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Need for expanded HPV genotyping for cervical screening ☆

ABSTRACT

The focus for HPV genotyping has largely been on types 16 and 18, based on their high prevalence in cervix cancer. However screening is focussed on the detection of high grade precursor lesions (CIN3 and CIN2), where other types have a greater role. While HPV16 retains its high predictive value in this context, HPV31 and especially HPV33 emerge as important types with higher positive predictive values (PPVs) than HPV18. Additionally full typing indicates that types 39, 56, 59 and 68 have much lower PPVs than types 16, 18, 31, 33, 35, 45, 51, 52 and 58 and they should be considered as 'intermediate risk' types, whereas type 66 should not be treated as having an increased risk. Available data are summarized to support this view.

The ATHENA (Addressing The Need for Advanced HPV Diagnostics) trial was a very large registration trial for the use of Roche's Cobas human papillomavirus (HPV) test in primary cervical screening and for the triage of atypical squamous cells of unknown significance (ASC-US). Over 42,000 women aged 25y or older were enrolled. The study has provided convincing evidence that HPV testing alone as the primary screening modality is more sensitive than cervical cytology at all ages and is as sensitive as HPV co-testing with cytology in women aged 30y and over [1]. As a result of this study, Cobas is now licenced by the Food and Drug Administration (FDA) in the United States for primary screening in women aged 25y and older and for ASC-US triage in women aged 21y and older. The Cobas test is based on polymerase chain reaction (PCR) amplification of HPV DNA using liquid-based cervical cytology samples and detects HPV 16 and 18 separately with a consensus pool for 12 other high-risk HPV types. This trial has confirmed that positivity for HPV 16 carries a higher risk than a pool of other high risk types for the detection of high grade cervical intraepithelial neoplasia (CIN) [2]. However based on data from this trial, Monsonego et al. [3] have suggested that typing only for HPV types 16 and 18 is all that is needed to assess the risk of high-grade cervical intraepithelial neoplasia (CIN grade 2 (CIN2) or CIN grade 3 (CIN3)) in a screening context. While important, this is a gross oversimplification based on currently available data, where further discrimination of risk based on extended HPV typing is clearly apparent.

Firstly, while much less common than HPV 16, HPV 33 has similar predictive power for detection of high-grade CIN (CIN2 and CIN3) and HPV 33 also carries a high risk for invasive cervical cancer. This is seen in a number of other large studies assessing HPV genotype-specific cervical disease risks (Tables 1 and 2). HPV 33 has a higher positive predictive value for CIN2+ and CIN3+ than HPV 18, for all studies, except in a study conducted in Kaiser Permanente Northern California (KPNC) where the risk was virtually equal. Similarly, HPV 31 consistently stands out as being higher risk than other 'high risk HPV types' and has a higher risk than HPV 18 for most of the studies shown in Table 1. For squamous cancers, HPV 16 is clearly dominant and HPV 18 fares somewhat better, typically ranking second in relative risk (Table 2B). HPV 45 also emerges in the top four HPV genotypes causing invasive cervical cancer, but it ranks lower for high-grade precursor lesions. This type has been combined with HPV18 in some assays (notably Hologic Aptima). Only for adenocarcinoma (including adenosquamous cancer) does HPV 18 carry the highest relative risk (Table 2B). Data on full HPV typing is quite sparse for adenocarcinoma in situ (AIS), but again in the available data HPV 18 carries the highest relative risk.

Another large international study of cancer with full genotyping was reported by Sanjose et al. [24] involving 10,575 cases. No control data were given in that study, but a contemporary study of negative cytology was reported by many of the same authors [25]. There were not enough data to compute confidence intervals but the rankings for squamous cancer would be 16, 45, 33,18 and 31, whereas for adenocarcinoma they would be 45, 18, 16, 33, 31.

