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Published in:
Journal of General Virology

DOI:
[10.1099/vir.0.80001-0](https://doi.org/10.1099/vir.0.80001-0)

2004

[Link to publication](#)

Citation for published version (APA):
Naucler, P., Da Costa, F. M., Ljungberg, O., Bugalho, A., & Dillner, J. (2004). Human papillomavirus genotypes in cervical cancers in Mozambique. *Journal of General Virology*, 85(Pt 8), 2189-2190.
<https://doi.org/10.1099/vir.0.80001-0>

Total number of authors:
5

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Received 30 January 2004

Accepted 13 May 2004

Human papillomavirus genotypes in cervical cancers in Mozambique

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The distribution of human papillomavirus (HPV) types in cervical cancers is essential for design and evaluation of HPV type-specific vaccines. To follow up on a previous report that HPV types 35 and 58 were the dominant HPV types in cervical neoplasia in Mozambique, the HPV types in a consecutive case series of 74 invasive cervical cancers in Mozambique were determined.

The most common worldwide major oncogenic HPV types 16 and 18 were present in 69 % of cervical cancers, suggesting that a vaccine targeting HPV-16 and -18 would have a substantial impact on cervical cancer also in Mozambique.

A previous study on human papillomavirus (HPV) genotypes in Mozambique, reported that the HPV type distribution was unusual. The most common worldwide oncogenic HPV type 16 was infrequent and HPV type 35 was dominant (Castellsague *et al.*, 2001). The authors drew attention to the fact that type-specific HPV vaccines are currently being produced (Koutsky *et al.*, 2002) and proposed that the type composition of such vaccines should be modified for different populations to reflect the HPV type distribution in the population. To investigate further this important issue, we analysed the HPV types present in a comprehensive case series of invasive cervical cancers from Mozambique.

From June 2002 to April 2003, all women with suspected cervical cancer at the Department of Gynaecology at the Central Hospital of Maputo, the capital of Mozambique, were asked to participate. Following written consent, two biopsies were taken from each tumour, one was formalin-fixed and used for histological diagnosis, the other biopsy was frozen for HPV DNA detection. Human immunodeficiency virus (HIV) testing was performed on serum samples and a questionnaire recorded socio-demographic factors. Ethical approval was obtained from the Commission of Investigation and Ethics at the Central Hospital in Maputo and from Lund University Research Ethics Committee in Sweden.

Biopsies and serum samples were successfully obtained from 88 of 94 patients and transported to Sweden for HPV analysis. Histopathological diagnosis was evaluated in Mozambique and in Sweden. Fourteen patients were excluded because invasive cervical cancer could not be confirmed and two samples were negative in the specimen adequacy test (β -globin PCR). One patient had adenocarcinoma, the others squamous carcinoma. The

mean age was 46 years. HPV DNA was detected using general primer PCR (GP5+/GP6+ primers) and HPV DNA typing was performed by reverse dot-blot hybridization (RDBH) assay with full-genomic clones (Forslund *et al.*, 2002) of HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. GP5+/6+ PCR-negative samples were analysed further using type-specific PCR for HPV-16 and -18 and with another HPV general primer system (MY09/11), followed by HPV typing by sequencing. The last few still HPV-negative samples were also amplified with multiply primed rolling-circle amplification (RCA) (Rector *et al.*, 2004) before GP5+/6+ PCR and RDBH. A repeat analysis of 25 % of the samples found identical results. HIV testing was performed using AxSYM (Abbot), followed by confirmation using RIBA HIV-1/HIV-2 SIA (Chiron).

The HPV prevalence was 66 of 72 (92 %) using GP5+/GP6+ primers. This increased to 68 of 72 (94 %) after testing with type-specific PCR and MY09/11 PCRs and reached 70 of 72 (97 %) with prior amplification with RCA before the PCR. It appears that the combination of RCA and PCR is a promising new strategy to minimize false-negative results in diagnostic virology.

The most common HPV types were 16 and 18, being present in 69 % of tumours (Table 1). Although coexistence with other HPV types was common (13, 7, 3 and 1 women were infected with 2, 3, 4 and 5 HPV types, respectively), a substantial proportion of cases (36 %) had a single HPV infection with either HPV-16 or -18.

Suggested reasons for common multiple HPV infections include impaired immune tolerance and concomitant CIN (cervical intraepithelial neoplasia) lesions within the specimen (Davies *et al.*, 2001). Thirteen of 72 (18 %) patients

Table 1. HPV genotype distribution among 72 invasive cervical cancer patients in Mozambique

HPV type	Present in cervical cancers <i>n</i> (%; 95 % CI)
16	18 (25 %; 15–35)
16, 45	4 (6 %)
16, 18	3 (4 %)
16, 18, 45; 16, 35, 59;	2 (3 %) each
16, 18, 31, 35; 16, 18, 33; 16, 18, 33, 45; 16, 18, 33, 45, 51; 16, 31;	1 (1 %) each
16, 33; 16, 33, 45; 16, 35; 16, 35, 45, 59; 16, 35, 66; 16, 52	
All 16	40 (56 %; 45–68)
18	8 (11 %; 3, 8–18)
18, 35; 18, 66	1 (1 %) each
All 18	19 (26 %; 16–36)
All 16 and/or 18	50 (69 %; 58–80)
33	2 (3 %)
35	7 (10 %; 3, 1–17)
All 35	14 (19 %; 10–28)
45	7 (10 %; 3, 1–17)
All 45	17 (24 %; 14–34)
56	1 (1 %)
58	1 (1 %)
68	1 (1 %)
Any HPV	70 (97 %)

were HIV-positive, but multiple HPV infections were not more common among HIV-positive women (age-adjusted odds ratio, 1.0; 95 % CI, 0.25–4.0). Almost all patients had advanced stage tumours that may have resulted in immunosuppression.

Our findings that HPV-16 and -18 are the most frequent HPV infections associated with cervical cancer in Mozambique is in concordance with the overall world distribution of HPV types in cervical cancer (Clifford *et al.*, 2003), but is not in line with a study by Castellsague *et al.* (2001) who investigated 239 healthy women and 23 women with cervical dysplasia in Mozambique, and found HPV-35 and 58 to be the most common HPV types. We investigated the HPV type distribution in invasive cervical cancer. Different HPV types are associated with different cancer risks (Clifford *et al.*, 2003), and circulation of HPV types among women without cancer may therefore not accurately reflect which HPV types cause invasive cervical cancer in a population. Furthermore, in many countries it is difficult to obtain representative population-based samples from healthy women or women with asymptomatic lesions. Recruitment of symptomatic women with cancer at the major site offering health care in the country may therefore have resulted in a more representative sample of oncogenic HPV types. However, it should be noted that HPV-35 was not uncommon in our series, being found in 19 % of patients.

Continued investigation and monitoring of which HPV types that actually cause cervical cancer in different countries is undoubtedly an important endeavour. Our study suggests that HPV vaccines targeting HPV-16 and

-18, the two worldwide most frequent oncogenic HPV types, would have a substantial impact on cervical cancer also in Mozambique.

Acknowledgements

Financial support was provided by the Swedish Cancer Society. Conflict of interest: Professor Dillner has acted as consultant for Merck, a company pursuing research on HPV vaccines.

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