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Comparative Efficacy of Hybrid Capture 2 and Real-Time PCR in Detecting High-Risk HPV Genotypes for Cervical Cancer Screening

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Abstract

Human papillomavirus (HPV) infection is a leading cause of cervical cancer, making early detection critical for effective prevention and treatment. Among the diagnostic methods available, Hybrid Capture 2 (HC2) and Real-Time Polymerase Chain Reaction (PCR) are widely used for detecting high-risk HPV genotypes, particularly HPV 16 and 18, which account for the majority of cervical cancer cases. This review aims to compare the efficacy of HC2 and Real-Time PCR in terms of sensitivity, specificity, and clinical utility in cervical cancer screening. HC2 is a well-established method that detects a broad range of HPV types, but it has notable limitations, such as cross-reactivity, which can lead to false positives. Its lower specificity makes it less reliable for distinguishing between high-risk and low-risk infections, resulting in unnecessary follow-ups and potential overtreatment. Conversely, Real-Time PCR offers higher specificity by directly amplifying and detecting viral DNA sequences, allowing for precise identification of high-risk HPV genotypes. This method also enables viral load quantification, providing additional clinical insights into the severity of infection and risk of disease progression. The comparative analysis suggests that while HC2 remains a useful tool for large-scale screening due to its ability to detect a wide range of HPV infections, Real-Time PCR is superior in terms of accuracy and clinical relevance. Its precise detection capabilities make it more effective for targeted screening and risk stratification in clinical settings. In conclusion, Real-Time PCR's enhanced specificity and ability to reduce false positives present a significant advantage in improving cervical cancer screening outcomes, making it a more reliable tool for early detection and prevention strategies.

Keywords: *Human papillomavirus,* Polymerase Chain Reaction (PCR), DNA sequences, cervical cancer, transmitted infection

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INTRODUCTION

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection worldwide and a major cause of cervical cancer, which remains one of the leading causes of cancer-related deaths among women. There are over 150 different types of HPV, but the high-risk genotypes – particularly HPV 16 and 18 – are responsible for approximately 70% of all cervical cancer cases. HPV infects epithelial cells, and while most infections are transient and asymptomatic, persistent infection with high-risk HPV types can lead to the development of cervical intraepithelial

neoplasia (CIN), which can progress to invasive cervical cancer if left undetected [1]. Globally, cervical cancer accounts for more than 500,000 new cases and over 250,000 deaths annually, with a disproportionate burden in low- and middle-income countries where access to effective screening and prevention measures is limited. Therefore, early detection of high-risk HPV genotypes is crucial for preventing the progression of cervical cancer, making accurate diagnostic tools a key component of public health strategies.

CURRENT SCREENING TECHNIQUES

Historically, cervical cancer screening has relied on the Papanicolaou (Pap) smear, which examines exfoliated cervical cells for abnormalities. While the Pap smear has been instrumental in reducing cervical cancer incidence in developed countries, it has limitations, including low sensitivity, subjectivity in interpretation, and the inability to directly detect HPV. As a result, many cases of high-grade CIN and early cervical cancer may be missed, especially in resource-limited areas. To address these limitations, HPV testing has emerged as a more sensitive method for early detection. HPV tests directly identify the presence of high-risk HPV DNA, enabling more accurate and earlier detection of potential cervical lesions before they progress to cancer [2, 3]. This makes HPV testing particularly valuable in primary screening and as a triage tool for women with abnormal Pap resultsThis review aims to compare two commonly used HPV detection methods: Hybrid Capture 2 (HC2) and Real-Time Polymerase Chain Reaction (PCR). HC2 has been widely adopted in large-scale screening programs due to its ability to detect a broad range of high-risk HPV types. However, it has limitations, such as cross-reactivity with low-risk HPV types, leading to false positives and unnecessary clinical interventions. In contrast, Real-Time PCR offers greater specificity, accurately identifying high-risk genotypes and quantifying viral load, which is critical for determining the risk of disease progression. This review focuses on evaluating the sensitivity and specificity of these two diagnostic tools and their impact on clinical decision-making in cervical cancer screening. By comparing their strengths and weaknesses, the review provides insights into which method offers greater efficacy in detecting high-risk HPV and improving patient outcomes [4].

