Evidence review for recommendations: Chapter 6 management of oncogenic HPV (16/18) detected

Analysis of NCSR data to estimate risk of serious disease in those with HPV16/18 detected: detection of incident infections compared to prevalent infections

Background

This analysis of data from the National Cancer Screening Register (NCSR) was undertaken to inform a review of the National Cervical Screening Program (NCSP) guidelines in 2023.

Detection of HPV16/18 is associated with elevated risk of serious disease (even in conjunction with negative cytology) and colposcopy referral is recommended for screening participants with these test results. However, previous studies (all conducted outside Australia) have shown that the risk of serious disease is lower in those with a previous negative HPV test (incident detection) than in those with no previous information about HPV status (prevalent detection)[1,2,3,4]. Starting from late 2022, people eligible for cervical screening will begin attending for their second round HPV screening test (ie some people attending will have had at least one previous negative HPV test).

The current review of the guidelines includes a review of the international literature[a] and an analysis of NCSR data to estimate the risk of serious disease (CIN3+) in those with incident vs prevalent detection of HPV (16/18), to ascertain if it may be low enough to consider deferring colposcopy referral in some cases, where there is a previous HPV negative test result.

Methods

Data source

Aggregate data were extracted from the NCSR for a cohort of people attending for routine cervical screening over the period 1 December 2017 to 31 December 2022 (inclusive). Data was extracted on 24 May 2023 and results considered up until 31st December 2022, to allow time for results to be uploaded to the NCSR.

Eligibility

Individuals were eligible for this analysis if they attended routine cervical screening (reason for test: primary screening) between 1 December 2017 and 31 December 2022 (inclusive); if they were aged 25-74 years at the time of the routine screening test; if they had HPV16/18 detected on the primary HPV test; and if they had a record that colposcopy and/ or histology has occurred within 1 year of their primary HPV 16/18 positive test result.

Outcomes

The outcomes of interest were serious cervical abnormalities, defined as CIN3+ and cancer (primary outcomes) and CIN2+ (secondary outcome). Each of the outcomes was classified based on the most serious histological outcome available within 12 months of the HPV16/18+ test result, and which occurred no later than 31st December 2022. These would predominantly reflect the outcomes resulting from the initial

[a] See accompanying evidence reviews (2 PECOs) available at: <final link>

colposcopy (was constrained to occur within 12 months of the screening test), rather than following a 12-month follow-up HPV test. Individuals with no histology result available within the timeframe were classified as CIN2+ not identified (<CIN2) as in all cases there was a record of subsequent colposcopy but no biopsy was taken. Individuals with a record that a histology sample was collected, but where the histology result was not available, were classified as having no outcome within the relevant timeframe and were excluded from the analysis.

Data analysis

Estimates were made of the risk of detecting serious disease in those with a negative HPV test result in the previous 6 years (incident detection), and in those with no previous HPV test result available (prevalent detection). Prevalent HPV infections were further dichotomised into whether or not people were 2 or more years overdue for screening at the time of their HPV (16/18) test result (see Table 1). Incident infections were not dichotomised in this way as at the time of this analysis, it was not possible for anyone with a previous negative primary HPV test (which must have occurred on 1 December 2017 or later) to be 2 or more years overdue for a primary HPV test (this cannot occur until 1 December 2024 or later).

Outcomes were also stratified by LBC result and age group.

We also calculated 95% confidence intervals (CI) for all crude and cumulative rates. All analyses on aggregate data provided by the NCSR were performed using Excel.

Table 1: Definitions for incident versus prevalent detection of infections

Detection categories	Definition
Incident*	Individuals with a negative primary HPV test within the 6 years prior to their HPV16/18+ test result
Prevalent	Individuals with no HPV test result available prior to their HPV16/18+ test result
Prevalent (<2 years overdue)	individuals who had a negative primary cytology test <4 years before the detection of prevalent infection on a routine primary screening test or anyone who is aged <27 years
Prevalent (2+ years overdue)	In individuals who are aged 27 years or more who have no record of a negative primary cytology test <4 years before the time of the prevalent infection on a routine primary screening test

*Overdue categories not specified in relation to incident detection, as at the time of this analysis, it was not possible for someone with a previous negative HPV test to be 2+ overdue for a primary HPV test.

Results

In total, 96,222 screening participants had HPV 16/18 detected on a primary screening test between 1 December 2017 and 31 December 2022; of these, 84,577 (87.9%) had a record of colposcopy and/or histology within 12 months of their HPV16/18 test result. There were 2,295 incident and 69,621 prevalent infections. Further information about the demographics and test results in this cohort is available in Supplementary Table 1.

Cumulative detection rates for CIN3+ and cancer within 12 months of a result of HPV 16/18 detected on a primary screening test are shown in **Error! Reference source not found.**, stratified by LBC result and age.

In the absence of a known LBC result, the risk of detecting CIN3+ was significantly lower for those with an incident infection than those with a prevalent infection in every age group. The lower risk associated with incident compared to prevalent HPV16/18 infections was also observed in each category of LBC results. For both incident and prevalent infections, the risk of CIN3+ was higher in younger age groups and tended to decrease with increasing age after 45-49 years.

Cancer detection was much rarer for incident HPV16/18 infections than for prevalent infections, and at the time of analysis was only identified in those with negative or pHSIL+/ glandular LBC results (although there were only 585 incident infections with pLSIL/LSIL LBC results).

The risk of CIN3+ and cancer detection within 12 months, stratified for prevalent infections based on whether the screening participant was up-to-date or less than two years overdue for screening compared to those who were two or more years overdue at the time the prevalent detection of HPV16/18, is shown in Table 3. Among those with prevalent detection of HPV16/18 at primary screening, the risk was higher among those who were two or more years overdue for screening at the time than among those who were less overdue/ not overdue (although the difference was not significant in some age groups). The pattern of lower risk of serious disease among those with incident compared to prevalent HPV16/18 infections continued to hold, even when restricted to prevalent infections among those who were on-time or less than two years overdue at the time of their prevalent detection. The pattern of higher CIN3+ risk in younger age groups (seen for incident detection and for prevalent detection overall, not stratified by whether the person was overdue or not) remained true for prevalent detection regardless of whether the person was 2 or more years overdue or not. Cancer outcomes were rarer, and so differences between age groups were often not significant; however, the one case where those aged 50-74 years were significantly more likely to have cancer detected within 12 months that women aged 25-49 years was in the group who were 2 or more years overdue and had pHSIL+ or any glandular LBC result.

Table 2: Risk of detecting CIN3+ or cancer among those with colposcopy recorded within 12 months of HPV (16/18) detection

