Cancer Epidemiology 61 (2019) 89–94

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Prevalence and characteristics of HPV-driven oropharyngeal cancer in France

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ARTICLE INFO

Keywords:
Human papillomavirus (HPV)
cancer(s)
neoplasm(s)
oral/oropharynx/oropharyngeal
tonsil/tonsillar
epidemiology
prevalence
France

ABSTRACT

Background: France has one of the highest incidence of head and neck cancers in Europe. Despite this, the epidemiological impact of high-risk human papilloma virus (HR-HPV) remains poorly investigated.
Methods: We prospective assessed the proportion of oropharyngeal cancers due to HR-HPV in 15 hospitals throughout France. HPV-status was determined by p16-immunohistochemistry, and by detection of HPV-DNA using *in situ* hybridization. Cancers were classified as HPV-driven if both p16-immunohistochemistry and HPV-DNA assays were positive. Demographical and clinical features were recorded.
Results: 291 patients with palatine-tonsil or tongue-base cancers were recruited from March-2011 to July-2012. Of these, 43.1% of samples were p16-positive and 37.7% were positive for both p16 and HPV-DNA. Prognosis was significantly better in patients with HPV-driven cancers, with smoking negatively impacting patients' oncological outcomes.
Conclusion: In France, more than a third of tonsillar and tongue base cancers are HPV-driven. More research concerning the evolution of HPV-driven cancers over time is needed.

1. Introduction

France has one of the highest incidences of head and neck cancers in Europe with approximately 14 650 new cases diagnosed in 2012 [1].

Despite this high incidence, the epidemiological impact of high-risk HPV (HR-HPV) remains poorly investigated. Few studies have been published [2–4], some significantly limited by small sample sizes, inadequately defined HPV-status, and methodological shortcomings.

Therefore, in 2011, UNICANCER a network of French Comprehensive Cancer Centers launched the prospective epidemiologic HPV-ORO study (ID-RCB: 2009-A0120354). We aimed to assess the prevalence of oropharyngeal cancer (OPC) due to HR-HPV in France and to characterize the clinical features and oncological outcomes of OPCs by HPV-status. In the present article, we report our results and

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https://doi.org/10.1016/j.canep.2019.05.007
Received 28 January 2019; Received in revised form 14 May 2019; Accepted 17 May 2019
Available online 31 May 2019

