Differences in the genomic and transcriptomic landscapes of Human Papillomavirus (HPV)-positive neuroendocrine neoplasms and HPV-positive carcinomas

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Background

- HPV is an infectious cause of several malignancies. Neuroendocrine neoplasms (NEN) are highly heterogeneous, ranging from low-grade indolent tumors to high-grade clinically aggressive carcinomas.
- Aside from cervical NENs, most have not traditionally been associated with HPV, but our initial studies uncovered a subset of NENs that are HPV 16/18 positive.
- To identify actionable differences between HPV+ NEN and non-NENs, genomic and transcriptomic landscapes were investigated.

Methods

- 101,343 solid tumors were sequenced at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing (NGS) of DNA (whole or hybrid exome) and RNA (whole or hybrid transcriptome) and assayed for HPV16/18 positivity (HPV+) via DNA sequencing.
- Mutation prevalence for pathogenic SNVs/indels (-Mt) and copy number amplification (CNA) were calculated.
- Expression of Ki-67 mRNA (*MKI67)* was used to infer high-grade vs low-grade NEN.
- Differentially regulated pathways were assessed by gene set enrichment analysis (GSEA).
- Fisher's exact/χ^2 tests were applied as appropriate with p-values adjusted for multiple comparisons ($p < .05$).

Results

Pan-tumor prevalence of HPV16/18

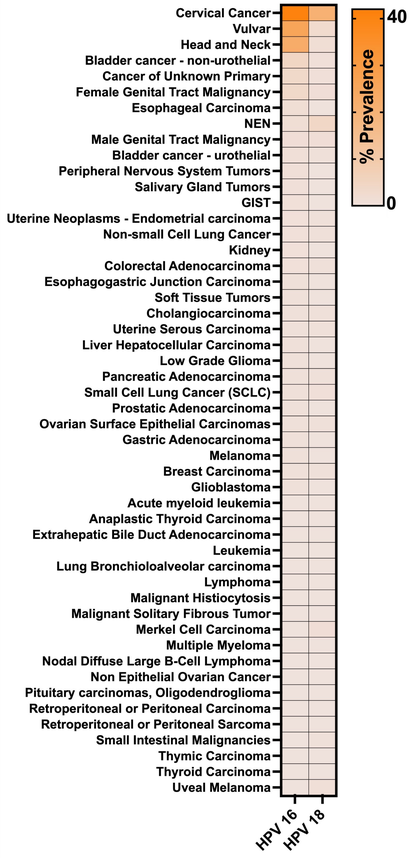

Figure 1: Prevalence of HPV16 or HPV18 positivity by NGS across a variety of solid tumors.

NEN prevalence of HPV16/18 by site and grade

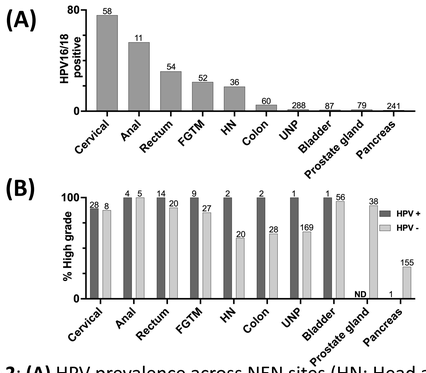

Figure 2: **(A)** HPV prevalence across NEN sites (HN: Head and neck, UNP: Unknown Primary). **(B)** Prevalence of high grade NENs across sites and between HPV positive or negative tumors (no difference in prevalence between +/- tumors was observed, $p > 0.05$ for comparison of grade between HPV+/-, numbers shown are the total sample size).

	NEN Cervical HPV +	non-NEN Cervical HPV+	Statistic	*p*-value
Count (N)	39	1052		
Median Age [range]	50 [25 - 76]	49 [24-90]	t-test	0.99
Female	100% (39/39)	99.7% (1049/1052)	chi-square	0.99
	NEN HN HPV +	**Non-NEN HN HPV +**	**Statistic**	***p*-value**
Count (N)	7	580		
Median Age [range]	65 [49 - 77]	65 [21 - 90]	t-test	0.905
Female	28.6% (2/7)	9.0% (52/580)	chi-square	0.19
	NEN AR HPV +	**Non-NEN AR HPV +**	**Statistic**	***p*-value**
Count (N)	6	324		
Median Age [range]	62.5 [48-72]	63 [31 -90]	t-test	0.90
Female	83.3% (5/6)	78.7% (255/324)	chi-square	0.99

Table 1: Demographic information for sites of focus (AR: Anal/rectal).

Genomic landscape of select sites

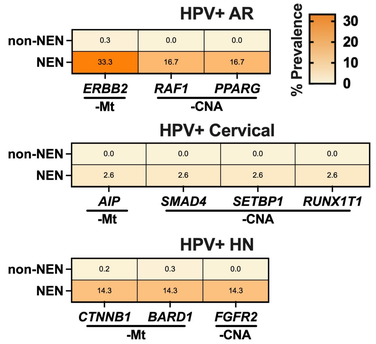

Figure 3: Genomic landscape of indicated sites for HPV+ NEN and non-NEN tumors. Alterations show are all statistically significant between non-NEN and NEN tumor ($p < 0.05$).

Gene set enrichment analysis (GSEA)

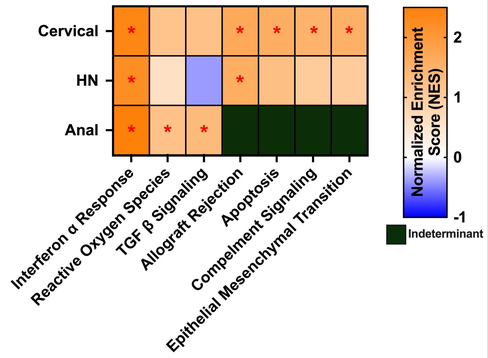

Figure 4: GSEA comparing NEN vs non-NEN tumors at the indicated sites. High NES indicates gene set enrichment in non-NEN tumors. A red asterisk indicates statistical significance ($p < 0.05$, FDR < 0.2).

Study Highlights

- HPV+ NENs have alterations that vary by anatomic site.
- Our data suggest that non-NEN HPV+ tumors are enriched for gene sets related to interferon alpha signaling

Conclusions

- We uncovered a category of HPV+ NENs with distinct genomic and transcriptomic landscapes compared to non-NEN tumors.

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