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Review Article

A systematic review and meta-analysis on the attribution of human papillomavirus (HPV) in neuroendocrine cancers of the cervix

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HIGHLIGHTS

- 85% of all small-cell neuroendocrine cancers of the cervix were caused by HPV.
- 88% of all large-cell neuroendocrine cancers of the cervix were caused by HPV.
- HPV vaccination will prevent most neuroendocrine cancers of the cervix.

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ABSTRACT

Background. There remains uncertainty about the role of human papillomavirus (HPV) infection in causing small-cell neuroendocrine carcinoma (SCNC) and large-cell neuroendocrine carcinoma (LCNC) of the cervix. To clarify the role of HPV in the development of SCNC and LCNC, we conducted a systematic review and meta-analyses.

Methods. PubMed and Embase were searched to initially identify 143 articles published on or before June 1, 2017. Studies were limited to methods that tested for HPV in the cancer tissue directly to minimize misattribution. Thirty-two studies with 403 SCNC and 9 studies of 45 LCNC were included in the analysis.

Results. For SCNC, 85% (95% confidence interval [95%CI] = 71%–94%) were HPV positive, 78% (95%CI = 64%–90%) were HPV16 and/or HPV18 positive, 51% (95%CI = 39%–64%) were singly HPV18 positive, and 10% (95%CI = 4%–19%) were singly HPV16 positive. In a subset of 5 SCNC studies (75 cases), 93% were positive for $p16^{INK4a}$ by immunohistochemistry and 100% were HPV positive. For LCNC, 88% (95%CI = 72%–99%) were HPV positive, 86% (95%CI = 70%–98%) were positive for HPV16 or HPV18, 30% were singly HPV18 positive (95%CI = 4%–60%), and 29% (95%CI = 2%–64%) were singly HPV16 positive.

Conclusions. In conclusion, most SCNC and LCNC are caused by HPV, primarily HPV18 and HPV16. Therefore, most if not all SCNC and LCNC will be prevented by currently available prophylactic HPV vaccines.

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Contents

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1. Introduction

Approximately 95% of all cervical cancer is either squamous cell carcinoma (SCC) or adenocarcinoma (ADC) histology. The remaining approximately 5% of cervical cancer histologies is composed of a number of rare histologies, most common of which are high-grade neuroendocrine carcinomas, which are composed of small-cell neuroendocrine carcinoma (SCNC), large-cell neuroendocrine carcinoma (LCNC), and a smaller subset of low-grade neuroendocrine tumors also termed typical and atypical carcinoid tumors. Of neuroendocrine tumors, SCNC is the most common.

The morphologic features of SCNC and LCNC of the cervix resemble those of SCNC of the lung and have been described elsewhere [1]. Clinically, SCNC and LCNC are more aggressive, more likely to metastasize and is more lethal, than SCC and ADC of the cervix [2–4].

The rational for prophylactic HPV vaccination is the widespread recognition that almost all SSC and ADC of the cervix are caused by HPV. Because of their rarity, cervical neuroendocrine tumors have been variably recognized as being caused by human papillomavirus (HPV) infection [2–6]. Certainly, it is important to understand the etiologic fraction of SCNC and LCNC caused by HPV to understand the future impact of prophylactic vaccination against HPV. First-generation HPV vaccines that prevent virtually all HPV16 and HPV18 infections [7,8] are expected to prevent approximately 70–80% of all cervical cancer. The second-generation vaccine that prevents HPV16, 18, 31, 33, 45, 52, and 58 infections is expected to prevent approximately 90% of cancers [9]. To address the question of how much SCNC and LCNC might be prevented by currently available HPV vaccines, we conducted a systematic review and meta-analysis of case series of SCNC and LCNC that tested for HPV and $p16^{INK4a}$, a HPV-related marker.

2. Methods

We aimed to identify studies of the association of HPV with SCNC and LCNC. Studies were excluded if 1) SCNC were found with another lesion but detection of HPV was not shown to be specifically in the SCNC tissue, for example, by in situ hybridization, and 2) HPV detection was done on Pap/cervical specimen and not on the tumor tissue itself. We used the latter exclusion criteria to avoid the possibility of contamination due to other HPV infections in the lower genital tract that might have been sampled by Pap/cervical collection. HPV detection in the tumor itself provides a stronger case for causality.

