Research Article

Analysis of the Peninsula Health Colposcopy Service Data of One Year Since Transitioning to the New Cervical Screening Program

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Abstract

Aims: We aim to analyze the data from our colposcopy clinic since its transition to the new cervical screening program to determine its effectiveness in clinical practice.

Materials and Methods: We extracted data from hospital electronic records, which was analyzed by a bio-statistician. Associations and concordance between referring (Human Papilloma Virus) HPV types, Liquid Based Cytology (LBC), colposcopic impression and cervical biopsy were calculated and analyzed.

Results: Data from 262 women who attended our colposcopy clinic from December 2017 to November 2018 was analyzed. Our study showed that the volume of referrals had increased by 6-fold since the implementation of the new cervical screening program in Australia. HPV Other (non 16/18) had the highest prevalence among women referred and accounted for the highest number of high-grade referrals to our unit.

Conclusion: 83.3% of referrals with HPV Other (non 16/18) had abnormal cytology. HPV Other appears to be the most pathogenic of all HPV subtypes. The concordance between colposcopic impression and cervical biopsy was 61.9%.

Keywords: Cytology and GYN Pathology; HPV Infection and CIN

1. Introduction

The new risk-based cervical screening program was implemented in Australia in December 2017. It was based on partial genotyping to classify the type of HPV and then reflex LBC on the same sample to determine if

a cervical cytological abnormality was present. This was to determine the patient's risk rating and triaging for colposcopy. This new screening program was supposed to have equivalent or better sensitivity, specificity and positive predictive value to that of the Pap smear. Using HPV as a primary screening tool was expected to reduce the number of false negatives and the reflex LBC testing to reduce the number of false positives, thereby decreasing the number of referrals to the colposcopy clinic and unnecessary follow ups. Comparisons of HPV testing with cytology in two randomized controlled trials (RCT) showed increased detection of Cervical Intraepithelial Neoplasia 2 (CIN2) or worse over subsequent screening rounds, compared with women who were tested with cytology only [1]. HPV 16 or 18 positive had been associated with increased incidence of CIN3 or worse up to 10 years later when cervical abnormalities were left untreated [2]. HPV 16, 18 and 45 accounted for 94% of HPV-related cervical cancers [3]. Studies had shown that HPV 16 and 18 were associated with CIN that were more likely to progress than regress [4-5].

1.1 Aim

The aim of this study was to analyze the data of the colposcopy clinic of Peninsula Health from December 2017 to November 2018 to streamline the clinical practice. The analysis focussed on the prevalence of different types of HPV in the local population, their association with referring LBC (LBC as mentioned in the referral letter of the referring doctor), concordance between the referring LBC and colposcopic impression, and concordance between the colposcopic impression and histological confirmation of the concurrent cervical biopsy. This colposcopy clinic is the only public colposcopy clinic in the Peninsula area of Melbourne and serves a population of approximately 400, 000. The clinic is held once a week and is run 5 gynaecologists,

who take turns supervising registrars allocated to the clinic.

2. Materials and Methods

Data were extracted from the hospital's electronic medical records and analyzed by the bio-statistician. Different associations and concordance were calculated and analyzed. The analyses were conducted in the R program using epi.R package [6]. Two by two tables, chi-squared tests, odds ratio with 95% confidence interval were computed from the observed count data and presented.

3. Result

Women referred to our colposcopy clinics had their cervical screening in different laboratories using HPV-type specific DNA tests. Before December 2017, the average number of new referrals to our colposcopy clinic was 4 per week. Under the new system, there has been a 6-fold increase in this number. A total of 262 women were referred to the colposcopy clinic in the time frame of the study. 34 of 262 women referred to the Peninsula Health colposcopy clinic were under 25 years of age: 4 were aged 18-20 years and 30 were 21-25 years. The new cervical screening program recommends screening from 25 years onwards, but these women had HPV testing earlier either due to risk factors or at clinician discretion. 60 women were aged 26-30 years, 82 aged 31-40 years, 51 aged 41- 50 years, 20 aged 51-60 years, 13 aged 61-70 years, 1 aged 71-80 and 1 aged 81-85 years (see Table 1). HPV Other (non 16/18) accounted for the highest proportion of referrals, 41.2%, followed by HPV 16, 23.6%. Other referred HPV subtypes include HPV 18, 6.1%, HPV 16 & Other, 6.9%, HPV 18 & Other, 3.4%, HPV 16 & 18, 0.76%, HPV 16 &18 & Other, 0.38% and HPV hasn't detected, 0.38%. HPV testing was not done in 17.1% women and their referral was based on LBC (see Table 2). The breakdown of the referring LBC included normal, high

