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Cohort profile: indigenous human papillomavirus and oropharyngeal squamous cell carcinoma study - a prospective longitudinal cohort

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ABSTRACT

Purpose Our aims are to: (1) estimate prevalence, incidence, clearance and persistence of oral human papillomavirus (HPV) infection among Indigenous Australians; (2) identify risk factors associated with oropharyngeal squamous cell carcinoma (OPSCC)-related HPV types (HPV 16 or 18); (3) develop HPV-related health state valuations and; (4) determine the impact on OPSCC and cervical cancers, and the cost-effectiveness of extending publicly-funded HPV vaccination among Indigenous Australians.

Participants Participants were recruited from February 2018 to January 2019. Twelve-month follow-up occurred from March 2019 to March 2020. Participants provided socio-demographic characteristics, health-related behaviours including tobacco and alcohol use and sexual history. Health state preferences in regard to HPV vaccination, knowledge regarding HPV infection, OPSCC and cervical cancer were collected using a two-stage standard gamble approach. Participants provided saliva samples and DNA for microbial genotyping was extracted.

Findings to date Of the 910 participants who were positive for β-globin at baseline, 35% had any oral HPV infection. The most prevalent HPV types were 13 or 32 (Heck's disease; 23%). The second most prevalent types were associated with OPSCC (HPV 16 or 18; 3.3%). Of the 645 participants who were positive for β-globin at 12-month follow-up, 43% had any HPV infection. Of these, 33% were HPV types 13 or 32 and 2.5% were HPV 16 or 18. Some 588 participants had β-globin positive oral samples at baseline and 12-month follow-up. The prevalence of any oral HPV infection increased from 34% at baseline to 44% at 12-month follow-up; due to increases in HPV types 13 or 32 (20% at baseline and 34% at 12-month follow-up).

Future plans Further funding will be sought to continue follow-up of this cohort, and to include (after a full medical history) a thorough clinical examination of the external head and neck; a complete oral examination and examination of the oropharynx. Blood tests for early stage OPSCC will also be undertaken.

Strengths and limitations of this study

- ► One of the largest, most contemporary cohorts in Australia (indeed, of an Indigenous population in the world) that has examined prevalence of oral human papillomavirus (HPV) infection and associated risk factors, and that will have follow-ups at key time points.
- ► Established Indigenous Reference Group who provide governance and oversight of all study processes, strong rapport with South Australian Indigenous community and excellent participant buy-in and retention.
- ► There are very few insights into Indigenous oral HPV prevalence and its association with oropharyngeal squamous cell carcinoma (OPSCC). Our large and reasonably representative study population will, in time, be able to answer questions that Indigenous communities want answered with respect to rates of, and risk factors for, HPV-associated OPSCC.
- ► A 24-month follow-up has been hampered due to social distancing restrictions necessitated by the COVID-19 pandemic. Many Indigenous communities remain closed.

INTRODUCTION

Human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) is a cancer with one of the most rapidly increasing incidences in high-income countries.[1] The increased incidence, which is especially notable among men and younger cohorts, may be attributable to increased carriage of high-risk genotypes of HPV (especially HPV 16 or 18) via increased oral exposure to infected anogenital sites with changing sexual behaviours (as opposed to smoking and alcohol consumption; the more traditional risk factors).[2 3] Although estimates vary by setting, the proportion of OPSCC attributable to HPV has been cited in high-income

countries as between 65% and 83%.[4–6] It is important to note that, while the incidence of HPV-associated OPSCCs are increasing, the incidence of non-HPV associated OPSCCs are decreasing.[3]

Cancer is a leading cause of death in Australia, with almost 50 000 cancer deaths reported annually.[7] While advancements have been made to improve the survival of Australians living with cancer, these improvements have not been equally distributed. Aboriginal and Torres Strait Islanders (hereafter respectfully termed 'Indigenous') are the first peoples of Australia and represent 3.3 per cent of the total Australian population.[8] Indigenous Australians have a slightly higher rate of cancer diagnosis but are approximately 50% more likely to die from cancer than non-Indigenous Australians.[9] Evidence suggest that Indigenous Australians with cancer are up to 10 years younger at diagnosis, more likely to present in recent diagnostic years, to be resident of geographically remote locations, and to have primary cancer sites of head and neck, lung, liver and cervix.[10] Risk of cancer death among Indigenous Australians has been associated with advanced stage at first observation, with more Indigenous than non-Indigenous cases having distant metastases at diagnosis.[9] There are higher rates of OPSCC among Indigenous relative to non-Indigenous Australians,[11] although the HPV attributable fraction remains unknown.

