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Effectiveness of Co-Testing in Cervical Cancer Screening Program in Macau SAR

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Abstract

Background: Cervical cancer remains a significant public health concern in Macau SAR despite the implementation of a cervical cancer screening program and HPV vaccination. To improve early detection, Macau SAR introduced HPV DNA testing alongside cytology (co-testing) as the primary screening method in 2019. This study evaluates the effectiveness of co-testing in identifying cervical precancerous lesions (CIN2+) compared to cytology alone. **Methods:** We conducted a retrospective analysis of women aged 30 - 65 years who participated in the routine cervical cancer screening program in Macau SAR Primary Healthcare Centers from 2019 to 2022. Data from over 70,000 women were analyzed, comparing the detection rates of CIN2+ through co-testing and cytology alone. Women with abnormal cytology or positive HPV results were referred for colposcopy. **Results:** The introduction of co-testing led to a significant increase in the detection of CIN2+, particularly in women with atypical squamous cells of undetermined significance (ASCUS) or negative for intraepithelial lesion or malignancy (NILM) cytology results. Between 2019 and 2022, the percentage of women with ASCUS/NILM and any high-risk HPV (hrHPV) positive who were diagnosed with CIN2+ after colposcopy were 24%, 13%, 10% and 7.5% respectively. This highlights the ability of co-testing to identify high-risk individuals who would have been missed by cytology alone. **Discussion:** Our findings demonstrate the effectiveness of co-testing in improving the sensitivity of cervical cancer screening in Macau SAR. The inclusion of HPV DNA testing allows for better risk stratification of women with ASCUS/NILM cytology, leading to more targeted referrals for colposcopy and timely detection of precancerous lesions. The initial high positive rate in 2019 (24%) might be attributed to the small sample size and potentially reflects a backlog of undiagnosed cases prior to co-testing implementation. **Conclusion:** The implementation of co-testing in Macau SAR's cervical cancer screening program significantly improves the early detection of

precancerous lesions, particularly in women with ambiguous cytology results. This proactive approach contributes to reducing cervical cancer morbidity and mortality and improving women's health outcomes in Macau SAR.

Keywords

Cervical Cancer, Co-Testing, HPV DNA Testing, Liquid-Based Cytology, Thin Prep, Colposcopy, Cervical Cancer Screening Program

1. Objective

Cervical cancer is a global health issue and one of the leading causes of cancer morbidity and mortality worldwide. It is the fourth most common cancer among women globally, with an estimated 604,000 new cases and 342,000 deaths in 2020 [1]. A large majority of cervical cancer (more than 95%) is due to the human papillomavirus (HPV). Fortunately, cervical cancer can be cured if diagnosed at an early stage and treated promptly.

Macao Special Administrative Region implemented a free cervical cancer screening program in 1985 and included the human papillomavirus (HPV) vaccine in the vaccination plan for women under the age of 18 in 2013. Despite the primary prevention with HPV vaccination and secondary prevention with cervical cancer screening by Pap smear, the decline in the incidence of cervical cancer remained stagnant (see Table 1). In 2019, the government started co-testing: high-risk human papillomavirus testing (HPV DNA) and Thin-Prep cytology test (ThinPrep) which are done together as the primary screening methodology for cervical cancer in the screening program. This study explored the effectiveness of co-testing in the early diagnosis of cervical precancerous lesions by comparing the number of CIN2+ cases identified through co-testing versus liquid-based cytology screening alone.

Table 1. Cervical cancer incidence, cumulative risk and mortality in Macau SAR from 2014 to 2020.

Year	Ranking (incidence)	New cases registered	Crude Incidence rate (1/100,000)	Death cases	Crude Mortality rates (1/100,000)
2014	7	29	9.2	9	2.8
2015	8	25	7.7	6	1.8
2016	6	38	11.4	12	3.6
2017	6	34	9.9	9	2.6
2018	7	34	9.7	13	3.7
2019	10	20	5.6	11	3.1
2020	7	37	10.3	11	3.1

2. Methods

This retrospective analysis utilized data from women aged 30 to 65 years who underwent cervical cancer screening at Macau SAR Primary Healthcare Centers between January 1, 2019, and December 31, 2022. Inclusion criteria included complete cervical cytology and human papillomavirus (HPV) testing results. Patients with a prior history of cervical cancer or incomplete cytology and/or HPV results were excluded.