grade (HSIL), possible high grade (pHSIL), low grade (LSIL), possible low grade (pLSIL), unsatisfactory and not done. There were 98 high grade or possible high grade LBC in the referrals, 86, low grade or possible low grade LBC, 2 unsatisfactory, 74 negative LBC and 2 where LBC was not done (see Table 3). When evaluating the relationship between the different HPV subtypes and abnormal reflex LBC, HPV Other (non 16/18) appeared to be the most pathogenic of the HPV subtypes. 90 out of 108 women (83.3%) referred to HPV Other (non 16/18) had abnormal LBC. Of these women, 62 had high grade or possible high grade reflex LBC (68.8%), 28 had low grade or possible low grade LBC (31.1%), 17 had normal LBC and 1 was unsatisfactory. A total of 62 out of 98 of all the patients (63.2%) referred to the highest grade or possible high grade reflex LBC were HPV Other (non 16/18) positive. When compared to other HPV types, HPV Other accounted for the highest proportion of abnormal referred LBC, both high and low grades in our study (see Table 4 and 5). Of the 262 women who attended the Peninsula Health colposcopy clinic, 257 underwent colposcopy. Five patients did not undergo colposcopy due to lack of consent or difficulty performing a speculum examination. We evaluated the relationship between referred LBC subtypes and colposcopic impression. 51 women had a high-grade colposcopy and of them, 42 had high-grade or possible high-grade referred LBC, 5 had low-grade or possible low-grade referred LBC, three had negative LBC and one did not have LBC done. 111 women had low-grade abnormal colposcopic impression. Of these women, 45 had low-grade or possible low-grade referred LBC, 47 high-grade or possible high-grade referred LBC, 18 negative referred LBC and one was unsatisfactory. Of the 88 patients with normal impression at colposcopy, 47 had negative referred LBC, 32 low-grade or possible low-grade referred LBC, seven high-grade or possible high-

grade referred LBC, one unsatisfactory LBC and 1 in whom LBC was not done (see Table 6).

There was a moderately strong correlation between the referred LBC result and colposcopic impression (Cramer' s V= 0.29). The odds ratio for a high-grade colposcopic impression with a high-grade referring LBC was 4.24 (95% CI, 2.17- 8.29%, P value <0.001). There was a positive correlation between low-grade colposcopy impression with a low-grade referring LBC with an odds ratio of 1.87 (95% CI, 1.02- 3.44%, P value 0.042). The odds ratio of having a normal colposcopy with a negative referring LBC is 6.24 (95% CI, 3.47-11.22%, P value <0.001). The odds ratio of possible high- grade referring LBC correlates with a high-grade colposcopy was 4.80 (95% CI, 2.38- 9.67%, P value <0.001). We also evaluated the correlation between referred HPV and colposcopic impression. The odds ratio of HPV 16 correlating with low-grade colposcopy was 2.59 (95% CI, 1.07- 6.26%, P value 0.03) and of HPV Other with high-grade colposcopy was 1.96 (95% CI, 1.01- 3.79%, P value 0.044). The odds ratio of HPV Other and normal colposcopy was 0.47 (95% CI, 0.24-0.91%, P value 0.022). See Table 7. The women aged below 25 were analyzed separately. In our study, HPV Other (non 16/18) had the highest prevalence in these younger women, accounting for 18 in 34 referrals (52%). 19 women had low-grade or possible low-grade referring LBC, twelve had high-grade or possible high-grade referring LBC, two had negative LBC and one had unsatisfactory LBC. Of the 19 women with low-grade referring LBC, four had high-grade changes on concurrent cervical biopsy at colposcopy. Of them, three were positive for HPV Other and underwent Large Loop Excision of the Transformation Zone (LLETZ), all of them confirming CIN2 or higher on histology. Of the twelve with high grade referring LBC, four had a high-grade proven cervical biopsy at colposcopy. Two of them underwent

