Applied statistics as an essential tool for the success of the relationship between epidemiology and clinics: the study of the involvement of Human Papillomavirus with oropharyngeal cancer.

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A multidisciplinary team composed by epidemiologists, statisticians, pathologists, and laboratory technicians at ICO started around 10 years ago to study the relationship between Human Papillomavirus (HPV) infection and oropharyngeal cancer (OPC). A large international study^{ref1} including 3680 samples was conducted to estimate fractions (AF) of head and neck cancers (HNCs) attributable to HPV using six biomarkers. We observed that HPV contribution to HNCs was substantial but highly heterogeneous by cancer site, region, and sex, and confirmed the important role of HPVs in OPC. In 2018, we started to collaborate with the oncologist's team from the hospital given the different nature and better outcomes of OPC associated with HPV infection they were observing in the clinical practice. The etiologic role of HPV in OPC was well established at that time point. Nevertheless, information on survival differences by anatomic sub-site or treatment remained scarce. Simultaneously, a novel clinical stage classification for HPV-related OPC was just accepted for HNCs tumors classification, based on p16INK4a (p16) detection. However, it was still unclear the HPV-relatedness definition with best diagnostic accuracy and prognostic value. So, we conducted several studies to determine in a cohort of patients (pts) from Barcelona which could be the best definition to classifying HPV-related OPC ptsref2 and to assess the determinants of HPV infection and prognostic values of OPC pts based on p16 and HPV detection^{ref3}. We observed that HPV-relatedness definition does impact on TNM classification and the survival of p16+/HPV- pts was worse than p16+/HPV+. So, we extended our research to a multicenter study collecting multinational individual pt data including retrospective cohorts of consecutively recruited OPC pts previously analyzed^{ref4}. The study included 7654 OPC pts from 13 different centers. We identified significantly different proportion of p16+/HPV- pts by geographical region, being highest in the areas with lowest HPV-AFs (r=-0.7, p=0.003). 5-year overall survival was different depending on p16/HPV detection: 81.1% (95% CI 79.5-82.7) for p16+/HPV+, 40.4% (38.6-42.4) for p16-/HPV-, 53.2% (46.6-60.8) for p16-/HPV+, and 54.7% (49.2-60.9) for p16+/HPV-, and the prognosis of discordant p16+/HPV- tumors also differed on smoking status. In conclusion, pts with discordant OPC (p16-/HPV+ or p16+/HPV-) had a significantly worse prognosis than pts with p16+/HPV+ OPC, and a significantly better prognosis than pts with p16-/HPV- OPC. Along with routine p16, HPV testing should be mandated for clinical trials for all pts. In Figure 1 we detail the contribution of the statistician in each study.

Figure 1: Timeline of the studies conducted and the role of the statistician.

	EPIDEMIOLOGY	STATISTISTICS	c	LINICS	>
2013	Castellsagué X et al. HPV Involvement in Head and Neck Cancers: Comprehensive Assessment of Biomarkers in 3680 Patients. <i>J Natl Cancer Inst.</i> 2016; 108(6):djv403. (ref1)	 To centralize the recriutment and sample testing To collect the information provided by all the test performed To compute the HPV attributable fractions To adjust logistic regression models to asses the determinants of HPV positivity 			
2018	Taberna M et al. HPV-relatedness definitions for classifying HPV-related oropharyngeal cancer patient do impact on TNM classification and patients' survival. <i>PLoS One</i> . 2018 Apr 17;13(4):e0194107. (ref2) Mena M et al. Double positivity for HPV-DNA/p16ink4a	 To design a centralized database to collect information from 4 different centres To estimate the rates of OS by means of the Kaplan-Meier and Nelson-Aalen methods To adjust univariate Cox models (proportional hazard model) for each stage classification To compare Cox models using AIC (Akaike Information 	AJCC AJCC Cancer Staging		
	is the biomarker with strongest diagnostic accuracy and prognostic value for human papillomavirus related oropharyngeal cancer patients. <i>Oral Oncol.</i> 2018 Mar;78:137-144. (ref3)	Criterion) • To compare the risk of death and recurrence among HPV- related and non-related OPC using the same cohort of patients adjusting proportional-hazards models		€ tyring	per .
2023	Mehanna H et al. Prognostic implications of p16 and HPV discordance in oropharyngeal cancer (HNCIG- EPIC-OPC): a multicentre, multinational, individual patient data analysis. <i>Lancet Oncol.</i> 2023 Mar;24(3):239-251. (ref4)	 To design a centralized database to collect information from 13 different centres To asses the determinants of biomarkers combinations (p16+/HPV+, p16+/HPV-, p16-/HPV+, p16-H/HPV-) using multinomial regression models To compare the risk of death and recurrence among HPV- related and non-related OPC using the same cohort of patients admention to the same cohort of patients 	Teactip Hordinage/IC RPActual-out/coge/IC Nov-IPP employage/IC Nov-IPP employage/IC Nov-IPP employage/IC Nov-IPP employage/IC	opige princy manipular RN posts To mongo Print too ThomPM No desp	(P): spectrum and/o (P): spectrum is an in- (P): status is from their printing in minimum in (P) they printing in minimum in (P) they printing in (P) the
	To be continued	adjusting proportional-hazards models		energi t ana	