Int J Clin Exp Med 2016;9(8):16682-16688
www.ijcem.com /ISSN:1940-5901/IJCEM0026080

Original Article

Cytokine variants predict outcome of squamous cell carcinoma of the oropharynx

Wenbin Yu[1*], Lijun Zhu[2*], Yuncheng Li[3], Guojun Li[4,5]

[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Head and Neck surgery, Peking University Cancer Hospital & Institute Beijing, China; [2]Department of Oral and Maxillofacial Surgery, Guangdong General Hospital & Guangdong Academy of Medical Sciences, 106 Zhongshan 2nd Rd, Guangzhou 510080, China; [3]Department of Otolaryngology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China; Departments of [4]Head and Neck Surgery, [5]Epidemiology, The University of Texas MD Anderson Cancer Center, Houston TX 77030, USA. [*]Equal contributors and co-first authors.

Received February 16, 2016; Accepted June 8, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: Genetic variants of genes in inflammation/immune response pathways may control the mechanisms of HPV clearance and HPV escape of immune surveillance and thus may affect both tumor HPV status and possibly related outcomes of squamous cell carcinoma of the oropharynx (SCCOP) patients. We determined tumor HPV16 status and genotyped selected polymorphisms in key genes involved in inflammation/immune response pathways in 401 incident SCCOP patients. Logistic regression models, Kaplan-Meier analysis, and Cox proportional hazards regression were used to evaluate associations and survival. Compared to the patients with the corresponding variant or common homozygous genotypes, the patients with the common homozygous genotypes of *IL1β* orvariant genotypes of *IL10* in inflammation/immune response pathway had significantly 3.3-6.0 times likely to be HPV16-positive tumors among SCCOP patients, respectively. Furthermore, the patients with 4-5 combined risk genotypes of 5 polymorphisms exhibited a significantly greater association with HPV16-positive tumor status (OR, 12.4, 95% CI, 4.1-24.3), and the association is in a statistically significant dose-effect relationship (P<0.001). In HPV16-positive SCCOP patients only, the combined unfavorable genotypes of 5 cytokine variants were also significantly associated with increased risk of overall death after adjustment for important prognostic confounders and the association is in a statistically significant dose-effect relationship (P<0.001). These results suggest that genetic polymorphisms in cytokine genes may individually or, more likely, jointly affect individual susceptibility to HPV tumor status and constitute the confounding effect on HPV-related clinical outcomes. Validation of our findings is needed.

Keywords: Polymorphisms, HPV, cytokine, biomarkers, survival, oropharyngeal cancer

Introduction

Approximately 13,510 new cases of squamous cell carcinoma of the oropharynx (SCCOP), a subtype of squamous cell carcinoma of the head and neck (SCCHN), are diagnosed, and 2,330 deaths result from these cancers annually in the U.S. [1, 2]. Human papillomavirus (HPV) accounts for a growing proportion of cases, particularly in young adults [1, 3]. The most common high-risk type of HPV is HPV16, which is found in approximately 60-80% of SCCOPs [4-6] and in 90-95% of HPV-positive SCCOPs [7, 8]. Since HPV-positive SCCOP is etiologically and clinically distinct from HPV-negative SCCOP [6, 9], HPV status may be highly relevant to SCCOP prognosis besides the TNM stage and smoking [9]. Thus, it is an urgent need to identify this unique subgroup of patients for appropriate treatment of this disease.

The 5-year relative overall survival rate for patients with SCCOP is approximately 50%, despite advances in diagnostic and therapeutic approaches [10]. Although the treatment and prognosis of SCCOP are dependent on certain clinical features (e.g., previous treatment, performance status, and disease stage) and lifestyle factors (e.g., smoking, alcohol drinking,

and HPV status), the current prognostic markers are inadequate for making individualized treatment decision for SCCOP patients. Primarily based on tumor TNM stage clinicians make treatment decisions for SCCOP patients, while HPV status has recently emerged as a key prognostic marker. Reports on the impact of HPV status on SCCOP prognosis have been controversial and inconsistent because SCCOP has significantly heterogeneous clinical outcomes. Thus, the biomarkers for identification of individual SCCOP patients at high risk for poor clinical outcomes is of utmost clinical relevance, and such new biomarkers for further stratifying SCCOP patients are needed to ensure appropriate treatment.