Australia introduced a national, publicly-funded HPV vaccination programme in 2007, the first country to do so.[12] It has since achieved high vaccination coverage across both sexes and resulted in reduced prevalence of HPV infections.[13 14] In a study investigating HPV vaccination coverage and course completion rates among Indigenous adolescents, Brotherton and colleagues reported that, although overall HPV vaccine coverage was high, completion of the three courses required was generally low.[15] However, other studies have demonstrated that vaccine impact has been similar in Indigenous and non-Indigenous Australians,[16–18] consistent with data suggesting strong protection from one vaccine dose. Cervical screening participation is, however, lower among Indigenous Australian women.[19]

As with cervical cancer, it is likely that subclinical oral HPV infections that persist for decades precede development of HPV-associated OPSCC.[20] However, information on population estimates of oral HPV infection (ie, HPV detected in saliva) are scarce. In a systematic review involving nine studies that collected oral HPV data from 3762 cancer-free, HIV-negative individuals from around the world, Wood and colleagues reported that 7.5% had an oral infection with any HPV type at baseline.[21] In a study involving 307 Australian university students (age range 18–35 years), 7 (2.3%) tested positive for oral HPV infection; 3 for HPV 18, 1 each of HPV 16, HPV 67, HPV 69 and HPV 90.[22] Four had high-risk HPV (HPV 16 and HPV 18). Those positive for an oral HPV infection were more likely to have received oral sex from more partners in their lifetime.

The critical issue with high risk oral HPV infections in regards to OPSCC (or any HPV-related head and neck cancer) is persistent oral HPV carriage.[23] In a large

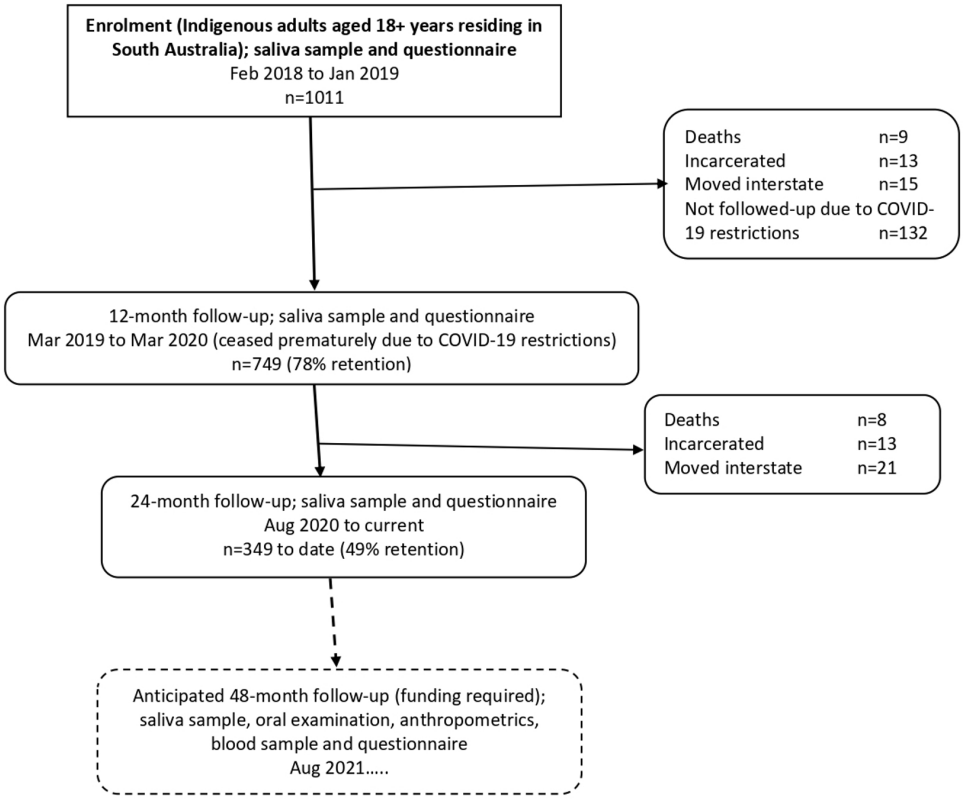

Figure 1 Flow diagram of participants through key stages of the cohort study.

Table 1 Broad categories of variables collected at baseline, 12-month and 24-month follow-up

Phase	Measurements
Baseline	► Saliva sample to test for oral HPV infection. ► Self-report information on socio-demographic characteristics, health-related behaviours including tobacco and alcohol use, sexual history, general and oral health-related quality of life, experiences of racism and cultural identity. ► Health state preferences and utilities on oral HPV infection, HPV vaccination and oropharyngeal squamous cell carcinoma.
12-month follow-up	► Saliva sample to test for oral HPV infection. ► Self-report information on health-related behaviours including tobacco and alcohol use, physical activity, pain, recent life events and self-rated oral and general health. ► Health state preferences and utilities on HPV infection, HPV vaccination and cervical cancer (women only).
24-month follow-up	► Saliva sample to test for oral HPV infection. ► Self-report information on sleeping behaviours, recent life events, experiences of racism, self-perceived oral and general health and social support.

HPV, human papillomavirus.

cohort study examining incidence and clearance of oral HPV carriage among men who were HIV-negative and with no anogenital cancer, Kreimer and colleagues reported that, during the first 12 months of follow-up, 4.4% acquired an incident oral HPV infection, with 1.7% of these 4.4% being oncogenic HPV types and 0.6% of the 4.4% being HPV 16.[20] Acquisition of an oral oncogenic HPV infection was significantly associated with tobacco smoking and not being in a long-term monogamous relationship, and was similar across included countries, age groups and reported sexual behaviours. The median duration of carriage was 6.9 months for any oral HPV, 6.3 months for oncogenic HPV types and 7.3 months for HPV 16 specifically. Eight of the 18 incident oral HPV 16 infections persisted for 6 or more months. The authors concluded that newly acquired oral carriage of oncogenic HPV in healthy men was rare and that most cleared within 1 year.

