Cervical cancer, a gender-specific disease, is caused by infection with the human papillomavirus (HPV) (World Health Organization [WHO], 2007, 2014). Genital HPV infection is the most common sexually transmitted infection in the United States and in other countries, with infection rates ranging from 14%–90% (Centers for Disease Control and Prevention [CDC], 2014; Forman et al., 2012; WHO, 2007, 2014). More than 100 types of HPV have been identified, about 40 of which can infect the genital area (CDC, 2014). High-risk types of HPV cause virtually all cervical cancer; cause most anal cancers; and cause some vaginal, vulvar, penile, and oropharyngeal cancers (Forman et al., 2012). The International Agency for Research on Cancer (IARC) assessed the carcinogenic risk of the biologic agents and classified HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 as carcinogenic to humans (WHO, 2007). Most high-risk HPV infections are asymptomatic, with most infections clearing in one to two years (Koutsky, 1997; Spitzer, 2006). However, the transient nature of the infection may cause cytologic abnormalities, which may progress to invasive cancers.

Although HPV vaccination and cervical cancer screening have been demonstrated to be effective in prevention of cervical cancer in developed countries (CDC, 2010; Markowitz et al., 2013; National Cancer Institute [NCI], 2014; WHO, 2014), these methods are too expensive for use in resource-limited and developing countries. Therefore, a need exists for inexpensive prevention methods to detect cervical precancers and cancers earlier in these countries. Several screening strategies have
been adapted as options for countries with limited resources (Blumenthal, Lauterbach, Sellors, & Sankaranarayanan, 2005; Jeronimo et al., 2014; Sankaranarayanan, Nessa, Esmay, & Dangou, 2012; WHO, 2005). Visual inspection with 3%–5% acetic acid (VIA) has emerged as a promising cost-effective method for women who live in resource-limited countries (Jeronimo et al., 2014; WHO, 2005). The objectives of this article are to examine and discuss (a) the burden of cervical cancer in developing countries, (b) the socioeconomic determinants of primary and secondary prevention of cervical cancer, (c) VIA and Lugol’s iodine (VILI) as alternative methods of screening for resource-limited countries, and (d) the implications of using visual inspection methods in reducing cervical cancer burden in developing countries.

Cervical Cancer Burden in Developing Countries

Cervical cancer is the fourth most common cancer among women worldwide, with about 528,000 new cases and more than 266,000 deaths reported annually (WHO, 2015). About 85% of cervical cancer occurs in developing countries, where most women have never been screened, and it tends to be diagnosed in later stages when treatment is less viable (Baseman & Koutsky, 2005; WHO, 2012). A comprehensive meta-analysis of 194 studies (Bruni et al., 2010) to assess the burden of HPV infection in women (N = 1,016,719) with normal cytologic findings demonstrated that 12% of women worldwide with normal cytologic findings carry detectable cervical HPV infections; however, rates of infection differ greatly by region, from 2%–35%. The Caribbean, Eastern, Southern, and Western regions in Africa had the highest prevalence (22%–35%), and Western Asia, North America, and Western Europe had the lowest prevalence (2%–7%). Studies of women with cytologic abnormalities have reported the prevalence of HPV infection increasing in direct proportion to the severity of the lesion, reaching about 90% in women with invasive cervical cancer (Guan et al., 2012). IARC launched GLOBOCAN (Global Burden of Cancer) in 2008 to provide a more accurate assessment of the burden of global cancer. According to the GLOBOCAN 2008 database, the estimated HPV-associated burden of cancer showed that the highest burden and mortality exists in developing countries, where a five-year survival rate of less than 20% exists in countries with a low human development index (HDI) compared with a more than 65% survival rate in countries with a high HDI (Forman et al., 2012).

The incidence of and mortality from cervical cancer have declined in North America and Western Europe during the past 50 years because of the increased availability of cytologic screening with Papanicolaou (Pap) smears and the introduction of HPV vaccination in 2006 (CDC, 2007, 2010; Markowitz et al., 2013; WHO, 2005, 2014). However, cervical cancer is a major source of morbidity and mortality in lower socioeconomic settings. In Africa, 99 new cases of cervical cancer are diagnosed per 100,000 women annually, and 60.1 per 100,000 women die from that cancer compared with a 14.4 incidence rate and 7.1 deaths per 100,000 women in North American (Ferlay et al., 2015). The prevalence of cervical cancer has increased faster than would be expected relative to the slow improvement of life expectancy in developing countries, which is as low as 51 years in sub-Saharan Africa (compared to 79 years in the United States and 84 years in Japan) (WHO, 2013). The lower life expectancy in developing countries would, theoretically, not allow most of the population to reach the age at which noninfectious diseases, such as cancer and cardiovascular diseases, occur. However, the survivors of infectious diseases are now facing the threat of noninfectious diseases, such as cancer, in these resource-limited countries. Previously, HIV/AIDS-related mortality outweighed the risk of dying from cervical cancer in HIV/AIDS-endemic regions. However, improvement in the screening and treatment of HIV has resulted in significantly decreased HIV/AIDS-related mortality (Bendavid & Bhattacharya, 2009). This means that women will live longer but will now face the risk of developing invasive cervical cancer, particularly cervical cancer that occurs among relatively young women. The disease not only affects the mortality of the woman herself, but also has negative consequences for her children and family. The disproportionately high burden of cervical cancer in developing countries exists because of the few primary and secondary prevention measures in place to detect precancerous and early-stage cervical cancer that are cost effective and accessible.

Socioeconomic Determinants of Primary and Secondary Prevention of Cervical Cancer

Because carcinogenic HPV infections cause virtually all cervical cancer, cervical cancer can be prevented by HPV vaccinations in younger women and cancer screening in older women. Two HPV prevention vaccines are now available. Bivalent HPV2 targets two oncogenic types (HPV 16 and 18) and quadrivalent HPV4 targets four subtypes of HPV: two oncogenic types (HPV 16 and 18) and two nononcogenic types (HPV 6 and 11). