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Perspective

Preventive Oncology International: A brief history of HPV self-collected vaginal specimens for cervical cancer screening

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ABSTRACT

Since 1998, Preventive Oncology International, Inc. (POI) has been at the forefront of studying human papillomavirus (HPV) self-collection for cervical cancer screening, with a significant focus in China. Through multiple clinical trials over the past 25 years, POI has explored various aspects related to self-collection methodologies. In 2004–2006, POI established that self-collection could be equivalent to direct endocervical samples. Subsequently, a large randomized trial involving 10,000 patients in 2010 further confirmed that self-collected vaginal specimens, tested for high-risk HPV (hrHPV) using a PCR-based assay with high analytic sensitivity, could effectively replace endocervical specimens with minimal loss of sensitivity and a slight decrease in specificity. Throughout the years, POI's research has encompassed several crucial topics, including patient acceptance, the development of new cost-effective, simpler, and faster assays, exploring different collection devices, devising efficient methods of specimen transport, and implementing population-based screening systems. The findings strongly support the integration of self-collection methodologies into cervical cancer control programs worldwide, particularly in medically underserved regions. As HPV self-collection continues to evolve, ongoing research and innovations are expected to play a pivotal role in achieving the global mission of combating cervical cancer.

1. Introduction

With increased attention to human papillomavirus (HPV) self-collection as primary screening for cervical cancer,[1] we were inspired to reflect on our personal journey and the "timeline of discovery" and "awareness" in the field. Twenty-five years ago, Preventive Oncology International, Inc. [POI], a US-based non-profit organization with a mission to eliminate cervical cancer, initiated collaborations with Chinese academic institutions, driven by a shared vision of combining humanitarian care with scientific investigation. Our collaborations started with the Department of Epidemiology at the Cancer Institute/Hospital of the Chinese Academy of Medical Sciences (CICAMS) in Beijing. We shall be forever grateful to Zhiwei Dong PhD., the Institute Director, who acted favorably to our collaboration offer in November 1997. Beginning in 2008, our center of operations moved to the Department of OB/Gyn at Peking University Shenzhen Hospital in Shenzhen, China. These two great collaborations guided us to unique populations and locations in China, such as in rural Shanxi or Guizhou, which both have large populations with a high need and a high prevalence of disease. Initial trials introduced liquid-based cytology and HPV testing into China.

2. The trials

In 1998, we conducted our first pilot study in Shanxi, Province,[2] which was followed by Shanxi Province Cervical Cancer Screening Study (SPOCCS), published in 2001.[3] This unique study, involving1997 participants from an unscreened population aged 35–45 with a 4.4% incidence of cervical intraepithelial neoplasia 2(CIN 2), CIN 3, and cancer

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[CIN2+]), provided us with valuable insights into various screening and diagnostic technologies. The screening tests in SPOCCS included self-collected vaginal specimens tested for high-risk HPV (hrHPV) (at the suggestion of Attila Lorencz, at the time scientific director of Digene Corporation), liquid-based cervical cytology, practitioner-collected endocervical specimens tested for hrHPV, visual inspection of the cervix following application of 5% acetic acid (VIA), fluorescent spectroscopy, and colposcopy with biopsies. In SPOCCS, the test for hrHPV was Hybrid Capture II (HC II), the self-collected vaginal specimens were obtained from the upper vagina with a dacron swab. All 1997 participating subjects had histology confirmed with a minimum of four cervical biopsies and an endocervical curettage (POI micro-biopsy protocol of directed and random biopsies).[3] The study results showed that the sensitivity of self-collected vaginal specimens for CIN 2+ (82.6%, 71/86) was lower than that of similarly tested endocervical specimens (95.4%, 82/86, $p < .001$). However, the specificity of the self-collected vaginal specimens [85.6%, 1,642/1,911] was similar to that of the endocervical specimens (85.2%, 1629/1,911, $p = .056$).[3]