Given the high risk of Indigenous Australians having OPSCC, the aims of this study were to, in partnership with South Australian Indigenous communities and key Indigenous stakeholders, estimate the prevalence, incidence, clearance and persistence of oral HPV infection among Indigenous Australians. Other objectives of the overall study (not reported here) include: (1) identifying risk factors associated with OPSCC-related HPV types (HPV 16 or HPV 18); (2) developing and testing HPV-related health state valuations for use among Indigenous Australians and; (3) using this information, combined with already available data on cervical HPV infection in this population, determine the impact on both oropharyngeal and cervical cancers and the cost-effectiveness of extending publicly-funded HPV vaccination among Indigenous Australians. To the best of our knowledge, there has been no other reported findings of oral HPV infections among other Indigenous groups globally, meaning our study is the first to report on these important findings.

COHORT DESCRIPTION

Who is in the cohort?

This prospective longitudinal cohort study was developed in partnership with local Indigenous communities in South Australia. The study is governed by an Indigenous Reference Group, with data collected by trained Indigenous research officers.[24] To be eligible, participants needed to identify as being Aboriginal and/or Torres Strait Islander, be aged 18+ years and be a South Australian resident. Participants were primarily recruited through Aboriginal Community Controlled Health Organisations (ACCHOs), who were key stakeholders in the study. The study had strong buy-in from the Indigenous community, with several potential participants contacting the principal investigator (LMJ) by phone asking what they needed to do to be involved. All participants provided signed informed consent.

How often have they been followed up?

Participants were recruited from February 2018 to January 2019 across eight sites in South Australia. Extensive Indigenous community consultation had occurred in the 2 years prior to recruitment, which enabled partnering ACCHOs to be involved as equal partners in the co-design process. Participants were recruited through these partnering ACCHOs and through other word-of-mouth avenues (contacts of the Indigenous Reference Group, for example). The Indigenous Reference Group was established to provide oversight and cultural guidance on recruitment strategies and data collection. This included Indigenous community members, councillors and health workers, and was chaired by an Indigenous health manager.

The 1011 participants recruited represented 5% of Indigenous South Australian adults who were eligible to be recruited during the recruitment period; 8.2% of those who were eligible to be recruited in non-metropolitan

Table 2 Baseline and 12-month follow-up/loss to follow-up characteristics (%, 95% CI)

	Indigenous oral HPV-OPSCC study		
	Baseline (n=1011)	12-month follow-up (n=749)	12-month loss to follow-up (n=264)
Socio-demographic			
Sex			
Male	33.6 (30.7 to 36.5)	31.3 (28 to 34.7)	40.2 (34.2 to 46.1)
Female	66.4 (63.5 to 69.3)	68.7 (65.3 to 72)	59.8 (53.9 to 65.8)
Age group (years)			
≥37	52.2 (49.1 to 55.3)	55.6 (52 to 59.1)	**42.8 (36.8 to 48.8)**
<37	47.8 (44.7 to 50.9)	44.4 (40.9 to 48)	**57.2 (51.2 to 63.2)**
Geographical location			
Non-metropolitan	62.7 (59.7 to 65.7)	60.9 (57.3 to 64.4)	68.1 (62.4 to 73.7)
Metropolitan	37.3 (34.3 to 40.3)	39.6 (35.6 to 42.7)	31.9 (26.3 to 37.6)
Level of education*			
High school or less	68.2 (65.3 to 71.1)	65.9 (62.5 to 69.3)	74.6 (69.3 to 79.9)
Trade/TAFE/university	31.8 (28.9 to 34.7)	34.1 (30.7 to 37.5)	25.4 (20.1 to 30.7)
Income§			
Centrelink or other	76 (73.3 to 78.7)	73.9 (70.7 to 77.1)	**82 (77.3 to 86.7)**
Job	24 (21.3 to 26.7)	26.1 (22.9 to 29.3)	**18 (13.3 to 22.7)**
Healthcare card ownership			
Yes	79 (76.4 to 81.5)	77.3 (74.2 to 80.4)	83.6 (79 to 88.2)
No	21 (18.5 to 23.6)	22.7 (19.6 to 25.8)	16.4 (11.8 to 21)
Number of people in house previous night			
>4	36.4 (33.3 to 39.5)	36.2 (32.6 to 39.8)	37 (30.8 to 43.2)
≤4	63.6 (60.5 to 66.7)	63.8 (60.2 to 67.4)	63 (56.8 to 69.2)
Own car			
No	44.6 (41.5 to 47.6)	40.8 (37.3 to 44.4)	**55.2 (49.1 to 61.3)**
Yes	55.4 (52.4 to 58.5)	59.2 (55.6 to 62.7)	**44.8 (38.7 to 50.9)**
Tobacco smoking status			
Current smoker	59.4 (56.3 to 62.5)	58.7 (55.1 to 62.4)	61.4 (55.3 to 67.4)
Ex-smoker	11.8 (9.8 to 13.9)	13.6 (11.1 to 16.2)	6.8 (3.6 to 9.9)
Never smoked	28.8 (25.9 to 31.6)	27.7 (24.3 to 31)	31.9 (26.1 to 37.7)
How often consume alcohol			
Daily	3.7 (2.6 to 5)	3.7 (2.3 to 5.1)	3.9 (1.5 to 6.2)
Weekly	23.6 (20.9 to 26.2)	24.1 (21 to 27.3)	22 (16.9 to 27.1)
Monthly	36.6 (33.6 to 39.6)	35.7 (32.2 to 39.2)	39 (33 to 45)
Never	36.1 (33.1 to 39.1)	36.4 (32.9 to 39.9)	35.1 (29.3 to 41)
Use of non-prescription tobacco substitutes (vape, e-cigarette)			
Currently smoke	12.1 (10 to 14.2)	12.6 (10.2 to 15.1)	10.6 (6.8 to 14.4)
Don't now but used to	19 (16.5 to 21.5)	18.5 (15.6 to 21.3)	20.5 (15.5 to 25.5)
Never smoked	68.9 (66 to 71.8)	68.9 (65.5 to 72.3)	68.9 (63.2 to 74.6)
Use of recreational drugs			
Currently use	20.9 (18.3 to 23.4)	19.8 (16.9 to 22.7)	23.8 (18.6 to 29)
Don't now but used to	33 4 (30.5 to 36.3)	33.8 (30.4 to 37.3)	32.2 (26.5 to 37.9)
Never used	45.7 (42.6 to 48.8)	46.3 (42.7 to 49.9)	44.1 (38 to 50.1)
Ever been found to be with HPV (self-reported)			

