Literature Review

Viral Intrusion: Unveiling the Role of Human Papillomavirus in Primary Lung Cancer – A Systematic Review and Meta-analysis

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Abstract

Background: The role of human papillomavirus (HPV) in lung carcinogenesis remains debated. This systematic review and meta-analysis evaluated the association between HPV infection and lung cancer risk, as well as its potential prognostic implications.

Method: A systematic search of PubMed, ScienceDirect, and Google Scholar (2015–2025) identified observational studies reporting HPV status in both lung cancer cases and non-cancer controls. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a random-effects model. Assessment of heterogeneity was performed using the I^2 statistic, and publication bias was examined using a funnel plot and Egger's test. Studies lacking control groups or effect sizes were narratively summarized.

Results: Nine studies (n=3,871,842) were included, yielding a pooled OR of 2.62 (95% CI=1.86–3.68), indicating higher odds of lung cancer among HPV-infected individuals. Substantial heterogeneity was observed (I^2=83.3%; P<0.001), and publication bias was detected (Egger's test P=0.015). An additional 26 studies were narratively synthesized, many detecting HPV DNA mainly types 16 and 18 in lung tumors, particularly among non-smokers, females, and EGFR-mutated adenocarcinomas. Considerable variation in geographic origin, histology, detection method, and specimen type was also observed.

Conclusion: HPV infection is significantly associated with an increased risk of lung cancer, suggesting its possible role as a risk and prognostic biomarker. However, the presence of publication bias and heterogeneity underscores the need for further large-scale, standardized studies to validate these findings.

Keywords: carcinogens, human papillomavirus, lung cancer, meta-analysis

INTRODUCTION

Lung cancer, a malignancy that originates in the epithelial cells lining the bronchi and alveoli of the lungs, is a primary global health concern and the leading cause of cancer-related deaths worldwide.[1,2] According to GLOBOCAN estimates, lung cancer accounted for 2.2 million new cases and 1.8 million deaths in 2020, rising to 2.5 million new cases and 1.82 million deaths by 2022.[3,4]

Men consistently show a higher incidence rate than women. While high-income countries have seen a decline in cases following successful smoking cessation programs, incidence continues to rise in many middle-income countries due to ongoing tobacco use and environmental pollution.[5] Notably, the prevalence and mortality burden are disproportionately higher in Asia compared to Europe. This reflects differences in tobacco consumption patterns, air quality, and access to early detection programs.

In Indonesia, lung cancer is a significant cause of mortality, with 38,900 new cases and 34,300 deaths reported in 2022. The age-standardized incidence rates were considerably higher in men (21.3 per 100,000) than in women (6.4 per 100,000).[6] Projections suggest that if no preventive measures are taken, the incidence could double by 2040.[7]

Multiple causes are linked to the development of primary lung cancer, including tobacco smoking, environmental exposures to particulate matter, genetic susceptibility, and viral infections.[8,9] Among these, HPV infection has attracted increasing attention due to its well-established oncogenic role in anogenital and oropharyngeal cancers.[10] HPV, particularly high-risk types such as HPV-16 and HPV-18, has been detected in lung tumors, especially squamous cell carcinomas, and is associated with an increased lung cancer risk, especially in never-smokers, women, and Asian populations.[11,12]

Although the precise routes of HPV transmission to the lungs are not fully understood, the virus may travel through oral-genital contact, inhalation of infected droplets, or hematogenous (bloodstream) spread. Oral HPV infection is widespread, with a higher prevalence in men (10%) than women (3.6%), and is often transmitted through oral sex.[13–16] While the body's immune system typically clears these infections, persistent oral HPV infection, particularly with high-risk types like HPV-16 and HPV-18, is a significant concern due to its strong association with oropharyngeal cancers.

Evidence is growing for a link between HPV and lung cancer, particularly in specific populations. A strong association has been observed in Asian populations, particularly among women and never-smokers.[11,12] Research has shown that HPV-infected individuals may have a significantly increased risk of developing lung cancer, with a robust link to squamous cell carcinoma.[12] Despite these findings, the exact role of HPV in lung carcinogenesis remains a subject of ongoing debate.

Thus, this systematic review aims to examine the association between HPV

infection and lung cancer and to explore its potential prognostic significance.

METHOD

A systematic literature search was conducted across PubMed, ScienceDirect, and Google Scholar to identify studies published between January 2015 and January 2025, as illustrated in Figure 1. A total of 320 potential studies were retrieved from three electronic databases. After initial screening, 288 studies underwent further evaluation. Of these, 252 studies were excluded based on study design, with the majority being experimental studies. In accordance with the inclusion criteria, there are nine possible studies.

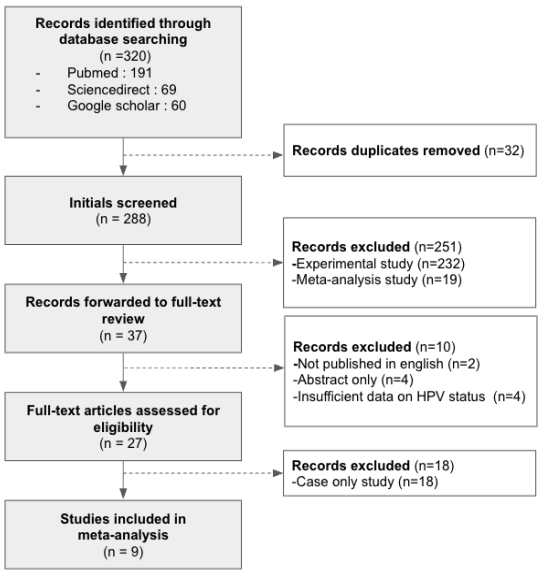


Figure 1. Flow diagram of the systematic literature search

The search terms that used were combined ("Human papillomavirus" OR "HPV") AND ("Lung cancer" OR "Pulmonary carcinoma") AND (risk OR association OR prevalence OR incidence). This process adhered to the PRISMA guidelines and was limited to observational human studies published in the English language. The reference lists of relevant articles were also manually screened to find additional studies.

