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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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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).

Table 1
Studies included in meta-analysis of HPV in the small-cell and large-cell neuroendocrine carcinomas of the cervix.

Study	Publication year	Study location	N (cases)[¥]	HPV testing method	HPV types detected	%HPV+	%HPV18+[†]	%HPV16+[†]	%HPV16 and HPV18[£]	%HPV16+/HPV18+[‡]	%p16 IHC+
Small-cell neuroendocrine											
Hara [31]	1990	Japan	3	TS ISH (DNA)	HPV6, 11, 16, and 18	0.0%	0.0%	0.0%	0.0%	0.0%	n/a
Pao [13]	1991	Taiwan	12	E6 and E7 PCR	HPV16, 18, 31, and 33	0.0%	0.0%	0.0%	0.0%	0.0%	n/a
Stoler [15]	1991	U.S.	20	Type-specific ISH (RNA)	HPV16 and 18	85.0%	70.0%	15.0%	0.0%	85.0%	n/a
Abeler [14]	1994	Norway	25	Type-specific ISH (DNA)	HPV6, 11, 16, and 18	68.0%	40.0%	28.0%	0.0%	68.0%	n/a
Wolber [33]	1991	USA	9	ISH	HPV6/11, 16/31/33/35, and 18	44.4%	44.4%	0.0%	0.0%	44.4%	n/a
Ambros [36]	1991	USA	11	TS PCR/Southern Blot	HPV16 and 18	81.8%	36.4%	45.5%	9.1%	81.8%	n/a
Kashiwabara [42]	1992	Japan	2	L1 PCR and RFLP	All HPV types	100.0%	100.0%	0.0%	0.0%	100.0%	n/a
Menon [35]	1995	India	1	TS ISH	HPV16 and 18	100.0%	100.0%	0.0%	0.0%	100.0%	n/a
Hsu [32]	1997	Taiwan	1	PCR	n/a	100.0%	100.0%	0.0%	0.0%	100.0%	n/a
Yang [43]	1997	Taiwan	2	PCR and RFLP	All HPV types	100.0%	100.0%	0.0%	0.0%	100.0%	n/a
Mannion[**] [34]	1998	USA	8	TS ISH	HPV6/11, 16/18, and 31/33	87.5%	n/a	n/a	n/a	87.5%	n/a
Wistuba [40]	1999	USA	8	TS PCR	HPV16, 18, 31, 33	50.0%	25.0%	25.0%	0.0%	50.0%	n/a
Herrington [39]	1999	UK/S. Africa	25	GP5+/6+; hybridization	HPV6, 11, 16, 18, 31, 33, 35, 39, 42–45, 51, 52, 56, 58, and 66	100%	44.0%	52.0%	0.0%	96.0%	n/a
Wang [18]	2001	Taiwan & USA	11	Consensus L1 primer PCR and RFLP; TS PCR	Pan-HPV; HPV16 and HPV18	90.9%	81.8%	9.1%	0.0%	90.9%	n/a
Shyu [30]	2001	Taiwan	3	MY09/11 PCR and TS PCR	Pan-HPV; HPV16 and HPV18	100.0%	33.3%	33.3%	33.3%	100.0%	n/a
Masumoto [19]	2003	Japan	10	L1 PCR; sequencing	All HPV Types	100.0%	90.0%	10.0%	0.0%	100.0%	90.0%
Wang [17]	2004	USA	22	SPF10/INNO-LiPA	HPV6, 11, 16, 18, 31, 33–35, 39, 40, 42–45, 51, 52–54, 56, 58, 59, 66, 68, 70, and 74	100.0%	77.3%	18.2%	4.5%	100.0%	90.9%
Ishida [20]	2004	Japan	10	L1 PCR and RFLP	HPV6, 11, 16, 18, 31, 33, 42, 52, and 58	80.0%	80.0%	0.0%	0.0%	80.0%	n/a
Mathew-Greers[***] [44]	2004	Mexico	2	PGMY/Line Blot	HPV6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51–56, 58, 59, 61, 62, 64, 66–73, 81, 82, 82v, 83, 84, and 89	100.0%	0.0%	100.0%	0.0%	100.0%	n/a
Alphandery [21]	2006	Italy	1	TS PCR	16 and 18	100.0%	100.0%	0.0%	0.0%	100.0%	n/a
Wang[*] [22]	2006	Taiwan	26	L1 consensus PCR; HPV16 & HPV18 TS PCR	Pan-HPV; HPV16 and HPV18	69.2%	65.4%	3.8%		69.2%	n/a
Horn [23]	2006	Germany	9	GP5+/6+ PCR; sequencing	All HPV types	88.8%	11.1%	44.4%	0.0%	55.5%	100.0%
Nofech-Mozes [24]	2010	Canada	5	AMPLICOR	High-risk HPV (pooled)	100.0%	n/a	n/a	n/a	n/a	n/a
Kong [25]	2010	USA	1	HR-HPV ISH	High-risk HPV (pooled)	100.0%	n/a	n/a	n/a	n/a	100.0%
Wang [16]	2010	Taiwan	8	GP6+ and SPF1 consensus primer PCR; Easychip HPV BlotMembrane Genotyping	HPV6, 11, 16, 18, 26, 31–33, 35, 37, 39, 42–45, 51–56, 58, 59, 61, 62, 66–72, 74, and 81–85	87.5%	62.5%	0.0%	0.0%	62.5%	n/a
Bian [38]	2011	China	1	Nested PCR	n/a	100.0%	100%	0.0%	0.0%	100.0%	n/a
Siriaunkgul [26]	2011	Thailand	89	GP5+/6+ PCR	HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 66, and 68	92.1%	59.6%	15.7%	n/a	86.5%	n/a
Ramalingam [27]	2012	USA	2	ISH	High-risk HPV (pooled)	100.0%	n/a	n/a	n/a	n/a	100.0%
Ayatollahi [61]	2013	Iran	13	GP5+/6+ PCR; TS PCR	High-risk HPV (pooled); HPV16 and HPV18	30.8%	n/a	n/a	n/a	15.4%	n/a
Cavalcanti [28]	2016	USA	1	TS PCR	HPV16 and 18	0.0%	0.0%	0.0%	0.0%	0.0%	n/a

