ACTA ONCOLOGICA
2019, VOL. 58, NO. 3, 267–272
https://doi.org/10.1080/0284186X.2018.1546059

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ORIGINAL ARTICLE

Association between oropharyngeal cancers with known HPV and p16 status and cervical intraepithelial neoplasia: a Danish population-based study

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ABSTRACT

Background: Persistent infection with high-risk genotypes of human papillomavirus (HPV) is the main risk factor in the development of uterine cervical precancerous lesions and cervical cancer (CC), and cases of HPV-induced oropharyngeal squamous cell carcinoma (OPSCC) is increasing in the Western world. We investigated the association between HPV and p16 status and previous results of cervical examinations, including cytological and histological tests, in females with OPSCC.

Material and Methods: We included females diagnosed with an OPSCC in Eastern Denmark from 2000 to 2014. OPSCCs were assessed for p16-overexpression and HPV DNA PCR. History of cervical tests was obtained from the Danish Pathology Registry. The cytology and histological results were categorized in accordance with the 2014 Bethesda System (TBS) and WHO. Hence, we divide the cervical results into two groups. Group I were negative for intraepithelial lesion or malignancy and group II had epithelial cell abnormalities and subdivided after increasingly neoplastic severity from A-D. Chi^2-tests and Fischer's exact tests were performed to compare the two groups.

Results: A total of 417 women with OPSCC were identified; 203 with HPV-positive tumors (49%) of which cervical cytology or histology were available in 172 women (85%). Among these, 22 (13%) patients had a cervical history of $\geq$ IIC. A total of 171 out of 214 women in the HPV-negative group (80%) were examined with cytology and 17 had a history of $\geq$ IIC. No significant difference in diagnoses of (pre)cancerous lesions between the OPSCC HPV-positive and negative groups were observed (χ^2 test $p = .28$, Fischer's exact test $p = .29$).

Conclusion: HPV status in oropharyngeal tumors was not correlated with a history of $\geq$ IIC in cervical examinations. The effect on cervical dysplasia may be masked by a higher incidence of smoking among the OPSCC HPV-negative group.

ARTICLE HISTORY
Received 17 July 2018
Accepted 5 November 2018

Introduction

Human papillomavirus (HPV) genital infection is common among both men and women. Most infections are transient, but high-risk genotypes of HPV can cause persistent infections, leading to cervical precancerous lesions and cervical cancer (CC) in women [1]. High grade lesions are characterized as cervical intraepithelial neoplasia(CIN) 2 and -3, and considered intermediate stages in the cancer progression, often developing within 5 years of infection with these high-risk HPV types [2]. Women with high-grade CIN have a long-term risk of not only cervical cancer, but also anal, vulvar, and vaginal cancers, when compared to the general population [3–5]. Additionally, a few studies have exposed an association between high-grade CIN and head and neck cancer [6,7]. It is well established that HPV infection is also associated with head and neck cancer, in particular oropharyngeal squamous cell carcinoma (OPSCC) [8].The main risk factor of OPSCC in most parts of the Western world is currently HPV infection, while more traditional risk factors like high consumption of alcohol and smoking tobacco accounts for a smaller proportion [9]. In Eastern Denmark in the period from 2011 to 2014, approximately 62% of patients with OPSCC had HPV-positive tumors and the overall incidence rate of OPSCCs were 4.5 per 100,000 [10].

The main objective of this study was to investigate the frequency in history of cervical intraepithelial neoplasia and cervical cancer in all women diagnosed with OPSCC in Eastern Denmark from 2000 to 2014 stratified by HPV/p16 tumor status, in order to ascertain whether the infection with (carcinogenic) HPV in one site predisposes to HPV-related cancer in oropharynx.

Material and methods

Study population

All female patients diagnosed with OPSCC in Eastern Denmark from 2000 to 2014 were included [11,12]. Patients were identified through the Danish Head and Neck Cancer

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Supplemental data for this article can be accessed here.

(DAHANCA) Database and in the Danish Pathology Register (DPR). The DAHANCA database collects information from date of diagnosis to follow-up on patients with head and neck cancer. The DPR holds data reported by all pathology departments through an online, real-time system, on all cytological and histological examinations performed in Denmark. Registration is mandatory by law. The population was identified using the computerized Civil Registration System which provides all Danish residents with a unique personal identification number (PIN) [13]. The PIN is used in all national registers and allowed accurate merging between the two nationwide Danish registries described above. Further, all patient characteristics, including smoking history and clinical outcome were obtained from the patient files.

