Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis

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Particular types of human papillomavirus (HPV) infection may preferentially progress from high-grade squamous intraepithelial lesions (HSIL) to squamous cell carcinoma of the cervix (SCC). We performed a meta-analysis of published data to compare HPV type distribution in HSIL and SCC. HPV16, 18 and 45 were each more prevalent in SCC than HSIL, whereas the reverse was true for other oncogenic types including HPV31, 33, 52 and 58. These data suggest that HSILs infected with HPV16, 18 and 45 preferentially progress to SCC. This may have implications for follow-up protocols of future HPV-based cervical cancer screening programmes and for HPV vaccine trials.

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Epidemiological studies have established human papillomavirus (HPV) infection as the central cause of invasive cervical cancer (ICC) and its precursor lesions (Walboomers et al, 1999). However, only a fraction of precancerous lesions progress to ICC. A strong candidate factor for differential progression is HPV type (Lorincz ICC. A strong candidate factor for differential progression is HPV type (Lorincz et al, 1992).

Identifying HPV types that preferentially progress from high-grade squamous intraepithelial lesions (HSIL) to ICC has implications not only for follow-up protocols in ICC screening programmes, but also for prophylactic type-specific HPV vaccine trials. For ethical reasons, final outcome measures in such trials will be the prevention of HSIL. However, it is important to know whether the HPV type distribution in HSIL is representative of those that go on to cause cancer.

Articles presenting HPV type-specific prevalence data were identified from Medline. Studies had to include at least 20 cases of squamous cell or histologically unspecified cervical cancer (Clifford et al, 2002) and/or 20 histologically verified cases of HSIL. In this study, HSIL refers both to lesions classified by the Bethesda system, that is, CIN2/3, and those classified separately as CIN2 and CIN3. Studies had to use polymerase chain reaction (PCR)-based assays to identify HPV, and to present prevalence of at least one HPV type other than HPV6, 11, 16 or 18 (Clifford et al, 2002). Studies had to use PCR primers (5318 SCC, 3502 HSIL). The SCC : HSIL ratios were calculated for all cases tested for HPV, and thus represents the prevalence in either single or multiple infections.

Overall, HPV prevalence was slightly higher in SCC cases (87.6%) than HSIL (84.2%) (SCC:HSIL ratio 1.04, 95% CI 1.03–1.06) (Table 2). HPV16 was the most common type in both SCC (54.3%) and HSIL (45.0%), but was more prevalent in SCC (ratio of 1.21, 95% CI 1.16–1.26). HPV18 was also more prevalent in SCC (12.6%) than in HSIL (7.0%), with a ratio of 1.79 (95% CI 1.56–2.10). HPV45 was associated with a ratio of 1.85 (95% CI 1.35–2.91), similar to that of HPV18. All other HR types included were additionally calculated within more homogeneous study subgroups: (i) studies that did not report any multiple infections (6558 SCC, 2182 HSIL), (ii) studies testing for HPV from biopsies (7128 SCC, 1483 HSIL), and (iii) studies using ‘broad'-spectrum PCR primers (5318 SCC, 3502 HSIL). The SCC:HSIL ratios were calculated separately for HSILs classified by the Bethesda system and for CIN3 only. Across all these subanalyses, SCC:HSIL ratios remained consistent for HPV16 (range: 1.04–1.25), HPV18 (1.46–1.93) and HPV45 (1.20–4.61). HPV31, 33, 35, 52 and 58 were consistently associated with ratios of 0.3–0.9, with the exception of HPV58 for biopsy studies (1.06, 95% CI 0.73–2.08).