LBC	Age (years)	N		CIN3+ (% [95% CI])		Cancer (% [95% CI])	
		Incident	Prevalent	Incident	Prevalent	Incident	Prevalent
Unknown (any)	25-29	178	8,308	6.2 [2.6 - 9.7]	21.3 [20.4 - 22.2]	0.0 [0.0 – 2.1]	0.6 [0.4 - 0.7]
	30-34	286	11,676	2.4 [0.7 - 4.2]	26.6 [25.8 - 27.4]	0.0 [0.0 – 1.3]	1.8 [1.5 - 2.0]
	35-39	271	10,159	3.7 [1.4 - 5.9]	24.7 [23.8 - 25.5]	0.4 [0.0 - 1.1]	2.3 [2.0 - 2.6]
	40-44	350	8,974	3.4 [1.5 - 5.3]	19.2 [18.4 - 20.0]	0.0 [0.0 – 1.0]	2.0 [1.7 - 2.2]
	45-49	330	8,066	3.9 [1.8 - 6.0]	14.0 [13.3 - 14.8]	0.0 [0.0 – 1.1]	1.7 [1.4 - 2.0]
	50-54	292	6,503	2.7 [0.9 - 4.6]	8.7 [8.0 - 9.4]	0.0 [0.0 – 1.3]	1.2 [0.9 - 1.4]
	55-59	244	5,769	1.6 [0.0 - 3.2]	6.9 [6.3 - 7.6]	0.4 [0.0 - 1.2]	1.0 [0.7 - 1.2]
	60-64	174	4,910	1.1 [0.0 - 2.7]	5.8 [5.2 - 6.5]	0.0 [0.0 – 2.1]	0.8 [0.6 - 1.1]
	65-69	122	3,535	0.8 [0.0 - 2.4]	4.8 [4.1 - 5.5]	0.0 [0.0 – 3.0]	0.9 [0.6 - 1.3]
	70-74	48	1,721	0.0 [0.0 – 7.4]	4.6 [3.6 - 5.6]	0.0 [0.0 – 7.4]	0.8 [0.3 - 1.2]
	25-74	**2,295**	**69,621**	**3.0 [2.3 - 3.7]**	**16.9 [16.6 - 17.1]**	**0.1 [0.0 - 0.2]**	**1.5 [1.4 - 1.5]**
Negative	25-49	935	24,464	1.1 [0.4 - 1.7]	6.5 [6.2 - 6.8]	0.1 [0.0 - 0.3]	0.4 [0.3 - 0.5]
	50-74	597	15,706	0.7 [0.0 - 1.3]	2.2 [2.0 - 2.4]	0.0 [0.0 – 0.6]	0.3 [0.2 - 0.4]
	25-74	**1,532**	**40,170**	**0.9 [0.4 - 1.4]**	**4.8 [4.6 - 5.0]**	**0.1 [0.0 - 0.2]**	**0.4 [0.3 - 0.4]**
pLSIL/LSIL	25-49	376	11,317	5.6 [3.3 - 7.9]	12.5 [11.8 - 13.1]	0.0 [0.0 – 1.0]	0.3 [0.2 - 0.4]
	50-74	209	4,033	2.4 [0.3 - 4.5]	4.8 [4.2 - 5.5]	0.0 [0.0 – 1.7]	0.3 [0.1 - 0.4]
	25-74	**585**	**15,350**	**4.4 [2.8 - 6.1]**	**10.4 [10.0 - 10.9]**	0.0 [0.0 – 0.6]	**0.3 [0.2 - 0.4]**
pHSIL+/ glandular	25-49	94	11,175	22.3 [13.9 - 30.8]	64.3 [63.5 - 65.2]	0.0 [0.0 – 3.8]	5.9 [5.4 - 6.3]
	50-74	43	2,251	14.0 [3.6 - 24.3]	41.9 [39.9 - 44]	2.3 [0.0 - 6.8]	7.0 [5.9 - 8.0]
	25-74	**137**	**13,426**	**19.7 [13.0 - 26.4]**	**60.6 [59.8 - 61.4]**	**0.7 [0.0 - 2.2]**	**6.0 [5.6 - 6.5]**

Table 3: Risk of detecting CIN3+ or cancer among those with colposcopy recorded within 12 months of HPV (16/18) detection: prevalent detection stratified by time since last test

