Site and sex-specific differences in the effect of vitamin D on human papillomavirus infections: analyses of NHANES 2009–2014

Persistent human papillomavirus (HPV) infection with oncogenic HPV types (or the high-risk HPV types) is responsible for about 90% of anal and cervical cancers; 70% of oropharyngeal, vaginal and vulvar cancers; and more than 60% of penile cancers.¹ Vitamin D seems to support the immune system by possible strengthening of innate and adaptive immune responses,^{2–4} and has been found to be protective against acute respiratory infections^{2 3 5} and cervicovaginal HPV infection among females.⁴ Here, we report the associations between vitamin D levels and HPV infection prevalence at oral, genital and anal sites of the high-risk and low-risk HPV types among men and women nationally in the USA. We used the National Health and Nutrition Examination Survey data, conducted by the National Center for Health Statistics from 2009 to 2014. These cross-sectional surveys involve a household interview, followed by physical examination and laboratory testing in a mobile examination centre (MEC), and are nationally representative of the civilian, non-institutionalised US population. After excluding individuals who had received one or more dose of HPV vaccine, who had never had anal, vaginal or oral sex and who had missing/invalid results for vitamin D or HPV, 4620 males and 4343 females aged 18–59 years representing 68 920 825 and 63 480 356 individuals nationally were included in the analyses. HPV infection

was categorised into low-risk (6, 11, 40, 42, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 81, 82, 82 subtype IS39, 83, 84, 89(cp108)) and high-risk (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82) HPV types. Serum 25-hydroxyvitamin D (25(OH)D) (sum of 25(OH)D2 and 25(OH)D3) indicated the vitamin D level which was categorised into <20 ng/mL (deficient) and ≥20 ng/mL (sufficient).⁴ MEC sample weights were used to provide national-level estimates. Relative risk (RR) of HPV infection in different groups was assessed using bivariate logistic regression models. We found that, among males, neither oral nor penile low-risk or high-risk HPV infections were significantly associated with vitamin D level. Among females, at cervical site, vitamin D deficiency was associated with a higher likelihood of both low-risk (1.41; 95% CI 1.23 to 1.61; $p < 0.001$) and high-risk (1.25; 95% CI 1.04 to 1.49; $p = 0.014$) HPV infection. However, only oral low-risk HPV infection (3.22; 95% CI 1.73 to 6.01; $p < 0.001$) was more likely among vitamin D-deficient women (table 1). Sex and site differences in HPV infection are important because of the growing incidence of oropharyngeal squamous cell carcinomas (OPSCCs) which mainly affects males. Vitamin D has been shown to be an immunoregulator.⁶ Our findings indicate that vitamin D deficiency, which is speculated to be associated with immune dysregulation, might have less impact on high-risk oral HPV infection among males, and might imply different clearance and persistence propensity of HPV. This would suggest that males might be less likely to be affected by the immunomodulatory effects of vitamin D. The key clinical and research implication of this finding is that the control of OPSCC among men through prevention

of HPV infection such as via HPV vaccine might need separate evaluations, instead of generalising the findings from HPV infections at other sites or among females.

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Table 1 HPV infection in vitamin D-deficient and vitamin D-sufficient males and females

	Prevalence of HPV infection in vitamin D deficient and vitamin D sufficient			Risk ratio of HPV infection in vitamin D deficient vs vitamin D sufficient	
	Vitamin D deficient Proportion (N)	Vitamin D sufficient Proportion (N)	P value	RR (95% CI)	P value
Males					
Oral low-risk	5.5% (92)	5.5% (168)	0.985	1.00 (0.72 to 1.40)	0.985
Penile low-risk	16.1% (249)	14.0% (420)	0.406	1.18 (0.79 to 1.74)	0.406
Oral high-risk	7.2% (103)	7.4% (189)	0.886	0.97 (0.73 to 1.30)	0.886
Penile high-risk	9.9% (158)	9.3% (276)	0.718	1.07 (0.72 to 1.60)	0.718
Females					
Oral low-risk	3.4% (36)	1.0% (39)	<0.001	3.22 (1.73 to 6.01)	<0.001
Cervical low-risk	43.3% (703)	35.0%	<0.001	1.41 (1.23 to 1.61)	<0.001
Oral high-risk	1.9% (21)	1.5% (44)	0.423	1.29 (0.68 to 2.44)	0.425
Cervical high-risk	26.1% (430)	22.0% (692)	0.014	1.25 (1.04 to 1.49)	0.014

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REFERENCES

- 1 Division of Cancer Prevention and Control, HPV-Associated Cancer Statistics. Centers for Disease Control and Prevention. 2018.
- 2 Juzeniene A, Ma L-W, Kwitniewski M, *et al.* The seasonality of pandemic and non-pandemic influenzas: the roles of solar radiation and vitamin D. *Int J Infect Dis* 2010;14:e1099–105.
- 3 Sacco RE, Nonnecke BJ, Palmer MV, *et al.* Differential expression of cytokines in response to respiratory syncytial virus infection of calves with high or low circulating 25-hydroxyvitamin D3. *PLoS One* 2012;7:e33074.
- 4 Shim J, Pérez A, Symanski E, *et al.* Association between serum 25-hydroxyvitamin D level and human papillomavirus cervicovaginal infection in women in the United States. *J Infect Dis* 2016;213:1886–92.
- 5 Sabetta JR, DePetrillo P, Cipriani RJ, *et al.* Serum 25-hydroxyvitamin D and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS One* 2010;5:e11088.
- 6 Di Rosa M, Malaguarnera M, Nicoletti F, *et al.* Vitamin D3: a helpful immuno-modulator. *Immunology* 2011;134:123–39.