HPV DNA analyses and p16 immunohistochemistry of OPSCC

Expert head and neck pathologists reviewed histological specimens of OPSCC. All histological specimens were assessed for the expression of p16 using immunohistochemistry (IHC) on the tumor slides. Tumors exhibiting a staining with >75% positive tumor cells were defined as p16-positive [14]. The squamous cell carcinoma diagnosis was examined using hematoxylin and eosin stained materials and the tumors were divided into specific tonsillar -, base of tongue -, and nonspecific tonsillar squamous cell carcinoma (STSCC, BSCC or NSTSCC) based on clinical information and tissue specific structures [15]. HPV DNA analysis was conducted on the formalin-fixed paraffin-embedded (FFPE) tumor specimens as previously described [11,15]. In this study, only patients with OPSCC that had positive HPV DNA and p16 IHC overexpression were categorized as HPV positive and all patients either HPV+/p16-, HPV-/p16+ or HPV-/p16- are referred to as HPV negative ($n = 214$) [16]. Women with an unknown HPV/p16 status, these were excluded.

Cervical cancer screening

Current guidelines from 2012 in Denmark recommends screening for cervical cancer every three years for women aged 23–49 years, every five years for women aged 50–59 years and terminating at 60–64 years of age following a normal HPV test [17]. The DPR contains information on dates and results from all opportunistic and organized cervical cytologies, as well as all histologies performed, and serves as the administrative system for women attending the cervical screening program [18]. Structurally, the DPR is based on the Danish version of Systematized Nomenclature of Medicine (SNOMED) [19]. We have retrieved information by cross-referencing each unique patient PIN and specific SNOMED codes to determine the number of screenings and degree of cervical dysplasia before diagnosis of OPSCC. Cervical cytology were categorized according to the 2014 Bethesda System (TBS) [20,21] and the histological test were categorized according to the WHO [22]. Women with more than one episode of cervical lesions were included only once with the worst diagnosis. We divided cervical cytology and histological examinations into group I (negative for intraepithelial lesion or malignancy) and group II (epithelial cell abnormalities). Group II where subdivided into four subgroups (A-D) with increasingly neoplastic severity as illustrated in Supplementary Table S1.

Statistical analysis

Statistical analyses were performed in R version 3.5.0 [23]. The Pearson Chi-square test was used to compare patients categorized as HPV positive oropharyngeal tumors with the HPV negative tumors, to evaluate the distribution of cervical cytology. Differences in tumor location, T- and N-stage, and status at follow-up were also assessed by the Pearson Chi-square test. Student *t*-test was used to compare cervical cytology/histology and number of pack years (py) according to HPV status including 95% confidence intervals (95% CI). The Wilcoxon test was used to compare median age. In categories with less than 5 patients, the Fisher's exact test was used to compare the groups. We used ordinal logistic regression to evaluate the three categories of cervical examination results between HPV-positive and –negative women adjusted for age and smoking. We categorized the results of cervical examinations into group I-IIAB and IICD, and performed a logistic regression adjusted for age and smoking. A *p*-value below .05 was considered statistically significance.

Results

Approximately 5.6 million inhabitants live in Denmark, of which Eastern Denmark comprises 46% [24]. Within this population, a total of 417 women (median age 61.2; 203 HPV-positive) were diagnosed with an OPSCC between 2000 and 2014 (Table 1).

For patients with HPV/p16-positive OPSCC, the cervical cytology/histology results were available for 172/203 patients (85%). A normal cervical cytology result (Group I) was identified in 130 of these patients, atypical cells or low-grade squamous cell abnormalities (Group IIA-B) was recorded for 20 patients while 22 patients were diagnosed with high-grade squamous cell abnormalities or CC (Group IIC-D). Within the OPSCC HPV-negative group the cervical cytology/histology outcomes were recorded in 171 out of 214 patients (80%). Of these patients, 141 were in Group I, 13 in Group IIA-B and 17 in Group IIC-D.