Table 1 (*continued*)

Study	Publication year	Study location	N (cases)[¥]	HPV testing method	HPV types detected	%HPV+	%HPV18+[†]	%HPV16+[†]	%HPV16 and HPV18[£]	%HPV16+/HPV18+[‡]	%p16 IHC+
Kuji[*] [29]	2017	Japan	29	Multiplex PCR (PapiPlex)	HPV6, 11, 16, 30, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66	72.4%	62.1%	10.3%	0.0%	72.4%	n/a
Alejo (unpublished)	2017	Global	33	SPF10/INNO-LiPA	HPV6, 11, 16, 18, 31, 33–35, 39, 40, 42–45, 51, 52–54, 56, 58, 59, 66, 68, 70, and 74	87.9%	36.4%	45.5%	0.0%	84.8%	78.6%
Large-cell neurocrine											
Mannion [34]	1998	USA	5	TS ISH	HPV6/11, 16/18, and 31/33	60.0%	n/a	n/a	0.0%	60.0%	n/a
Yun [46]	1999	New Zealand		TS PCR	HPV16, 18, and 31	100.0%	0.0%	100.0%	0.0%	100%	n/a
Wistuba [40]	1999	USA	2	TS PCR	HPV16, 18, 31, and 33	50.0%	50.0%	0.0%	0.0%	50.0%	n/a
Grayson [47]	2002	S. Africa	12	ISH	HPV6, 11, 16, 18, 31, and 33	75.0%	16.7%	58.3%	0.0%	75.0%	n/a
Powell [48]	2008	USA	1	ISH; L1 PCR and RFLP	All HPV	100.0%	0%	100%	0.0%	100%	n/a
Wang [49]	2009	Taiwan	7	L1 consensus PCR (primers MY11/GP61); TS PCR	Pan-HPV; HPV16 and 18	83.3%	83.3%	0.0%	0.0%	83.3%	n/a
Siriaunkgul [26]	2011	Thailand	5	MY09/11, Nested GP5+/6+ PCR	HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 66, and 68	100.0%	80.0%	20.0%	0.0%	100.0%	n/a
Murakami [50]	2013	Japan		Hybrid capture 2	High-risk HPV (pooled)	0.0%	n/a	n/a	n/a	n/a	n/a
Alejo	2017	Global	11	SPF10/INNO-LiPA	HPV6, 11, 16, 18, 31, 33–35, 39, 40, 42–45, 51, 52–54, 56, 58, 59, 66, 68, 70, and 74	90.9%	18.2%	63.6%	0.0%	81.8%	n/a