To further explore the differences between self-collected vaginal specimens and endocervical specimens, we conducted a similar cross-sectional trial (Shanxi Province Cervical Cancer Screening Study II, [SPOCCS II]) of 8497 women in 2003.[4] Like the original SPOCCS, SPOCCS II used HC II as the test for hrHPV. SPOCC II differed from SPOCCS in that colposcopy with five biopsies was limited to women with positive hrHPV in either endocervical or self-collected vaginal specimens or those with cervical cytology of atypical squamous cells of uncertain significance or worse (ASC-US+); late in the trial, 462 women with negative hrHPV tests in both endocervical and self-collected vaginal specimens and cytology of ASC-US also did not undergo colposcopy. Limiting colposcopy and biopsy to this subset of subjects missed a few diagnoses of CIN 2+ as, in SPOCCS, 98.8% (83/84) women with CIN 2+ had a positive hrHPV test from an endocervical specimen or had cervical cytology of low grade squamous intraepithelial lesion or worse (LSIL+), and only 1/225 women with cytology of ASC-US and negative endocervical hrHPV was found to have CIN 2+. To potentially increase the sensitivity of the self-collected vaginal specimen in SPOCCS II, the vaginal specimen was collected with a conical-shaped brush rather than with a dacron swab. As with SPOCCS, in SPOCCS II, the sensitivity of self-collected vaginal specimens for CIN 2+ tested for hrHPV (87.5%, 328/375) was lower than that of similarly tested endocervical specimens (96.8%, 363/375, $p < .001$). In contrast, in SPOCCS II, the specificity of the self-collected vaginal specimens for CIN 2+ (77.2%, 6,272/8,122) was also lower than that of similarly tested endocervical specimens (79.7%, 6470/8,122, $p < .001$). The change in method of collection of the vaginal specimen (from dacron swab in SPOCCS to conical brush in SPOCCS II) was not beneficial as the sensitivity of self-collected vaginal specimens for CIN 2+ tested for hrHPV in SPOCCS II (85.5%, 328/375) was like that of self-collected vaginal specimens similarly tested in SPOCCS (82.6%, 71/83, $p = .23$).[4] In SPOCCS II, the sensitivity for CIN 2+ of cervical cytology with a cutpoint of ≥ASC-US (88.3%, 331/375) was lower than that of endocervical specimens tested for hrHPV (96.8%, 363/375, $p < .001$) but comparable to that of self-collected vaginal specimens tested for hrHPV (87.5%, 328/375, $p = .82$). Nearly two decades before the WHO's recommendation, we recognized the impossibility of implementing a traditional Pap screening system for reaching hundreds of millions of women in medically underserved communities. Therefore, we explored the potential of molecular hrHPV testing on self-collected vaginal specimens as an alternative method for cervical cancer screening in these populations. Therefore, we explored the potential of molecular hrHPV testing on self-collected vaginal specimens as an alternative method for cervical cancer screening in these populations.

To further understand why the sensitivity and specificity for CIN 2+ of the self-collected vaginal specimens tested for hrHPV with HC II were lower than the endocervical specimens and to explore the viral load within the vagina and endocervix, in 2006–2007, we conducted the Shanxi Province Cervical Cancer Screening Study III (SPOCCS III).[5] SPOCCS III was a cross-sectional cervical cancer screening study involving 2625 subjects. Each woman had five specimens collected, including endocervix, upper and lower vagina, perineum, and self-collected specimens. All five specimens were tested for hrHPV with HC II. For the 397 women with positive hrHPV results in either endocervical or self-collected vaginal specimens using HC II, all 5 anogenital specimens were tested for hrHPV with Linear Array (a PCR-based HPV genotyping assay, Roche, Pleasanton, CA, USA). In line with previous findings from SPOCCS and SPOCCS II, the sensitivity of self-collected vaginal specimens for CIN 2+ tested for hrHPV with HC II (80.9%, 38/47) was lower than that of endocervical specimens (97.9%, 46/47, $p = .008$) in SPOCCS III. However, the sensitivity of self-collected vaginal specimens for CIN 2+ tested for hrHPV with Linear Array (95.7%, 45/47) was comparable to that of endocervical specimens tested for with Linear Array (100.0%, 47/47, $p = 1.0$). In SPOCCS III, we analyzed the mean signal strength of hrHPV tests using HC II in different anatomical locations. Among the 34 women with true-positive hrHPV tests by HC II, the mean signal strength was higher in the endocervix (688.2 RLU/CO) compared to the self-collected vaginal specimens (273.5 RLU/CO, $p = .004$). Similarly, in the upper vagina, the mean signal strength (110.0 RLU/CO) was higher than that in the lower vagina (51.0 RLU/CO, $p = .015$) among these women. For the 165 women with positive hrHPV by Linear Array in both direct endocervical and self-collected vaginal specimens, the mean signal strength was (329.1 RLU/CO). This exceeded that of the 55 women with hrHPV test positive by Linear Array only in the self-collected vaginal specimen where the mean signal strength was 21.1 RLU/CO($p < .001$). Based on the findings from SPOCCS III, we concluded that the lower sensitivity of the self-collected vaginal specimens was attributed to a lower hrHPV viral load in the vagina. To potentially increase the sensitivity of self-collected vaginal specimens, we suggested two approaches. First, using an hrHPV assay with higher analytic sensitivity, such as Linear Array, which can detect lower copies of viral DNA (10–100 copies) compared to HC II (about 5000 copies at its positive cut-point). Second, considering the use of a collection device that can obtain a larger specimen to enhance the chances of capturing sufficient hrHPV DNA for accurate detection. The lower specificity of the self-test was associated with specimens with positive hrHPV in the vagina and negative hrHPV in the endocervix; these vaginal specimens had a very low viral load, indicating that these infections were likely recently acquired.[6] However, during that period, the available PCR assays for HPV, i.e. Linear Array, were impractical laboratory tests not suitable for large-scale clinical use. Of note, the “analytic” similarity of HPV testing using PCR for self and direct samples was reported in 2001, by Gravitt et al. in her manuscript exploring how to conduct longitudinal monitoring of HPV infection.[7]