As Table 2 presents, no significant difference in diagnosis of pre/cancerous lesions between the positive and negative group were found (χ^2 test $p = .28$, Fischer's exact test $p = .29$). We then divided the female patients into two groups; those with a history of category I and IIA-B and those in category IIC-D. We found no significant difference between these groups ($p = .5$). When investigating the group of women in group IIC-D, adjusting for both age and smoking, we found the same ratio of HPV expression in the OPSCC's ($p = .4$). Women with a history of IIC-D had a 1.35 greater odds of getting a HPV/p16-positive OPSCC. Women who smoked had 2.68 greater odds of getting HSIL or CC

Table 1. Tumor characteristics in relation to HPV-status in women with OPSCC.

	Cases		HPV-positive		HPV-negative		*p*-value*
Cases	417	100%	203	48.7%	214	51.3%	
Age at diagnosis							
Median	61.2		59.8		62.3		.006[b] (−5 – −0.9)
Oropharynx							
NSTSCC	101	100%	13	12.9%	88	87.1%	<.001[c]
STSCC	204	100%	134	65.7%	70	34.3%	
BSCC	112	100%	56	50%	56	50%	
N-stage							
0	101	100%	30	29.7%	71	70.3%	<.001[c,d]
1	210	100%	145	69%	65	31%	
2abc	92	100%	21	22.8%	71	77.2%	
3	11	100%	4	36.4%	7	63.6%	
x	3	100%	3	100%	0	0%	
T-Stage							
1	86	100%	46	53.5%	40	46.5%	<.001[c,d]
2	203	100%	120	59.1%	83	40.9%	
3	80	100%	23	28.75%	57	71.25%	
4A/4B	43	100%	9	21%	34	79%	
Non-graded	5	100%	5	100%	0		
TNM Stage (UICC-8)							
I	180	100%	150	83.3%	30	16.7%	<.001[d]
II	66	100%	34	51.5%	32	48.5%	
III	68	100%	13	19.1%	55	80.9%	
IV	98	100%	1	1%	97	99%	
Unknown TNM-stage	5	100%	5	100%	0	0%	

BSCC: base of tongue tonsillar squamous cell carcinoma, NSTSCC: nonspecific tonsillar squamous cell carcinoma, STSCC: specific tonsillar squamous cell carcinoma, x: unknown stage.

Table 1 illustrates the oropharyngeal tumor characteristics stratified by HPV tumor status, showing a significant difference in age at diagnosis, tumor location, N-stage, T-stage, and TNM stage.

*p-value of HPV-positive group (HPV+/p16+) compared to HPV-negative (HPV+/p16−, HPV−/p16+, and HPV−/p16−).

[a]Student t-test.

[b]Wilcoxon test.

[c]χ^2 test.

[d]Fisher's exact test.

Table 2. Relationship between cervical cytology and histology and HPV status in women with OPSCC.

Cervical examinations	HPV-positive		HPV-negative		Total	*p*-value*	*p*-value**
Total	172	100%	171	100%	343	.28[a]	.4[b] I/IIAB – IICD
I	130	75.6%	141	82.5%	271		.51[c]
IIAB	20	11.6%	13	7.6%	33		I – IIAB
IICD	22	12.8%	17	9.9%	39		.88[c] IIAB – IICD

Table 2 illustrates cervical examination results categorized in 3 groups in relation to HPV tumor status in OPSCC. Subdivision of cervical examinations, group I-IIA-D is explained under Supplementary Table 1.

[a]χ^2 test.

[b]logistic regression, [c]Ordinal logistic regressions.

*p-value of HPV-positive group (HPV+/p16+) compared to HPV-negative group (HPV+/p16−, HPV−/p16+, and HPV−/p16−).

**After adjusting for age and smoking.

compared to nonsmokers, although not statistically significant.

The association between patient characteristics and tumor HPV status is presented in Table 3.

Women with HPV-negative OPSCC were more likely to have a history of heavy smoking (>20 py) resulting in an average of 20.6 pack years (py) more than the HPV-positive group.

Both groups of women had the same participation rate to the cervical screening program. A total of 343 (82%) had one or more cervical results identified in the medical history, leaving 74 patients uninvestigated. Females with HPV-negative OPSCC attended significantly fewer times in the program and the majority having performed only 1–5 cervical screenings.

Discussion

In this study, we aimed to explore the correlation between cervical and oropharyngeal HPV infections to obtain further knowledge regarding the pathogenesis of HPV infection, its interactions and potential systemic implications.