LLETZ and their histology confirmed CIN 2 or 3. The other two chose to repeat colposcopy in 6 months. This implied that abnormal cytology, if detected, should have close follow up or treatment even in those below 25 years of age. There was no consensus in our unit to repeat colposcopy or perform LLETZ for those with biopsy-proven high-grade changes and the decision seemed to be individualized to clinician choice. Given that 8 of 12 with high-grade referring LBC were low-grade or normal on the initial cervical biopsy, it seemed reasonable to repeat colposcopy in 6 months. Preliminary data from the PRINCess trial suggests there is a 43% likelihood of regression of CIN 2 in women below age of 25 [7]. A study evaluating cervical screening in 4767 women under 25 years old showed that only 63 women (2.5%) had CIN 2-3 confirmed on LLETZ. This study concluded that screening women under the age of 25 may cause unnecessary referral to colposcopy and subjecting women to anxiety and psychosocial morbidity [8]. Till more evidence is available, the management of high-grade cervical abnormalities for women aged 25 is controversial, largely due to limited data around safety and benefit in this group. A total number of 168 patients were biopsied in our colposcopy clinic. For the purposes of data comparison, we grouped cervicitis, inflammation, HPV effect only, CIN1 and LSIL as low-grade biopsy, whereas CIN 2-3 and HSIL were grouped as high grade biopsy. Of the 51 women with high-grade colposcopic impression, 24 had a high-grade proven biopsy (47%), 21 had low grade, three had normal biopsies and three were not biopsied. In other words, all women with biopsy proven high-grade abnormal changes had abnormal colposcopic impression (sensitivity 100%). Of the 111 women with low-grade colposcopic impression, 80 women had a low-grade proven biopsy (72%), 20 had a high-grade proven biopsy, 5 had normal biopsies and 6 were not biopsied. Of 88 women with a normal colposcopy impression, 11 women had a low-grade biopsy, 1 had a normal biopsy and 76 women were not biopsied. The number of patients who had the low-grade colposcopy impression with concordant low-grade cervical biopsy result was 80/111 (72%) and 24/51 (47%) in the high-grade group. Together, this correlated to 61.9% concordance (104 in 168 biopsies). The odds ratio of high-grade biopsy with a high-grade colposcopic impression was 8.49 (95% CI, 4.14-17.39%, P value <0.001) and of low-grade biopsy with the low-grade colposcopic impression was 8.55 (95% CI, 4.88-14.99%, P value <0.001). See Table 8.

Age	Number of Referrals	Percentage of referrals
Below 21	4	1.5%
21-25	30	11.4%
26-30	60	22.9%
31-40	82	31.3%
41-50	51	19.4%
51-60	20	7.6%
61-70	13	4.9%
71-80	1	0.3%
81-85	1	0.3%
Total	262	100%

Table 1: number of referrals in different age groups.

HPV Types	Number of Referrals	Percentage of Referrals
HPV Other	108	41.2%
HPV 16	62	23.6%
HPV 18	16	6.1%
HPV 16 & Other	18	6.9%
HPV 18 & Other	9	3.4%
HPV 16 & 18	2	0.76%
HPV 16, 18 & Other	1	0.38%
HPV Not Detected	1	0.38%
HPV not done	45	17.1%
Total	262	100%

Table 2: number of referrals with different types of HPV.

Referring LBC	Numbers	Percentage of Referrals
High grade (HSIL)	54	20.6%
Possible high grade (pHSIL)	44	17.2%
Low grade (LSIL)	53	20.2%
Possible low grade (pLSIL)	33	12.2%
Unsatisfactory	2	0.8%
Negative	74	28.2%
Not done	2	0.8%
Total	262	100%

Table 3: Number of referrals with different referring LBC.