Secondly, other individual HPV genotypes within commonly grouped categories of "other" high-risk HPV genotypes do not carry equal risk [4], and some – notably HPV 39, 56, 59, 66 and 68 would be better considered as 'intermediate risk' and potentially have less active clinical management than other high-risk HPV genotypes, e.g., if cytology negative repeat screening at 2–3 years rather than after one year. Further analyses and new data indicate that type 66 carries little or no risk, and should be dropped altogether from the group of 'increased risk' HPV types [5,6]. The International Agency for Research on Cancer (IARC) dropped its assessment of sufficient evidence for carcinogenicity for HPV66 in 2009 [7].

Lastly, there is little discrimination between types 16 and 18 in the report of Monsonego et al. [3], whereas again numerous

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Table 1
Prevalence of HPV 16, 18, 31, 33 and positive predictive value (PPV) or relative risk (RR, where indicated) for CIN2+ and CIN3+ in different studies.

Study [ref]	HPV type	Population prevalence % (95% CI)	CIN2+		CIN3+	
			PPV (95% CI)	rank	PPV (95% CI)	rank
ATHENA (N=40 901) [[3], (Table 3)]	16	2.1 (1.9, 2.2)	19.5 (16.8, 22.3)	1	14.7(12.2, 17.3)	1
	18	.82 (.73, .91)	8.4 (5.64, 11.9)	4	6.9 (4.4, 10.2)	4
	31	1.0 (.92, 1.1)	15.2 (11.9, 19.0)	2	8.0 (5.5, 11.0)	2
	33	.28 (.23, .33)	9.7 (4.96, 16.8)	3	7.1 (3.1, 13.5)	3
NMHPVPR (N=47 617, 3y FU) [[13], Table 1; [14], Table 3]]	16	3.5 (3.3, 3.6)	10.9 (6.1, 12.7)	1.5	8.0 (6.5, 9.6)	1
	18	1.2 (1.1, 1.3)	5.7 (3.4, 7.9)	4	2.9 (1.5, 4.3)	4
	31	1.8 (1.7, 1.9)	7.3 (4.7, 9.9)	3	3.1 (1.9, 4.4)	3
	33	.50 (.43, .57)	10.9 (5.8, 16.0)	1.5	5.2 (1.8, 8.6)	2
FUTURE I (N=1694, 3y FU) [[15], Table 1]	16	13.9 (12.4, 15.5)	9.2 (6.0, 13.2)	2	1.7 (0.0, 3.8)	3
	18	5.8 (4.8, 6.9)	4.4 (1.4, 10.0)	4	0 (-)	–
	31	8.0 (6.8, 9.3)	8.9 (5.0, 14.5)	3	3.2 (0.0, 8.8)	2
	33	2.9 (2.2, 3.7)	14.0 (6.26, 25.8)	1	4.1 (0.0, 10.5)	1
KPNC (3y FU) (N=18 810, HPV+, cyto neg, >30y) [[6], Tables 2 and 3)]	16	14.7 (14.2, 15.2)	16.7 (15.5, 17.9)	1	10.6 (.89, 11.4)	1
	18	6.3 (6.0, 6.7)	9.4 (8.3, 10.7)	4	5.9 (5.2, 6.7)	2
	31	10.1 (9.7, 10.5)	10.2 (9.3, 11.3)	3	4.5 (4.1, 5.0)	4
	33	2.2 (2.0, 2.4)	8.9 (7.1, 11.0)	6	5.9 (4.8, 7.2)	3
			HPV 52-2nd; HPV35-5th			
Predictors 2 (referral) N=1067 [[4], Table 3 and new data[a]]	16	30.2 (27.4, 33.0)	57.8 (52.2, 63.2)	2	42.3 (37.0, 47.8)	1
	18	5.4 (4.1, 7.0)	29.3 (18.1, 42.8)	4	15.2 (6.34, 28.9)	6
	31	7.6 (6.1, 9.4)	39.5 (28.8, 51.0)	3	22.2 (13.7, 32.8)	3
	33	7.7 (6.2, 9.4)	59.8 (48.3, 70.4)	1	31.0 (20.5, 43.1)	2
					HPV35-4th; HPV52-5th	
New Mexico [[16], Table 2 and new data for CIS only[a]] (RR) N=5020	16	7.4 (6.6, 8.3)			5.8 (5.2, 6.3)	1
	18	2.3 (1.8, 2.8)			1.8 (1.5, 2.2)	4
	31	2.9 (2.4, 3.5)			2.7 (2.4, 3.1)	3
	33	.92 (.65, 1.3)			3.4 (3.0, 3.8)	2
Sweden 14y risk (N=11 685) [[17], Tables 1, 2 and 4]	16	2.4 (2.18, 2.74)	42.8 (36.4, 49.8)	2	34.5 (28.4, 41.5)	1
	18	.62 (.49, .79)	39.4 (28.4, 52.8)	4	29.7 (19.6, 43.4)	3
	31	1.0 (.84, 1.22)	41.9 (31.1, 54.6)	3	28.4 (18.2, 42.7)	4
	33	.38 (.27, .51)	54.2 (37.6, 72.5)	1	34.1 (19.2, 55.6)	2
Controls in Vaccine trials (15–26y) (N=17 590) [[18], Tables 1 and 3]	16	8.8 (8.4, 9.3)	26.3 (24.1, 28.6)	1	15.5 (13.7, 17.4)	1
	18	3.6 (3.4, 3.9)	12.5 (10.0, 15.3)	4	5.6 (4.0, 7.7)	4
	31	4.4 (4.1, 4.8)	18.3 (15.7, 21.2)	3	8.6 (6.7, 10.8)	3
	33	2.0 (1.8, 2.2)	23.5 (19.2, 28.2)	2	13.4 (10.1, 17.4)	2
POBASCAM Baseline- (N=44 102) [19, Tables 1 and 2]	16	1.6 (1.5, 1.8)	20.8 (17.9, 24.0)	1	17.1 (14.4, 20.0)	1
	18	.42 (.37, .49)	7.4 (4.1, 12.3)	3	5.3 (2.6, 9.6)	3
	31	.64 (.57, .72)	7.1 (4.4, 10.8)	4	5.0 (2.8, 8.2)	4
	33	.27 (.22, .32)	14.4 (8.6, 22.1)	2	12.7 (7.3, 20.1)	2
Denmark [[20], Tables 1 and 2] (N=40 382)	16	5.4 (5.1, 5.9)	15.7 (14.1, 17.3)	1	13.2 (11.8, 14.7)	1
	18	2.4 (2.2, 2.5)	10.2 (8.4, 12.3)	3	8.1 (6.5, 10.0)	3
	31	3.8 (3.6, 4.0)	9.3 (7.9, 10.9)	4	6.3 (5.1, 7.6)	4
	33	1.7 (1.6, 1.9)	13.2 (10.8, 16.0)	2	9.0 (7.0, 11.3)	2