Only one study by Rietbergen *et al.* previously investigated the association between HPV-positive OPSCC and precancerous cervical lesions [25]. A statistically significant difference between cervical history in women with HPV-positive and negative OPSCC was found, but this study had several limitations such as a small study population, single center and no adjustments for potential confounders (e.g., smoking and age). We investigated a larger group of women ($n = 417$) and found no significant differences in their history of cervical dysplasia or worse before or after adjusting for potential confounders.

We found that females with HPV-positive OPSCC did not have significantly different history of high-grade squamous cell abnormalities and cervical cancer (group IIC-D) compared to the HPV-negative group. Of the HPV-negative OPSCC group, 83% and 76% of the HPV-positive OPSCC group had a normal result. This result corresponds to the finding in the Danish population, where 80% of all cytologies have normal cells [26].

The incidence of cervical cancer in the Danish population is found to be markedly higher than in Iceland, Norway or Sweden [27] and has one of the highest occurrences in Europe [26]. We found that 1.2% of females in our cohort

Table 3. Patient characteristics in relation to HPV-status in women with OPSCC.

	Cases		HPV-positive		HPV-negative		*p*-value*
Cases	417	100%	203	48.7%	214	51.3%	
Pack years							
Mean	27.2		16.8		37.4		<.001[a] (−25 – −16.1)
0	95	100%	72	75.8%	23	24.2%	<.001[c]
< 10	25	100%	17	68%	8	32%	
11–20	48	100%	32	66.7%	16	33.3%	
>20	215	100%	70	32.6%	145	67.4%	
Unkown	34	100%	12	35.3%	22	64.7%	
Cervical screening program							
Participates	*343*	*100%*	*172*	*50.1%*	*171*	*49.9%*	.2[c]
Non-participates	*74*	*100%*	*31*	*41.9%*	*43*	*58.1%*	
Cervical examinations							
Mean participants	6.9		8.3		5.4		<.001[a] (1.6 – 4.1)
Mean all patients	5.6		7		4.3		<.001[a] (1.5 – 3.8)
1–5	167	100%	62	37.1%	105	62.9%	<.001[d]
6–10	126	100%	74	58.7%	52	41.3%	
11–15	27	100%	18	66.7%	9	33.3%	
16–20	11	100%	8	72.7%	3	27.3%	
21–25	7	100%	6	85.7%	1	14.3%	
>25	5	100%	4	80%	1	20%	
Status at follow-up							
Dead	192	100%	39	20.3%	153	79.7%	<.001[c]
Alive	225	100%	164	72.9%	61	27.1%	

Table 3 illustrates the patient characteristics stratified by HPV tumor status in OPSCC, showing a significant difference in pack years, cervical examinations performed, status at follow-up. No difference is observed in amount of participates in the cervical screening program.
[a]Student *t*-test.
[b]Wilcoxon test.
[c]χ^2 test.
[d]Fisher's exact test.
**p*-value of HPV-positive group (HPV+/p16+) compared to HPV-negative group (HPV+/p16−, HPV−/p16+, and HPV−/p16−).

had a history of CC (HPV-positive group =3, HPV-negative group =2).

One possible explanation for the finding of the same amount of (pre)cancerous cervical lesions among the two OPSCC groups could be distinct HPV infections associated with OPSCC compared to the type causing HSIL and CC. HPV16 is the most common infection in both CC and OPSCC, whereas the other most frequent types in respectively cervical and oropharyngeal cancer differs. A study by Carlander et al. of 700 patients with OPSCC, demonstrated that 86% of HPV-positive tumor types were HPV16, 6.3% were HPV33 and 4.0% were HPV35 [15]. In Denmark, 70% of cervical dysplasia is due to HPV types 16 and 18 [28], Further studies found that in Europe the most prevalent types of HPV infection found in cervical lesions were HPV16, -52, and -31 [29]. This supports the hypothesis of different types of viral infection. Interestingly, one study investigated the HPV16 gene expression profiles in CC and OPSCC and found that the viral load was very low in OPSCC compared to CC and that the viral oncogene mRNA levels and expression profiles were very different between CC and OPSCC, and suggested distinctive viral oncogenic mechanisms in the two cancers [30]. Although their study was limited in number of patients, it could support a theory of different HPV pathogeneses. In future studies, it would be interesting to compare HPV genotypes in the cervical and oropharyngeal tumors from the same patients, to clarify if it is in fact the same HPV-type in both locations.