n/a = data not available.
[*] HPV data were presented for small- and large-cell neuroendocrine tumors combined, of which small-cell was in the majority (>80%).
[**] Included mixed small- and large-cell neuroendocrine carcinomas (n = 2) and small-cell neuroendocrine, large-cell neuroendocrine, and squamous cell carcinomas (n = 1).
[***] Assumed to be small-cell (vs. large-cell) neuroendocrine carcinomas.
[¥] Only cases that had valid HPV testing.
[†] Single infections only.
[£] Both HPV16 and HPV18 were detected in the tissue specimen. The result does not imply that both infections were the cause of the cancer, just that cancer could be attribute to one or the other HPV infection.
[‡] Single and double infections that included HPV16 and/or HPV18.

4. Discussion

We demonstrate that a large proportion of SCNC and LCNC of the cervix are caused by HPV, primarily HPV16 and HPV18. By restricting to studies with HPV genotyping on the lesional tissue itself, we reduced the likelihood that the HPV detected was due to contamination by HPV infections present elsewhere in the lower genital tract. We further conclude, from the high p16 IHC positivity observed in the subset of studies that tested for it, that the HPV DNA in these tumors was transcriptionally active and likely the cause of the SCNC and LCNC. Interestingly, there was a much greater proportion of HPV18 than HPV16 in SCNC, suggestive of a different biology than other histologic types of cervical cancer including LCNC, which had a similar proportion of HPV16 and HPV18 that is more like adenocarcinoma [10].

Although there had been reasonable agreement that HPV causes SCNC and LCNC of the cervix [2–4], some publications still report that HPV does not cause SCNC and LCNC [5,6] as does some social media (e.g., https://www.facebook.com/SmallCellCC/). There may be several explanations of this. This tumor is so rare and in earlier studies may have been subject to misclassification due to insensitive HPV testing. Indeed, one early case series study of 12 SCNC of the cervix did not detect HPV in any cases [13]; this study might be considered an outlier and may well have been due to assay technical factors. Study-to-study differences in analytic sensitivity for HPV detection may have contributed to, in part, the significant heterogeneity in HPV prevalence in SCNC. Indeed, methods of HPV detection evolved over time and may have increased in analytic sensitivity. As a consequence, the fraction of HPV-positive cancers may be underestimated.

Given the strict criteria for inclusion in these meta-analyses, we suggest that HPV has a direct role in causing most if not all SCNC and LCNC. Although the final HPV positivity was not 100%, HPV testing of cancer tissues from cases that are unequivocally caused by HPV (e.g. squamous cell carcinoma of the cervix) are rarely 100% positive [10] due to insensitivity of the HPV testing method on formalin-fixed, paraffin-embedded tissue.

Second, it is important to differentiate between what causes the cancer and whether screening tests are effective in identifying women who have those cancers. Thus, although HPV may cause SCNC and LCNC, screening tests may fail to detect precursor lesions before they become invasive [51] or after cancer is already present. Cytology-based methods are well known to miss glandular disease [52–55]. Poor sampling of a distal, glandular lesion and/or lower viral load may cause the HPV-related SCNC or LCNC to test clinically negative for HPV even though it is HPV-related tumor in part because the positive cutoff for clinical HPV tests is set to trade off a slight degree of sensitivity for better specificity [56]. Of note, there is no recognized “neuroendocrine” precursor either