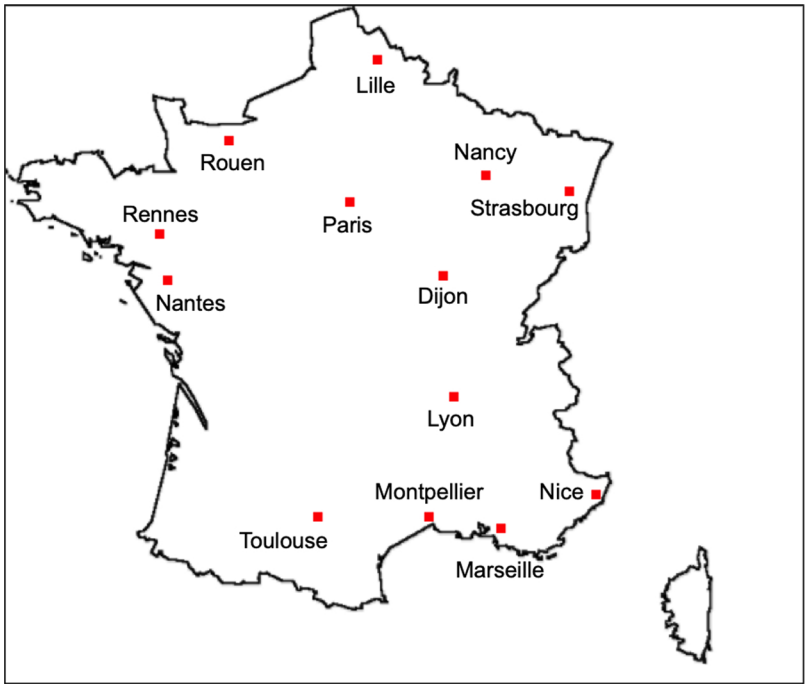

Fig. 1. Geographic location of the participating centers in metropolitan France.
This map shows the geographic location of the centers that participated in our study.
These hospitals are representative of those treating head and neck cancers in France and their geographic distribution cover the whole country.
The number of patients is provided in brackets: Paris (2 centers, n = 45), Rouen (n = 3), Nancy (n = 26), Strasbourg (n = 15), Toulouse (n = 32), Nantes (n = 13), Marseille (n = 34), Rennes (N = 12), Lille (n = 3), Lyon (n = 2), Dijon (n = 26), Montpellier (n = 45), Nice (n = 7) and Guadeloupe (n = 8, West Indies – not on the map).

discuss the implications of this emerging disease in France.

2. Methods

2.1. Study design

Patients were prospectively recruited in 15 hospitals (10 comprehensive cancer centers and 5 university hospitals) throughout France from March-2011 to July-2012 (Fig. 1). Only patients with tonsillar or tongue-base squamous cell carcinoma (SCC) were eligible, as HPV-driven head and neck cancers occur almost exclusively in these anatomical regions [4–6]. Consequently, patients with SCC in the vallecular, the soft palate, or the posterior pharyngeal wall were not eligible.

We selected centers representative of those treating head and neck cancer patients in France and all eligible patients were prospectively and consecutively enrolled at each center.

Epidemiological, clinical, pathological, and oncological data recorded were centralized at the Institut Bergonié for analysis (see supplementary-data, file-1).

2.2. HPV testing

Tumor samples were initially assessed with p16 immunohistochemistry (IHC) (CINtec p16 Histology Kit, Roche mtm laboratories AG, Heidelberg, Germany). In samples overexpressing p16-protein in > 70% of tumor cells, the presence of HPV-DNA was tested by *in situ* hybridization (ISH) (Inform HPV-III probe cocktail, Ventana Medical Systems, Tucson, AZ, USA). The corresponding tonsillar or tongue-base SCCs were considered HPV-driven if both assays were positive. The IHC and ISH protocols are described in the Supplementary-data (file-2).

2.3. Statistical analysis

Overall survival (OS) was defined as the interval between registration to the date of death or censorship (i.e., the patient's last follow-up date). Disease-free survival (DFS) was defined as the interval between registration until the date of first documented disease recurrence or censorship.

OS and DFS curves were estimated by the Kaplan-Meier method. Survival between groups was compared by logrank tests in univariate analysis. In multivariable analyses, a Cox proportional hazards model was used to adjust for covariates of statistical significance in univariate analysis. The Wald test was used to estimate the 95% confidence intervals (CIs) of hazard ratios. All statistical tests were two-sided and p values < 0.05 were considered statistically significant.

3. Results

3.1. Study population

Between March 2011 and July 2012, 291 patients were enrolled. Of these, 15 patients were not analyzed: eight patients without and two patients with non-exploitable p16-IHC results, 2 patients without HPV-DNA results, and 3 patients without the protocol required imaging. The study analyzed 276 patients with a mean age of 59.9 years (range: 34-89). The majority of patients were men (209, 75.7%). Overall, 220 patients (79.7%) had a history of smoking with 109 (39.5%) smoking at diagnosis. The smoking level was above 20 pack/year in 154/220 patients (70%) with a history of smoking. Of the 276 patients, 111 (40.2%) had up-front surgery alone or combined with adjuvant treatment. The remaining 165 (59.8%)patients had up-front radiotherapy or chemoradiation depending on the disease stage. The choice of treatment, either surgery, radiotherapy, or chemoradiation, was at each sites discretion. The patient and disease characteristics are shown in Table 1.