[a] See Supplementary Tables for detailed breakdown of disease categories.

studies indicate these two HPV genotypes have very different roles in disease management. In particular while HPV 16 carries a higher risk of CIN2 or greater (CIN2+) at screening, but HPV18 does not. Its special role is more related to the fact that it is relatively more common in cancer and is also associated with adenocarcinoma and CIN lesions in the endocervical canal (Table 2). These lesions are less often detected by cytology and less visible on colposcopy. Evidence for an increased risk of disease with HPV 18 is largely based on longitudinal follow up and is not seen cross-sectionally [[8] and Refs. in Tables]. While HPV 16 positivity alone may well be grounds for referral to colposcopy, HPV 18 positivity alone will not be associated with higher CIN2+ detection rates. Repeat HPV 18 positivity to establish persistence could potentially be a better option in the absence of a cytologic abnormality. Further the prevalence of HPV 18 in cancer does not automatically qualify it as a more important HPV genotype for screening purposes, as many HPV18 related cancers are endocervical, and precursors are often not visible on colposcopy, so its detection may not lead to cancer prevention.

Thus, clinically useful information is contained in a finer classification of HPV genotypes [4] with one approach being to provide separate read outs for HPV 16, 18, 31, 33 and two pools – one of 'high risk' types (HPV 35, 45, 51, 52, 58) and one of 'intermediate risk' types (HPV 39, 56, 59, 68). While this is not the only possible extended genotyping approach, and these observations should not lead to immediate changes in current screening recommendations, it is clear that separate assessment of HPV 33 and 31 needs to be reconsidered, as this is not possible with currently approved HPV tests such as the Cobas test. Whether HPV 45 should be included with HPV 18 is also an open question in need of further data. A

Table 2
Population prevalence of HPV 16, 18, 31, 33, 45 and relative risk with 95% confidence intervals for A) squamous cancer (SCC), B) Adenocarcinoma (ADC, including adenosquamous cancer) and C) adenocarcinoma in situ (AIS).