LBC	Age (years)	N			CIN3+ (% [95% CI])			Cancer (% [95% CI])		
		Incident	Prevalent		Incident	Prevalent		Incident	Prevalent	
			<2 years overdue	2+ years overdue		<2 years overdue	2+ years overdue		<2 years overdue	2+ years overdue
Any	25-49	1,415	22,918	24,265	3.7 [2.8 - 4.7]	16.6 [16.1 - 17.1]	26.5 [26.0 - 27.1]	0.1 [0.0 - 0.2]	0.8 [0.7 - 0.9]	2.6 [2.4 - 2.8]
	50-74	880	13,870	8,568	1.7 [0.8 - 2.6]	4.8 [4.4 - 5.1]	9.8 [9.2 - 10.4]	0.1 [0.0 - 0.3]	0.3 [0.2 - 0.4]	2.1 [1.8 - 2.4]
	25-74	**2,295**	**36,788**	**32,833**	**3.0 [2.3 - 3.7]**	**12.1 [11.8 - 12.5]**	**22.2 [21.7 - 22.6]**	**0.1 [0.0 - 0.2]**	**0.6 [0.5 - 0.7]**	**2.4 [2.3 - 2.6]**
Negative	25-49	935	13,247	11,217	1.1 [0.4 - 1.7]	5.9 [5.5 - 6.3]	7.3 [6.8 - 7.8]	0.1 [0.0 - 0.3]	0.3 [0.2 - 0.4]	0.5 [0.4 - 0.7]
	50-74	597	10,124	5,582	0.7 [0.0 - 1.3]	1.9 [1.7 - 2.2]	2.6 [2.2 - 3.1]	0.0 [0.0 – 0.6]	0.2 [0.1 - 0.3]	0.5 [0.3 - 0.6]
	25-74	**1,532**	**23,371**	**16,799**	**0.9 [0.4 - 1.4]**	**4.2 [3.9 - 4.4]**	**5.8 [5.4 - 6.1]**	**0.1 [0.0 - 0.2]**	**0.3 [0.2 - 0.3]**	**0.5 [0.4 - 0.6]**
pLSIL/LSIL	25-49	376	5,474	5,843	5.6 [3.3 - 7.9]	11.4 [10.6 - 12.2]	13.4 [12.6 - 14.3]	0.0 [0.0 – 1.0]	0.2 [0.1 - 0.3]	0.4 [0.2 - 0.5]
	50-74	209	2,414	1,619	2.4 [0.3 - 4.5]	4.4 [3.6 - 5.3]	5.4 [4.3 - 6.5]	0.0 [0.0 – 1.7]	0.2 [0.0 - 0.4]	0.3 [0.1 - 0.7]
	25-74	**585**	**7,888**	**7,462**	**4.4 [2.8 - 6.1]**	**9.3 [8.6 - 9.9]**	**11.7 [11.0 - 12.4]**	**0.0** [0.0 – 0.6]	**0.2 [0.1 - 0.3]**	**0.4 [0.2 - 0.5]**
pHSIL+/ glandular	25-49	94	4,119	7,056	22.3 [13.9 - 30.8]	57.9 [56.4 - 59.4]	68.1 [67.0 - 69.2]	0.0 [0.0 – 3.8]	3.0 [2.4 - 3.5]	7.6 [6.9 - 8.2]
	50-74	43	1,098	1,153	14.0 [3.6 - 24.3]	32.0 [29.2 - 34.7]	51.4 [48.5 - 54.3]	2.3 [0.0 - 6.8]	1.5 [0.8 - 2.3]	12.1 [10.3 - 14.0]
	25-74	**137**	**5,217**	**8,209**	**19.7 [13.0 - 26.4]**	**52.4 [51.1 - 53.8]**	**65.8 [64.7 - 66.8]**	**0.7 [0.0 - 2.2]**	**2.7 [2.2 - 3.1]**	**8.2 [7.6 - 8.8]**

Comparison of findings from NCSR analysis and literature review: short-term risk in those with prevalent vs incident infections

Results from our analysis of NCSR data reflecting the NCSP in Australia were compared with published data from a large US cohort reported in Demarco 2020[1] and Egemen 2020[2] (Table 4). Both of these US analyses included individuals aged 25-65 years who underwent routine 3-yearly co-testing between 2003 and 2017 at Kaiser Permanente Northern California (KPNC) who were members of the KPNC/National Cancer Institute guidelines cohort with an HPV and a cytology test result at initial screen. There are some known differences between the KPNC cohort and NCSR data:

- The KPNC cohort includes those aged 25-65 (compared to those aged 25-74 years being included in NCSR data).
- In the KPNC cohort, those with HPV detected and negative (NILM) cytology were only referred for colposcopy if they were persistently HPV positive on two tests (and from 2006 on), whereas in Australia those with HPV16/18 with negative cytology are referred for colposcopy immediately. Therefore, the group seen at colposcopy with negative cytology in the KPNC cohort are plausibly higher risk (this may be the reason for the blue NILM cell, where risk in the NCSR cohort with NILM cytology could be lower).
- The KPNC cohort is in general potentially lower risk, however, as they undergo 3-yearly co-testing (may explain blue ASC-US/LSIL cell for those with incident HPV16 detection).