Where sample size permitted, subanalyses were also stratified by region. When estimated from studies within Asia, Europe and South/Central America, respectively, there was no material difference in SCC:HSIL ratios for HPV16 (1.46, 1.17, 1.40), HPV18 (1.74, 2.02, 1.46), HPV45 (4.35, 1.39, 1.20), HPV33 (0.56, 0.62, 0.76), HPV35 (0.66, 0.85, 0.97) and HPV58 (0.37, 0.47, 0.48).
HPV16 or HPV16/18 vaccines may be an underestimate of the beneficial effect on the prevention of ICC. Even in countries with established screening programmes, women still die from rapidly progressing cancers that escape periodic examination. Given that HPV16, 18 and 45 appear to have greater progressive potential, and in the event that future cervical screening programmes include HPV typing, women infected with HPV16, 18 and 45 may require closer surveillance than women infected with other HR HPV types.

Our findings suggest that worldwide, HSIL infected with HPV16, 18 or 45 are more likely to progress to SCC than HSIL infected with other HR types. This could be interpreted in two ways: either these types have a greater potential to induce fully malignant transformation, and/or these infections somehow preferentially evade the host immune system. Compared to other HR types, HPV16, 18 and 45 may require closer surveillance than women infected with other HR HPV types.

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Appendix

Study methods and type-specific prevalence of human papillomavirus by study and by region are summarised in Table A1.

Correction: The reference to “Obstet Gynecol 79: 328–337” should be corrected to “Obstet Gynecol 79: 328–337” in the Appendix section.
# Table A1