Studies were included if they (1) reported original observational data (case-control and cohort); (2) involved adult patients with histologically confirmed lung cancer; (3) assessed HPV infection using molecular or clinical methods; and (4) included a control group without cancer, allowing for calculation of odds ratios (ORs) or comparable effect sizes. Studies without control groups were excluded from meta-analysis but considered for narrative synthesis. Experimental in vitro or in vivo studies, reviews, editorials, and duplicated reports were excluded.

Molecular methods refer to PCR-based HPV DNA detection (including type-specific PCR), used in seven of the nine included studies, all of case-control design. Clinical methods refer to HPV/lung cancer case ascertainment from International Classification of Diseases (ICD) coded administrative health insurance data, used in the two retrospective cohort studies, which did not perform direct molecular HPV testing.

Three reviewers independently screened titles, abstracts, and full texts using Rayyan (https://rayyan.ai), a web-based tool for systematic reviews. The three reviewers resolved discrepancies through group discussion until consensus was reached. No AI-assisted or automated screening features were used; all screening decisions were made manually.

Risk of bias was critically appraised in accordance with the Cochrane Handbook

guidelines using the ROBINS-I (Risk of Bias in Non-randomized Studies - of Interventions/Exposures) tool. Three reviewers independently evaluated each study across seven domain areas: bias due to confounding, selection of participants, classification of exposures, deviations from intended exposures, missing data, measurement of outcomes, and selection of the reported result. In line with Cochrane recommendations, quality assessment was based on domain-specific judgments (Low, Moderate, Serious, or Critical Risk of Bias).

For each included study, extracted for the author's name, publication year, country of study, study design, sample type, histological subtype of lung cancer, HPV detection method, reported HPV subtypes, and key findings. For meta-analysis, odds ratios (ORs) and 95% confidence intervals (CIs) were extracted or calculated from available raw data.

Meta-analysis was conducted using a random-effects model to account for between-study variability. Pooled ORs with 95% CIs were calculated. For the two cohort studies, ORs were likewise derived directly from raw 2×2 contingency data (HPV-positive/negative counts among lung cancer cases and controls), ensuring a consistent effect-size metric across all nine pooled studies rather than mixing OR and RR estimates. Heterogeneity was assessed using the I^2 statistic, with values >75% indicating substantial heterogeneity. Publication bias was evaluated through funnel plot asymmetry and Egger's test. All statistical analyses were performed using STATA 17.

RESULT

There are nine possible studies, including seven case-control studies and two cohort studies. Moreover, according to the Cochrane Risk of Bias ROBINS-I tool, these nine studies were ultimately included in this meta-analysis (Table 1).

Table 2 summarizes the characteristics of the nine included studies, including study design, study location, HPV genotype detected, and the number of lung cancer (LC) cases and non-cancer controls with and without HPV infection. Six studies were conducted in Asia, two in Europe, and one in the United States.

The types of specimens analyzed included paraffin-embedded tissues, frozen biopsy samples, and administrative health insurance data. Histological subtypes of lung cancer reported across the studies included squamous cell carcinoma (SCC), adenocarcinoma (AC), small cell lung cancer (SCLC), and undifferentiated carcinoma. Study-specific histological distributions are detailed in Table 2.

Control tissues were obtained from individuals diagnosed with benign pulmonary diseases or from healthy subjects. In total, the pooled sample comprised 3,871,842 individuals, of whom 1,964 individuals (0.05%) were lung cancer patients who were HPV-positive, compared to 962,404 individuals (24.85%) HPV-positive individuals in the control group.

A meta-analysis was conducted of nine observational studies to assess the relationship between HPV infection and the risk of developing lung cancer. As shown in

the forest plot (Figure 2), the pooled ORs using a random-effects model were 2.62 (95% CI=1.86–3.68), suggesting that individuals with HPV infection had significantly higher odds of developing lung cancer compared to those without HPV infection.

Table 1. Risk of bias assessment of the included observational studies using the Cochrane ROBINS-I framework

Study (year)	Study Design	Confounding	Selection of Participants	Classification of Exposure	Missing Data	Measurement of Outcome	Overall Risk of Bias
Yu et al (2015)[17]	Case-control	Low	Low	Low (PCR)	Low	Low	Low Risk
Robinson et al (2016)[18]	Case-control	Moderate	Low	Low (PCR)	Low	Low	Moderate Risk
Lu et al (2016)[19]	Case-control	Moderate	Low	Low (PCR)	Low	Low	Moderate Risk
Shikova et al (2017)[20]	Case-control	Moderate	Low	Low (PCR)	Low	Low	Moderate Risk
Rezaei et al (2021)[21]	Case-control	Low	Low	Low (PCR)	Low	Low	Low Risk
Hussen et al (2021)[22]	Case-control	Low	Low	Low (PCR)	Low	Low	Low Risk
Alikanoğlu & Karaçay (2024)[23]	Case-control	Low	Low	Low (PCR)	Low	Low	Low Risk
Lin et al (2016)[24]	Retrospective Cohort	Low	Low	Moderate (ICD codes)	Low	Low	Moderate Risk
Huang et al (2022)[25]	Retrospective Cohort	Low	Low	Moderate (ICD codes)	Low	Low	Moderate Risk

Note: ICD=International Classification of Diseases; PCR=polymerase chain reaction.