Continued

Table 2 Continued

	Indigenous oral HPV-OPSCC study		
	Baseline (n=1011)	**12-month follow-up (n=749)**	**12-month loss to follow-up (n=264)**
Yes	2 (1.1 to 2.9)	2.4 (1.3 to 3.6)	0.8 (0 to 1.8)
No	81.2 (78.8 to 83.6)	81.3 (78.5 to 84.1)	81 (76.2 to 85.8)
Don't know	16.8 (14.5 to 19.1)	16.3 (13.6 to 18.9)	18.3 (13.6 to 22.9)
Ever received HPV vaccination (self-reported)			
Yes	8.3 (6.6 to 10)	7.6 (5.7 to 9.5)	10.3 (6.6 to 14)
No	57.7 (54.6 to 60.7)	58.5 (54.9 to 62)	55.5 (49.5 to 61.6)
Don't know	34 (31.1 to 37)	33.5 (30.5 to 37.4)	34.2 (28.4 to 40)
Ever had tonsils taken out			
Yes	12.6 (10.5 to 14.7)	13.9 (11.4 to 16.5)	8.9 (5.4 to 12.5)
No	82.1 (79.7 to 84.5)	80.3 (77.4 to 83.2)	87.2 (83 to 91.3)
Don't know	5.3 (3.9 to 6.7)	5.8 (4.1 to 7.5)	3.9 (1.5 to 6.3)
In life, how many passionately kissed			
≥4	64.8 (61.7 to 67.9)	66.5 (62.9 to 70.1)	60.2 (53.9 to 66.4)
<4	35.2 (32.1 to 38.3)	33.5 (29.9 to 37.1)	39.8 (33.6 to 46.1)
Ever given oral sex			
Yes	64.5 (61.4 to 67.7)	66.8 (63.2 to 70.4)	58.2 (51.9 to 64.5)
No	35.4 (32.3 to 38.6)	33.2 (29.6 to 36.8)	41.8 (35.5 to 48.1)
If yes, how old when first gave oral sex			
<16 years	24.3 (20.8 to 27.8)	21.8 (17.9 to 25.7)	32.1 (24.2 to 40)
16+years	75.7 (72.2 to 79.2)	78.2 (74.3 to 82.1)	67.9 (60 to 75.8)
Number of people given oral sex to in lifetime			
>3	43.6 (39.6 to 47.7)	43.6 (38.9 to 48.2)	43.8 (35.4 to 52.2)
≤3	56.4 (52.3 to 60.4)	56.4 (51.8 to 61.1)	56.2 (47.8 to 64.6)
Ever received oral sex			
Yes	64.8 (61.7 to 67.9)	67.6 (64 to 71.2)	**57 (50.6 to 63.3)**
No	35.2 (32.1 to 38.3)	32.4 (28.8 to 36)	**43 (36.7 to 49.4)**
If yes, how old when first received oral sex			
<16 years	27.3 (23.7 to 31)	27.7 (23.5 to 31.9)	26.2 (18.5 to 33.8)
16+ years	72.7 (69 to 76.3)	72.3 (68.1 to 76.5)	73.8 (66.2 to 81.5)
Received oral sex by how many people in lifetime			
>3	49 (44.9 to 53.1)	48.5 (43.8 to 53.2)	50.8 (42.1 to 59.4)
≤3	51 (46.9 to 55.1)	51.5 (46.8 to 56.2)	49.2 (40.6 to 57.9)
Sexual intercourse with another person			
Yes	94.8 (93.3 to 96.2)	95.2 (93.5 to 96.8)	93.6 (90.5 to 96.8)
No	5.2 (3.8 to 6.7)	4.8 (3.2 to 6.5)	6.4 (3.2 to 9.5)
If yes, how old when first had sex			
<16 years	41 (37.7 to 44.4)	42.3 (38.3 to 46.1)	37.6 (31.1 to 44.1)
16+ years	59 (55.6 to 62.3)	57.8 (53.9 to 61.7)	62.4 (55.9 to 68.9)
Altogether, how many people had sex with			
≥4	63.3 (60 to 66.6)	66.1 (62.4 to 69.9)	55.3 (48.6 to 62)
<4	36.7 (33.4 to 40)	33.9 (30.1 to 37.6)	**44.7 (38 to 51.4)**
In lifetime, sexual encounters have been mostly			
Heterosexual	93.2 (91.5 to 94.8)	93.5 (91.6 to 95.4)	92.2 (88.8 to 95.7)