| First author | Reference | Country | PCR primers used to identify all HPV +ve cases | CINII/CINIII/HSIL | HPV-specific prevalence (% of all cases tested) | No. cases |
|--------------|-----------|---------|-----------------------------------------------|-------------------|-----------------------------------------------|-----------|
|              |           |         |                                               |                   |                                               |           |
| **Africa**   |           |         |                                               |                   |                                               |           |
| La Ruche     | Int J Cancer (1998) | Ivory Coast | Exfol. cells | MY09/11 | 49 | 0/0/0/49 | 77.6 | 30.6 | 10.2 | 0.0 | 6.1 | 8.2 | 4.1 | 0.0 | 4.1 | 0.0 | 2.0 | 0.0 |
| de Vuyst     | Sex Transm Dis (2003) | Kenya | Exfol. cells | SPF10 | 29 | 0/0/0/29 | 96.6 | 34.5 | 3.4 | 6.9 | 6.9 | 1.4 | 6.9 | 24.1 | 17.2 | 0.0 | 3.4 | 10.3 | 6.9 | 0.0 | 10.3 |
| **Africa sub-total** | | | | | 78 | 0/0/0/78 | 84.6 | 32.1 | 7.7 | 2.6 | 6.4 | 11.5 | 6.4 | 0.0 | 3.8 | 3.8 | 0.0 | 10.3 |
| **Asia**     |           |         |                                               |                   |                                               |           |
| Chan MKM     | Gynecol Oncol (1996) | China | Exfol. cells | MY09/11 | 45 | 10/35/0/0 | 55.6 | 24.4 | 8.9 | 0.0 | 0.0 | 4.4 |
| Chan PKS     | J Med Virol (1999) | China | Exfol. cells | MY09/11 | 89 | 29/60/0/0 | 58.4 | 25.8 | 4.5 | 0.0 | 1.1 | 1.1 |
| Wu CH        | Sex Transm Dis (1994) | China | Fixed | TS-PCR only | 34 | 13/15/0/0 | 76.5 | 35.3 | 20.6 | 0.0 | 4.4 |
| Nagai Y      | Gynecol Oncol (2000) | Japan | Exfol. cells | L1C1/L1C2 | 58 | 0/58/0/0 | 96.6 | 37.9 | 3.4 | 15.5 | 6.9 | 0.0 |
| Saito J      | J Obstet Gynecol Pract (2001) | Japan | Exfol. cells | L1C1/L1C2 | 38 | 0/0/0/38 | 100.0 | 34.2 | 18.4 | 0.0 | 0.0 |
| Sasagawa T   | Cancer Epidemiol Biomarkers Prev (2001) | Japan | Exfol. cells | LCR-E7 | 137 | 0/0/0/137 | 91.2 | 35.8 | 2.2 | 2.2 | 9.5 | 2.2 |
| **Asia sub-total** | | | | | 726 | 62/243/52/369 | 76.4 | 31.4 | 6.9 | 1.0 | 4.9 | 11.2 | 6.4 | 0.0 | 3.8 | 3.8 | 0.0 | 10.3 |
| **Europe**   |           |         |                                               |                   |                                               |           |
| Baay MFD     | Eur J Gynecol. Oncol (2001) | Belgium | Fixed | GP5+/6+ | 97 | 42/55/0/0 | 82.5 | 56.2 | 6.2 | 0.0 | 6.2 | 2.1 | 2.1 | 0.0 | 1.0 | 1.0 | 0.0 |
| Tachezy R    | Hum. Genet. (1999) | Czech Republic | Exfol. cells | MY09/11 | 88 | 0/0/0/88 | 58.0 | 43.2 | 5.7 | 3.4 | 1.1 | 6.8 |
| Sebbelov     | Res Virol. (1994) | Denmark | Fixed | GP5/6 | 34 | 0/34/0/0 | 91.2 | 85.3 | 0.0 | 0.0 | 29.4 |
| Bergeron B   | Am J Surg Pathol (1992) | France | Fresh | L1 primers | 53 | 0/0/0/53 | 92.5 | 56.6 | 3.8 | 1.9 |
| Merkelbach-Brue S | Diagn Mol. Pathol (1999) | Germany | Fixed | GP5/6 | 88 | 2/67/0/0 | 78.4 | 61.4 | 1.1 | 3.4 | 1.1 |
| Meyer T      | Int J Gynecol Cancer (2001) | Germany | Fixed | GP5/6 | 288 | 0/0/288 | 94.4 | 46.2 | 6.2 | 1.4 | 13.2 | 9.4 | 1.7 | 5.6 | 3.1 | 0.7 | 1.4 | 1.0 | 0.3 | 1.4 |
| Nindi I      | J Clin Pathol (1999) | Greece | Exfol. cells | GP5+/6+ | 65 | 31/34/0/0 | 87.7 | 56.9 | 6.2 | 1.5 | 18.5 | 7.7 |
| Nindi I      | Int J Gynecol Pathol (1997) | Greece | Exfol. cells | GP5+/6+ | 85 | 0/0/0/85 | 83.5 | 36.5 | 2.4 | 5.9 | 12.9 |
| Labropoulou V | Sex Transm Dis (1997) | Greece | Fixed | MY09/11 | 50 | 0/0/0/50 | 88.0 | 36.0 | 12.0 | 6.0 | 0.0 | 4.0 |
| Paraskevaidis E | Gynecol Oncol (2001) | Greece | Exfol. cells | MY09/11 | 28 | 0/0/28 | 89.3 | 35.7 | 1.1 | 13.2 | 4.3 | 1.1 |
| Sebbelov     | Res Virol. (1994) | Greenland | Fixed | GP5/6 | 30 | 0/30/0/0 | 63.3 | 70.0 | 3.3 | 6.7 | 1.0 |
| Butler D     | J Pathol (2000) | Ireland | Fixed | TS-PCR only | 27 | 0/27/0/0 | 85.2 | 70.4 | 3.7 | 3.7 | 0.0 | 0.0 |
| O’Leary JJ   | Hum. Pathol. (1998) | Ireland | Fixed | GP5/6 | 20 | 0/20/0/0 | 95.0 | 95.0 | 0.0 | 0.0 | 0.0 |
| Laxoni       | Pathologica (2000) | Italy | Fixed | GP5+/6+ | 36 | 19/17/0/0 | 100.0 | 50.0 | 8.3 | 2.8 | 2.8 | 5.6 | 5.6 | 2.8 | 0.0 | 0.0 |