3.2. HPV prevalence and patients characteristics

The p16-protein was overexpressed in 119 patients (43.1%). HPV-DNA detection by ISH was available for 239 patients. Overall, 90 patients (37.7%) had HPV-driven cancers (positive for both p16-protein and HPV-DNA). Age was not significantly different between HPV-positive and HPV-negative patients. HPV-driven cancers occurred more frequently in male than female (the same observation was made in HPV-negative patients). Patients with HPV-driven OPCs have higher socio-professional levels ($p = 0.002$) than those with HPV-negative tumors. Smoking was significantly more frequent among HPV-negative patients ($p < 0.001$). Although, 52/90 HPV-positive patients (57.8%)

Table 1
Patients characteristics and TNM staging according to p16 expression and HPV status.

	p16 status			HPV status		
	p16-positive	p16-negative	p-value	HPV-driven	Not HPV-driven	p-value
n (%)	119 (43.1)	157 (57.9)	-	90 (37.7)	149 (62.3)	-
Age, years			ns			ns
Mean	60.6	59.2		60.3	59.1	
Median	61	58		59.5	58	
Sex, n (%)			ns			ns
Male	87 (73.1)	122 (77.7)		64 (71.1)	114 (76.5)	
Female	32 (26.9)	35 (22.3)		26 (28.9)	35 (23.5)	
Socio-professional category, n (%)			0.01			0.002
High	75 (63)	46 (29.3)		56 (62.2)	59 (39.6)	
Low	38 (32)	101 (64.3)		18 (20)	55 (36.9)	
Unknown	6 (5)	10 (6.4)		16 (17.8)	35 (23.5)	
Smoking, n (%)			< 0.05			< 0.001
Smokers*	74 (62.2)	146 (93)		52 (57.8)	139 (93.3)	
Never smokers	45 (37.8)	11 (7)		38 (42.2)	10 (6.7)	
Pack/year > 20[a]	39[a] (32.7)	115[a] (73.2)		24[c] (26.7)	55[c] (36.9)	
Active smokers at diagnosis[b]	29[b] (24.3)	80[b] (50.9)		19 (21.1)	78 (52.3)	
T stage, n (%)			< 0.05			0.0014
T1	24 (20.2)	14 (8.9)		21 (23.3)	12 (8)	
T2	45 (37.8)	46 (29.4)		30 (33.3)	44 (29.5)	
T3	28 (23.5)	44 (28)		24 (26.7)	42 (28.2)	
T4	21 (17.6)	52 (33.1)		14 (15.6)	50 (33.6)	
Tx	1 (0.9)	1 (0.6)		1 (1.1)	1 (0.7)	
N stage, n (%)**			< 0.05			< 0.001
N0	18 (15.1)	37 (23.6)		11 (12,2)	32 (21.5)	
N1	78 (65.5)	29 (18.5)		59 (65.6)	29 (19.5)	
N2	15 (12.6)			14 (15.6)		
N2a		5 (3.2)			5 (3.4)	
N2b		46 (29.3)			43 (28.9)	
N2c		28 (17.8)			28 (18.7)	
N3	8 (6.8)	9 (5.7)		6 (6.6)	9 (6)	
Nx		3 (1.9)			3 (2)	
M stage, n (%)			ns			ns
M0	117 (98.4)	142 (90.5)		88 (97.8)	134 (89.9)	
M1	1 (0.8)	6 (3.8)		1 (1.1)	6 (4.1)	
Unknown	1 (0.8)	9 (5.7)		1 (1.1)	9 (6)	

IHC: immunohistochemistry; HPV: human papillomavirus; ISH: In situ hybridization; ns: no significant difference.
[a] data was not available for 8 patients p16-positive and 7 patients p16-negative.
[b] data was not available for 1 patient p16-positive and 7 patients p16-negative.
[c] number of pack years is unknown for 1 patient HPV-positive and for 7 patients HPV-negative.
* The smoker category includes former and current smoker.
** In the 8th TNM edition [22], 2 distinct classifications have been developed according to HPV status. In the current study, the comparison was strictly limited to patients without neck lymph node metastasis (N0) versus those who have lymph node metastasis (independently of the size, number, and location of the metastatic nodes).

were current or former smokers and 24 (26.7%) smoked > 20 pack/year. HPV-negative patients had more advanced primary tumors compared to those with HPV-driven cancer (p = 0.0014). The nodal staging distribution was also significantly different according to HPV-status. In particular, HPV-negative patients were more likely to have tumors staged N0 than those of HPV-positive patients (< 0.001).