Continued

Table 2 Continued

	Indigenous oral HPV-OPSCC study		
	Baseline (n=1011)	12-month follow-up (n=749)	12-month loss to follow-up (n=264)
Homosexual	0.8 (0.2 to 1.4)	0.8 (0.1 to 1.4)	0.9 (0 to 2.1)
Bisexual	6 (4.5 to 7.6)	5.7 (4 to 7.5)	6.9 (3.6 to 10.2)
Current relationship status			
Stable long-term	50.6 (47.3 to 53.8)	52.1 (48.3 to 55.9)	46.2 (39.7 to 52.6)
Short-term	5.4 (3.9 to 6.9)	4.5 (2.9 to 6)	8.1 (4.6 to 11.6)
Single	44 (40.8 to 47.3)	43.5 (39.7 to 47.2)	45.7 (39.3 to 52.2)

*TAFE stands for 'Technical and Further Education' and provides training for vocational occupations.
†Difference statistically significant as denoted by non-overlapping 95% CIs.
‡Ownership of a government-administered healthcare card is means-tested, and enables access to services such as publicly-funded dental care.
§Centrelink is the government agency responsible for welfare payments to those means-tested to be eligible.
HPV, human papillomavirus; OPSCC, oropharyngeal squamous cell carcinoma.

locations and 3% of those in metropolitan locations. Participants were followed-up at 12 months (March 2019 to March 2020), with data for 749 participants obtained (78%; suspended early due to COVID-19 restrictions). Follow-up at 24 months is currently occurring (data for 349 participants obtained thus far). Some Indigenous communities remain closed. A flow diagram of participants through the baseline, 12-month and 24-month stages of the study is provided in figure 1.

What has been measured?

Details of broad categories of variables collected at baseline, 12-month and 24-month follow-up are provided in table 1. Self-report questionnaires at baseline included information on socio-demographic characteristics, health-related behaviours including tobacco and alcohol use, sexual history, general and oral health-related quality of life, experiences of racism and cultural identity. Health state preferences and utilities on oral HPV infection, HPV vaccination and OPSCC were also collected. Utilities are fundamental values that represent the strength of an individual's preferences for specific health-related outcomes. Measuring health utilities involves defining a set of health states of interest and valuing those health states. It is important to estimate utilities in relation to HPV infection, cervical cancer and oropharyngeal cancer among Indigenous Australians because the frame of reference regarding the burden of cancer and cancer treatment is likely to differ in meaningful ways in relation to the non-Indigenous population. Examples may be due to the substantial travel required for many Indigenous Australians, and subsequently time away from family, community and Country (in the Indigenous Australian context, connection with 'Country' is of great significance. It goes far beyond physical elements and is fundamental to identity). Racism experienced in many hospital or other healthcare based encounters are likely to contribute to the cancer burden faced by Indigenous Australians because it may prevent many from attending for screening and cancer-related care. There may be inherent distrust and fear of hospital systems not apparent in non-Indigenous populations, and the specific treatment-associated morbidity may be valued differently. It is important to capture this information so that it can be used to directly calculate quality-adjusted life years and to, in turn, be translated into hospital policy regarding Indigenous patient journeys with treatment of HPV infection (eg, removal of tissue with HPV infection surgically or via laser), cervical and oropharyngeal cancer. Although health state valuations appropriate for modelled economic evaluations have been undertaken for cervical HPV infections, including cancer and precancerous lesions[25 26] and for genital warts,[27] there is a paucity of information on health state valuations for other HPV cancer states including OPSCC. There is a particular dearth of information on HPV-related health state valuations as they apply to Indigenous Australians.

At 12-month follow-up, self-reported information included health-related behaviours including tobacco and alcohol use, physical activity, pain, recent life events and self-rated oral and general health. Health state preferences and utilities on HPV carriage, HPV vaccination and cervical cancer were collected among women only. At 24-month follow-up, self-reported data currently being collected includes information on sleeping behaviours (after feedback from participants, with many reporting their views that lack of good quality sleep was impacting on much of their health, social and emotional well-being), recent life events, experiences of racism, self-perceived oral and general health and social support.