HPV Subtype	HSIL or pHSIL Numbers	Percentage of Referrals
HPV Other	62	63.2%
HPV 16	9	9.1%
HPV 18	2	2.0%
HPV 16+ Other	6	6.1%
HPV 18 + Other	2	2.0%
Not done	17	17.3%
Total	98	100%
Total	262	100%

Table 4: Number of referrals and High Grade Change (HSIL or pHSIL) by HPV Subtypel.

			Referring LBC							
			HSIL	LSIL	neg	not done	PHSIL	PLSIL	unsatisfactory	Total
Referring HPV	16 +18 + other	Count	0	1	0	0	0	0	0	1
		% within Referring LBC	0.0%	1.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%
	HPV 16	Count	8	8	34	0	1	10	1	62
		% within Referring LBC	14.8%	15.1%	45.9%	0.0%	2.3%	30.3%	50.0%	23.7%
	HPV 16 + 18	Count	0	0	1	0	0	1	0	2

		% within Referring LBC	0.0%	0.0%	1.4%	0.0%	0.0%	3.0%	0.0%	0.8%
HPV 16 + other	Count	4	1	10	0	2	1	0	18
	% within Referring LBC	7.4%	1.9%	13.5%	0.0%	4.5%	3.0%	0.0%	6.9%
HPV 18	Count	2	5	6	0	0	3	0	16
	% within Referring LBC	3.7%	9.4%	8.1%	0.0%	0.0%	9.1%	0.0%	6.1%
HPV 18 + other	Count	0	0	6	0	2	1	0	9
	% within Referring LBC	0.0%	0.0%	8.1%	0.0%	4.5%	3.0%	0.0%	3.4%
HPV not detected	Count	0	0	0	0	0	1	0	1
	% within Referring LBC	0.0%	0.0%	0.0%	0.0%	0.0%	3.0%	0.0%	0.4%
HPV other	Count	29	16	17	0	33	12	1	108
	% within Referring LBC	53.7%	30.2%	23.0%	0.0%	75.0%	36.4%	50.0%	41.2%
not done	Count	11	22	0	2	6	4	0	45
	% within Referring LBC	20.4%	41.5%	0.0%	100.0%	13.6%	12.1%	0.0%	17.2%
Total	Count	54	53	74	2	44	33	2	262
	% within Referring LBC	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 5: Referring HPV and Referring LBC Crosstabulation.

			Colposcopy Impression						
			glandular	HG	LG	normal	not done	unsatisfactory	Total
Referring LBC	HSIL	Count	1	22	28	2	0	1	54
		% within Colp Impression	100.0%	43.1%	25.2%	2.3%	0.0%	16.7%	20.6%
	LSIL	Count	0	4	29	17	2	1	53
		% within Colp Impression	0.0%	7.8%	26.1%	19.3%	40.0%	16.7%	20.2%
	neg	Count	0	3	18	47	3	3	74
		% within Colp Impression	0.0%	5.9%	16.2%	53.4%	60.0%	50.0%	28.2%

			glandular	HG	LG	normal	not done	unsatisfactory	Total
	not done	Count	0	1	0	1	0	0	2
		% within Colp Impression	0.0%	2.0%	0.0%	1.1%	0.0%	0.0%	0.8%
	PHSIL	Count	0	20	19	6	0	0	45
		% within Colp Impression	0.0%	39.2%	17.1%	6.8%	0.0%	0.0%	17.2%
	PLSIL	Count	0	1	16	14	0	1	32
		% within Colp Impression	0.0%	2.0%	14.4%	15.9%	0.0%	16.7%	12.2%
	unsatisfactory	Count	0	0	1	1	0	0	2
		% within Colp Impression	0.0%	0.0%	0.9%	1.1%	0.0%	0.0%	0.8%
Total		Count	1	51	111	88	5	6	262
		% within Colp Impression	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 6: Referring LBC and Colposcopy Impression.