3.3. Oncologic outcomes and follow-up data

The median follow-up was 3.7 years (95% CI: 3.61-3.77). Overall, survival outcomes were significantly longer in HPV-positive and p16-positive patients compared with those HPV-negative and p-16 negative. The 3-year OS rate was 85% in HPV-positive patients compared to 60% in those HPV-negative (p < 0.001). Similarly, the 5-year OS rate was 80% in HPV-positive patients and 40% in those HPV-negative (p < 0.001). In addition, the 3-year DFS rate was 80% in the HPV-positive patients compared to 46% in those HPV-negative (p < 0.001). Similarly, the 5-year DFS rate was 68% in HPV-positive patients and 28% in those HPV-negative (p < 0.001).

The 3-year OS rate was 85% in p16-positive patients compared to 60% in those p16-negative (p < 0.001). Similarly, the 5-year OS rate was 80% in p16-positive patients compared to 40% in those p16-negative (p < 0.001). In addition, the 3-year DFS rate was 79% in p16-positive patients compared to 48% in those p16-negatives. Similarly, the 5-year DFS rate was 68% in p16-positive patients and 28% in those p16-negative patients (p < 0.001).

In the p16-positive and HPV-positive populations, multivariate analysis identified age and smoking as having a significant negative impact on OS (see Table 2) and DFS (see Table 3). Survival curves and the interaction between clinical parameters (age, sex, smoking, T and N stage) and oncological outcomes are depicted in Table 2 and 3 and in the supplementary data (file 3 and 4).

4. Discussion

This prospective study shows that HR-HPVs are responsible for 37.7% of tonsillar and tongue-base SCC. To define HPV-status accurately we used a combination of two biomarkers, which we tested sequentially. We initially tested the presence of p16-protein by IHC and if p16 was overexpressed we then tested the presence of HPV-DNA by ISH. HPV-driven OPCs required both biomarkers to be positive. Although, this approach is widely accepted [7], it is important to highlight that HPV-DNA detection by ISH, lacks sensitivity with possible false negatives [7]. In our study, 43.1% of samples were p16-

Table 2
Interaction between clinical parameters and overall survival in p16-positive and HPV-positive patients (multivariate analysis).

	p16-positive OPC			HPV-driven OPC		
	HR	95% CI	p-value	HR	95% CI	p-value
Age, years			0.0035			0.0011
< 50	1.00	-		1.00	-	
[50-59]	0.32	0.07-1.47		0.15	0.02-0.93	
[60-69]	0.53	0.15-1.93		0.47	0.10-2.23	
< 70	3.08	0.78-12.10		4.56	0.99-20.90	
Sex			0.0926			0.1203
Male	1.00	-		1.00	-	
Female	0.17	0.02-1.34		0.19	0.02-1.54	
Smoker			0.0352			0.0055
No	1.00	-		1.00	-	
Yes	3.40	1.10-10.61		6.43	1.73-23.94	
T stage			0.5935			0.1163
T1-3	1.00	-		1.00	-	
T4	1.34	0.46-3.9		2.69	0.78-9.22	
N stage			0.2850			0.2044
N1-2	1.00	-		1.00	-	
N3	2.31	0.60-8.9		3.05	0.54-17.12	

OPC: oropharyngeal cancer; HPV: human papillomavirus; HR: hazard ratio; CI: confidence interval.

Table 3
Interaction between clinical parameters and disease-free survival in p16-positive and HPV-positive patients (multivariate analysis)

	p16-positive OPC			HPV-driven OPC		
	HR	[95% CI]	p-value	HR	[95% CI]	p-value
Age, years			0.0015			0.0083
< 50	1.00	-		1.00	-	
[50-59]	0.52	0.16-1.68		0.29	0.07-1.15	
[60-69]	0.71	0.24-2.15		0.54	0.15-1.97	
< 70	3.58	1.06-12.07		2.88	0.73-11.40	
Sex			0.1075			0.1256
Male	1.00	-		1.00	-	
Female	0.41	0.14-1.21		0.37	0.11-1.32	
Smoker			0.0219			0.0252
No	1.00	-		1.00	-	
Yes	2.75	1.16-6.52		3.22	1.16-8.95	
T stage			0.1683			0.1634
T1-3	1.00	-		1.00	-	
T4	1.82	0.78-4.24		2.15	0.73-6.29	
N stage			0.0543			0.0334
N1-2	1.00	-		1.00	-	
N3	3.08	0.98-9.69		4.54	1.13-18.32	

OPC: oropharyngeal cancer; HPV: human papillomavirus; HR: hazard ratio; CI: confidence interval.

positive and 37.7% were p16-positive with HPV-DNA detected. We thus estimate that HPV-driven tonsilar and tongue base cancer's prevalence in France is probably between 37.7 % and 43.1%.