HUMAN PAPILLOMAVIRUS AND CERVICAL CANCER: A GLOBAL CHALLENGE

HPV is one of the most common viral infections globally, with over 80% of sexually active individuals contracting the virus at some point in their lives. Of the more than 150 identified HPV types, around 12 are classified as high-risk for their role in causing cancers, particularly cervical cancer. The two most dangerous high-risk genotypes, HPV 16 and HPV 18, are responsible for about 70% of all cervical cancer cases worldwide. HPV is also linked to other anogenital cancers, such as vaginal, vulvar, penile, and anal cancers, as well as oropharyngeal cancers. Despite the availability of preventive vaccines and screening programs, cervical cancer remains a major public health issue, especially in low- and middle-income countries (LMICs) where access to HPV vaccination and regular screening is limited [5].

Globally, cervical cancer is the fourth most common cancer in women, with an estimated 604,000 new cases and 342,000 deaths in 2020. The burden is disproportionately high in developing regions, which account for approximately 85% of the global incidence of cervical cancer. In countries with limited access to screening, the disease is often detected at advanced stages, contributing to higher mortality rates. In contrast, high-income countries have seen significant reductions in cervical cancer rates due to widespread implementation of Pap smear tests and HPV testing. However, even in these regions, disparities persist, with marginalized communities experiencing higher morbidity and mortality due to socioeconomic barriers to healthcare access [6, 7].

HPV INFECTION AND CERVICAL CANCER PATHOGENESIS

The pathogenesis of HPV-induced cervical cancer begins with the virus infecting the basal epithelial cells of the cervix through micro-abrasions in the mucosa. HPV infection is usually transient, with the immune system clearing the virus within 1–2 years in most individuals. However,

in a minority of cases, particularly with high-risk HPV types like HPV 16 and 18, the infection persists, leading to the integration of viral DNA into the host genome. This integration disrupts the regulation of viral oncogenes, E6 and E7, which inactivate tumor suppressor proteins p53 and retinoblastoma (Rb) [8].

Persistent HPV infection with high-risk genotypes is the most significant risk factor for the development of CIN, a precursor to cervical cancer. CIN is categorized into three grades: CIN 1 (mild dysplasia), CIN 2 (moderate dysplasia), and CIN 3 (severe dysplasia or carcinoma in situ). While CIN 1 lesions often regress spontaneously, CIN 2 and CIN 3 are more likely to progress to invasive cervical cancer if left untreated. The progression from CIN to invasive cancer can take 10–20 years, providing a critical window for early detection and intervention. However, without effective screening, the progression remains unnoticed in many women, particularly in LMICs, where cervical cancer continues to be a major cause of mortality.

Persistent high-risk HPV infections are directly implicated in the pathogenesis of cervical cancer. This underscores the need for reliable diagnostic methods to detect HPV early and prevent the progression of cancer. Effective screening programs, combined with HPV vaccination, offer the best strategy for reducing the global burden of cervical cancer, particularly in regions where access to healthcare is limited [9].

DIAGNOSTIC METHODS FOR HPV DETECTION

HC2 is a widely used diagnostic method that detects a broad range of high-risk HPV types through RNA-DNA hybridization and chemiluminescence. It is effective for large-scale screening due to its ability to process many samples and provide semi-quantitative viral load data. However, HC2 has limitations, including cross-reactivity with non-HPV DNA and low-risk HPV types, leading to false positives. Additionally, it cannot distinguish between individual HPV genotypes, which is crucial for assessing specific cancer risks like those posed by HPV 16 and 18.

