Original contribution

Detection of human papillomavirus in sinonasal carcinoma: systematic review and meta-analysis

Kari Syrjänen MD, PhD, FIAC [a,b,]*, Stina Syrjänen DDS, PhD, FDSRCSEd(hon) [c]

[a]*Department of Oncology & Radiotherapy, Turku University Hospital, Savitehtaankatu 1, FIN-20521 Turku, Finland*
[b]*Teaching and Research Institute, Barretos Cancer Hospital, Barretos, Sao Paulo, Brazil*
[c]*Department of Oral Pathology and Radiology, Institute of Dentistry, University of Turku, Turku, Finland*

Summary Since first suggested (in 1983), the etiological role for human papillomavirus (HPV) in sinonasal carcinomas has been subject to constantly increasing interest. To perform systematic review and formal meta-analysis of the literature reporting on HPV detection in sinonasal squamous cell carcinomas (SCC), literature was searched through May 2012. The effect size was calculated as event rates (95% CI), with homogeneity testing using Cochran Q and I^2 statistics. Meta-regression was used to test the impact of study-level covariates (HPV detection method, geographic origin, papilloma type) on effect size, and potential publication bias was estimated using funnel plot symmetry. Thirty-five studies were eligible, covering 492 sinonasal SCCs from different geographic regions. Altogether, 133 (27.0%) cases tested HPV-positive; effect size 0.305 (95% CI, 0.260-0.355; fixed effects model), and 0.330 (95% CI, 0.249-0.423; random effects model. In meta-analysis stratified by (i) HPV detection technique and (ii) geographic study origin, the between-study heterogeneity was significant only for the latter; P = .526, and P = .0001, respectively. In maximum likelihood meta-regression, HPV detection method (P = .511) and geographic origin of the study (P = .812) were not significant study-level covariates. Some evidence for publication bias was found only among polymerase chain reaction–based studies and among studies from Europe and North America but with negligible effect on summary effect size estimates. In sensitivity analysis, all meta-analytic results were robust to all one-by-one study removals. In formal meta-regression, the variability in HPV detection rates reported in sinonasal SCCs was not explained by the HPV detection method or geographic origin of the study.
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1. Introduction

Cancer of the nasal cavity and paranasal sinuses is a rare disease [1]. In Finland, the age adjusted incidence rates are 0.3/ 100 000 and 0.6/100 000 for women and men, respectively [2], probably reflecting the status more generally in Europe. Unfortunately, no such figures are available globally because GLOBOCAN or other IARC databases do not report sinonasal carcinomas as a separate entity [3]. During the past several years, a variety of agents have been implicated as risk factors of sinonasal cancer [4], including cigarette smoking and different occupational exposures, for example, working in the nickel and wood industries.

* Corresponding author. Department of Oncology & Radiotherapy, Turku University Hospital, Savitehtaankatu 1, FIN-20521 Turku, Finland.
E-mail address: kari.syrjanen@tyks.fi (K. Syrjänen).

The increased interest in sinonasal cancer parallels the research activity focused on their benign counterparts (sinonasal papillomas) since the 1980s, when the evidence on possible causal role of human papillomavirus (HPV) was first provided [5–7]. Papillomas of the sinonasal mucosa have been recognized since 1854, when first described with the name inverted papilloma [8]. Since then, the literature on sinonasal papillomas has expanded rapidly, covering several thousands of cases reported in large clinical studies [9,10].

There are 2 peculiar features in the natural history of sinonasal papillomas: (i) the tendency to recurrence even after radical treatment, and (ii) a substantial potential for malignant transformation [10–14]. Based on a meta-analysis of the reports covered until 1992, the overall recurrence rate is substantial (32%), varying from 0% to 100% [14]. Similarly, the reported prevalence of metachronous and synchronous malignancy varies within a wide range, 3% to 16% and 0% to 100%, respectively [9,13,15]. These 2 characteristics strongly implicate an infectious etiology of sinonasal papillomas, their clinical behavior closely resembling that of recurrent respiratory papillomatosis [9,13].