Inflammation/immune response pathway controls a wide variety of basic cellular functions [11]. The genes in this pathway affect all facets of immune/inflammation response systems [12] and further play important roles in the development and progression of infection-associated cancers. It controls the mechanisms of HPV clearance and HPV escape from immune surveillance, which may affect both tumor HPV status and the outcomes of SCCOP patients. We have previously selected the genetic variants in key genes involved in Inflammation/immune response pathway and assessed their associations with risk of SCCHN or SCCOP, however, very few studies have been done on associations of the similar genetic variants with HPV status and clinical outcome of SCCOP. Therefore, in the present study, we assessed the distribution of genotypes of the genes involved in inflammation/immune response pathway in tumors HPV status among patients with SCCOP and survival of SCCOP patients.

Materials and methods

Study subjects

From December 1996 to May 2011, a total of 401 SCCOP patients were consecutively recruited, without restrictions on age, sex, ethnicity, or clinical stage, as part of an ongoing molecular epidemiological study at The University of Texas MD Anderson Cancer Center. These patients were newly diagnosed and previously untreated and had histopathologically confirmed SCCOP with tumor tissue specimens available for further analysis. Institutional Review Boards of UT MD Anderson Cancer Center approved the study, and written informed consent was obtained from all study subjects before they were enrolled. The details of the subject recruitment have been previously described [11]. All participants had 30 ml of blood drawn for genotyping. Participants also completed an epidemiological questionnaire that included demographic data, smoking history, and alcohol exposure.

The patients' medical records were reviewed under the direct supervision of the senior author and staff head and neck surgeon. Primary tumor subsite, clinical stage, treatment, medical comorbidities, and vital status, as assessed between the initial and final patient contact, were recorded. All patients included in the survival analyses were treated with chemoradiation for curative intent.

Tumor HPV16 determination

The patients' paraffin-embedded tissue specimens were tested for HPV16 DNA in the E6 and E7 regions using polymerase chain reaction (PCR)-based, type-specific assays that were modified as previously described [13, 14]. Assays of the samples were run in triplicate, with positive and negative controls (Siha and TPC-1 cell lines, respectively). β-Actin was used as a DNA quality control. Southern blot analysis confirmed the specificity for HPV16 E6 and E7 using a Roche Diagnostics labeling and hybridization system (Roche Applied Science, Indianapolis, IN) (7). A random 5% of the samples were retested, and the results of retesting were 100% concordant.

Genotyping

The patients' whole blood samples (1.0 ml) were centrifuged, and leukocyte cell pellets were obtained from the buffy coat. Genomic DNA was extracted from each pellet using the QIAamp DNA Blood Mini Kit (QIAGEN Inc., Valencia, CA) according to the manufacturer's instructions. Samples were then genotyped for polymorphisms in the following genes in inflammation/immune response pathway (*IL1β* and *IL10*). Using the methods previously reported [15, 16]. At least 10% of the samples were randomly selected for retesting and provided 100% concordant results.

Statistical analysis

All statistical analyses were performed using Statistical Analysis System software (SAS ver-

Table 1. Distribution of selected variables and cytokine genotyping in SCCOP patients by HPV16 status

Variable	HPV16 (+) patients (N = 301)		HPV16 (-) patients (N = 100)		*P* value*
	No.	%	No.	%	
Age					0.712
≤54 years	166	55.0	56	56.0	
>54 years	135	45.0	44	44.0	
Sex					0.011
Male	271	90.0	79	79.0	
Female	30	10.0	21	21.0	
Ethnicity					0.128
Non-Hispanic white	286	95.0	90	90.0	
Others	15	5.0	10	10.0	
Tobacco smoking					0.038
Ever	156	51.8	69	69.0	
Never	145	48.2	31	31.0	
Alcohol drinking					0.811
Ever	235	78.1	76	76.0	
Never	66	21.9	24	24.0	
Genotyping					
IL1β (-1060T>C)					0.001
CC	190	63.1	32	31.8	
CT/TT	111	36.9	68	68.2	
IL1β (14T>C)					0.020
CC	213	70.8	41	40.9	
CT/TT	88	29.2	59	59.1	
IL1β (-580C>T)					0.0001
TT	162	53.9	27	27.3	
CT/CC	139	46.1	73	72.7	
IL10 (-853T>C)					0.030
CC	136	45.3	77	77.3	
CT/TT	165	54.7	23	22.7	
IL10 (-626A>C)					0.001
CC	136	45.3	81	80.9	
CA/AA	165	54.7	19	19.1	