From 2019 to 2022, 17,563, 18,737, 20,829, and 15,374 women aged 30 to 65 years participated in the routine cervical cancer screening program at Macau SAR Primary Healthcare Centers, respectively. Data regarding the number of women screened annually were obtained from the Macau SAR Health Bureau's cervical cancer screening program database, which captures the total population of eligible women for cervical cancer screening within the catchment area. It is important to note that these numbers may not be representative of the entire eligible population in the region, as some women may have pursued screening at other private hospitals or clinics.

In accordance with the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, patients with abnormal cytology and/or HPV test results were referred for colposcopy. HPV testing was performed using the Roche cobas® 4800 HPV assay system, which automates and simultaneously distinguishes between HPV-16/18 genotypes and 12 other high-risk HPV genotypes. High-risk HPV (hrHPV) genotypes are associated with an increased risk of cervical cancer development. This study focused on 14 hrHPV genotypes, including HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, and -68, as detected by the Roche cobas® 4800 HPV assay.

Notably, the cobas® 4800 HPV test demonstrated a greater degree of sensitivity and specificity in detecting high-risk HPV (hrHPV) genotypes than the Digene HC2 hrHPV test, as reported in a 2014 study by Cui *et al.* [2]. The Cobas test showed a significantly higher specificity than HC2 test in the detection of CIN2+ and CIN3+ (66.46% vs 43.67% and 65.42% vs 42.86%, $p < 0.001$) as reported in a 2022 study by Liu *et al.* [3].

Cytology refers to the examination of a liquid-based thin-prep slide to detect cervical cells and perform cytology classification and diagnosis. ThinPrep tends to be more sensitive and specific than conventional smears in detecting cervical dysplasia. The increased sensitivity results in an increase in cytologic diagnosis of cervical atypia, LGSIL, HGSIL, and invasive cervical carcinoma [4].

From 2019 to 2022, the Macau SAR Health Bureau conducted 695, 741, 863 and 905 colposcopy examinations respectively. Colposcopy results were interpreted by experienced gynecologists according to the 2012 American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines. The retrospective analysis on this study using colposcopy was stratified into 5 groups according to the baseline cytology and HPV test results as follows: 1) HSIL/ASC-H/AGC, 2) **hrHPV 16/18+ and ASCUS/NILM**, 3) hrHPV 16/18+ and HSIL/ASC-H, 4) **other**

hrHPV+ and ASCUS/NILM, 5) **other hrHPV+ and LSIL**. The following groups: hrHPV 16/18+ and ASCUS/NILM, other harp+ and ASCUS/NILM, other hrHPV+ and LSIL and samples whose final pathological results were CIN2+ were further described in this study.

3. Results

The proportion of women diagnosed with CIN2+ after colposcopy varied by baseline cytology and HPV results. Among women with baseline hrHPV16/18+ and ASCUS/NILM, the proportion diagnosed with CIN2+ was 32% (29/90), 20% (28/137), 13% (22/172), and 11% (18/162) from 2019 to 2022, respectively. For those with other hrHPV+ and ASCUS/NILM, the proportion diagnosed with CIN2+ was 16% (18/106), 8% (22/262), 9% (30/350), and 6% (28/450) from 2019 to 2022, respectively. Finally, among women with other hrHPV+ and LSIL, the proportion diagnosed with CIN2+ was 22% (8/36), 12% (11/90), 14% (11/77), and 8% (7/93) from 2019 to 2022, respectively.

	Percentage of CIN2+ diagnosed by colposcopy			
Baseline Co-testing Result	2019	2020	2021	2022
HSIL/ASC-H/AGC	48%	42%	45%	37%
hrHPV 16/18+ and ASCUS/NILM	32%	20%	13%	11%
hrHPV 16/18+ and HSIL/ASC-H	50%	61%	67%	53%
other hrHPV+ and ASCUS/NILM	16%	8%	9%	6%
other hrHPV+ and LSIL	22%	12%	14%	8%

Chart: Percentage of final pathological reports for combination testing as CIN2+.

With the incorporation of HPV DNA test since 2019, women with ASCUS/NILM detected by cytology can be further stratified to high-risk group for colposcopy based on a positive hrHPV DNA result. From 2019 to 2022, 196, 399, 522 & 612 women with any hrHPV positive and ASCUS/NILM were referred for colposcopy, respectively. 24% (47/196), 13% (50/399), 10% (52/522) and 7.5% (46/612) were diagnosed with CIN2+ after the final pathology report on colposcopy in each year.

	Number and Percentage of CIN2+ diagnosed by colposcopy			
Baseline Co-Testing Result	2019	2020	2021	2022
Any hrHPV+ and ASCUS/NILM	47/196 (24%)	50/399 (13%)	52/522 (10%)	46/612 (7.5%)

Chart: Percentage of final pathological reports for combination testing as CIN2+.