Comparison of HPV type distribution in HSIL and SCC

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| Study | Country | Location | Sample Size | HPV Type | HPV16/18 | HPV31/33 | HPV45 | HPV51/52 | HPV56/58 | HPV6/11 | HPV13 | HPV15 | HPV39 | HPV42/43 | HPV53 | HPV54 | HPV57 | HPV61 | HPV62 | HPV70 | HPV71 | HPV73/74 | HPV82 | HPV8 | HPV97 | HPV99 | Notes |
|-------|---------|----------|-------------|----------|----------|----------|-------|----------|----------|----------|-------|-------|-------|----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Zerbini M | Italy | Exfol. cells | MY09/11 | 89 | 0/0/0/89 | 79.8 | 50.6 | 3.4 | 2.2 | 7.9 | 9.0 |
| Medeiros R | Portugal | Fixed biopsies | MY09/11 | 78 | 10/68/0/0 | 85.9 | 82.1 | 0.0 | 1.3 |
| Bosch | Spain | Exfol. cells | MY09/11 | 157 | 0/157/0/0 | 70.7 | 49.0 | 0.6 | 1.3 | 5.7 | 0.6 |
| Kalantari M | Sweden | Exfol. cells | MY09/11 | 164 | 69/95/0/0 | 82.9 | 36.0 | 7.3 | 7.3 | 10.4 |
| Zehbe I | Sweden | Fixed biopsies | GPS+/6+ | 103 | 55/48/0/0 | 95.1 | 50.5 | 9.7 | 1.9 | 7.8 | 9.7 | 1.9 | 0.0 | 7.8 | 1.9 | 0.0 |
| Bollen LJM | The Netherlands | Exfol. cells | SPF1/0 | 216 | 44/172/0/0 | 97.7 | 56.9 | 13.9 | 19.4 | 11.6 | 8.3 |
| Cornelissen MTE | The Netherlands | Fixed biopsies | MY09/11 | 89 | 16/73/0/0 | 88.8 | 52.8 | 6.7 | 12.4 | 5.7 | 0.6 |
| Reesink-Peters N | The Netherlands | Exfol. cells | SPF10 | 216 | 44/172/0/0 | 97.7 | 56.9 | 13.9 | 19.4 | 11.6 | 8.3 |
| Arends MJ | UK | Fixed biopsies | GPS+/6+ | 40 | 20/20/0/0 | 60.0 | 50.0 | 10.0 | 0.0 |
| Cuzick J | UK | Exfol. cells | TS-PCR only | 73 | 12/61/0/0 | 91.8 | 63.0 | 20.5 | 26.0 | 16.4 | 2.7 |
| Giannoudis A | UK | Fixed biopsies | GPS+/6+ | 118 | 31/87/0/0 | 100.0 | 68.6 | 4.2 | 0.0 | 14.4 | 11.0 | 3.4 | 0.8 | 2.5 | 0.0 | 2.5 | 0.8 | 2.5 |
| Herrington CS | UK | Exfol. cells | TS-PCR only | 38 | 12/26/0/0 | 92.1 | 50.0 | 7.9 | 18.4 | 7.9 |
| Southern SA | UK | Fixed biopsies | GPS+/6+ | 26 | 0/26/0/0 | 100.0 | 61.5 | 7.7 | 0.0 | 15.4 | 3.8 |
| Europe sub-total | | | | 2271 | 406/1181/0/684 | 87.1 | 52.6 | 6.5 | 2.4 | 2.6 | 0.3 | 2.5 | 1.5 | 0.6 | 1.8 | 1.6 |