*Two-sided χ^2 test.

sion 9.3; SAS Institute, Cary, NC). Chi-square tests were used to assess differences in the distributions of selected demographic characteristics (including age, sex, ethnicity, tobacco smoking, and alcohol drinking) and the genotype frequencies of HPV16-positive and HPV16-negative SCCOP. Associations between the genotypes and tumor HPV16 positivity were estimated by calculating odds ratios (ORs) and 95% confidence intervals (95% CI) using univariate and multivariate logistic regression analyses. Overall survival (OS) was defined as the date of the patient's first appointment at MD Anderson Cancer Center to date of death from any cause or last follow-up. Participants who were alive at the end of the study period or lost to follow-up were considered censored. The Kaplan-Meier method was used to compare survival between patients with different genotypes. We also evaluated whether the genotypes modulated survival and whether the genotypes were associated with risk of death among the SCCOP patients by fitting a Cox proportional hazards model that included age, sex, ethnicity, smoking history, alcohol consumption, disease T and N stage, comorbidity, and treatment as covariates. We further analyzed the genotype data by dividing the adverse genotypes into subgroups of SNPs that significantly affected overall survival in multivariable logistic regression models. All tests were 2-sided, and a P value < 0.05 was set for statistical significance.

Results

Among 401 patients with incident SCCOP, 301 (75%) had tumors positive and 100 (25%) had tumors negative for HPV16 DNA. Relevant demographic characteristics, as well as smoking and alcohol history, for HPV16-positive versus HPV16-negative patients are shown in **Table 1**. Generally, HPV16-positive patients were more likely to be male and never-smokers compared with HPV16-negative patients (P = 0.011 for sex and P = 0.038 for tobacco smoking), but the differences in age, ethnicity, and alcohol drinking were not statistically significant (P = 0.712, P = 0.128, and P = 0.811, respectively).

The HPV16-positive patients were more likely to have the variant genotypes for *IL10* and the common homozygous genotypes for *IL1β* compared with the HPV16-negative patients. The patients with the variant genotypes of *IL10* had a 3- to 6-fold higher risk [OR, 4.3, 95% CI, 1.3-13.9 for *IL10 (-853T>C) and* OR, 5.8, 95% CI, 1.6-20.7 for *IL10 (-626A>C)*] compared with the those with the corresponding common homozygous genotypes, while the patients with the common genotype of *IL1β* had a 70% reduced risk, of having an HPV16-positive tumor compared with the patients with the corresponding variant genotypes [HR, 0.3, 95% CI,

Table 2. Association of combined risk genotypes of 5 polymorphisms in inflammation/immune response pathway with tumor HPV16 status in SCCOP patients

No. of risk genotypes	HPV16-positive tumors (n = 301)		HPV16-negative tumors (n = 100)		Adjusted OR (95% CI)[a]
	N	%	N	%	
0[†]	114	37.9	22	22.0	1.0
1	168	55.8	51	51.0	1.6 (1.1-5.3)
2-3	14	4.6	15	15.0	5.6 (2.8-8.1)
4-5	5	1.7	12	12.0	12.4 (4.1-24.3)
Trend					< 0.001

[†]Ref. = Reference group. [a]Adjusted for sex, age, ethnicity, smoking and alcohol drinking status.

Table 3. Effect of combined unfavorable genotypes of the 5 polymorphisms in inflammation/immune response pathway on OS among tumor HPV16-positive SCCOP patients

No. of unfavorable genotypes	Total (N = 301)		Overall deaths (N = 40)		Adjusted HR (95% CI)[a]
	N	%	N	%	
0[†]	114	37.9	10	25.0	1.0
1	168	55.8	21	52.5	1.7 (0.9-4.7)
2-3	14	4.6	5	12.5	6.1 (2.1-9.4)
4-5	5	1.7	4	10.0	10.8 (3.2-29.3)
Trend					< 0.001

[†]Ref. = Reference group. [a]Adjusted for age, sex, ethnicity, smoking status, alcohol drinking status, T-stage, N-stage, treatment, and comorbidity in a Cox regression model.