A. Squamous cancer

Study	HPV type	Population prevalence % (95% CI)	Prevalence in squamous cancer % (95% CI)	Rel risk for squamous cancer (95% CI)	Rank
IARC (world) [[21,22], Table 2; Table 2] N=15, 613 normal, 9494 SCC	16	1.8 (1.6, 2.0)	55.2 (54.2, 56.2)	30.6 (27.2, 34.4)	1
	18	.66 (0.54, 0.80)	12.8 (12.1, 13.5)	19.4 (15.9, 23.7)	2
	31	.69 (0.56, 0.83)	3.8 (3.4, 4.2)	5.5 (4.4, 6.9)	5
	33	.53 (0.42, 0.66)	3.7 (3.3, 4.1)	7.0 (5.5, 8.9)	4
	45	.51 (0.41, 0.64)	4.6 (4.1, 5.2)	9.0 (7.0, 11.5)	3
New Mexico [[16], Table 2 and new data for SCC only[a]] N=4007 controls, 660 SCC	16	7.4 (6.6, 8.3)	58.0 (54.2, 61.8)	7.8 (6.9, 8.9)	1
	18	2.3 (1.8, 2.8)	9.8 (7.7, 12.4)	4.3 (3.2, 5.9)	3
	31	2.9 (2.4, 3.5)	4.2 (2.8, 6.1)	1.4 (.97, 2.3)	6
	33	.92 (0.65, 1.3)	4.8 (3.3, 6.8)	5.2 (3.3, 8.4)	2
	45	2.2 (1.8, 2.8)	6.5 (4.6, 8.7)	2.9 (2.0, 4.1)	4 HPV35 5th
Denmark [[20], Tables 1 and 2] (N=40 382, 19 SCC)	16	5.4 (5.1, 5.9)	57.9 (33.5, 79.7)	10.8 (7.3, 15.9)	1
	18	2.4 (2.2, 2.5)	10.5 (13.0, 33.1)	4.4 (1.2, 16.4)	4
	31	3.8 (3.6, 4.0)	5.3 (1.3, 26.0)	1.4 (0.21, 9.4)	5
	33	1.7 (1.6, 1.9)	10.5 (13.0, 33.1)	6.1 (1.63, 22.5)	3
	45	1.9 (1.8, 2.1)	15.8 (3.38, 39.6)	6.7 (2.3, 19.3)	2

B. Adenocarcinoma (including adenosquamous)

Study	HPV type	Population prevalence % (95% CI)	Prevalence in adenocarcinoma % (95% CI)	Rel risk for adenocarcinoma (95% CI)	Rank
IARC (world) [[23], Table 2] N=157 cases, 1609 controls	16	4.7 (3.7, 5.9)	42.7 (34.8, 50.8)	9.0 (6.8, 12.0)	3
	18	1.2 (.71, 1.8)	31.8 (24.6, 39.7)	27.0 (16.3, 44.6)	1
	31	0 (0.0, .2)	0 (0, 2.3)	–	–
	33	.06 (.02, .35)	.6 (.01, .35)	10.2 (.64, 163)	2
	45	.68 (.34, 1.2)	3.8 (1.4, 8.1)	5.6 (2.1, 15.1)	4
New Mexico [[16], Table 2 and new data for ADC only[a]] N=122 ADC, 4007 controls	16	7.4 (6.6, 8.3)	36.9 (28.3, 46.1)	5.0 (3.9, 6.4)	2
	18	2.3 (1.8, 2.8)	28.9 (20.9, 37.6)	12.6 (8.9, 17.8)	1
	31	2.9 ((2.4, 3.5)	3.3 (0.90, 8.2)	1.1 (.42, 3.0)	4
	33	.92 (0.65, 1.3)	0 (0, 3.0)	0	–
	45	2.2 (1.8, 2.8)	.8 (.02, 4.5)	1.5 (.55, 3.9)	3
Denmark [[20], Tables 1 and 2] (N =40 382, 8 ADC)	16	5.4 (5.1, 5.9)	0 (0, 36.9)	0	–
	18	2.4 (2.2, 2.5)	87.5 (47.3, 99.7)	36.8 (28.1, 48.1)	1
	31	3.8 (3.6, 4.0)	12.5 (.32, 52.7)	3.3 (.53, 21.8)	2
	33	1.7 (1.6, 1.9)	0 (0, 36.9)	0	–
	45	1.9 (1.8, 2.1)	0 (0, 36.9)	0	–