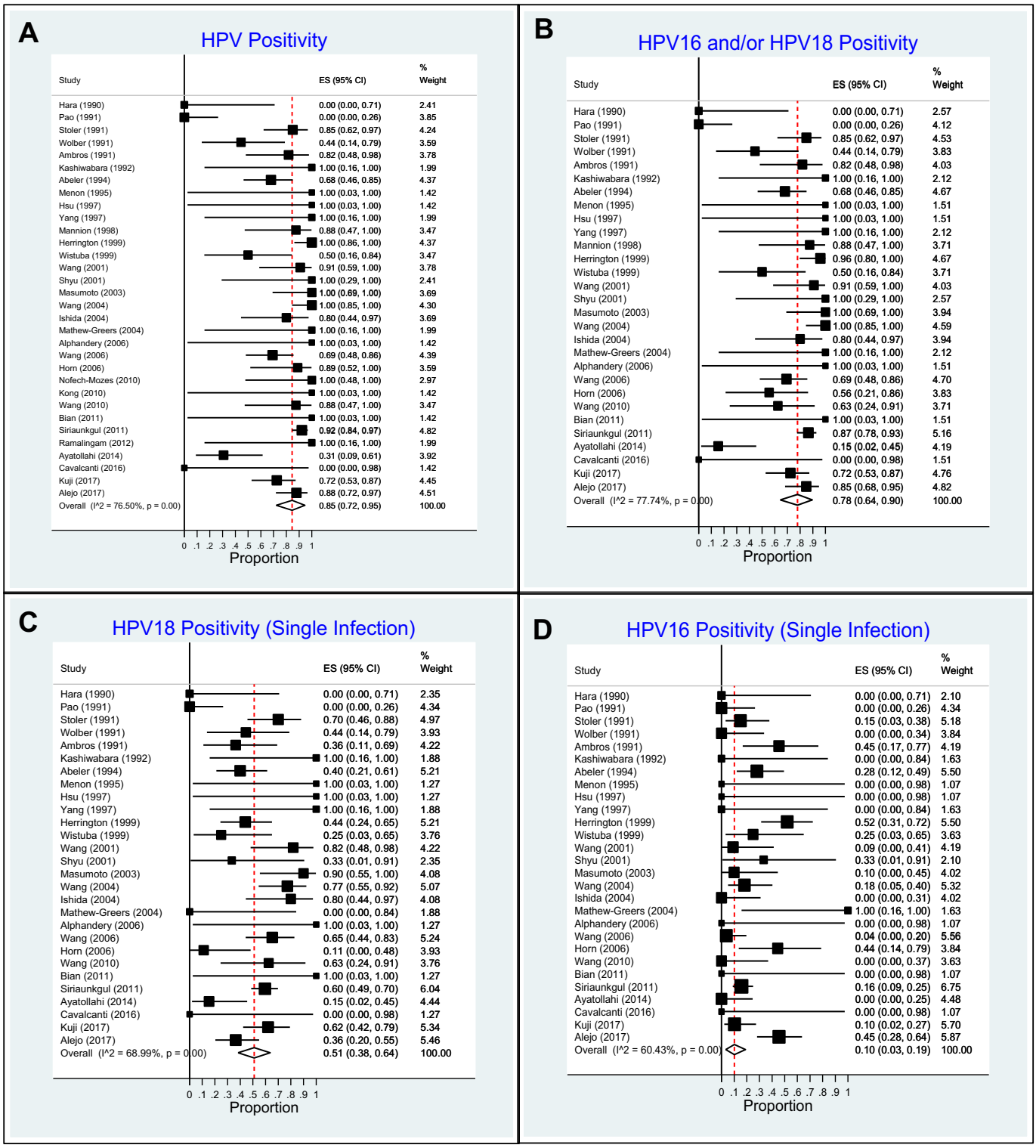

Fig. 1. Results of meta-analyses for the proportion of small-cell neuroendocrine carcinoma of the cervix that tested positive for any HPV (A), HPV16 and/or HPV18 (B), HPV18 only (C), and HPV16 only (D).

cytologically or histologically that would enable intervention prior to becoming invasive cancer.