Table 2. Characteristics of the nine eligible studies in the meta-analysis

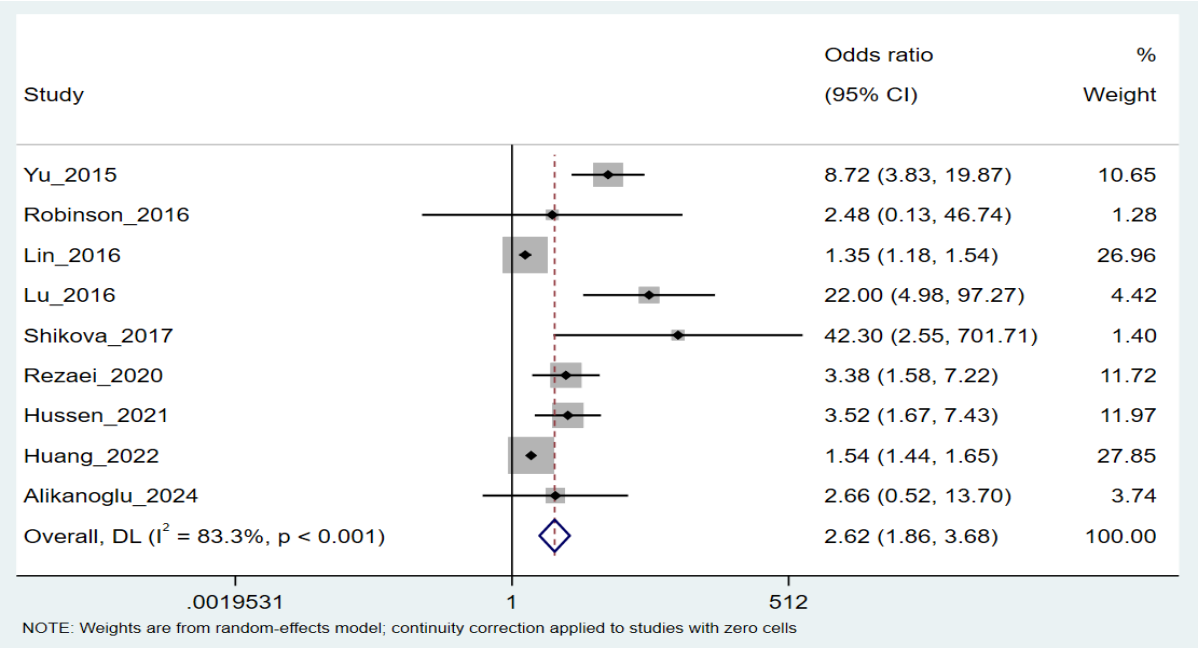
Study (year)	Country	Study Design	HPV detection method	HPV types detected	Histological Subtype(s)
Yu et al (2015)[17]	China	Case-control	PCR	16,18	SCC, AC, SCLC
Robinson et al (2016)[18]	USA	Case-control	PCR	16, 18, 39, 44, 51, 52, 68	NSCLC (SCC, AC)
Lu et al (2016)[19]	China	Case-control	PCR	16, 18	NSCLC (SCC, AC)
Shikova et al (2017)[20]	Bulgaria	Case-control	PCR	16, 18	SCC, AC, adenosquamous, SCLC, other
Rezaei et al (2021)[21]	Iran	Case-control	PCR	6, 11, 16, 18, 33	SCC, AC, SCLC
Hussen et al (2021)[22]	Iraq	Case-control	PCR	6, 11, 16, 18, 33	SCC, AC, SCLC
Alikanoğlu & Karaçay (2024)[23]	Turkey	Case-control	PCR	---	SCC, AC, other (small/large-cell, LCNEC)
Lin et al (2016)[24]	Taiwan	Retrospective Cohort	ICD-based	Based on ICD	Not specified (population-based cohort)
Huang et al (2022)[25]	Taiwan	Retrospective Cohort	ICD-based	Based on ICD	AC

Note: AC=adenocarcinoma; ICD=International Classification of Diseases; LCNEC=large-cell neuroendocrine carcinoma; NSCLC=non-small cell lung cancer; PCR=polymerase chain reaction; SCC=squamous cell carcinoma; SCLC=small-cell lung cancer.

Among the included studies, Huang et al and Lin et al contributed the largest weights to the meta-analysis (27.85% and 26.96%, respectively), reflecting their relatively large sample sizes and narrow confidence intervals.[24,25] In contrast, studies such as Robinson and Shikova had smaller weights and wider confidence intervals due to small sample sizes or less precise estimates.[18,20]