C. Adenocarcinoma in Situ (AIS)

Study	HPV type	Population prevalence % (95% CI)	Prevalence in AIS % (95% CI)	Rel Risk for AIS (95% CI)	Rank
New Mexico [[16], Table 2 and new data[a] for AIS only] N=4007 controls, 25 AIS	16	7.4 (6.6, 8.3)	48.0 (27.8, 68.0)	6.5 (4.2, 9.9)	2
	18	2.3 (1.8, 2.8)	48.0 (27.8, 68.0)	21.1 (13.4, 33.3)	1
	31	2.9 (2.4, 3.5)	0 (0, 13.7)	0	–
	33	.92 (.65, 1.3)	0 (0, 13.7)	0	–
	45	2.2 (1.8, 2.8)	4.0 (0.10, 20.4)	1.8 (.26, 12.3)	3
Controls in Vaccine trials 15–26y [[18], Tables 1 and 3] N=17 590, 19 AIS	16	8.8 (8.4, 9.3)	78.9 (54.4, 93.9)	8.9 (7.1, 11.3)	2
	18	3.6 (3.4, 3.9)	36.8 (16.3, 61.6)	10.7 (5.9, 19.1)	1
	31	4.4 (4.1, 4.8)	0 (0, 17.6)	0	–
	33	2.0 (1.8, 2.2)	5.3 (.13, 26.0)	2.5 (.38, 17.5)	3
	45	2.4 (2.2, 2.6)	5.3 (.13, 26.0)	1.9 (0.29, 13.3)	4
Denmark [[20], Tables 1 and 2] (N=40 382, 23 AIS)	16	5.4 (5.1, 5.9)	43.5 (23.2, 65.5)	8.1 (5.1, 12.9)	4
	18	2.4 (2.2, 2.5)	60.9 (38.5, 80.3)	25.6 (18.3, 35.7)	1
	31	3.8 (3.6, 4.0)	30.4 (13.2, 52.9)	8.1 (4.4, 15.0)	5
	33	1.7 (1.6, 1.9)	21.7 (7.5, 43.7)	12.5 (5.7, 27.2)	2
	45	1.9 (1.8, 2.1)	17.4 (5.0, 38.8)	8.9 (3.7, 21.9)	3

[a] See Supplementary Tables for detailed breakdown of disease categories.

finer level of genotyping along with other discriminators not used in current HPV testing algorithms such as viral load [5,9], methylation status [10,11] and HPV variant status (esp for HPV 16 [12]) deserve further research to find combinations that optimally use sample information to stratify risk of high grade disease, both at the time of screening and in the longer term, and to use this information to improve management algorithms.

It is important to recognise that the aim of screening is to prevent cancer and that the HPV distribution in cancers may not accurately reflect the relative importance of different types in doing this, as some cancers will not be detected by screening. Cancer prevention is based on recognizing and treating precursor

lesions before they become cancer. Doing this effectively and still avoiding overtreatment should be the primary goal of a cervical cancer screening programme.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pvr.2016.05.004.

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Jack Cuzick*
Wolfson Institute of Preventive Medicine, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, United Kingdom
E-mail address: j.cuzick@qmul.ac.uk

Cosette Wheeler
Department of Pathology, University of New Mexico Health Sciences Center, Albuquerque, NM 87131, USA

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* Corresponding author.