In contrast, Real-Time PCR directly amplifies HPV DNA, offering higher specificity and sensitivity. Real-Time PCR can accurately distinguish between different HPV genotypes, reducing false positives and providing precise information on high-risk types. It also allows for the quantification of viral load, which helps in assessing the severity of infection and predicting the likelihood of progression to cervical cancer. This makes Real-Time PCR a more reliable and clinically useful tool, especially for early detection and tailored patient management [10].

Comparative Analysis of HC2 and Real-Time PCR

Sensitivity and Specificity

HC2 is a broad-based HPV detection method, widely used for its ability to identify multiple high-risk genotypes simultaneously. While this makes it suitable for large-scale screening, HC2 has limitations in sensitivity and specificity. The method can miss specific genotypes or produce false positives due to cross-reactivity with non-HPV DNA or low-risk HPV types. This lack of specificity is particularly problematic when distinguishing between high-risk types, such as HPV 16 and 18, which are most strongly associated with cervical cancer. In contrast, Real-Time PCR offers significantly higher specificity by directly amplifying and detecting the DNA of individual HPV genotypes. This precision enables Real-Time PCR to accurately identify high-risk genotypes, particularly HPV 16 and 18, without the cross-reactivity issues inherent in HC2.

Clinical Relevance

The clinical implications of false positives in HC2 are significant, as they can lead to unnecessary follow-ups, invasive procedures, and psychological distress for patients. False positives also burden healthcare systems with extra costs and resource demands, especially in settings where follow-up capabilities are limited. Real-Time PCR addresses these challenges by providing precise identification

of specific HPV types, thereby improving clinical decision-making. Its ability to quantify viral load and detect persistent infections ensures that patients at the highest risk of cervical cancer are prioritized for treatment, while minimizing unnecessary interventions for those at lower risk. This targeted approach reduces the overall burden on healthcare systems, streamlining care and improving patient outcomes.

IMPACT ON CERVICAL CANCER SCREENING PROGRAMS

HC2's broad detection capabilities make it an effective tool for large-scale screening programs, particularly in low-resource settings where high-throughput and cost-effective options are essential. Its ability to detect multiple HPV genotypes simultaneously allows for widespread application in population-level screening efforts. However, the lack of genotype-specific information limits its utility in tailored patient management. Real-Time PCR, though more technically demanding, provides more accurate detection of high-risk HPV genotypes, enabling better-targeted follow-ups and reducing overtreatment. Its precision in identifying patients at higher risk of developing cervical cancer allows healthcare providers to focus resources more effectively

Cost-Effectiveness

While Real-Time PCR offers superior accuracy, it comes at a higher cost compared to HC2. The upfront expenses for equipment and testing are greater, making HC2 a more attractive option for initial screening in low-resource settings. However, when considering long-term cost-effectiveness, Real-Time PCR may provide greater value by reducing the number of unnecessary follow-ups, biopsies, and treatments caused by false positives. By providing more accurate risk assessments, Real-Time PCR could ultimately lower the overall costs associated with cervical cancer screening and treatment, particularly in high-risk populations where tailored management is crucial.

CONCLUSIONS

The comparison of HC2 and Real-Time PCR demonstrates that while HC2 is a valuable tool for broad HPV screening, particularly in large-scale programs and resource-limited settings, it has limitations in specificity, often leading to false positives. Real-Time PCR, on the other hand, offers superior specificity and sensitivity, particularly for detecting high-risk genotypes like HPV 16 and 18, and provides the added benefit of viral load quantification, making it a more accurate and clinically useful tool for cervical cancer prevention. Given these advantages, adopting more precise diagnostic tools like Real-Time PCR in clinical practice could significantly improve early detection and reduce unnecessary follow-ups, ultimately enhancing cervical cancer prevention efforts. However, a balanced approach that combines both methods may be optimal, with HC2 used for initial broad screening and Real-Time PCR employed for more targeted follow-up in settings where resources allow. This flexible approach can ensure effective and cost-efficient cervical cancer screening based on the specific healthcare context.

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