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 pts[ref2] 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.