0.1-0.7 for *IL1β (-1060T>C),* HR, 0.3, 95% CI, 0.1-1.0 for *IL1β (14T>C),* and HR, 0.3, 95% CI, 0.1-0.9 for *IL1β (-580C>T),* respectively]. Because there was no interaction effect between these 5 polymorphisms on the tumor HPV16 status, we categorized subjects into 4 combined genotype groups based on the level of HPV16 positivity related risk genotypes as shown in **Table 2**. This allowed us to evaluate the association of tumor HPV16 status in SCCOP with the combined *IL1β* and *IL10* risk genotypes. Compared with the patients with 0 unfavorable genotypes, the patients with 1, 2-3, and 4-5 unfavorable genotypes exhibited a significant association with tumor HPV16 positivity (OR, 1.6, 95% CI, 1.1-5.3, OR, 5.6, 95% CI, 2.8-8.1, and OR, 12.4, 95% CI, 4.1-24.3, respectively). The dose-effect relationship between the combined risk genotypes and the tumor HPV16 positivity in SCCOP was also statistically significant ($P < 0.001$).

Survival among HPV16-positive SCCOP patients were analyzed with respect to the death from all causes (OS). Of the 301 HPV16-positive SCCOP patients treated with chemoradiation for curative intent at our institution, 40 (13%) have died, with a median follow-up duration of 28.6 months. Univariate Kaplan-Meier survival analyses demonstrated that SCCOP patients carrying the variant genotypes of *IL1β (14T>C)* had significantly worse OS than the patients with the corresponding alternative genotypes (log-rank test, $P < 0.05$). In multivariable Cox proportional hazard regression analysis, compared with SCCOP patients having common homozygous genotypes of *IL1β (14T>C)*, the patients with the variant genotypes had a significantly 5-fold increased risk of overall death (HR, 4.9, 95% CI, 1.6-8.9), while no significant associations were found for other 4 polymorphisms of *IL1β* and *IL10* genes. As shown in **Table 3**, after we combined the 5 polymorphisms, while analysis of combined unfavorable genotypes of 5 polymorphisms of *IL1β* and *IL10* indicated that, compared to HPV16-positive SCCOP patients with no variant genotype, those with one, two or three, and four or five unfavorable genotypes of the five polymorphisms had a1. 7-, 6.1-, and 10.8-fold increased risk of overall death, respectively (HR, 1.7, 95% CI, 0.9-4.7; HR, 6.1, 95% CI, 2.1-9.4, and HR, 10.8, 95% CI, 3.2-29.3, respectively). The risk was therefore significantly dose-effect manner (Trend test, $P < 0.001$).

Discussion

In this study, these polymorphisms might lead to functional changes of these genes in this molecular pathway, which control HPV clearance and escape from immune surveillance. The interplay between HPV E6 and E7 and the key molecular regulators in these pathways alters gene regulation, thereby leading to the accumulation of genetic or epigenetic abnormalities. Our results support that genetic polymorphisms in the likely functional regions of the genes in inflammation/immune response pathway may cause the individual differences in HPV tumor status that confound the effects of HPV status on clinical outcomes.

Studies have demonstrated that HPV16 infection is one of the main etiologic risk factors for

SCCOP, causing the increased incidence of SCCOP [17]. HPV can be found in the upper aerodigestive tract in more than 10% of the general population [18]. The characteristic of cryptic invaginations of the oropharynx allows for greater exposure of basal epithelial cells in the epithelium to HPV infection [17], but only a small percentage of those infected develop SCCOP, probably because of lowered immune response and HPV clearance due to inter-individual genetic variations.