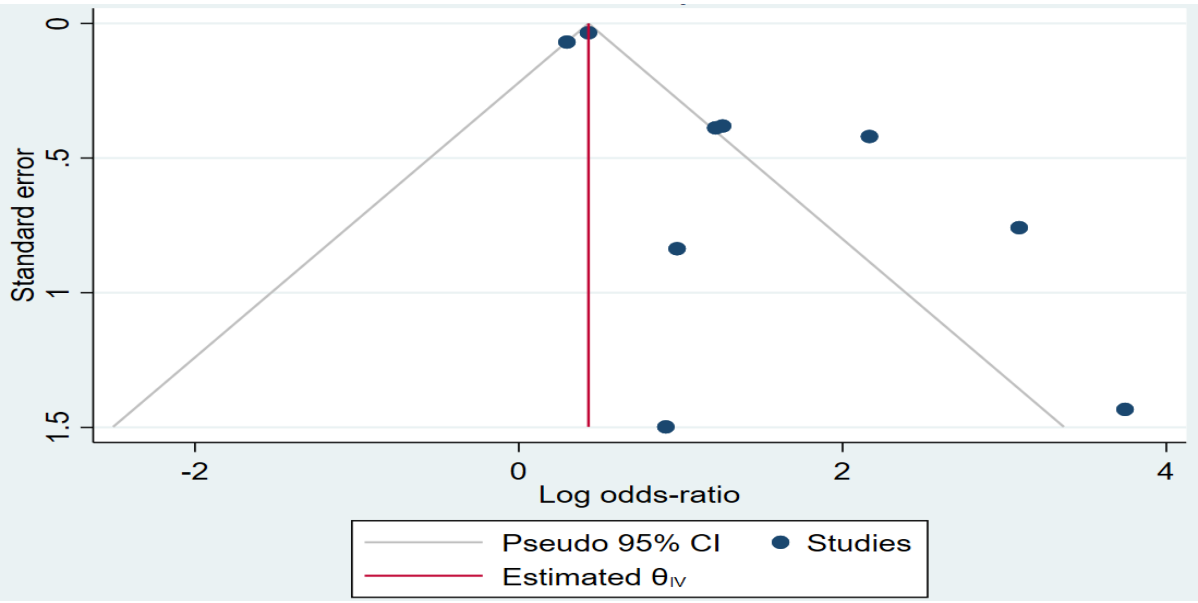
Substantial heterogeneity was observed among the studies (I^2=83.3%; P<0.001), indicating considerable variability in effect sizes. This heterogeneity may be attributable to differences in study design, HPV detection methods, population characteristics, or geographic regions. Despite this heterogeneity, the direction of association was generally consistent across most studies. These findings support a potential etiological role of HPV infection in the development of lung cancer, although further research is warranted to explore underlying mechanisms and adjust for potential confounders.

Visual inspection of the funnel plot (Figure 3) suggested asymmetry, with relatively few studies on the left side, indicating potential publication bias. This observation was supported by Egger's test for small-study effects, which demonstrated a statistically significant result (bias = –2.14; 95% CI= –3.73 to –0.55; P=0.015). These findings suggest that smaller studies may have disproportionately reported stronger associations between HPV infection and lung cancer, raising concerns that small-study effects and publication bias may have influenced the overall estimate.



Note: A horizontal line represents a study with its odds ratio (OR) and 95% confidence interval (CI); the size of the square indicates a study weight; the diamond represents the pooled OR estimate.

Figure 2. Forest plot of the association between HPV infection and lung cancer using a random-effects model



Note: The vertical red line represents the estimated overall effect; the diagonal lines represent the pseudo 95% confidence limits.

Figure 3. The funnel plot displays the log odds ratio against the standard error of each study, assessing publication bias for studies evaluating the association between HPV infection and lung cancer

In addition to the nine studies included in the meta-analysis, 17 observational studies were reviewed but excluded from the quantitative synthesis due to the absence of a control group or a lack of effect size reporting (Table 4). Nevertheless, these studies provided relevant evidence on the presence and potential role of HPV in lung cancer, particularly through molecular detection or population-level associations.

Several studies using PCR-based detection reported the presence of high-risk HPV DNA, most commonly HPV 16 and 18, in lung cancer tissues, with detection rates ranging from 6.8% to 78%. Notably, some studies observed a higher HPV prevalence in non-smokers, females, and patients with EGFR mutations or adenocarcinoma histology, suggesting potential subgroup-specific susceptibility.

Conversely, other studies detected no HPV at all or failed to demonstrate a significant association between HPV status and lung cancer risk. Argyri et al and Silva et al both reported no high-risk HPV in small-cell and non-small-cell lung cancer specimens, respectively.[26,27] Some studies have also investigated surrogate markers, such as p16 or E6/E7 mRNA expression, to assess viral activity. However, the expression was often inconsistent or limited to a small subset of HPV DNA-positive samples.

In addition to tissue-based studies, three Mendelian randomization analyses utilized GWAS-derived genetic instruments as proxies for HPV infection to explore its causal relationship with lung cancer. While one study suggested a significant association between HPV E7 type 16 and squamous cell carcinoma, the others reported no consistent causal link, particularly when applying bidirectional approaches or sensitivity analyses

Table 4. Overview of Non-pooled Observational Studies Assessing the Role of HPV in Lung Cancer