Other studies showed that women with CIN2 or worse had a greater risk of a head and neck squamous cell cancer, but did not stratify OPSCC by HPV status [7]. Another theory proposed is that women with immune dysregulation are more susceptible to HPV infection because of impaired ability to clear the virus, hereby having a higher risk of persistent infection and a subsequent risk of HPV induced OPSCC. This theory is supported by evidence among immunosuppressed individuals (e.g., HIV infected), finding a 2- to 3-fold higher prevalence of oropharyngeal HPV-infection and of CIN2 or worse cervical lesions, compared to the general population [29,31], and also a longer persistency of HPV infection and of higher risk of CIN3 + [32,33]

The HPV/p16 negative group had significantly less cervical examinations performed compared to the patients with HPV/p16 positive tumors, and of the negative group a total of 43 had no medical history registered. This could indicate that this group of women had more unnoticed episodes of precancerous lesions and cervical cancer than was detected in our study. This observation supports the finding that there is no correlation between cervical lesions and HPV-status of OPSCC. This could even suggest that the HPV-negative group has a higher occurrence of precancerous lesions. The reason for the differences in attending the cervical screening program could be explained by the difference in age at diagnosis for OPSCC (median age: HPV-positive =59.8 years and HPV-negative =62.3 years) or difference in socioeconomic status [18]. Cervical cancer screening was introduced in 1960s in Denmark; since then, the free of charge screening procedure has been gradually implemented, and in 2006, all Danish women between 23–64 years were invited to the screening program [34].

When investigating other causes of CC and CIN, tobacco smoking was shown to be a risk factor for both CIN3, CIS and CC, even after adjusting for HPV infection [35,36]. Furthermore, a review by the International Agency for Research on Cancer

Table 4. Relationship between smoking status and cervical cytology and histology in women with HPV positive OPSCC.

HPV-positive							
Cervical examinations	Non-smoker		Previous-smoker		Current-smoker		*p*-value*
IICD	3	5.26%	12	13.79%	6	24%	.19[1]
IIAB	7	12.28%	11	12.64%	2	8%	
I	47	82.46%	64	73.56%	17	68%	
Total	57	100%	87	100%	25	100%	
HPV-negative							
IICD	1	7.69%	5	9.80%	11	10.68%	.67[1]
IIAB	0	0.00%	6	11.76%	6	5.83%	
I	12	92.31%	40	78.43%	86	83.50%	
Total	13	100%	51	100%	103	100%	

Table 4 illustrates cervical examination results categorized in three groups in relation to smoking habits comparing HPV tumor status in OPSCC. Subdivision of cervical examinations, group I-IIA-D is explained under Supplementary Table S1. [1]Fisher's exact test.
*p-value of HPV-positive group (HPV+/p16+) compared to HPV-negative group (HPV+/p16−, HPV−/p16+, and HPV−/p16−).

(IARC) classified smoking not only as a risk factor, but as a cause of CC [37]. We found that one of the biggest clinical differences between our populations were their smoking habits. It has been well established that tobacco is a predominant risk factor of OPSCC [38]. For the women with HPV-negative OPSCC, the average tobacco consumption was 37.4 pack years. A hypothesis could be that the incidence of cervical examination result with CIN2 or worse in the HPV-negative OPSCC group could be explained by both smoking and HPV infection. This would mask a higher incidence of HPV-related cervical neoplasia in women with HPV-positive OPSCC, whom smoke less than their HPV- OPSCC counterparts. Table 4 illustrates the relationship of HPV tumor status and smoking habits. It was striking that women with HPV-negative OPSCC, regardless of smoking habits, only differed by 3% in occurrence of class IIC-D, whereas women with HPV-positive OPSCC had a prevalence of 24% and 5% for smokers and nonsmokers, respectively. This finding could suggest an interaction between HPV infection in cervix and smoking in relation to formation of IICD. Such a correlation has been described previously, finding the risk of HPV infection 1.9 times higher among smokers versus nonsmokers [39]. We found that the women in group IIC-D were diagnosed with OPSCC in average 20.4 years after their cervical dysplasia.

The strengths of our study were the ability to obtain high-quality, individual-level data from nationwide registries, which eliminated the risk of selection bias and recall bias.

In conclusion, no association was found between women with HPV/p16-positive and -negative OPSCC regarding history of cervical intraepithelial neoplasia. This would suggest different pathogenesis and carcinogenic mechanisms in the two different virus related tumors or different clinical characteristics among these women.

Funding

None.

Disclosure statement

The authors declare no conflicts of interest.

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