			Colp Impression						
			glandular	HG	LG	normal	not done	unsatisfactory	Total
Referring HPV	16 +18 + other	Count	0	0	0	1	0	0	1
		% within Colp Impression	0.0%	0.0%	0.0%	1.1%	0.0%	0.0%	0.4%
	HPV 16	Count	1	5	18	31	2	5	62
		% within Colp Impression	100.0%	9.8%	16.2%	35.2%	40.0%	83.3%	23.7%
	HPV 16 + 18	Count	0	0	0	2	0	0	2
		% within Colp Impression	0.0%	0.0%	0.0%	2.3%	0.0%	0.0%	0.8%
	HPV 16 + other	Count	0	5	5	6	1	1	18
		% within Colp Impression	0.0%	9.8%	4.5%	6.8%	20.0%	16.7%	6.9%
	HPV 18	Count	0	1	8	7	0	0	16
		% within Colp Impression	0.0%	2.0%	7.2%	8.0%	0.0%	0.0%	6.1%
	HPV 18 +	Count	0	0	3	6	0	0	9

other	% within Colp Impression	0.0%	0.0%	2.7%	6.8%	0.0%	0.0%	3.4%
HPV not detected	Count	0	0	0	1	0	0	1
	% within Colp Impression	0.0%	0.0%	0.0%	1.1%	0.0%	0.0%	0.4%
HPV other	Count	0	31	52	25	0	0	108
	% within Colp Impression	0.0%	60.8%	46.8%	28.4%	0.0%	0.0%	41.2%
not done	Count	0	9	25	9	2	0	45
	% within Colp Impression	0.0%	17.6%	22.5%	10.2%	40.0%	0.0%	17.2%
Total	Count	1	51	111	88	5	6	262
	% within Colp Impression	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 7: Referring HPV and Colposcopy Impression Crosstabulation.

			Biopsy Result				Total
			HG	LG	normal	not done	
Colp Impression	HG	Count	24	21	3	3	51
		% within Biopsy Result	54.5%	18.6%	33.3%	3.4%	20.0%
	LG	Count	20	80	5	6	111
		% within Biopsy Result	45.5%	70.8%	55.6%	6.7%	43.5%
	normal	Count	0	11	1	76	88
		% within Biopsy Result	0.0%	9.7%	11.1%	85.4%	34.5%
	not done	Count	0	1	0	4	5
		% within Biopsy Result	0.0%	0.9%	0.0%	4.5%	2.0%
Total		Count	44	113	9	89	255
		% within Biopsy Result	100.0%	100.0%	100.0%	100.0%	100.0%

(unsatisfactory and glandular have been removed so n=255)

Table 8: Colposcopy Impression and Biopsy Result.

4. Discussion

One of the expectations of the HPV-based cervical screening program was that it would reduce the number of referrals to colposcopy clinics in the long run because of its low false positive and negative rates. However, in the past year since the implementation of the new cervical screening test, there had been a major increase in the average number of referrals to our Peninsula

Health colposcopy clinic. The average number of referrals of 4 per week under the previous Pap-smear based screening system rose to 24 per week, a 6 fold rise. Since there had been no increase in the resources to the colposcopy clinic, it had resulted in increased waiting times for women to be seen in our colposcopy clinic to about 12 months. In the long term, this new system of screening was expected to give major cost savings. However, major fluctuations in rates of colposcopy referrals and follow up were also expected [9]. It is vital that in the short term, data from individual colposcopy clinics is audited to review the impact of these changes, while this new program is still getting established. According to these authors [9], referrals to colposcopy clinics are expected to decline in future, when mostly the incident disease will be detected. The advantage of partial HPV genotyping is that it allows identification of most oncogenic HPV types, which are then referred for colposcopy, not all HPV types. Although HPV 16 and 18 are the commonest oncogenic HPV types and account for 70% of cervical cancers and pre-cancerous cervical lesions, HPV Other (non16/18) also account for a high volume of referrals and a significant cause of disease. In our study, HPV Other (non 16/18) had the most numbers of referrals to our clinic (41.2%), followed by HPV 16 (23.6%). Other large studies around the world also have reported a high prevalence of HPV Other (non 16/18). A study of 38,000 women in China showed that HPV 52 is the most common HPV genotype in patients with cervical pre-cancerous changes, followed by 16, 58, 39, 18, and 56 [10]. In another study, it is estimated that the prevalence of HPV Other (non 16/18) is three times higher than HPV 16/18 [11]. In a Sydney-based study, the incidence of HPV 16 and 18 combined was 2.2% (95% CI, 2.1-2.3%) and the incidence of HPV Other (non 16/18) was more than double, 5.9% (95% CI, 5.8-6.0%) in primary screening [12]. This study also showed that in women who are HPV 16 or 18 positive,