This range is higher than the 27.1% reported in the Papillophar study [4], the only published French prospective study. The lower prevalence reported in the Papillophar study may be due to the study's patient population and definition of HPV-status. The Papillophar study included not only patients with tonsil and tongue-base SCC, as in our study, but also those with other oropharyngeal sub-localizations (posterior pharyngeal wall, soft palate, and vallecula) not usually associated with HPV-driven cancers [5,6]. Moreover, the Papillophar study defined HPV-driven OPCs as those with HPV-DNA detected by polymerase chain reaction and expressing E6/E7 mRNA [4].

Compared with other European studies (Table 2), the prevalence of HPV-driven OPCs in France is lower than that reported in Northern Europe and higher than in Southern and Eastern Europe [68–19]. The reasons for this variation are unknown but several factors may contribute including tobacco consumption level (higher levels of consumption may lower the relative proportion of HPV-induced tumors), sexual behaviors, and potential confounding factors – as most studies were monocentric and retrospective. Indeed, significant national variations in the prevalence of HPV-induced OPC have been reported [4,6].

Our demographical and clinical data corresponds with that published for HPV-driven OPC. This disease affects mainly men [4,10,20] and patients with a good socio-professional status [21]. Neck lymph node metastases are frequent at diagnosis [4,10]. As reported, almost 60% of our HPV-positive cancer patients were current or former smokers [4,10]. Although tobacco consumption, in pack-years, was significantly lower than that of HPV-negative patients.

Furthermore, about a quarter of HPV-positive patients in France had high exposure to smoking, > 20 pack-years, which contrasts with that reported in North America and Northern Europe [22].

Regarding oncologic outcomes, as expected p16-positive and HPV-driven cancer patients had higher OS and DFS rates at 3 and 5-years compared with those p16-negative and HPV-negative. Furthermore, smoking had a significantly negative impact on prognosis of p16-positive and HPV-positive patients.

Although our study has several advantages, a national prospective design with an accurately defined HPV-status, there are some limitations.

- Firstly, our cohort size is modest and represents only about 10% of tonsil and tongue base SCC diagnosed annually in France [1]. However, our sample size is comparable to most of the European series published [68–19] (these series having the disadvantage of being retrospective and monocentric - Table 4).

- Secondly, our study estimates the prevalence of HPV-driven OPC over a specific and short period of just over a year, but does not assess the evolution over time, which is a major issue, particularly for public health policies.

Recently, analysis of data from 11 French cancer registries (covering 14% of the French metropolitan population) from 1980-2012, found that the incidence of head and neck cancers in sites at risk of being HPV-driven (C01.9, C02.4, C09, C10 and C14.2) have decreased less drastically than in sites where smoking is the main risk factor [23]. This suggests that in France, HPV-driven OPCs incidence is increasing. Unfortunately, these registries did not collect tumor HPV-status data.

Finally, we defined HPV-driven cancers as those positive for both p16 and HPV-DNA by ISH. Currently, E6/E7 mRNA expression is the gold standard for defining HPV status [7]. However, when we initiated this study HPV-RNA expression could only be determined in fresh frozen tumor samples that were not available for our study.

5. Conclusion

Our study indicates that in France, HPV-driven tonsilar and tongue base cancer's prevalence is probably between 37.7 % and 43.1%. For a more comprehensive understanding of HPV-driven OPC the evolution of disease over time needs to be studied.

Author Statement

All the authors have contributed to this study

All the authors agree to submit this paper to cancer epidemiology journal

All the authors have no conflict of interest to disclose.

Conflict of interest statement

The authors have nothing to declare.

Table 4
Selected publications describing the prevalence of HPV-driven OPC in several European countries.