The Shenzhen Cervical Cancer Screening Trial II (SHENCCAST II), published in 2012, provided evidence that the sensitivity of self-collected vaginal specimens for detecting CIN 3+ could be increased to match that of endocervical specimens when using the appropriate assay, irrespective of the collection device used.[8] SHENCCAST II was a cross-sectional cervical cancer screening study in which 8,556 women had endocervical specimens tested for hrHPV by HC II, Cervista (a signal-amplification method of detecting hrHPV with virtually identical performance to HC II in detecting CIN 3+),[9] and MALDI-TOF (a PCR-based matrix-assisted laser desorption/ionization time-of-flight mass spectrometry method); and self-collected vaginal specimens tested for hrHPV by Cervista and MALDI-TOF. The women participating in SHENCCAST II were randomly assigned to have their self-collected vaginal specimens obtained with samplers having a flocked nylon head or with a conical-shaped brush. When tested with Cervista, the flocked nylon head did not lead to an increased sensitivity of the self-collected vaginal specimens. The sensitivity of self-collected vaginal specimens obtained with the flocked nylon head for detecting CIN 3+ (71.6%, 58/81) was similar to that of the self-collected vaginal specimens obtained with the conical-shaped brush (76.6%, 46/60, $p = .92$). The sensitivity for CIN 3+ of self-collected vaginal specimens tested for hrHPV by Cervista (70.9%, 100/141) was

lower than that of the endocervical specimens tested for hrHPV by Cervista (95.0%, 134/141, $p < .001$). The sensitivity for CIN 3+ of the self-collected vaginal specimens tested for hrHPV by MALDI-TOF (94.3%, 133/141) was identical to that of the endocervical specimens tested for hrHPV by MALDI-TOF (94.3%, 133/141, $p = 1.0$). The specificity for CIN 3+ of the self-collected vaginal specimens tested for hrHPV by MALDI-TOF (87.5%, 7,370/8,415) was lower than that of the endocervical specimen similarly tested (89.4%, 7,526/8,415, $p < .001$). The conclusion from SHENCCAST II was that self-collected vaginal specimens tested for hrHPV with a PCR-based assay with high analytic sensitivity (e.g. MALDI-TOF) could be used as a substitute for endocervical specimens without losing sensitivity, and with a minor decrease in specificity [8].

In SHENCCAST II, we also introduced rapid processing using the PCR-based MALDI-TOF. The use of this technology was part of our vision to develop models with self-collection that could significantly increase the number of people screened compared to what current laboratory tests could handle. In 2011 we collaborated with BGI (BGI Shenzhen, China) to develop and test SEQHPV, which was the first PCR-based assay to utilize next-generation genomic sequencing.[10] SEQHPV proved to be a groundbreaking development as it offered very high throughput at a low cost while maintaining exceptional sensitivity and specificity.[11]

Over the years, our focus has been on seeking or developing technologies that would pair with self-collection and could enhance a centralized laboratory concept adaptable to massive screening programs. To achieve this, we conducted several studies on patient acceptance of self-collection[12–14] and developed very simple collection kits.[15] We then focused on specimen transport to avoid the cost and complexities provided by alcohol-containing transport liquids. We first studied and then developed inexpensive solid media transport cards.[15–18] The cards were attractive since they were light and compact, and gave patients positive feedback by changing color when the sample was placed on the card. As we progressed, we identified and tested the auto-punch system, leading to the development of new models that simplified the laboratory handling of solid media transport cards.[19] Most recently, to further reduce cost and simplify collection and transport, we explored the transport of brush specimens in a tube without the use of any transport media ("dry transport"). Additionally, we conducted studies to ensure the maintenance of sample integrity even after a two-week waiting period for processing, simulating remote screening, and transport scenarios.[20,21]