Genetic variation can contribute greatly to the treatment outcome and prognosis of cancer by affecting the interactions between cancer cells and tumor microenvironment, including cytokine-induced inflammation and immune response [19]. The combination of polymorphisms in the cellular pathway may cause extensive biological variations that affect cancer physiology, treatment outcome, and prognosis because the response to genotoxic stress caused by radiation or chemotherapy is an important factor in determining the treatment response and outcome. Inflammation/immune response pathway may play roles in regulating the growth of HPV-infected cells, and viral persistence, disease progression, and/or malignant transformation could involve escape from these mechanisms. The genetic polymorphisms in the inflammation/immune response pathways may affect their biological function and interactions with the HPV E7 and E6 proteins. Therefore, such genetic variants in promoter or coding regions, which are believed to influence the expression levels or functional efficiency of their respective cytokines, could constitute a confounding effect on HPV-related clinical outcomes and modify the efficiency of HPV clearance. We have previously reported the risk of SCCHN associated with polymorphisms of genes in several molecular pathways [20-24]. In this study, we further examined the associations of some of these polymorphisms with HPV16 tumor status among patients with incident SCCOP. We found that the distributions of genotypes of some polymorphisms differed significantly between HPV16-positiveand HPV16-negative SCCOP patients. Furthermore, after adjusting for other confounding variables (and accounting for multiple comparisons) we found that the combined genotypes of the selected genetic variants of genes in several pathways were strongly associated with increased risk of HPV16 positivity among SCCOP patients. These results suggest that the presence of certain polymorphisms may a marker of HPV16 positivityin SCCOP patients. Similarly, the significance of these findings was also observed in inflammation/immune response pathway.

In HPV16-positive SCCOP patients, mutation of genes is rare. The genetic polymorphisms, therefore, may affect inter-individual variation in clinical outcomes. In this study, we found that the genetic variants in inflammation/immune response pathway also modify survival in patients with HPV16-positive SCCOP. We found that the variant genotypes of the selected *IL1β* (14T>C) polymorphism can predict an increased risk of overall death among tumor HPV16-positive SCCOP patients. It could be that the HPV16-positive patients with different variant genotypes have different responses to radiation-induced apoptosis, as all of the SCCOP patients studied received radiotherapy.

Exploitation of the association between inherited genetic polymorphisms and HPV status and related outcome using a pathway-based genotyping approach may provide a comprehensive clinical tool for the prognosis and prevention of SCCOP. Knowing the HPV status of SCCOP patients has important prognostic implications and may influence future treatment and prevention strategies. However, larger studies to carefully assess the clinical validity and utility of potential markers before implementation are required. Genetic polymorphisms could define the individualized molecular profiles of HPV-positive SCCOP, leading to individualized treatment and prevention. Such profiles could also potentially optimize patient stratification for clinical trials testing HPV-targeted therapies.

Our study has several limitations. Firstly, the majority of SCCOP cases in our study were non-Hispanic white patients; thus, the generalizability of our results to other ethnic populations may be limited. Secondly, since the outcome event rate of death in this study was lower than expected, the statistically significant results could be by chance due to the small number of outcome events and the short duration of follow-up. Third, although the findings from some groups were significant, the fairly small patient numbers may have limited the interpretation of our findings. Finally, the hospital-based nature

of the study as well as other unknown confounding factors, such as sexual behavior characteristics or infection with other high-risk HPV types, could have led to selection bias. In conclusion, genetic polymorphisms may affect tumor HPV status among SCCOP patients. The genetic polymorphisms that we identified in inflammation/immune response pathway may affect biological function and interactions with the HPV E6 and E7 proteins, thus affecting the tumor HPV status and related outcomes of SCCOP patients. Therefore, these genetic polymorphisms could serve as predictors of HPV-positive tumors and survival in SCCOP patients. Understanding the genetic profile of SCCOP is imperative for the successful application of HPV vaccines and future cancer prevention efforts.

Disclosure of conflict of interest

None.

Abbreviations

HPV, human papillomavirus; SCCOP, squamous cell carcinomas of the oropharynx; SNPs, single nucleotide polymorphisms; OR, odds ratio; SCCHN, squamous cell carcinomas of the head and neck.

Address correspondence to: Yuncheng Li, Department of Otorhinolaryngology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan 430022, China. Tel: 027-85351630; Fax: 02785351706; E-mail: whxhent30@163.com; Dr. Guojun Li, Department of Head and Neck Surgery, Unit 1445, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston TX 77030, USA. Tel: 713-792-0227; Fax: 713-794-4662; E-mail: gli@mdanderson.org

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