



Integration Frequencies of Viral Genomes Differ Among Cervical Cancers Infected by Different High Risk HPV Types: Evidence for Differences in the Oncogenic Potential of Individual HPV Types



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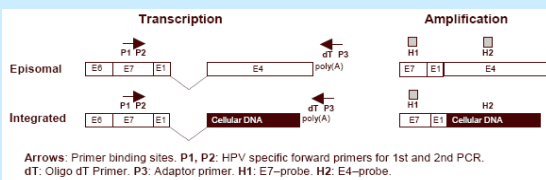
Objective:

Cervical cancer is induced by persisting high-risk human papillomavirus (HR-HPV) infections. HR-HPV integration is assumed to occur at the point of transition from high-grade lesions to micro-invasive carcinoma. Most previous reports investigating HPV integration focus only on HPV 16 and / or 18 associated lesions. No data were so far available concerning the integration profiles of other HR-HPV types.

In the present study, we compared the prevalence of integrated HR-HPV types of the five most commonly detected HR-HPV types (HPV 16, 18, 31, 33 and 45) using the APOT PCR system.

Materials and Methods

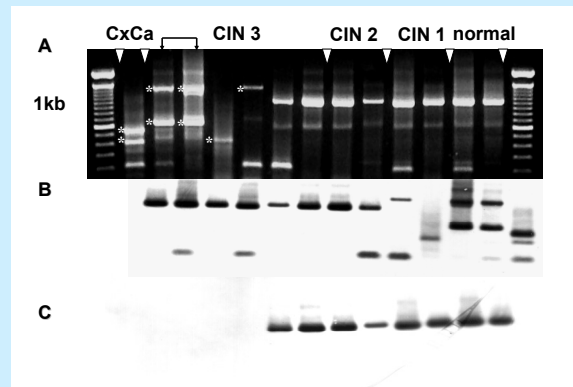
981 samples positive for HPV 16, 18, 31, 33 and 45 were selected from an ongoing epidemiological study and subjected to the APOT assay (Klaes et al., Cancer Research 59 (24),1999).



Results

- In samples derived from normal cervical epithelia (n = 186) or low-grade cervical lesions (CIN I, n = 108), no integrate-derived HPV transcripts were found.
- Integrate-derived HPV transcripts were found in 2.9% (5/172) of the CIN II samples, in 14% (46/325) of the CIN III samples and in 72% (137/190) of the patients with invasive cervical cancer.
- For the cervical carcinomas, differences were observed between HPV18-related (18, 45) and HPV16-related (16, 31 and 33) types. The highest integration frequency was found for HPV 18 (95%, 38/40) and 45 (89.6%, 26/29). HPV 31 and 33 were found to be integrated in 29.4% (5/17) and 32% (8/25), respectively. For HPV 16, a medium integration frequency of 75.9% (60/79) was observed.

APOT from HPV45-positive clinical samples of normal epithelia, preneoplastic lesions (CIN1-3) and cervical carcinomas (CxCa)



* - Integrate-derived transcripts ↓ - paired cytobrush and biopsy samples

Prevalence of integrate-derived transcripts in dysplastic and neoplastic lesions of the cervix

	Normal n (%)	CIN1 n (%)	CIN2 n (%)	CIN3 n (%)	CxCa n (%)	Total
HPV31	22 (0)	16(0)	29(0)	44 (6.8)	17 (29.4)	128
HPV33	23(0)	20(0)	35(0)	46(0)	25 (32)	149
HPV16	111(0)	61(0)	83 (6)	208 (15.8)	79 (75.9)	542
HPV45	8(0)	5(0)	12(0)	11 (81)	29 (89.6)	65
HPV18	22(0)	6(0)	13(0)	16 (6.2)	40 (95)	97
HPVs	186(0)	108(0)	172(2,9)	325 (14)	190 (72)	981

Statistically significant difference (p<0.001, Fisher test) was observed in the frequency of integration between different HPV types but not for HPV31,33 and HPV18,45.

Conclusions

Detection of integrated HR-HPV DNA points to advanced dysplasia or invasive cervical cancer. For cervical carcinomas, the frequency of integrated viral genomes appears to be related to individual HR-HPV types. HPV 18-related types seem to integrate significantly more frequent as compared to HPV 16-related types.

These data suggest that individual HR-HPV types may have different oncogenic activities and therefore confer different degrees of chromosomal instability to their host cells.