Table 4: Comparison of risk estimates from the NCSR with those from a large US cohort (KPNC)

a) CIN3+ detection

	HPV16/18			HPV16			HPV18		
	NILM	ASC-US/ pLSIL	LSIL	NILM	ASC-US/ pLSIL	LSIL	NILM	ASC-US/ pLSIL	LSIL
Prevalent									
NCSR analysis	4.8% (4.6 – 5.0)	10.4% (10.0 – 10.9)		5.1% (4.9 – 5.4)	12.1% (11.5 – 12.7)		4.2% (3.8 – 4.6)	6.1% (5.4 – 6.8)	
Demarco 2020[1] (KPNC) *^				5.30% (4.09 – 6.52)	8.99% (7.20 – 10.77)	11.27% (8.51 – 14.02)	3.00% (1.57 – 4.43)^^	3.54% (1.53 – 5.56)^^	3.05% (0.62 – 5.49)^^
Egemen 2020[2] (KPNC)*^	2.13% (1.95 - 2.31)	4.45% (4.18 – 4.71)	4.27% (3.97 – 4.56)						
Incident									
NCSR analysis	0.9% (0.4 – 1.4)	4.4% (2.8 – 5.1)		0.8% (0.3 – 1.5)	4.9% (3.0 – 7.5)		1.2% (0.5 – 2.7)	3.4% (1.3 – 7.3)	
Demarco 2020[1] (KPNC) *^				2.96% (0.88 – 5.03)^^	5.34% (2.66 – 8.03)	6.70% (3.28 – 10.13)	2.49% (0.39 – 4.59)^^	2.45% (-0.35 – 5.24)^^	3.48% (-1.40 – 8.36)^^
Egemen 2020[2] (KPNC)*^	0.74% (0.51 – 0.96)	2.03% (1.67 – 2.38)	2.10% (1.69 – 2.51)						

b) Cancer detection

	HPV16/18			HPV16			HPV18		
	NILM	ASC-US/ pLSIL	LSIL	NILM	ASC-US/ pLSIL	LSIL	NILM	ASC-US/ pLSIL	LSIL
Prevalent									
NCSR analysis	0.37%	0.29%		0.31%	0.27%		0.5%	0.36%	
Demarco 2020[1] (KPNC) *^				0.67% (0.27 – 1.07)	0.38% (0.02 – 0.74)	0.31% (-0.12 – 0.75)	0.20% (-0.16 – 0.55)	0.28% (-0.27 – 0.83)-	0.46% (-0.44 – 1.36)
Egemen 2020[2] (KPNC)*^	0.15% (0.10 – 0.19)	0.16% (0.11 – 0.21)	0.08% (0.04 – 0.12)						
Incident									
NCSR analysis	0.07%	-		-	-		0.21%	-	
Demarco 2020[1] (KPNC) *^				-	0.33% (-0.32 – 0.98)	0.89% (-0.35 – 2.14)	-	1.63% (-0.63 – 3.89)	-
Egemen 2020[2] (KPNC)*^	-	0.05% (0 – 0.11)	0.06% (0 – 0.13)						

Values in ( ) are 95%CI. Values in red are for any HC2 positive, not only 16/18+ (*a priori*, the detection rates in red would therefore be expected to be lower than those for 16/18+). Cells shaded in blue: NCSR outside range of study in literature review