| North America | Canada | Exfol. cells | MY09/11 | 58 | 0/0/0/58 | 98.3 | 75.9 | 8.6 | 0.0 | 27.6 | 5.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Adam E | USA | Exfol. cells | MY09/11 | 257 | 0/0/0/257 | 78.2 | 51.0 | 13.6 | 1.9 | 4.7 | 13.6 |
| Aoyama C | USA | Fixed biopsies | GPS+/6+ | 21 | 4/15/0/2 | 95.2 | 52.4 | 0.0 | 19.0 | 19.0 |
| Schiff M | USA | Exfol. cells | MY09/11 | 112 | 7/50/2/0 | 77.7 | 17.0 | 4.5 | 18.2 | 22.3 | 45.1 | 6.1 | 4.5 | 4.5 | 12.5 | 4.5 | 2.9 | 6.3 | 9.8 |
| North America sub-total | | | | 448 | 74/50/2/0 | 81.5 | 45.8 | 10.0 | 1.2 | 11.2 | 5.4 | 10.6 | 2.9 | 9.4 | 2.9 | 8.2 | 2.9 | 1.8 | 4.1 | 6.5 |
| South/Central America | Argentina | Exfol. cells | MY09/11 | 86 | 13/24/0/97 | 97.7 | 50.0 | 14.0 | 7.0 | 2.3 | 7.0 |
| Alonzo LV | Argentina | Biopsies | GPS+/6+ | 36 | 0/36/0/0 | 80.6 | 41.7 | 11.1 | 0.0 | 5.6 |
| Lorenzato F | Brazil | Exfol. cells | MY09/11 | 60 | 0/0/0/60 | 86.7 | 56.7 | 3.3 | 3.3 | 8.3 | 100.0 | 0.0 | 1.7 |
| Bosch | Colombia | Exfol. cells | MY09/11 | 125 | 0/125/0/0 | 63.2 | 32.8 | 0.0 | 2.4 | 2.4 | 1.6 |
| Herrero R | Costa Rica | Exfol. cells | MY09/11 | 125 | 0/0/0/125 | 88.8 | 44.8 | 5.6 | 2.4 | 6.4 | 3.2 | 9.6 | 7.2 | 3.2 | 0.8 | 3.2 | 7.2 | 0.8 | 3.2 | 0.0 |
| Ferrera A | Honduras | Exfol. cells | MY09/11 | 83 | 36/47/0/0 | 80.7 | 34.9 | 7.2 | 3.6 | 8.4 | 4.8 | 7.2 | 1.2 | 1.2 | 0.0 | 1.2 | 0.0 | 0.0 | 0.0 |
| Rattray | Jamaica | Exfol. cells | GPS+/6+ | 66 | 27/39/0/0 | 80.3 | 24.2 | 45.1 | 3.6 | 9.1 | 7.6 | 13.6 |
| Strickler HD | Jamaica | Exfol. cells | MY09/11 | 183 | 11/72/0/0 | 92.3 | 23.5 | 10.9 | 4.4 | 8.7 | 7.7 | 12.6 | 9.3 | 11.5 | 5.5 | 2.2 | 4.9 | 2.2 | 1.1 | 4.9 |
| Illades-Aguiar | Mexico | Fresh | MY09/11 | 27 | 0/0/0/27 | 85.2 | 37.0 | 3.7 | 0.0 | 14.8 | 14.8 | 3.7 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Torroella-Kouri M | Mexico | Exfol. cells | MY09/11 | 24 | 0/0/0/24 | 83.3 | 58.3 | 12.5 | 0.0 | 8.3 | 12.5 | 0.0 | 0.0 | 0.0 | 4.2 | 0.0 | 0.0 | 0.0 |
| South/Central America sub-total | | | | 815 | 187/343/0/285 | 84.3 | 36.9 | 7.1 | 4.4 | 6.4 | 5.5 | 10.2 | 5.4 | 5.5 | 2.5 | 2.0 | 4.7 | 1.1 | 1.4 | 2.0 |
| Total | | | | 4338 | 729/1824/51/1733 | 84.2 | 45.0 | 7.1 | 2.3 | 8.8 | 7.2 | 6.9 | 5.2 | 4.4 | 1.5 | 3.0 | 2.9 | 1.1 | 1.1 | 2.1 |

Exfol. Cells = exfoliated cells.