All epithelial sites have a population of neuroendocrine cells as part of their normal epithelial complement. Conceptually all epithelial sites renew their cellular compartments from a population of reserve (stem) cells that are theoretically capable of differentiating along various histologic lines. For instance in the cervix this reserve call population give rise to and renews squamous, endocervical glandular, and neuroendocrine population. Whether HPV infects reserve cells before or after they commit to a particular differentiation lineage is uncertain and may never be resolved [57,58]. Certainly the fact that neuorendocrine cancer are often admixed with adenocarcinomas suggests that for certain viruses like HPV18 the infection/transforming event occurs in a cell that has yet to be fixed in one lineage or another. Conversely, most pathologist do not believe that terminally differentiated cells, those cells that no longer are capable of cell division (i.e., fully

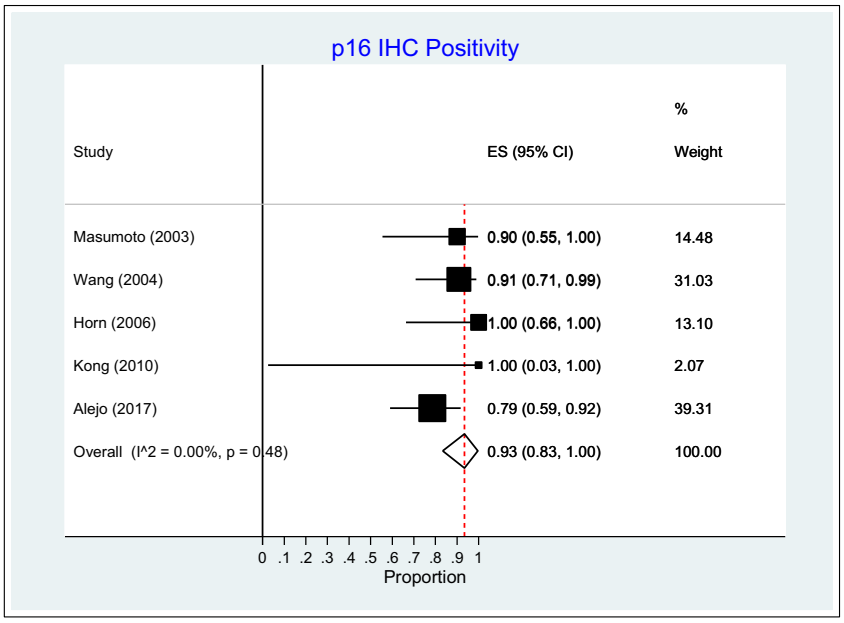

Fig. 2. Results of a meta-analysis for the proportion of small-cell neuroendocrine carcinoma of the cervix that tested positive for p16INK4a by immunohistochemistry (p16 IHC).