^^ authors did not provide a recommendation confidence score as patients with HPV 16 or 18 NILM or ASC-US, previously established special situations based on their known high risk of cancer (not observable through immediate CIN3+ risk estimates)

*^ confidence intervals obtained from https://lhncbc.nlm.nih.gov/LHC-research/LHC-projects/image-processing/cervixca.html accessed 190623

Discussion

NCSR data are consistent with other published data suggesting that the risk of serious disease is lower in those with newly detected HPV16/18, compared to those where these types are detected but the duration of the infection is unknown. In particular, cancer risk appears to be very low in those with newly detected HPV16/18 and no serious cytological abnormality (pHSIL or worse, or any glandular result).

These results aim to provide information to colposcopists and inform discussions with patients.

The risk of underlying serious disease is higher when LBC results are unknown, as in this situation the group includes some with pHSIL+/ glandular abnormalities on LBC; however this category was used to inform the situation where no LBC result is available at the time of colposcopy. This situation occurs when cervical screening is done on a self-collected sample, and is occurring more frequently (in September 2023, 26.4% of primary HPV tests were carried out on a self-collected sample, compared to 3.0% in June 2022).

Strengths and limitations

A strength of this analysis was that it is based on routinely-collected national data, and test information is close to complete (where tests occurred). In some cases where we could identify that histology had been collected but the result was not available, we excluded the individual from the analysis (rather than assume they did not have CIN2+).

Some methodological limitations should be considered while interpreting the results of this analysis. Firstly, disease ascertainment was incomplete, as not everyone in the cohort had a biopsy (although they all had at least one colposcopy). Our calculations assume that if no biopsy was collected, the outcome was <CIN2, but this would not always be the case. Therefore, all of our risk estimates are potentially underestimates. Guidelines recommend that those with negative, pLSIL or LSIL cytology and where no lesion is identified at colposcopy (Type 1, 2 or 3 TZ) can be managed with repeat HPV testing in 12 months. Our findings here reflect the worst outcome within 12 months (as in practice, there was only limited follow-up time available for those with incident detection) and so would not take into account disease detected at the follow-up test. Another limitation is the relatively small number of incident infections that could be included in the analysis, even from a national dataset, since at the time of the guidelines review, relatively few people had returned for their second HPV test, as it was only a few months since the earliest people to receive HPV screening were eligible to return, and in very few cases would 5 full years have elapsed between the two HPV tests. As well as being relatively small, the group with incident infections comprises people returning a shortly before or after the 5-year anniversary of their first HPV test. Individuals who are attending early or very soon after their test due date are potentially a lower risk group.

Supplementary data

Supplementary tables are provided in Excel, due to their size.

Supplementary Table 1: Cohort description

References

[1] Demarco M, Egemen D, Raine-Bennett TR, Cheung LC, Befano B, Poitras NE et al. A study of partial human papillomavirus genotyping in support of the 2019 ASCCP risk-based management consensus guidelines. J Low Genital Tract Dis 2020; 24:144-147.

[2] Egemen D, Cheung LC, Chen X, Demarco M, Perkins RB, Kinney W, Poitras N, Befano B, Locke A, Guido RS, Wiser AL, Gage JC, Katki HA, Wentzensen N, Castle PE, Schiffman M, Lorey TS. Risk Estimates Supporting the 2019 ASCCP Risk-Based Management Consensus Guidelines. J Low Genit Tract Dis. 2020;24(2):132-143.

[3] Gilham C, Sargent A, Peto J. Triaging women with human papillomavirus infection and normal cytology or low-grade dyskaryosis: evidence form 10-year follow up of the ARTISTIC trial cohort. BJOG 2020; 127:58-68.

[4] Veldhuijzen NJ, Polman NJ, Snijders PJF, Meijer CJLM, Berkhof J. Stratifying HPV-positive women for CIN3+ risk after one and two rounds of HPV-based screening. Int J Cancer. 2017;141(8):1551-1560.