0.812	0.555[1]	0.393–0.717
PCR	5 (p = 0.366)	0.391	0.252–0.549	0.607[2]	0.473–0.741
Meta-regression for all methods	Slope: –0.409 (95% CI: –0.968–0.148) (p = 0.150): Intercept: 2.389 (95% CI: –1.327–6.107) (p = 0.207)				
ISH	9 (p = 0.038)	0.534	0.232–0.812	1.000	
PCR	5 (p = 0.366)	0.391	0.252–0.549	0.052[3]	–0.158–0.262
Meta-regression (ISH/PCR)	Slope: –0.386 (95% CI: –1.469–0.697) (p = 0.484): Intercept: 2.231 (95% CI: –5.062–9.525) (p = 0.548)				

**Random effects model*
***Cochran's Q; IHC, immunohistochemistry*
[1]p = 0.126
[2]p = 0.087
[3]p = 0.626
ISH – in situ hybridization, PCR – polymerase chain reaction, Slope; effect parameter (= regression coefficient β_1), Intercept (= coefficient β_0)

Table 5. Effect of geographic origin of the study on the effect size in maximum likelihood meta-regression

Study-level covariates Geographic Origin of Study	No. of studies (homogeneity *p*-value)**	Effect size*		Difference in effect size estimates	
		Point estimate	95% CI	Difference in point estimates	95% CI
Other Asia	3 (p = 0.237)	0.631	0.173–0.933	1.000	0.321–0.604
Europe	5 (p = 0.027)	0.411	0.127–0.770	0.309[1]	–0.088–0.707
North America	7 (p = 0.339)	0.517	0.297–0.730	0.148[2]	–0.273–0.569
Meta-Regression for all areas	Slope: 0.409 (95% CI: –0.167–0.987) p = 0.164; Intercept: –1.373 (95% CI –2.944–0.196) p = 0.086				

**Random effects model*
***Cochran's Q*
[1]p = 0.139
[2]p = 0.510
Slope; effect parameter (= regression coefficient β_1), Intercept (= coefficient β_0)

(n = 7) from North America, there was some evidence for publication bias (Begg p = 0.088; Egger's p = 0.0691), and Duval and Tweedie's trim and fill (FE and RE) method imputed 2 hypothetically missing studies, with a marginal effect on adjusted point estimates (from 0.517 to 0.441).

Sensitivity analysis

Meta-analytic results seemed relatively robust to all (n = 14) one-by-one study removals, with little change in the magnitude and precision of the FE and RE summary point estimates of the effect size. The single most influential study was the one with the highest sample size (n = 31) [98], the removal of which would increase the summary effect size from 0.422 to 0.475 (FE model) and from 0.495 to 0.538 (RE model).

Discussion

The role of HPV in etiology of bronchial papillomas has received increasing interest since the late 1970s, when the first evidence was provided [79–82]. The accumulated literature has been reviewed most recently some 10 years ago [8, 84], but no formal meta-analysis has been published as yet. The formal meta-analysis presented in this communication covers all the published literature reporting HPV detection in bronchial SCPs (n = 15 studies), and also updates the author's own review of 2002 [84]. Importantly, the authors did not make any restrictions as to the HPV detection methods, although some of the early HPV detection techniques (IHC) are obsolete by now. This was just to validate by formal meta-analysis and meta-regression the frequently presented concept that the wide variation in HPV prevalence in bronchial SCPs might be explained by different detection techniques [8, 84]. The other study-level covariate addressed in this meta-analysis and meta-regression is the geographic origin of the study, also listed among potential causes of variation in HPV prevalence in respiratory tract neoplasia [84–86].

To evaluate 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 [87, 104–106]. The usual way of assessing whether true heterogeneity exists has been the Q test, originally introduced by Cochran (1954) [107]. Significant p-values in the Q test implicate true heterogeneity and warrant the use of a random effects (RE) model to test both within- and between-study variability. The Q statistic does not indicate the magnitude of true heterogeneity, however, but only its statistical significance [107]. On the other hand, the I^2 index, introduced by Higgins *et al.* (2003), measures the extent of true heterogeneity, expressed

as the percentage of the total between-study variability in the effect sizes [108]. 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 [104, 108].

Given the above considerations, there is little doubt that marked heterogeneity exists only between the studies ($n = 9$) using ISH, but not those using PCR ($n = 5$) methods, as estimated using the Q test and I^2 index (Table 2). This marked heterogeneity among studies comprising the bulk (9/15) of all included studies justifies the adoption of the RE model to analyze the summary statistics for heterogeneity [104–106]. Using the RE model, the most important conclusion implies that there is no true heterogeneity between the studies using different HPV detection techniques, as indicated by the non-significant homogeneity *p*-value ($p = 0.348$) for the between-study comparison, also when the FE model is used ($p = 0.355$). In other words, we can revisit the concept raised in some recent reviews [8, 84], suggesting that the differences in HPV prevalence reported in bronchial papillomas might be explained by the different HPV detection techniques. This statement is limited, however, by the relatively small number of studies reporting on HPV detection in these lesions.