4. Discussion

Cervical cancer ranks fourth in the world for common malignancies in women, accounting for about 6.9% of all female cancers. According to the Macao Cancer Registration Information (Macao Cancer Registration Annual Report), from 2008 to 2018, cervical cancer has been ranked among the top ten most common malignant tumors in women, and the 2nd in the most common malignant neoplasms in women aged 20 - 49 years [5]. Since cervical precancerous lesions generally take more than ten years to progress, regular cervical cancer screening programs are of great significance for the early diagnosis and treatment of cervical precancerous lesions. ASCCP evidence-based medicine guidelines also recommend co-testing as a method of screening for cervical cancer. Studies have shown that co-testing is 99.2% sensitive to CIN2+ and 87.3% specific, which is 4% higher than that of HPV-DNA detection alone, and approximately 45% higher than that of cytology detection alone [6].

While this study showed that approximately 24% of women with ASCUS/NILM and any hrHPV positive who have been referred to colposcopy were subsequently diagnosed with CIN2+ in 2019, the positive rate was higher than 10% that other study reported [7] and our data in 2020 and 2021. The discrepancy is likely attributable to the smaller sample size in 2019. The CIN2+ detection rates in this cohort during 2020 and 2021 align with those reported in other studies, though some variation exists. This variation may be influenced by a number of factors, including differences in sample collection techniques and interobserver variability in cytological interpretation.

Colposcopy with biopsy is an essential component of cervical cancer screening, enabling the visual identification and histological diagnosis of precancerous lesions. Nevertheless, there is still a room of improvement to its accuracy and reproducibility. Previous studies reported the sensitivity of colposcopy ranged from only 53.6% - 69.9%. The factors that may contribute to such performance include the lack of quality assurance measures, standardized colposcopy practice and procedures [8] [9]. Colposcopic interpretation can be challenging, particularly in cases with a cytological diagnosis of atypical squamous cells of undetermined significance (ASCUS). This category encompasses a spectrum of histologic findings, ranging from low-grade to high-grade lesions. Therefore, meticulous examination is essential when evaluating women with ASCUS cytology to ensure accurate identification and characterization of any underlying pathology.

Immediate referral of all women for colposcopy will greatly increase the number of colposcopic examinations, while conservative monitoring with repeat cytology may lead to a delayed diagnosis. Combining high-risk HPV DNA testing with cytology shows an advantage of increasing the detection rates for precancerous cervical lesions, and it was proven the most useful for women when their cytology was found to be ASC-US. The HPV DNA results in such case would be able to provide insights on the risk of underlying disease and inform the need of immediate colposcopy. For those with HPV negative results, they are safe to be

monitored with a longer duration [10].

The high volume of cervical cancer screenings in Macau SAR, coupled with a scarcity of qualified healthcare professionals, presents a challenge for maintaining consistent cytology interpretation accuracy. Reader fatigue in this setting could potentially lead to an increased rate of missed precancerous lesions. The integration of HPV DNA testing into the screening program in 2019 helps to mitigate this risk by providing an objective adjunct to cytology, particularly in cases with ambiguous cytological findings. This study did not collect data on demographic factors such as age, sexual history, or socioeconomic status. Future research should investigate the potential influence of these factors on the effectiveness of co-testing in Macau SAR.

In summary, the implementation of co-testing in Macau SAR significantly improves the accurate detection of cervical precancerous lesions, representing a critical advancement in cervical cancer prevention efforts.

5. Conclusion

This study demonstrates that the implementation of co-testing for cervical cancer screening by the Macau SAR Health Bureau since 2019 has effectively increased screening sensitivity. This enhanced sensitivity facilitates the early detection of moderate to severe cervical precancerous lesions, thereby reducing missed diagnoses and potentially decreasing cervical cancer morbidity and mortality. This improvement in early detection and intervention is expected to positively impact the quality of life for women in Macau SAR, carrying significant public health implications.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

Negative for Intraepithelial Lesion or Malignancy (NILM);
Low-Grade Squamous Intraepithelial Lesion (LSIL);
High-Grade Squamous Intraepithelial Lesion (HSIL);
Atypical Squamous Cells of Undetermined Significance (ASC-US);
Atypical Squamous Cells, Cannot Rule Out High Grade Squamous Intra-epithelial Lesion (ASC-H);
Atypical Glandular Cells (AGCs);
High risk HPV (hrHPV).