It is crucial to recognize that effective screening systems should address population-level challenges rather than focusing solely on isolated technologies.[22] This required that we initiate research on healthcare delivery systems that would allow our refined technologies to reach the people most in need. Therefore, using "community-based participatory modeling" we designed and then conducted a series of trials: first in Peru (PERCAPS)[23,24] and then in China (CHICAPS),[25] all with central processing at BGI Shenzhen. Then our colleagues in China, with special recognition to Xinfeng Qu, adapted our community-based self-collection modeling to an internet-based system.[26] Several years ago in the initial large trial using that system, 11 teams including 33 community workers and 22 local doctors screened 187,970 women in 29 days in downtown and rural Xinxiang, China, with only 0.05% uncorrectable errors. The largest number screened in one day was 14,890.[27] Due to the unique processing capacity at BGI for their Next Gen Assay (SEQHPV), it becomes easy to implement a massive expansion of this work however many important obstacles become clear. Evaluating and treating a large number of women with positive hrHPV tests is difficult. For example, in SHENCCAST II, when tested for hrHPV by MALDI-TOF, 13.8% (1,178/8,556) of women had positive hrHPV in their self-collected vaginal specimens and 11.9% (1,022/8,556) of women had positive hrHPV in their endocervical specimens.[8] While sensitivity issues were resolved, the major obstacle was specificity. Although secondary screening tests including cervical cytology, genotyping for hrHPV, viral load, dual staining for p16/Ki67, Methylation (host and viral), and automated visual evaluation have been studied,[28–35] none have yet been effective, affordable, and applicable to populations with less than an advanced health-care infrastructure. Likewise, although ablation of the cervical transformation zone with hot or cold cautery in some settings after positive self-collection might be considered, this may not be acceptable in many places. Of note, this has some historical relevance since 60–80 years ago, post-partum cauterization to "assist in cervical remodeling and repair" left the treated women with rare to no reported cases of cervical cancer.[36,37]

3. Future directions

So where does this all lead us today? There may be some countries that can establish nationwide policies and mandates. They have the potential to implement massive screening programs with centralized processing, and then dictate the application of diagnostic and risk-based management algorithms tailored to regional human and financial resources. However, it is extremely difficult to duplicate what we have seen a large organization like BGI do "in-house" in the areas of the world where today the greatest needs exist.

Many of us work in two distant worlds. Remember private/one-on-one care will always be simple. Patients return and time is invariably on our side to get the answer right. We will follow complex algorithms, and then employ the latest and greatest technologies to provide our patients with the best we can provide. However, this approach has a limited impact on cervical cancer control worldwide. For the millions of women without access to care we need thousands of providers/programs, receiving the results of inexpensive self-collected rapidly processed specimens, all armed with a simple risk-based diagnostic algorithm and inexpensive, easily transportable treatment technologies. Recently a collaboration between the NIH and Atila Biosystems (Sunnydale, CA, USA), updated the low-cost PCR-based assay "AmpFire HPV" (which reported 16, 18/45, and 12 type pool) to ScreenFire RS. The ScreenFire test reports positive results in four risk-based channels based on HPV genotyping, leading to more precise guidance for clinical care.[38] In summary, we now have self-collection techniques, fast and simple point-of-care assays with risk stratification capabilities, risk-based diagnostic algorithms, and mobile, safe treatment options. The challenge lies in integrating these various components into a cohesive system that can effectively address the cervical cancer burden. As investigators, our responsibility is to design, study, and implement such a system to make a meaningful impact in the fight against cervical cancer on a global scale.

Of course, HPV vaccination can and eventually will have a massive impact. This is already becoming evident in areas of the world with high vaccine penetration.[39] However, it will take decades to achieve the level of vaccine coverage needed to truly eliminate cervical cancer as a major public health problem.

Projecting further, are our specificity targets reasonable and/or necessary? Are there ways to make screening specificity less important? What if there were effective treatments so benign as to carry with them non-significant risk? And what if these future targeted medical therapies could be self-administered? This would further simplify the triage step of delineating risk. The current trials of topical Artesunate, now in Phase II (Frantz Viral Therapeutics, Cleveland, Ohio) potentially fall into this category.[40]

Many of you, like Preventive Oncology International, are intimately involved with studies designed to detect and prevent cancer. Our collective efforts promise to save millions of lives worldwide. And remember, Cervical HPV-related disease is only one part of the constellation of HPV-related neoplasia, which impacts the lives of both men and women. This common etiology may begin as a curse but ultimately can provide the roadmap to control cancers and their pre-cancers arising from multiple disease sites.

Disclosures

All authors were intimately involved with concept, design, conduct, analysis, and presentation of their work described in this manuscript.

All authors have advised multiple biotech companies and studied their products. Some POI studies have received product and funding from these same companies.

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Declaration of competing interest

The authors have no relevant financial or nonfinancial interests to disclose. All authors were intimately involved with the concept, design, conduct, analysis, and presentation of their work described in this manuscript. All authors have advised multiple biotech companies and studied their products. Some POI studies have received products and funding from these same companies.

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