



## Human papilloma virus in non-small cell lung cancer in never smokers: A systematic review of the literature



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### ABSTRACT

Non-small cell lung cancer (NSCLC) in never smokers has emerged as a global public health issue. The cause is still unclear, and few studies have focused on the prevalence of human papillomavirus (HPV) in the never smokers. We performed a systematic search of PubMed for articles of HPV infection in human subjects with NSCLC up to September 2012. Although smoking status was not fully reported in all studies, we contacted the authors by e-mail to supplement this information. Differences in the distribution of patients with and without HPV infection were tested with the Chi squared test. We identified 46 eligible articles, including 23 from Asian countries ( $N = 2337$  NSCLC cases), 19 from European countries ( $N = 1553$ ) and 4 from North and South America ( $N = 160$ ). The HPV prevalence was 28.1% (95% confidence interval (CI) 26.6–30.3%), 8.4% (95% CI 7.1–9.9%) and 21.3% (95% CI 15.2–28.4%), respectively. Eleven studies from East Asia ( $N = 1110$ ) and 4 from Europe ( $N = 569$ ) provided information on smoking status. The number of never smoker was 392 patients (33.9%) in East Asia and 54 patients (14.8%) in Europe. The HPV prevalence in East Asian countries was similar between never and ever smokers (33.9% vs 39.2%,  $P = 0.080$ ). Based on the literature confirming the presence of HPV in lung cancer in never smokers, the virus plays a role in carcinogenesis in the disease. There were different patterns of HPV prevalence between Asian and European countries in the never smokers as well as in ever smokers.

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### 1. Introduction

Lung cancer is one of the leading causes of cancer-related deaths worldwide. Although tobacco smoking is responsible for about 90% of lung cancer cases, the epidemiology of lung cancers remains partially unresolved since the vast majority of tobacco users do not develop such tumors. In fact, there were about 30% never smokers in Japan in a large cohort study including more than 20,000 patients with non-small cell lung cancer (NSCLC) [1]. In the global estimates, never smoker lung cancer mortality would rank as the seventh most common fatal cancer [2], and it is as common a cause of death as

cancer of the liver or of the esophagus [3]. NSCLC in never smokers has emerged as a global public health concern. Identification of the molecular mechanism for this disease is urgently needed to improve therapeutic strategies. In addition to tobacco smoking, a number of etiological factors have been proposed and the infection with oncogenic type of human papillomavirus (HPV) has been considered as one of those [4].

It is well known that certain HPV types cause essentially all human cervical cancer. Several studies have examined the possible involvement of HPV in non-genital cancers and have proposed the presence of HPV in esophageal, laryngeal, oropharyngeal, urothelial, breast, colon and lung cancers during the last two decades [5]. Since the virus can infect oral mucosa and subsequently larynx and bronchial tissue, this may be the main source of HPV detected in the lung [6]. Actually, Carpagnano demonstrated the presence of HPV in the exhaled breath condensate of lung cancer patients [7]. A meta-analysis showed that the prevalence of HPV in lung cancer is highly

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variable around the world and the higher frequencies are found in East Asian countries when compared with European countries [8]. The association between HPV infection and lung cancer was suggested to be geographical and race dependent.

Although HPV infection to NSCLC has been widely investigated in Asia, few studies have focused on prevalence of HPV in NSCLC in never smokers. We conducted and report here a systematic review on the issue above.

## 2. Materials and methods

### 2.1. Literature search and data extraction

We performed a systematic search of MEDLINE database using PubMed for articles of HPV infection in human subjects with NSCLC up to September 2012. Systematic search was performed using the keywords, “lung or bronchogenic”, “cancer or carcinoma or neoplasm” and “HPV or human papillomavirus.” All searches were limited to human studies and the English language. We included studies that used the lung tissue of patients diagnosed by histopathology to have primary NSCLC and excluded studies that used blood samples. The polymerase chain reaction (PCR) as the primary HPV detection method was included in our analysis. Therefore, studies were excluded because the primary method was in situ hybridization, immunohistochemistry, Southern blot, and Hybrid Capture II.

All studies were retrieved independently by two investigators (Y.H. and S.Y.) to assess the reliability of data extraction. After selection of potential studies, the investigators reviewed each other's selected studies and excluded inappropriate studies with the agreement of both. Disagreements were adjudicated by a third reviewer after referring to the original articles.

If the smoking status was not reported in a study, we contacted the authors by e-mail to supplement this information.

### 2.2. Statistical analysis

Differences in the distribution of patients with and without HPV infection were tested with the Chi squared test. The  $I^2$  statistics was used to assess heterogeneity across studies, and  $I^2 < 25$ ,  $25 \leq I^2 < 50$ , and  $50 \leq I^2$  was interpreted as signifying low-level, intermediate-level, and high-level heterogeneity, respectively [9].

A  $P$ -value  $< 0.05$  was considered statistically significant, and all reported  $P$ -values were two-sided. The Eggers' test and Begg's funnel plots were calculated using Comprehensive Meta-Analysis version 2 (Biostat Inc., Englewood, NJ). All other statistical analyses were performed with SPSS 16.0 for Windows software (SPSS, Chicago, IL).