An alternative view suggests that this variable HPV prevalence would be related to the different geographic regions of the study origin [8, 84]. To evaluate this concept, we performed our meta-analyses stratified by the geographic origin of studies (Table 3). Both the Q test and the I^2 index demonstrate a statistically significant heterogeneity ($p = 0.027$, $I^2 = 63.6\%$) only between the studies ($n = 5$) derived from Europe, but not among those from the other two geographic regions (Other Asia, North America). However, when the RE model was used to calculate the summary statistics, the homogeneity *p*-value was 0.792 for the between-strata comparison. This implies that the seemingly wide variation (11.8–63.6%) in HPV prevalence from different geographic regions is not significant according to the strict meta-analytical criteria. Noteworthy, however, is that the highest summary effect size estimates (63.1% for Other Asia) are based on a small number ($n = 3$) of studies only, while the lower estimates (41.1–51.7%) are derived from at least 5 to 7 studies (Table 3). In this respect, we should also keep in mind one of the shortcomings of the Q statistic, i.e., it has a poor power to detect true heterogeneity in a meta-analysis including a small number of studies, but excessive power to detect even insignificant variability when a large number of studies is included [87, 104–108].

We also performed meta-regression to formally compare these differences in summary effect sizes [92]. In meta-regression with the HPV detection method as the covariate, the regression coefficient for the effect parameter ($\beta 1$, or slope) was not statistically significant ($p = 0.150$). The same is true when the geographic origin of the study ($p = 0.164$) was tested for its impact as the study-level covariate. These data formally confirm that HPV detection method and geographic origin of the study are not significant study-level covariates accounting for the heterogeneity of HPV prevalence in bronchial papilloma studies. The results of meta-regression did not change if only the studies based on ISH and PCR were included in the analysis. Thus, despite the seemingly higher summary HPV prevalence derived from ISH studies (53.4%) as compared with the PCR studies (39.1%), this difference does not reach statistical significance ($p = 0.484$).

Some evidence for publication bias was detected, but this usually had an insignificant effect on the adjusted point estimates in stratified meta-analysis. There was no evidence for publication bias among ISH-based studies, and the slight publication bias revealed among the PCR studies resulted only in a negligible drop of the point estimates (from 39.1% to 37.3%). As to the geographic areas, some publication bias was evidenced only among the studies from North America. Thus, for this region, Duval and Tweedie's trim and fill (both FE and RE) method imputed 2 hypothetically missing studies, with a marginal impact on summary point estimates (51.7% to 44.1%). Thus, it remains to be seen whether the future studies from this region will report somewhat lower HPV prevalence than the summary effect size (51.7%) derived from the currently available studies.

In sensitivity analysis, based on one-by-one removal of all 15 studies, all meta-analytic results seemed relatively robust to all removals, with no major change in the magnitude or precision of either the FE or RE summary point estimates of the effect size (Fig. 1). In a meta-analysis based on such a small number of studies, and relatively small number of analyzed cases ($n = 89$), however, it is expected that the most influential studies are those based on the largest number of cases, and/or those with very low or very high event rates. In this analysis, such a single study was that by Popper *et al*. [98], reporting HPV prevalence of 35.5% (11/31) in a series of 31 bronchial SCPs. The relative (fixed) weight of this single study is 42.9, and even if reporting an effect size (0.355) far below the summary effect size (0.495) derived from all studies, removal of this study from the meta-analysis would increase the summary effect size (random) only from 0.495 to 0.538, i.e., by 4.3%. To be truly influential, any such hypothetical study should include over a hundred cases and demonstrate HPV prevalence markedly deviating (down- or upwards) from the summary effect size derived from the existing 15 studies.

Taken together, these meta-analytical results based on all published literature ($n = 15$ eligible studies) on HPV detection in bronchial squamous cell papillomas imply that HPV prevalence varies according to i) HPV detection method, and ii) geographic origin of the study. In stratified meta-analysis and meta-regression, however, this variability is not significantly associated with either of these two study-level covariates. Because not formally confirmed by the meta-regression, it seems premature to conclude that bronchial papillomas in different geographic regions have a different etiology, as hypothesized in some recent studies for bronchial cancer [109]. Large multi-center studies based on larger series, as well as prospective cohort studies, are needed to better elucidate the impact of HPV in pathogenesis of bronchial papillomas (papillomatosis), which are a not infrequent accompaniment of their (synchronous or metachronous) malignant counterparts, i.e., bronchial squamous cell carcinoma [2, 8, 11, 27, 39, 40, 50, 51, 57, 58, 66, 71, 84].

The authors declare no conflict of interests.

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Submitted: 18.12.2012
Accepted: 16.07.2013