It was not until 1983, however, that HPV was first suggested as a potential etiological agent of sinonasal papillomas and their malignant counterparts by us [5]. This striking hypothesis was based on immunohistochemical detection of HPV antigen expression in a single papilloma, soon confirmed by in situ hybridization (ISH) demonstrating HPV DNA both in benign and malignant sinonasal lesions [6,7]. Following these primary reports, interest in HPV and sinonasal cancer has increased steadily [16–21], as first reviewed in the early 2000s [9,13]. Basically, the evidence on HPV as a possible etiological agent in sinonasal cancer is derived from 2 major lines of research: (i) reports on malignant transformation of benign (HPV-associated) papillomas, and (ii) direct detection of HPV DNA in sinonasal carcinomas by different assays of polymerase chain reaction (PCR) [9,13].

By 2002, a total of 322 sinonasal carcinomas had been analyzed for HPV detection, of which 70 (21.7%) tested HPV positive [9]. Since then, a number of large studies have been published, substantially increasing the total number of sinonasal carcinomas analyzed for HPV [22–27]. Until now, however, no formal meta-analysis of this literature has been published, only conventional reviews [9,13]. Sinonasal carcinomas are intimately linked with their benign counterparts, sinonasal papillomas, which were recently subjected to the first formal meta-analysis by these authors [28]. Thus, it was felt appropriate to conduct a similar meta-analysis of the published data on HPV and sinonasal carcinoma as well. In the present communication, a systematic review and formal meta-analysis are reported, covering all the published literature without any restrictions concerning the HPV detection method or geographic origin of the study.

2. Material and methods

2.1. Data abstraction

We identified eligible studies by searching MEDLINE (via PubMed) and reference lists from original articles, book chapters and other reviews until May 2012. No language or date-of-publication limitations were imposed. The search terms included the following: papillomavirus, HPV, carcinoma, cancer, nasal, sinonasal, paranasal sinus, squamous cell, papilloma, and malignant transformation. We considered all publications that appeared in peer-reviewed journals eligible, irrespective of which method (see later) was used for HPV detection, provided that the report included exact numbers of analyzed cases and of those testing HPV-positive, necessary for calculation of the event rates (=HPV prevalence) and their 95% confidence intervals (95% CI).

Altogether, more than 900 abstracts were derived from the database, covering the years 1950 through 2012. Although most of the reported studies were case reports, case series, or clinical and/or epidemiological studies (including treatment reports), with no testing for HPV, the eligible studies were those including all the necessary information to enable calculation of the effect size estimates (ie, HPV prevalence). For the present meta-analysis, a total of 35 original studies were determined eligible, all including cases of sinonasal carcinomas analyzed for HPV detection. As these were included in a recent meta-analysis [28], all studies including only benign papillomas and/or samples from normal sinonasal mucosa were excluded from this meta-analysis. In this study, we did not make disctinction between de novo SCC and those accompanied by papillomas, however.

From the summaries and/or text of each eligible study, we abstracted the following information: histological types of carcinoma, HPV detection method, geographic region of the study, HPV genotypes analyzed and/or detected, total number of cases analyzed, number testing HPV-positive, percent HPV positivity, authors, and publication year. Only the studies reporting HPV in sinonasal squamous cell carcinomas (SCC) were included, omitting the anecdotal reports on other histological types (adenocarcinoma, undifferentiated carcinoma).

2.2. Statistical analyses

A specific software, Comprehensive Meta Analysis (Version 2.2.064; Biostat Inc, Englewood, NJ), was used to perform the meta-analysis. The software calculates the event rates (logit event rates, SE and variance) based on the events and sample size data. To assess overall heterogeneity in the event rates between the different studies, Cochran's Q (2-sided) homogeneity P value as well as I^2 statistics (for percentage of variation) were used [29]. To explore the eventual publication bias, funnel plots were drawn by plotting the logit event rates by their precision (1/SE) [30].