## 3. Results

### 3.1. HPV prevalence

We identified 46 eligible articles (supplemental Table A1), including 23 from Asian countries ( $N = 2337$  NSCLC cases), 19 from European countries ( $N = 1553$ ) and 4 from North and South America ( $N = 160$ ). The HPV prevalence was 28.1% (95% confidence interval (CI) 26.6–30.3%), 8.4% (95% CI 7.1–9.9%) and 21.3% (95% CI 15.2–28.4%), respectively. From these studies, there were regional differences between Asian, European and American studies (Fig. 1) including a significantly higher prevalence of HPV among lung cancer patients in Asia compared with European and American studies. When the analysis was limited to HPV types 16 and 18 which have higher oncogenic risk, a significantly higher prevalence was observed in Asia (23.1%, 95% CI 21.5–25.2%,  $N = 2307$ )

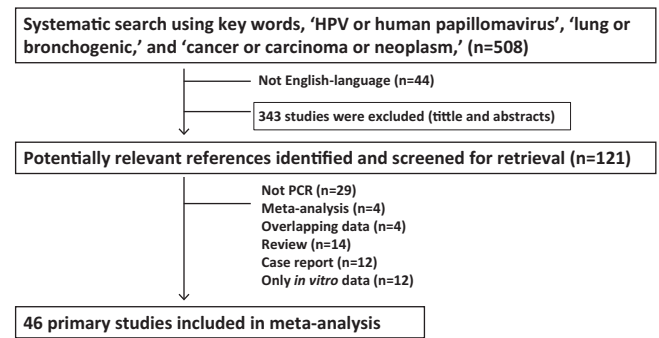


Fig. 1. Flow chart diagram showing retrieved citations from literature searches and the number of trials analyzed.

than in Europe (4.4%, 95% CI 3.5–5.2%,  $N = 1434$ ,  $P < 0.001$ ) or America (15.6%, 95% CI 10.3–22.1%,  $N = 160$ ,  $P = 0.003$ ). Apart from the worldwide regional difference, lung cancer associated with HPV infection was not evenly distributed within Japan. It was particularly high in Okinawa (43.9%, 95% CI 37.7–50.2%,  $N = 255$ ), south of mainland Japan, but it was notably low in Tokyo (0.3%, 95% CI 0.7–1.6%,  $N = 341$ ).

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.lungcan.2013.10.002>.

The prevalence of HPV in adenocarcinoma patients was slightly higher in Asia (9.8%, 95% CI 7.8–12.1%,  $N = 796$ ) than in Europe (6.8%, 95% CI 4.8–9.2%,  $N = 564$ ). Additionally, the prevalence of HPV in squamous cell carcinoma is significantly higher in Asia (33.2%, 95% CI 30.4–36.1%,  $N = 796$ ) than in Europe (9.5%, 95% CI 7.5–11.9%,  $N = 1090$ ,  $P < 0.001$ ).

### 3.2. HPV prevalence in lung cancer in never smokers

Because smoking status was not fully reported in all studies, we contacted the authors by e-mail to supplement this information. Eleven studies from East Asia [10–20] ( $N = 1110$ ), four from Europe [7,21–23] ( $N = 569$ ) and one from America [24] ( $N = 30$ ) provided information on smoking status (Table 1). These data showed the distribution of HPV infection with NSCLC in never smokers (31.4%, 95% CI 27.2–35.9%,  $N = 452$ ). However, there was no HPV detected in the two studies in Japan, one study in China, Italy and Croatia. Almost half of these studies in East Asia consisted of those from Japan. Geographically lung cancer associated with HPV in never smokers was not evenly distributed in Japan. It was relatively high in Kagoshima (23.7%, 95% CI 11.4–40.2%,  $N = 38$ ), the southwestern tip of the mainland Japan. The prevalence of HPV in never smokers was significantly higher in East Asia (33.9%, 95% CI 29.2–38.9%,  $N = 392$ ) than in Europe (14.8%, 95% CI 6.6–27.1%,  $N = 58$ ,  $P = 0.005$ ). While the HPV prevalence in East Asia was similar between never and ever smokers (33.9% vs 39.2%,  $P = 0.080$ ), it was significantly higher in never smokers than in ever smokers (14.8% vs 2.9%,  $P < 0.001$ ) in Europe (Fig. 2).

The pie chart in East Asian shows that not only smokers were prone to HPV but also never smokers (Fig. 3). The prevalence of HPV in never smokers was 68.7% (95% CI 58.6–77.6%,  $N = 105$ ) in Taiwan, 60.0% (95% CI 36.1–80.9%,  $N = 20$ ) in Korea, 23.8% (95% CI 17.6–31.0%,  $N = 168$ ) in central part of China and 12.4% (95% CI 6.8–20.2%,  $N = 105$ ) in Japan.

### 3.3. Publication bias

Potential publication bias was evaluated using the Eggers' test and Begg's funnel plots with log-transformed hazards calculated from prevalence rate (horizontal axis) as the outcome and their

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