Across baseline, 12-month and 24-month follow-ups, samples of whole mouth fluid to test for HPV carriage were/are being collected. Samples were collected through spitting and dribbling (no chewing of paraffin wax or rubber bands prior). This was collected in a

Table 3 Oral HPV+ types among South Australian Indigenous adults at baseline and 12-month follow-up (n=588)

	Total baseline N (%)	Total 12-month follow-up N (%)	Male baseline N (%)	Male 12-month follow-up N (%)	Female baseline N (%)	Female 12-month follow-up N (%)
Total (β-globin positive)	588 (100)	588 (100)	181 (100)	181 (100)	407 (100)	407 (100)
Positive 1+ oral HPV type	201 (34.2)	260 (44.2)	53 (29.3)	85 (47)	148 (36.4)	175 (43)
Positive oral HPV 13 or 32	119 (20.2)	198 (33.7)	26 (14.4)	64 (35.4)	93 (22.9)	134 (32.9)
Positive oral HPV 16 or 18	23 (3.9)	16 (2.7)	6 (3.3)	7 (3.9)	17 (4.2)	9 (2.2)
Positive IARC high-risk HPV*	50 (8.5)	42 (7.1)	19 (10.5)	15 (8.3)	31 (7.6)	27 (6.6)
HPV (+ve) types						
3	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
6	3 (1)	2 (0.8)	1 (1.9)	2 (2.4)	1 (0.7)	0 (0)
7	1 (0.5)	0 (0)	1 (1.9)	0 (0)	0 (0)	0 (0)
10	1 (0.5)	2 (0.8)	0 (0)	0 (0)	1 (0.7)	2 (1.1)
11	0 (0)	1 (0.4)	0 (0)	1 (1.2)	0 (0)	0 (0)
13	52 (25.9)	59 (22.8)	12 (22.6)	19 (22.6)	40 (27)	40 (22.9)
16	11 (5.5)	14 (5.4)	3 (5.7)	6 (7.1)	8 (5.4)	8 (4.6)
18	12 (6)	2 (0.8)	3 (5.7)	1 (1.2)	9 (6.1)	1 (0.6)
23	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
30	1 (0.5)	0 (0)	1 (1.9)	0 (0)	0 (0)	0 (0)
31	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
32	67 (33.3)	139 (53.7)	14 (26.4)	45 (53.6)	53 (35.8)	94 (53.7)
33	1 (0.5)	1 (0.4)	0 (0)	0 (0)	1 (0.7)	1 (0.6)
34	1 (0.5)	1 (0.4)	1 (1.9)	1 (1.2)	0 (0)	0 (0)
35	3 (1.5)	2 (0.8)	2 (3.8)	1 (1.2)	1 (0.7)	1 (0.6)
39	1 (0.5)	1 (0.4)	1 (1.9)	0 (0)	0 (0)	1 (0.6)
40	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
42	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
44	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
45	2 (1)	4 (1.5)	2 (3.8)	2 (2.4)	0 (0)	2 (1.1)
51	1 (0.5)	2 (0.8)	0 (0)	0 (0)	1 (0.7)	2 (1.1)
52	2 (1)	0 (0)	0 (0)	0 (0)	2 (1.4)	0 (0)
53	1 (0.5)	3 (1.2)	0 (0)	1 (1.2)	1 (0.7)	2 (1.1)
54	1 (0.5)	1 (0.4)	0 (0)	0 (0)	1 (0.7)	1 (0.6)
56	4 (2)	5 (1.9)	2 (3.8)	2 (2.4)	2 (1.4)	3 (1.7)
58	3 (1.5)	0 (0)	2 (3.8)	0 (0)	1 (0.7)	0 (0)
59	4 (2)	1 (0.4)	3 (5.7)	0 (0)	1 (0.7)	1 (0.6)
62	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.6)
66	6 (3)	10 (3.9)	1 (1.9)	3 (3.6)	5 (3.4)	7 (4)
67	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
68	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
69	4 (2)	0 (0)	2 (3.8)	0 (0)	2 (1.4)	0 (0)
72	5 (2.5)	7 (2.7)	0 (0)	0 (0)	5 (3.4)	7 (4)
73	1 (0.5)	1 (0.4)	0 (0)	0 (0)	1 (0.7)	1 (0.6)

Continued

Table 3 Continued

	Total baseline N (%)	Total 12-month follow-up N (%)	Male baseline N (%)	Male 12-month follow-up N (%)	Female baseline N (%)	Female 12-month follow-up N (%)
81	2 (1)	0 (0)	0 (0)	0 (0)	2 (1.4)	0 (0)
82	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
84	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
87	1 (0.5)	0 (0)	1 (1.9)	0 (0)	0 (0)	0 (0)
90	4 (2)	0 (0)	1 (1.9)	0 (0)	3 (2)	0 (0)
106	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
158	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)