36.4% (95% CI, 34.8-38.1%) had cytological cervical abnormalities; 21.1% (95% CI, 19.7-22.5%) of whom had low grade and 15.3% (95% CI, 14.2-16.6%) had high grade changes. In our study, HPV Other had the highest rate of cytological abnormalities, accounting for 63.2% of all our high-grade referrals, which is higher than the rate by the Sydney study of 35.2% (95% CI, 34.2-36.2%). HPV infection is necessary for the development of cervical neoplasia, but given only a small percentage of women infected with HPV developed HSIL, this indicates that HPV alone is insufficient for cervical cancer oncogenesis. Other co-variables, such as sexual, environmental, behavioural and socioeconomic factors may come into play. The distribution of HPV subtypes varies to some degree according to the geographical region [13]. Furthermore, the oncogenic potential within the same HPV type also varies. Sequential infection with different HPV types and simultaneous infection with more than one HPV types is not an uncommon phenomenon [14]. Infection with one HPV type and simultaneous clearance of another type happen independently.

Our study confirmed that colposcopy alone is not an effective screening tool. The efficacy of colposcopy to detect CIN largely depends upon the experience and training of the colposcopist, which can be highly variable. To increase the sensitivity of colposcopy, biopsies have to be from the abnormal areas of the transformation zone. Random biopsies do not increase sensitivity, however multiple biopsies do [15]. Using 2011 International Federation of Cervical Pathology and Colposcopic criteria, it is possible to distinguish normal cervix from CIN/ cancer with a sensitivity of 86% and specificity of 30% and to distinguish normal cervix/ CIN 1 from HSIL with sensitivity of 61% and specificity of 94% [16]. In our study, the concordance between low-grade colposcopy and biopsy was 72%, which is comparable to other studies. One study showed

a 78.5% correlation in the CIN 1 category and 84-88.6% in the CIN 2-3 category [17]. The colposcopy- biopsy concordance in our high-grade abnormal group is a mere 47%, which is lower than quoted other literature. Only 24 of the 48 biopsies in the high-grade colposcopic impression group had high-grade biopsy results, with the others being low-grade or normal. A possible reason for this may be the subjectivity around colposcopic features of HSIL. Biopsies will be misrepresentative of the pathology if not sampled from the abnormal areas of the transformation zone. Although trainees work in the clinic under the direct supervision of a gynaecologist, the accuracy of the biopsy site may be affected by the level of experience of the trainee. Our study showed that the volume of referrals had increased by 6-fold since the implementation of the new cervical screening program in Australia. HPV Other (non 16/18) had the highest prevalence among women referred and accounted for the highest number of high-grade referrals to our unit. On the basis of this, it is suggested that women with HPV Other (non 16/18) should be prioritized in the appointment schedule. All colposcopists must be credentialed by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) to minimise the subjectivity of recognizing the colposcopic features of different types of abnormalities. Colposcopy clinic capacity should be increased at least 6 fold to keep pace with the increased number of referrals. Moving forward, the number of HPV Other (non16/18) may continue to be on the rise given that women were previously vaccinated with the Cervarix and quadrivalent Gardasil vaccine, which do not cover for the other oncogenic HPV types.

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Disclosure

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