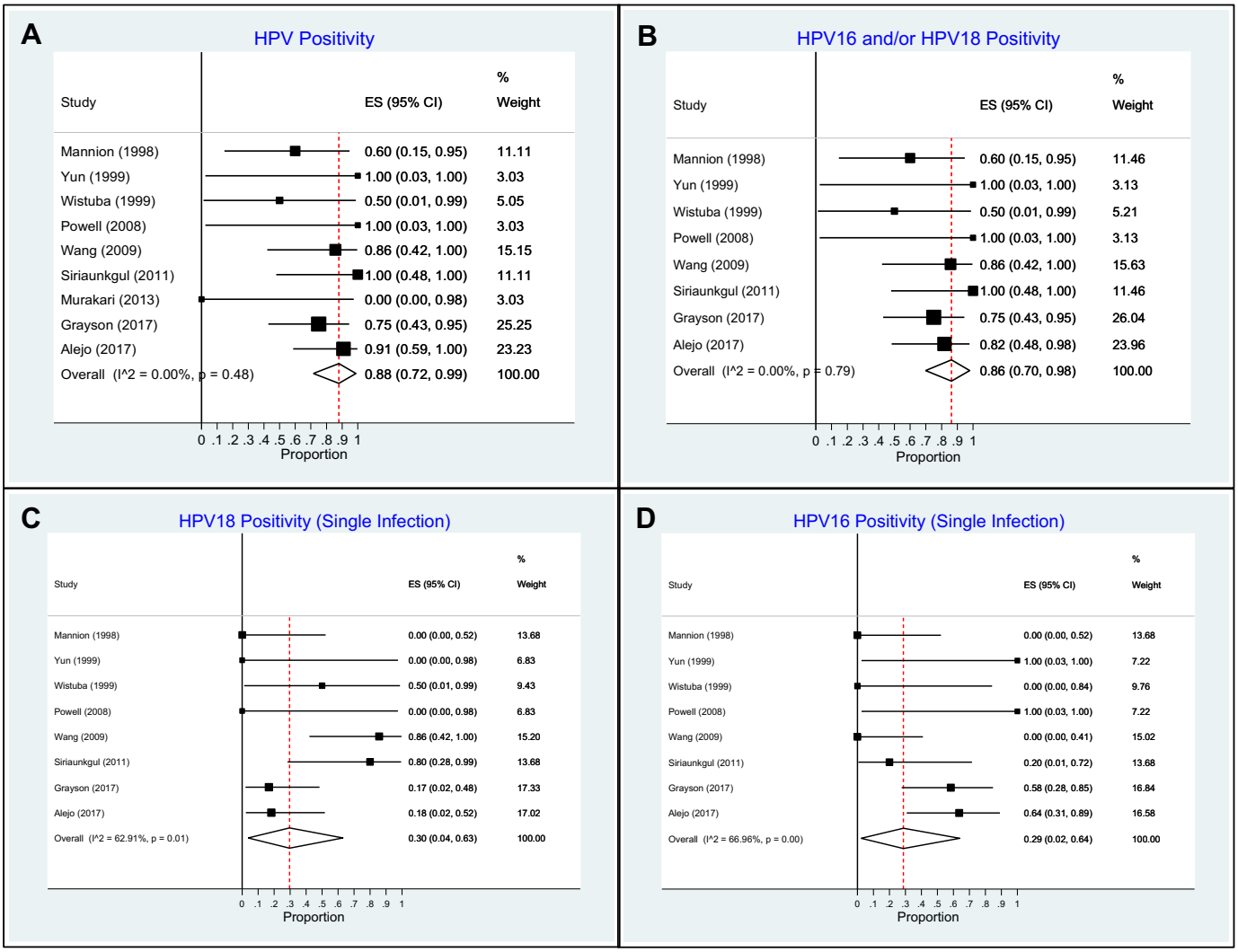

Fig. 3. Results of meta-analyses for the proportion of large-cell neuroendocrine carcinoma of the cervix that tested positive for any HPV (A), HPV16 and/or HPV18 (B), HPV18 only (C), and HPV16 only (D).

mature squamous cells or endocervical cells), "dedifferentiate" into a cancer or precancerous. Rather a cell compartment capable of proliferations also differentiates along certain histologic phenotypes.

We acknowledge some limitations in this analysis, in addition to the aforementioned study-to-study differences in analytic sensitivity for HPV. First, most studies focused on the detection of HPV16 and HPV18 and did not include detection of a broad range of individual HPV genotypes. We therefore could not accurately assess the potential differential impact of the 2nd-generation HPV vaccine against HPV16, 18, 31, 33, 45, 52, and 58 vs. 1st-generation HPV vaccines against HPV16 and HPV18. Of the SCNC studies that did include testing for all carcinogenic HPV genotypes, very few were caused for other carcinogenic HPV types: 1 case each of HPV35 [45], HPV45 [39], HPV33 and HPV52 [16], and HPV33 and HPV58 [26]. Thus, very few cases of SCNC appear to be caused by the weaker carcinogenic HPV genotypes and increased impact of the 2nd-generation HPV vaccine on the prevention of SCNC and LCNC may not be much greater than the 1st-generation HPV vaccines. A second limitation is that the small sample size for both SCNC and LCNC, especially LCNC. Finally, some of the p16 IHC positivity could be due to endometrial cancer misclassified as SCNC [59,60]. However, this seems an unlikely explanation of the p16 IHC results in this analysis give that all of the tissues tested by p16 IHC were HPV positive.

In conclusion, carcinogenic HPV, especially HPV16 and HPV18, causes a large proportion of SCNC and LCNC. Prophylactic HPV16 and HPV18 vaccination should prevent most if not all SCNC an LCNC.

Conflict of interest statement

MHS is a paid consultant and expert pathologist to Merck for Gardasil and Gardasil 9 development programs. The other authors disclose no competing interests.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2017.12.001.

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