Note: 37 HPV types.
*International Agency for Research on Cancer's (IARC) definition of high-risk HPV: HPV 16, HPV 18, HPV 31 to HPV 33, HPV 35 to HPV 39, HPV 45 to HPV 51, HPV 52, HPV 56, HPV 58, HPV 59 to HPV 66.[35]
HPV, human papillomavirus.

commercially available kit (OMNIgene OM-501; DNA Genotek, Canada), transported to a Queensland laboratory and stored at room temperature where DNA for microbial genotyping was extracted. Specifically, the Promega Maxwell viral kit for DNA extraction was used. β-globin PCR with the primers PCO3 and PCO4 were carried out on all samples to ensure the presence of human DNA, and that no PCR inhibiting agents were present.[28] All samples were analysed with a nested PCR system (MY09/11)[29] and GP5+/6+[30] that detects most mucosal HPV types and all high-risk HPV types that have oncogenic potential in mucosal tissue. All HPV DNA positive samples were sequenced to confirm viral DNA sequences. For the sequencing, HPV positive PCR products were purified with the Agencourt AMPure PCR purification kit in a magnetic 96-ring SPRIPlate. Sequencing reactions were performed containing the purified PCR products together with GP + primer and BigDye Terminator. Sequence reactions were purified with the Agencourt CleanSEQ dye-terminator removal kit in a magnetic 96-ring SPRIPlate. Direct sequencing was conducted, and sequence reactions were analysed with an automated DNA sequencer (ABI model 3100). The DNA sequences were compared with available sequences in GenBank through the NCBI BLASTn suite server (https://blast.ncbi.nlm.nih.gov/Blast.cgi). Participants with β-globin positive saliva samples were included in the data analysis (β-globin is a DNA integrity check; any samples with negative β-globin were invalid).

PATIENT AND PUBLIC INVOLVEMENT

The study's Indigenous Reference Group has been involved in the design, governance and general oversight of all phases of the research to date.

Study participants have been encouraged to communicate to the research team through Facebook and other social media platforms. Newsletters and community presentations are frequently shared with participants and relevant key stakeholder groups. Members of the study's Indigenous Reference Group have presented the study findings at international conferences.

FINDINGS TO DATE

Recruitment, 12-month follow-up and 12-month loss follow-up characteristics of the cohort are shown in table 2. At baseline,[31] two-thirds of participants were women (66%) and just over half (52%) were aged 37 years or older. The overall median age was 37 years (IQR 27–51 years), median age for men was 37 years (IQR 27–49 years) and median age for women was 38 years (IQR 27–52 years). Just under two-thirds resided in non-metropolitan locations, with the highest educational attainment of 68% being high school or less. Just over three-quarters received their income from Centrelink (government agency which provides welfare based on means testing) and 79% owned a healthcare card (means-tested, allows access to some health services, eg, dental public health services that otherwise incur out-of-pocket expenses). A very small proportion (2%) reported having ever been diagnosed with an HPV infection, with 17% not knowing. Less than one-tenth of participants (8%) reported having received HPV vaccination, with just over one-third (34%) not knowing. A higher proportion of participants who were not followed-up at 12 months were aged less than 37 years (at baseline), received their income from Centrelink, did not own their own car, had never received oral sex and had had sex with less than four people over their lifetime. There were many reasons for loss to follow-up, including our study population being highly mobile, lack of operational mobile phones through which to make initial contact, domestic violence issues meaning the household was no longer receptive to visitors, drug and alcohol issues and extensive time away due to cultural ceremonies and other community obligations.

Table 4 Incidence, persistence and clearance of oral HPV infection among Indigenous South Australians from baseline to 12-month follow-up (n=588)

	Baseline any oral HPV infection	12-month any oral HPV infection	N (%)
No infection	x	x	253 (43)
Incidence	x	√	134 (22.8)
Persistence	√	√	126 (21.4)
Clearance	√	x	75 (12.8)
	Baseline HPV 13 or 32	**12-month HPV 13 or 32**	**N (%)**
No infection	x	x	349 (59.4)
Incidence	x	√	120 (20.4)
Persistence	√	√	78 (13.3)
Clearance	√	x	41 (7)
	Baseline HPV 16 or 18	**12-month HPV 16 or 18**	**N (%)**
No infection	x	x	554 (94.2)
Incidence	x	√	11 (1.9)
Persistence	√	√	5 (0.9)
Clearance	√	x	18 (3.1)
	Baseline IARC high-risk HPV*	**12-month IARC high-risk HPV**	**N (%)**
No infection	x	x	513 (87.2)
Incidence	x	√	25 (4.3)
Persistence	√	√	17 (2.9)
Clearance	√	x	33 (5.6)

*International Agency for Research on Cancer's (IARC) definition of high-risk HPV: HPV 16, HPV 18, HPV 31 to HPV 33, HPV 35 to HPV 39, HPV 45 to HPV 51, HPV 52, HPV 56, HPV 58, HPV 59 to HPV 66.[35]
HPV, human papillomavirus.

