

Null Results in Brief

Lack of Association between Human Papillomavirus Type 16 and 18 Infections and Female Lung Cancer

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Abstract

Background: A carcinogenic role of human papillomavirus (HPV) in lung cancer development has been suggested through both clinical and laboratory research during the last two decades.

Methods: We did a population-based case-control study nested within the Finnish Maternity Cohort to assess the role of HPV16/18 infections in female lung carcinogenesis. The Finnish Maternity Cohort containing samples from more than 600,000 subjects were linked with nationwide cancer registries (1973-2006). Serum samples were retrieved from 311 women who developed lung cancer and 930 matched controls. The samples were analyzed for antibodies to HPV types 16 and 18 and cotinine (a biomarker of tobacco exposure). Conditional logistic regression-based estimates of odds ratios and 95% confidence intervals adjusted for cotinine levels were calculated.

Results: Overall, there was no evidence of increased risk of lung cancer associated with HPV 16 and 18 type-specific infections among nonsmokers and smokers, assessed via cotinine levels.

Conclusions: The question of HPV etiologic effect on lung carcinoma deserves further longitudinal studies using different HPV detection methods.

Impact: Our results bring new insights into female HPV lung cancer research. *Cancer Epidemiol Biomarkers Prev*; 19(7); 1879-81. ©2010 AACR.

Introduction

Lung cancer is the leading cause of cancer deaths worldwide (1). Its incidence (both in females and males) correlates with that of cervical cancer (1, 2). Smoking is an independent risk factor for both malignancies (3), but evidence for the involvement of human papillomavirus (HPV) in lung cancer is equivocal, based primarily on the detection of morphologic changes suggesting HPV in bronchial carcinogenesis, expression of HPV E6 expression in HPV16/18 DNA-positive lung tumors and *in vitro* transformation of bronchial epithelial cells by HPV16/18 (3, 4). Women with cervical cancer (an HPV-related cancer) have been reported to have an increased risk of developing secondary lung tumors (5, 6), and a recent meta-analysis suggested an association between HPV16/18 and lung tumors with odds ratios (OR) ranging from 3.5 [95% confidence interval (CI), 2.3-5.3] in Europe to 11.6 (95% CI, 9.5-14.2) in Asia (7). In our case-control

study nested in a cohort of 650,000 Finnish women, we found no association between HPV infection and subsequent risk of developing lung cancer.

Materials and Methods

Cohorts

The study base comprised the prospectively followed Finnish Maternity Cohort that, since 1983, has stored serum samples collected during the first trimester of pregnancy for screening of congenital infections (8).

Identification of cases and controls

All cases of lung cancer diagnosed between 1983 and 2006 in Finland, and registered at the population-based Finnish Cancer Registry were identified. The lung cancer cases and three controls/cases free of cancer at the time of diagnosis were selected by incidence density sampling and matched for age at serum sampling (± 2 years) and date of sample collection (± 2 months). We identified 311 cases and 930 controls. Permissions to link and to use the joint cohort data files were obtained from the Finnish Ministry of Health & Welfare and the institutional ethical review board.

Laboratory analyses

HPV16 and HPV18 antibodies were determined by standard virus-like particle ELISAs, as described (9, 10). The specificity and sensitivity of the assays varied between 95% and 99%, and 50% and 75%, respectively (11).

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doi: 10.1158/1055-9965.EPI-10-0356

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Serum cotinine levels were measured using a commercial immunoassay kit (OraSure Technologies), with a sensitivity of 96% to 97% and a specificity of 99% to 100% (9). A cotinine level of 20 ng/mL was used as the cutoff (9, 10).

Statistical analyses

ORs and 95% CIs were estimated by conditional logistic regression with STATA 10.0 (StataCorp LP). Both smoking-adjusted and smoking-stratified ORs were calculated. With 20% HPV16/18 seroprevalence, our approach had at least 80% statistical power to identify statistically significant ORs ($P = 0.05$) ranging between 0.00 to 0.05 and 1.6 to infinity.