Study	Country	Key Findings
Lee et al (2016)[28]	South Korea	High-risk HPV types showed no etiological correlation with primary SCC and AC in Korean patients.
Li et al (2016)[29]	China	HPV DNA was detected in 28.4% of lung adenocarcinoma tumors and was significantly associated with EGFR mutations, particularly in female non-smokers (P=0.012).
Gupta et al (2016)[30]	India	HPV was present in 6.8% of lung tumors, with a significant association observed in squamous cell carcinoma cases (P=0.01).
Li et al (2016)[31]	China	HPV DNA was found in 24% of lung tumors and was more common in non-smokers, patients with lymph node metastasis, and poorly differentiated tumors.
Kawaguchi et al (2016)[32]	Japan	The study found little association between HPV and NSCLC; TP53 and NFE2L2 mutations were more frequent in advanced stages.
Argyri et al (2017)[26]	Greece	No association was found between HPV infection and lung cancer.
de Oliveira et al (2018)[33]	Brazil	HPV was detected in 52.4% of tumor samples, suggesting active viral presence and a potential role in lung carcinogenesis.
Silva et al (2019)[27]	Brazil	No HPV DNA was identified in NSCLC samples analyzed.
He et al (2020)[34]	China	HPV infection was detected in 13 of 140 tumors and 16 of paired normal tissues; not linked to cancer risk but may impact platelet and lung function.
Zou et al (2021)[35]	Shenyang, China	HPV16 was associated with squamous cell carcinoma; E6/E7 mRNA expression was also detected in benign lesions, possibly due to transient infection.
Rojas et al (2022)[36]	Colombia, USA	HPV positivity was significantly associated with EGFR mutation and PD-L1 expression; HPV-positive patients had longer progression-free survival.
Sirera et al (2022)[37]	Spain	HPV-16 was the most frequent subtype; p16 expression was observed in both HPV-positive and negative tumors, with limited viral oncogene expression.
Sun et al (2023)[38]	Wuhan, China	A potential correlation was found between HPV infection and IL-1β and EGFR SNPs in non-smoking females.
Tsyganov et al (2023)[39]	Russia	HPV was found in 12.7% of NSCLC patients; HPV-positive patients had higher 5-year metastasis-free survival than HPV-negative (94% vs. 78%).
Han et al (2024)[40]	China	HPV E7 types 16 and 18 were significantly associated with increased risk of squamous cell lung cancer (OR=7.69).
Chen et al (2024)[41]	China	No causal relationship was found between HPV E7 proteins (type 16/18) and lung cancer or its subtypes in Mendelian randomization analysis.
Al Karsaneh et al (2024)[42]	Jordan	p16INK4a was expressed in 20% of NSCLC cases, but none of the HPV-positive tumors showed p16INK4a expression.

Note: HPV=Human Papillomavirus; DNA=deoxyribonucleic acid; SCLC=small-cell lung cancer; AC=adenocarcinoma; NSCLC=non-small cell lung cancer, EGRR=estimated glomerular filtration rate; mRNA=messenger ribonucleic acid; OR=odds ratio.

DISCUSSION

The pooled analysis demonstrated that HPV infection was associated with more than a twofold increase in lung cancer risk (OR=2.62; 95% CI=1.86–3.68). Importantly, this association remained consistent across most studies, despite substantial heterogeneity (I^2=83.3%). These findings suggest a potential etiological role of HPV in lung carcinogenesis.

These results are consistent with prior meta-analyses, which also reported increased odds of lung cancer among HPV-positive individuals, particularly for high-risk HPV types such as HPV-16 and HPV-18.[43] For example, a recent pooled analysis

estimated a global HPV prevalence of 13.5% in lung cancer cases, with the highest prevalence observed in Asia and the lowest in Europe.[12] In line with these findings, the association appears strongest in SCC, with weaker or borderline associations in AC. The higher prevalence observed in Asian studies may reflect regional differences in HPV epidemiology, host susceptibility, or detection practices

The high heterogeneity observed in this meta-analysis (I^2=83.3%) likely results from several contributing factors. First, the included studies employed a wide range of HPV detection methods, such as PCR assays on tissue specimens and ICD-based classification in administrative databases.[44,45] Second, study populations differed considerably in terms of geographic origin, sex distribution, and smoking status, all of which can influence both HPV prevalence and lung cancer risk.[15,46]

Third, variations in sample types and histological subtypes, including differences in the focus on adenocarcinoma, squamous cell carcinoma, or mixed types, further contributed to between-study variability. Additionally, differences in control group selection, particularly the use of healthy subjects versus patients with benign lung conditions, may have introduced selection bias.

Despite these inconsistencies, biological plausibility supports a potential role for HPV in lung cancer.[12,47] High-risk HPV oncoproteins E6 and E7 disrupt the function of key tumor suppressors, p53 and pRb. This process activates downstream pathways such as PI3K/Akt and MAPK, enhancing cell survival, proliferation, and genomic instability. The HPV genome also features a long control region (LCR) that enables the virus to persist in a latent state within basal cells and reactivate in response to environmental cues.[48,49] The integration of viral DNA into host chromosomes may sustain and lead to the overexpression of oncogenes, driving malignant transformation.[50]

Some evidence suggests that HPV-positive lung tumors may differ biologically. There are reports of distinct molecular signatures, links with EGFR mutations, and even differences in prognosis, such as improved progression-free survival in HPV-positive adenocarcinoma with EGFR mutations.[23,51]

Although the 17 additional observational studies summarized in Table 4 were not eligible for pooled quantitative synthesis due to the absence of a control group or an extractable effect size, their reported associations offer qualitative support for the biological plausibility of HPV's role in lung carcinogenesis and help contextualize the pooled findings. For instance, Li et al found a significant association between HPV DNA and EGFR mutations in advanced lung adenocarcinoma, while Rojas et al linked HPV positivity with improved progression-free survival in EGFR-mutant tumors.[31,36]

However, the potential role of HPV in lung carcinogenesis remains uncertain, given the heterogeneity in study populations, histological subtypes, and HPV detection methods, as well as the

mixed findings from Mendelian randomization studies. These limitations highlight the need for standardized detection methods and further well-designed studies to clarify this potential relationship.

Publication bias further complicates interpretation. Funnel plot asymmetry and Egger's test indicated that smaller studies tended to report stronger associations. This suggests that negative or null findings may be underrepresented in the literature. This raises the possibility that the overall risk estimate is inflated. In addition, the predominance of case-control designs among the included studies limits causal inference, as residual confounding, particularly from smoking, environmental exposures, or comorbidities, cannot be entirely ruled out.

Several limitations must be considered when interpreting these findings. First, the included studies were predominantly case-control designs, which limit causal inference. Second, we detected publication bias, with smaller studies more likely to report positive associations, potentially inflating the pooled estimate.