Country	Study type	Study duration	N° of cases	Outcomes
France (current study)	Multicentric Prospective	2011-2012	276	43.1% of cases were p16-positive and 37.7% were positive for both p16 and HPV-DNA
Denmark [8]	Multicentric Retrospective	2000-2010	632	58% of cases were p16-positive and HPV-DNA positive. 4.9% Annual increase during the study period – Study based on a cancer registry
Sweden [9]	Monocentric Retrospective	1970-2007	248	HPV-driven OPC (positive for both HPV-DNA and E6/E7 mRNA) increased from 23% between 1970-1979 to 79% between 2000-2007
Netherland [10]	Monocentric Retrospective	1990-2010	240	Samples positive for both p16 and HPV DNA increased from 5.1% in 1990 to 29.0% in 2010[a]
United Kingdom [6]	Multicentric Retrospective	2002-2011	1474	51.8% of OPCs are HPV-driven, no variation over time from 2002 to 2011[b]
Belgium[11](Flanders)	Multicentric Retrospective	2000-2010	249	24.7% of cases contained HPV-DNA by PCR. No data regarding p16 or E7/E7 mRNA expression
Germany [12]	Monocentric Retrospective	2004-2013	227	Samples positive for both p16 and HPV DNA increased from 28% in 2004-2006 to 59% in 2002-2013[c]
Slovenia [13]	Monocentric Retrospective	2007-2008	99	HPV E6/E7 mRNAs were identified in 20% of samples[d]
Switzerland [14]	Multicentric Retrospective	NA	338	43% of cases were both HPV DNA an p16-positive[e]
Spain [15] (Asturias)	Monocentric Retrospective	1990-2009	248	Samples positive for both p16 and HPV DNA increased from 1.8% in 1990 to 6.1% in 2009[f]
Poland [16]	Monocentric Retrospective	2006-2009	62	27.4% of cases contained HPV-DNA by PCR. No data regarding p16 or E7/E7 mRNA expression
Italy [17] (North-east Italy)	Monocentric Retrospective	2003-2012	63	20% of cases contained both HPV DNA and mRNA
Greece [18]	Monocentric Retrospective	1986-2007	31	38.7% of cases contained HPV-DNA by PCR. No data regarding p16 or E7/E7 mRNA expression
Romania [19]	Monocentric Retrospective	2010-2014	28	50% of cases contained HPV-DNA by PCR among which only one sample was positive for E6 mRNA

For some countries, several articles reporting HPV prevalence have been published. In this situation, we have selected the one with the largest cohort of patients or with samples collected from different area within country.

OPC: oropharyngeal cancer; HPV: human papillomavirus; PCR: polymerase chain reaction.

[a] HPV-positivity rate stratified per year was 2/39 (5%) in 1990, 3/37 (8%) in 1995, 6/42 (14%) in 2000, 12/59 (20%) in 2005 and 18/62 (29%) in 2010.

[b] Cases were collected from 11 recruiting centers distributed across the United Kingdom between 2002 and 2011. The study sample included 8.3% of the 17,739 OPSCCs diagnosed in the United Kingdom from 2002 to 2011.

[c] In this study, the authors assessed the fraction of HPV-related OPC in a cohort of 227 OPC treated between 2004 to 2013 in their institution (described in the table above). In addition they analyzed the registry data from six federal states of Eastern Germany and noted a significant increase in the trend of OPC incidence between 1998 and 2011 (of note, HPV status was not available in this registry).

[d] In this study, the authors also assessed the Slovenian cancer registry from 1983 to 2009 and noted that the incidence of head and neck cancers occurring in both HPV-related and those unrelated were decreasing (of note, HPV-status was not available in the registry).

[e] In this study, all patients were treated with primary surgery which may represent a selection bias.

[f] Patients were treated in the Hospital Universitario Central de Asturias where the vast majority of OPC patients in the Asturias, north western Spain are treated. A smaller study performed concerning patients treated in Madrid, that tested 102 samples collected from 2000 to 2008, reported that 26.5% of OPCs were HPV-related (Cerezo et al – Clin Trans Oncol 2014).

Acknowledgments

The authors would like to thank Trevor Stanbury PhD (Unicancer) for medical writing services.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.05.007.

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