Results

The seroprevalence of HPV16 and HPV18 infections among both cases and controls were 23% and 11%, respectively. HPV16 and HPV18 antibodies were detected in 19 (17%) and 10 (9%) lung cancer cases among nonsmokers and in 39 (24%) and 14 (9%) cancer cases among smokers, respectively. The prevalence of smoking, as defined by cotinine levels of ≥ 20 ng/mL, was 28% in the entire population and 53% among lung cancer cases. We found no increased risk of lung cancer associated with HPV16 and/or HPV18 seropositivity (Table 1), either in smoking or in nonsmoking women.

Discussion

The present study found no role for HPV, as defined by serum cotinine levels, in female lung cancers among nonsmokers and smokers (10, 12). Our data originated from

the Finnish Maternity Cohort, a large Nordic biobank, which offered an excellent opportunity to perform serologic studies aimed at verifying/disproving the role of different factors, e.g., infectious agents, in tumor development (8), including lung cancer (12), many years before cancer diagnosis.

The lack of consistency between our longitudinal study and previous studies could most likely be explained by the different study designs and HPV detection methods used. IgG anti-HPV antibodies are found in ~60% of women testing positive for cervical HPV DNA (13), whereas HPV virus-like particle-based ELISA has been important in the elucidation of the etiologic role of HPV and cervical cancer (11, 14). HPV seropositivity is associated with the number of sexual partners and cytologic lesions (15). On the other hand, detection methods for and rates of HPV DNA in lung cancer are subject to wide variation (4). In previous publications (4), the analyses was restricted to HPV DNA-positive women. Furthermore, most of these studies tested for HPV DNA at only one time point, which favored the detection of amplified HPV DNA in the cases, and controls testing HPV-positive just once most likely had a transient infection. This probably biased the measured lifetime HPV exposure and the effect of HPV infection. Such a problem does not exist for HPV-seropositive women because the possibility that HPV antibodies wane over time is highly unlikely (16).

Smoking is such an important risk factor for lung cancer that control of its effects is critical in the epidemiologic assessment of etiologic cofactors. Biochemical measurement of tobacco exposure may have induced misclassification because questionnaire data on smoking

Table 1. ORs and 95% CIs for lung cancer risk associated with HPV16, HPV18, and HPV16 and/or HPV18 antibodies stratified and adjusted by smoking status in a population-based cohort of fertile-aged women in Finland

HPV seropositive	No. (%) of positive		OR (95% CI)*
	Cases (n = 311)	Controls (n = 930)	
Nonsmokers [†]			
HPV16	19 (17)	166 (24)	0.81 (0.60-1.15)
HPV18	10 (9)	77 (11)	1.00 (0.60-1.50)
HPV16 and/or HPV18	22 (20)	185 (27)	0.80 (0.60-1.06)
Smokers [†]			
HPV16	39 (24)	26 (17)	1.10 (0.90-1.36)
HPV18	14 (9)	19 (13)	0.80 (0.50-1.14)
HPV16 and/or HPV18	42 (26)	33 (22)	1.04 (0.80-1.25)
Total*			
HPV16	61 (22)	194 (23)	1.02 (0.87-1.20)
HPV18	24 (9)	96 (11)	0.90 (0.71-1.11)
HPV16 and/or HPV18	67 (24)	220 (26)	0.96 (0.83-1.11)

*ORs calculated were adjusted for smoking.

[†]A nonsmoker was defined by cotinine levels of < 20 ng/mL, a smoker by cotinine levels of ≥ 20 ng/mL.

history would have permitted us to assess lifetime exposure to tobacco smoke. On the other hand, self-reporting underestimates the true prevalence (17), especially in pregnant women, and is inaccurate with regard to smoking exposure (18). Biochemical assessment integrates different aspects of true exposure, including tobacco composition, uptake, and distribution and individual differences in metabolism. Cotinine is a good marker of nicotine intake, which is the important carcinogen in tobacco smoke (19).

In conclusion, we reported a lack of association between HPV16/18 infections and female lung cancer from a large longitudinal nested case-control study.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

Tapio Luostarinen and Aljoona Aejmaleus are gratefully acknowledged for their excellent contributions to this research work.

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Received 04/04/2010; revised 04/24/2010; accepted 04/29/2010; published OnlineFirst 06/15/2010.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association
for Cancer Research

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Cancer Epidemiol Biomarkers Prev 2010;19:1879-1881. Published OnlineFirst June 15, 2010.

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