Third, detection methods and specimen types varied widely, reducing comparability across studies. Fourth, most studies did not adequately adjust for key confounders such as smoking, environmental exposures, or comorbidities. Finally, the small number of prospective and Mendelian randomization studies limits our ability to draw firm conclusions regarding causality.

Despite these limitations, our findings suggest that HPV infection may represent a risk factor and potential biomarker in lung cancer, especially among non-smokers, females, and patients with EGFR-mutated adenocarcinoma.[44,45] Clinically, this opens possibilities for integrating HPV testing into molecular profiling for lung cancer patients, which may help identify subgroups with distinct tumor biology or therapeutic responses.[52,53] It also raises awareness of the potential utility of HPV vaccination beyond its established role in preventing not only anogenital but also oropharyngeal and lung cancers.[54,55]

Nevertheless, due to variability in study quality, detection methods, and populations studied, HPV testing is not yet appropriate for routine clinical use in lung cancer screening or management.[56,57] More robust, prospective, and population-based studies are needed to confirm the prognostic value of HPV in lung cancer and to determine whether it could be effectively incorporated into future personalized prevention or treatment strategies.

CONCLUSION

This systematic review and meta-analysis demonstrated a significant association between HPV infection and increased risk of lung cancer, with a pooled odds ratio of 2.62. Although substantial heterogeneity and publication bias were detected, the findings suggest that HPV's particularly high-risk subtypes 16 and 18 may play a contributing role in lung carcinogenesis.

Beyond the quantitative synthesis, an additional 17 studies provided supporting molecular, clinical, and epidemiological evidence, including associations with EGFR mutations, female sex, non-smoking status, and better survival outcomes in HPV-positive patients. However, the evidence remains inconclusive due to variability in detection methods, study designs, and specimen types. These findings also highlight the potential of HPV as a risk factor and prognostic biomarker in lung cancer, particularly in specific subpopulations.

Future research should prioritize large-scale, prospective studies with rigorous HPV detection protocols and adjustment for key confounders, alongside mechanistic investigations into the oncogenic role of HPV in lung tissue. Integration of viral biomarkers into lung cancer screening or molecular profiling strategies may offer new insights into personalized cancer prevention and therapy.

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REFERENCES

1. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization Classification of Lung Tumors. Journal of Thoracic Oncology. 2015;10(9):1243–60. doi:10.1097/JTO.0000000000000630
2. Riely GJ, Wood DE, Ettinger DS, Aisner DL, Akerley W, Bauman JR, et al. Non–Small Cell Lung Cancer, Version 4.2024. Journal of the National Comprehensive Cancer Network. 2024;22(4):249–74. doi:10.6004/jnccn.2204.0023
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49. doi:10.3322/caac.21660
4. International Agency for Research on Cancer. GLOBOCAN 2022: World fact sheet. International Agency for Research on Cancer. 2022.
5. Islami F, Torre LA, Jemal A. Global trends of lung cancer mortality and smoking prevalence. Transl Lung Cancer Res. 2015;4(4):327–38.
6. Kementerian Kesehatan RI. Profil Kesehatan Indonesia 2023. Jakarta: Kementerian Kesehatan RI; 2023.
7. Ma J, Song Y, Bai X. Global, regional, and national burden and trends of early-onset tracheal, bronchus, and lung cancer from 1990 to 2019. Thorac Cancer. 2024;15(8):601–13. doi:10.1111/1759-7714.15227
8. Alberg AJ, Brock M V., Ford JG, Samet JM, Spivack SD. Epidemiology of Lung Cancer. Chest. 2013;143(5):e1S-e29S. doi:10.1378/chest.12-2345

9. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. The Lancet. 2017;389(10082):1907–18. doi:10.1016/S0140-6736(17)30505-6
10. Burd EM, Dean CL. Human Papillomavirus. Microbiol Spectr. 2016;4(4). doi:10.1128/microbiolspec.DMIH2-0001-2015
11. Liang H, Pan Z, Cai X, Wang W, Guo C, He J, et al. The association between human papillomavirus presence and epidermal growth factor receptor mutations in Asian patients with non-small cell lung cancer. Transl Lung Cancer Res. 2018;7(3):397–403. doi:10.21037/tlcr.2018.03.16
12. Xiong WM, Xu QP, Li X, Xiao RD, Cai L, He F. The association between human papillomavirus infection and lung cancer: a system review and meta-analysis. Oncotarget. 2017;8(56):96419–32. doi:10.18632/oncotarget.21682
13. McQuillan G, Kruszon-Moran D, Markowitz LE, Unger ER, Paulose-Ram R. Prevalence of HPV in Adults Aged 18–69: United States, 2011–2014. Centers for Disease Control and Prevention, National Center for Health Statistics. 2017.
14. D'Souza G, Wentz A, Kluz N, Zhang Y, Sugar E, Youngfellow RM, et al. Sex Differences in Risk Factors and Natural History of Oral Human Papillomavirus Infection. J Infect Dis. 2016;213(12):1893–6. doi:10.1093/infdis/jiw063
15. Gillison ML, Broutian T, Pickard RKL, Tong Z yue, Xiao W, Kahle L, et al. Prevalence of Oral HPV Infection in the United States, 2009-2010. JAMA. 2012;307(7):693–703. doi:10.1001/jama.2012.101
16. D'Souza G, Cullen K, Bowie J, Thorpe R, Fakhry C. Differences in Oral Sexual Behaviors by Gender, Age, and Race Explain Observed Differences in Prevalence of Oral Human Papillomavirus Infection. PLoS One. 2014;9(1):e86023. doi:10.1371/journal.pone.0086023
17. Yu Y, Liu X, Yang Y, Zhao X, Xue J, Zhang W, et al. Effect of FHIT loss and p53 mutation on HPV-infected lung carcinoma development. Oncol Lett. 2015;10(1):392–8. doi:10.3892/ol.2015.3213
18. Robinson LA, Jaing CJ, Campbell CP, Magliocco A, Xiong Y, Magliocco G, et al. Molecular evidence of viral DNA in non-small cell lung cancer and non-neoplastic lung. Br J Cancer. 2016;115:497–504. doi:10.1038/bjc.2016.213
19. Lu Y, Yu LQ, Zhu L, Zhao N, Zhou XJ, Lu X. Expression of HIF-1α and P-gp in non-small cell lung cancer and the relationship with HPV infection. Oncol Lett. 2016;12(2):1455–9. doi:10.3892/ol.2016.4751
20. Shikova E, Ivanova Z, Alexandrova D, Shindov M, Lekov A. Human