Of the 1011 participants recruited at baseline, 910 provided β-globin positive samples of whole mouth fluid. Of these 910, 35% were positive for any HPV infection.[31] This was 15 times the prevalence reported in a study of young non-Indigenous Australians,[21] and 5 times the prevalence reported in a systematic review involving USA, Brazil, Mexico and Finland.[21] Antonsson and colleagues described a longitudinal study (0, 6, 12 and 24 months) of 704 people from Brisbane (18–70 years old).[32] They reported an oral HPV prevalence of 10.7% (high-risk HPV prevalence 6.4%) at baseline in 636 people who tested positive for β-globin. The International Agency for Research on Cancer's (IARC) definition of high-risk HPV was used: HPV 16, HPV 18, HPV 31 to HPV 33, HPV 35 to HPV 39, HPV 45 to HPV 51, HPV 52, HPV 56, HPV 58, HPV 59 to HPV 66.[33] In our study, the most prevalent HPV types at baseline were those associated with Heck's disease (23% of the HPV types found); a relatively benign and rare condition caused by oral HPV types 13 or 32 that appears to be more prevalent among Indigenous populations around the world.[34 35] The next most prevalent types were those associated with OPSCC (HPV 16 or 18; 3.3% of the types found).

Of the 749 participants retained at 12-month follow-up, 645 provided β-globin positive samples of whole mouth fluid. Of these, 43% were positive for any HPV infection. The most prevalent HPV types at 12-month follow-up were again those associated with Heck's disease (33% of the HPV types found), followed by HPV types associated with OPSCC (HPV 16 or 18; 2.5% of the HPV types found). A total of 588 participants had samples at baseline and 12-month follow-up that were β-globin positive (table 3). The prevalence of any oral HPV infection increased from 34% to 44%. This increase was largely due to increases in HPV types 13 or 32 (Heck's disease); from 20% at baseline to 34% at 12-month follow-up. The prevalence of HPV 16 or 18 decreased from 3.9% at baseline to 2.7% at 12-month follow-up. The prevalence of high risk HPV types according to the IARC definition decreased from 8.5% at baseline to 7.1% at 12-month follow-up. The incidence, persistence and clearance of oral HPV infections from baseline to 12-month follow-up is documented in table 4. Around 43% of participants had no oral HPV infection at baseline or follow-up. The incidence (no infection at baseline, infection at 12-months follow-up) was 23%, while persistence (infection at baseline and 12-month follow-up) was 21%. Clearance (infection at baseline, no infection at 12-month follow-up) was 13%. Around 59% of participants had no HPV 13 or 32 infection at either baseline or 12-month follow-up. Incidence was 20%, persistence 13% and clearance 7%. Approximately 94% of participants had no HPV 16 or 18 infection at either baseline or 12-month follow-up. Incidence was 2%, persistence 1% and clearance 3%. Around 87% of participants had no IARC-defined high risk HPV infection at either baseline or 12-month follow-up. Incidence was 4%, persistence 3% and clearance 6%.

Strengths and limitations

We have established a prospective longitudinal cohort to examine, over time, the impacts of oral HPV infection on OPSCC among Indigenous Australians. The main strength of the study is the engagement of South Australian Indigenous communities. Their involvement and partnership were orchestrated through the study's Indigenous Reference Group, through the ACCHO stakeholder groups and by the Senior Aboriginal research officer (JH). This has, without doubt, contributed to the excellent recruitment and follow-up rate, which need to be taken into context. For example, this cohort study has been undertaken over vast distances (travelling 700 km to the west of the city of Adelaide, the capital of the State of South Australia; 400 km east, 800 km north), involving highly disadvantaged participants who have not always enjoyed positive research interactions. The fact that over 1000 participants were recruited in less than 12 months

demonstrates the widespread community support of the study aims and objectives. The main limitation is the lack of clinical examinations, anthropometrics and blood samples that would yield important biomarker estimates, with funding not provided for this in the first three waves of the study. The 12-month follow-up had to be suspended prematurely due to COVID-19 restrictions, with 24-month follow-ups delayed also because of this.

Further funding will be sought to continue follow-up of this cohort, and to include (after a full medical history) a thorough clinical examination of the external head and neck; a complete oral examination and examination of the oropharynx. Blood tests for early stage OPSCC will also be undertaken.[36] The study will yield important information on the prevalence, incidence, clearance and persistence of oral HPV infection among Indigenous Australians, with baseline estimates indicating a prevalence far in excess of those reported in other population groups. The study will, in future, be able to identify risk factors associated with OPSCC-related HPV types (HPV 16 or 18) among Indigenous Australians, examine development of early stage OPSCC and refer for treatment and contribute to refining HPV-related health state valuations for use among Indigenous Australians. This information, in partnership with the South Australian Indigenous community, will greatly facilitate policymakers, ACCHOs and health service providers to determine the impact of oral HPV infections on OPSCCs, and the utility, acceptance and cost-effectiveness of extending publicly-funded HPV vaccination among Indigenous groups.

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Patient consent for publication Not required.

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Data availability statement Data are available upon reasonable request. Study data are not freely available because of ethical and data protection constraints. The de-identified data are stored at the University of Adelaide and cannot be sent outside the institution. Proposals for possible collaborations in further analyses of the data should be addressed to Lisa Jamieson (lisa.jamieson@adelaide.edu.au) and will be reviewed by the Indigenous Reference Group and research team.

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