We conducted a literature review using PubMed to search Medline (US Library of Medicine, Bethesda, MD) and EMBASE for studies published on or before June 1, 2017. The search criterion was: (((((“neurosecretory systems”[MeSH Terms] OR (“neurosecretory”[All Fields] AND “systems”[All Fields]) OR “neurosecretory systems”[All Fields] OR “neuroendocrine”[All Fields]) OR (“endocrine system”[MeSH Terms] OR (“endocrine”[All Fields] AND “system”[All Fields]) OR “endocrine system”[All Fields] OR “endocrine”[All Fields]) OR small-cell[All Fields] OR “small cell”[All Fields] OR large-cell[All Fields] OR “large cell”[All Fields]) AND ((“neck”[MeSH Terms] OR “neck”[All Fields] OR “cervical”[All Fields]) OR (“cervix uteri”[MeSH Terms] OR (“cervix”[All Fields] AND “uteri”[All Fields]) OR “cervix uteri”[All Fields] OR “cervix”[All Fields]))) AND ((“neoplasms”[MeSH Terms] OR “neoplasms”[All Fields] OR “cancer”[All Fields]) OR (“carcinoma”[MeSH Terms] OR “carcinoma”[All Fields]))) AND (HPV[All Fields] OR (“papillomaviridae”[MeSH Terms] OR “papillomaviridae”[All Fields] OR “papillomavirus”[All Fields]) OR “papilloma virus”[All Fields])) NOT ((“lung”[MeSH Terms] OR “lung”[All Fields]) OR (“head”[MeSH Terms] OR “head”[All Fields]) OR (“neck”[MeSH Terms] OR “neck”[All Fields])).

We included only full reports (abstracts only were excluded) in English. A total of 143 publications were identified, and their titles and abstracts reviewed for relevance.

In addition, one unpublished, high-quality study (with permission from Drs. Laia Alemany and Silvia De Sanjose, personal communication) was included in this analysis. These cases were collected as part of a large, international survey study of HPV genotypes [10] in cancers related to or possibly related to HPV infection. Formalin-fixed, paraffin-embedded cervical cancer tissues from more 10,000 cervical cancers from around the world were confirmed to be cervical cancers and their histology assessed by pathology review, and then tested for HPV genotypes by PCR amplification using SPF-10 primers and testing of the HPV-positive amplimers for 25 HPV genotypes (6, 11, 16, 18, 31, 33–35, 39, 40, 42–45, 51–54, 56, 58, 59, 66, 68, 70, and 74) using LiPA25 as previously described [10].

We conducted a meta-analysis of the prevalence of any HPV type detected (HPV+), HPV16 alone (HPV16+), HPV18 alone (HPV18+), and HPV16 and/or HPV18 (HPV16+/HPV18+) in SCNC and LCNC using Metaprop [11]. For any HPV type detected, we considered any HPV detected in the study, even if it was only HPV16 and HPV18 or there was broad spectrum HPV detection (e.g., consensus PCR for low-risk and high-risk HPV genotypes) with no typing done. Multiple infections that included HPV16 or HPV18 were assigned to that category accordingly except in the situation in which HPV16 and HPV18 were detected together, which was not attributed to either category. That is, the prevalence of HPV16 and/or HPV18 does not equal the sum of prevalence of single HPV16 infection plus single HPV18 infections because multiple infections that include HPV16 and/or HPV18 infections are not included with the latter categories.

We also conducted a meta-analysis on the subset of SCNC studies that tested for $p16^{INKa}$, a marker of a transcriptionally active high-risk HPV infection [12], by immunohistochemistry (p16 IHC) as further evidence of HPV-related causality. This analysis was done among all specimens that underwent p16 IHC i.e., these analyses were not restricted to HPV-positive tissues.

3. Results

Table 1 shows the studies of SCNC [13–45] and LCNC [26,34,40,45–50] included in the respective meta-analyses. Four studies [22,29,34,44] included in the meta-analysis did not distinguish the HPV results in SCNC from LCNC but because most cases (>80%) were SCNC, they were included. Thirty-two studies with 403 SCNC cases and 9 studies with 45 LCNC cases were included in these analyses.

Fig. 1 shows the results of meta-analyses for HPV detected in SCNC: 85% (95% confidence interval [95%CI] = 72%–95%) were HPV+, 78% (95%CI = 64%–90%) were HPV16+/HPV18+, 51% (95%CI = 38%–64%) were HPV18+, and 10% (95%CI = 3%–19%) were HPV16+. There was significant heterogeneity between studies of HPV in SCNC ($p < 0.005$ for all comparisons).

We conducted several sensitivity analyses for SCNC for robustness. Excluding Pao [13], 89% (95%CI = 79%–96%) SCNC cases were HPV+. Excluding the largest study [26], 84% (95%CI = 70%–94%) SCNC cases were HPV+. Excluding the 5 studies that did not distinguish between SCNC and LCNC diagnoses [18,22,29,34,44], 84% (95%CI = 69%–96%) SCNC cases were HPV+. Restricted to 14 studies of 10 or more cases, 80% (95%CI = 65%–92%) SCNC cases were HPV+.

A subset of 5 SCNC studies also conducted p16 IHC (75 cases) (Fig. 2) [17,19,23,25,45]. The p16 IHC positivity of SCNC cases was 93% (95%CI = 83%–100%). In these studies, 100% (95%CI = 92%–100%) of SCNC were HPV+ (data not shown).

Fig. 3 shows the results of meta-analyses for HPV detected in LCNC: 88% (95%CI = 72%–99%) were HPV+, 86% (95%CI = 70%–98%) were HPV16+/HPV18+, 30% were HPV18+ (95%CI = 4%–60%), and 29% (95%CI = 2%–64%) were HPV16+. There was no significant heterogeneity between studies of HPV in LCNC ($p > 0.5$ for all comparisons).

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