papillomavirus prevalence in lung carcinomas in Bulgaria. Microbiol Immunol. 2017;61(10):427–32. doi:10.1111/1348-0421.12535

21. Rezaei M, Mostafaei S, Aghaei A, Hosseini N, Darabi H, Nouri M, et al. The association between HPV gene expression, inflammatory agents and cellular genes involved in EMT in lung cancer tissue. BMC Cancer. 2020;20:916. doi:10.1186/s12885-020-07428-6
22. Hussen BM, Ahmadi G, Marzban H, Azar MEF, Sorayyayi S, Karampour R, et al. The role of HPV gene expression and selected cellular MiRNAs in lung cancer development. Microb Pathog. 2021;150:104692. doi:10.1016/j.micpath.2020.104692
23. Alikanoğlu AS, Karaçay İA. Detection of High-Risk Human Papillomavirus (HPV), p16 and EGFR in Lung Cancer: Insights from the Mediterranean Region of Turkey. Viruses. 2024;16(8):1201. doi:10.3390/v16081201
24. Lin FCF, Huang JY, Tsai SCS, Nfor ON, Chou MC, Wu MF, et al. The association between human papillomavirus infection and female lung cancer. Medicine. 2016;95(23):e3856. doi:10.1097/MD.0000000000003856
25. Huang JY, Lin C, Tsai SCS, Lin FCF. Human Papillomavirus Is Associated With Adenocarcinoma of Lung: A Population-Based Cohort Study. Front Med (Lausanne). 2022;9:932196. doi:10.3389/fmed.2022.932196
26. Argyri E, Tsimplaki E, Marketos C, Politis G, Panotopoulou E. Investigating the role of human papillomavirus in lung cancer. Papillomavirus Research. 2017;3:7–10. doi:10.1016/j.pvr.2016.12.002
27. Silva EM, Mariano VS, Pastrez PRA, Pinto MC, Nunes EM, Sichero L, et al. Human papillomavirus is not associated to non-small cell lung cancer: data from a prospective cross-sectional study. Infect Agent Cancer. 2019;14:18. doi:10.1186/s13027-019-0235-8
28. Lee JE, Lee YM, Seong IO, Kang MW, Lee CS, Kim KH. No Detection of Episomal or Integrated High-Risk Human Papillomavirus in Nonsmall Cell Lung Carcinomas among Korean Population. Osong Public Health Res Perspect. 2016;7(6):356–9. doi:10.1016/j.phrp.2016.10.004
29. Li M, Deng F, Qian LT, Meng SP, Zhang Y, Shan WL, et al. Association between human papillomavirus and EGFR mutations in advanced lung adenocarcinoma. Oncol Lett. 2016;12(3):1953–8. doi:10.3892/ol.2016.4847
30. Gupta P, Haldar D, Naru J, Dey P, Aggarwal AN, Minz RW, et al. Prevalence of human papillomavirus, Epstein-Barr virus, and cytomegalovirus in fine needle aspirates from lung carcinoma: A case–control study with review of literature. Diagn Cytopathol. 2016;44(12):987–93. doi:10.1002/dc.23613

31. Li M, Zhang XL, Deng F, Qian LT, Meng SP, Shan WL, et al. Involvement of TP53 and TP16 expression in human papillomavirus-associated non-small cell lung cancer. Oncol Lett. 2016;12(5):3330–6. doi:10.3892/ol.2016.5087
32. Kawaguchi T, Koh Y, Ando M, Ito N, Takeo S, Adachi H, et al. Prospective Analysis of Oncogenic Driver Mutations and Environmental Factors: Japan Molecular Epidemiology for Lung Cancer Study. Journal of Clinical Oncology. 2016;34(19):2247–57. doi:10.1200/JCO.2015.64.2322
33. de Oliveira THA, do Amaral CM, de França São Marcos B, Nascimento KCG, de Miranda Rios AC, Quixabeira DCA, et al. Presence and activity of HPV in primary lung cancer. J Cancer Res Clin Oncol. 2018;144(12):2367–76. doi:10.1007/s00432-018-2748-8
34. He F, Xiong W, Yu F, Xiao R, Ye H, Li W, et al. Human papillomavirus infection maybe not associated with primary lung cancer in the Fujian population of China. Thorac Cancer. 2020;11(3):561–9. doi:10.1111/1759-7714.13282
35. Zou DJ, Zhao YB, Yang JH, Xu HT, Li QC, Wu GP. Expression and Significance of HPV16 E6/E7 mRNAs in the Bronchial Brush and TBNA Cells of Patients With Small Cell Lung Cancer. Technol Cancer Res Treat. 2021;20. doi:10.1177/15330338211019505
36. Rojas L, Mayorga D, Ruiz-Patiño A, Rodríguez J, Cardona AF, Archila P, et al. Human papillomavirus infection and lung adenocarcinoma: special benefit is observed in patients treated with immune checkpoint inhibitors. ESMO Open. 2022;7(4):100500. doi:10.1016/j.esmoop.2022.100500
37. Sirera G, Videla S, Saludes V, Castellà E, Sanz C, Ariza A, et al. Prevalence of HPV-DNA and E6 mRNA in lung cancer of HIV-infected patients. Sci Rep. 2022;12:13196. doi:10.1038/s41598-022-17237-5
38. Sun J, Xiang J, An Y, Xu J, Xiong Y, Wang S, et al. Unveiling the Association between HPV and Pan-Cancers: A Bidirectional Two-Sample Mendelian Randomization Study. Cancers (Basel). 2023;15(21):5147. doi:10.3390/cancers15215147
39. Tsyganov MM, Ibragimova MK, Rodionov EO, Cheremisina O V., Miller S V., Tuzikov SA, et al. Human Papillomavirus in Non-Small Cell Lung Carcinoma: Assessing Virus Presence in Tumor and Normal Tissues and Its Clinical Relevance. Microorganisms. 2023;11(1):212. doi:10.3390/microorganisms11010212
40. Han Z, Aizezi A, Ma L, Su Y, Fan L, Liu J. The association between human papillomavirus and lung cancer: A Mendelian randomization study. Infection, Genetics and Evolution. 2024;123:105646. doi:10.1016/j.meegid.2024.105646
41. Chen Y, Xu Z, Zhang Z, Wang X, Dong M. No genetic causal association between human papillomavirus and

lung cancer risk: a bidirectional two-sample Mendelian randomization analysis. Trials. 2024;25:582. doi:10.1186/s13063-024-08366-5

42. Al Karsaneh OA, Al Anber A, AlMustafa S, AlMa'aitah H, AlQadri B, Igbaria A, et al. Human Papillomavirus Is Rare and Does Not Correlate with p16INK4A Expression in Non-Small-Cell Lung Cancer in a Jordanian Subpopulation. Medicina (B Aires). 2024;60(4):660. doi:10.3390/medicina60040660
43. Karnosky J, Dietmaier W, Knuettel H, Freigang V, Koch M, Koll F, et al. HPV and lung cancer: A systematic review and meta-analysis. Cancer Rep. 2021;4(4):e1350. doi:10.1002/cnr2.1350
44. Zhang Y, Qiu K, Ren J, Zhao Y, Cheng P. Roles of human papillomavirus in cancers: oncogenic mechanisms and clinical use. Signal Transduct Target Ther. 2025;10:44. doi:10.1038/s41392-024-02083-w
45. Murphy J, Kennedy EB, Dunn S, McLachlin CM, Fung MFK, Gzik D, et al. HPV Testing in Primary Cervical Screening: A Systematic Review and Meta-Analysis. Journal of Obstetrics and Gynaecology Canada. 2012;34(5):443–52. doi:10.1016/S1701-2163(16)35241-0
46. Sequeira T, Pinto R, Cardoso C, Almeida C, Aragão R, Almodovar T, et al. HPV and Lung Cancer: A Systematic Review. Cancers (Basel). 2024;16(19):3325. doi:10.3390/cancers16193325
47. Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, et al. The Biology and Life-Cycle of Human Papillomaviruses. Vaccine. 2012;30(Supp5):F55–70. doi:10.1016/j.vaccine.2012.06.083
48. Doorbar J. Molecular biology of human papillomavirus infection and cervical cancer. Clin Sci. 2006;110(5):525–41. doi:10.1042/CS20050369
49. Maglennon GA, McIntosh PB, Doorbar J. Immunosuppression Facilitates the Reactivation of Latent Papillomavirus Infections. J Virol. 2014;88(1):710–6. doi:10.1128/JVI.02589-13
50. Klingelhutz AJ, Roman A. Cellular transformation by human papillomaviruses: Lessons learned by comparing high- and low-risk viruses. Virology. 2012;424(2):77–98. doi:10.1016/j.virol.2011.12.018
51. Stanley M. Immune responses to human papillomavirus. Vaccine. 2006;24(Supp1):S16–22. doi:10.1016/j.vaccine.2005.09.002
52. Rezazadeh A, Laber DA, Ghim SJ, Jenson A Ben, Kloecker G. The Role of Human Papilloma Virus in Lung Cancer: A Review of the Evidence. Am J Med Sci. 2009;338(1):64–7. doi:10.1097/MAJ.0b013e3181a393ba
53. Guo L, Liu S, Zhang S, Chen Q, Zhang M, Quan P, et al. Human papillomavirus infection as a prognostic marker for lung adenocarcinoma: a systematic review and meta-analysis. Oncotarget.

2017;8(21):34507–15. doi:10.18632/oncotarget.15671

54. Markowitz LE, Unger ER. Human Papillomavirus Vaccination. New England Journal of Medicine. 2023;388(19):1790–8. doi:10.1056/NEJMcp2108502
55. Drolet M, Bénard É, Boily MC, Ali H, Baandrup L, Bauer H, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis. 2015;15(5):565–80. doi:10.1016/S1473-3099(14)71073-4
56. Warren GW, Ostroff JS, Goffin JR. Lung Cancer Screening, Cancer Treatment, and Addressing the Continuum of Health Risks Caused by Tobacco. American Society of Clinical Oncology Educational Book. 2016;36:223–9. doi:10.1200/EDBK_158704
57. Galvan A, Noci S, Taverna F, Lombardo C, Franceschi S, Pastorino U, et al. Testing of human papillomavirus in lung cancer and non-tumor lung tissue. BMC Cancer. 2012;12:512. doi:10.1186/1471-2407-12-512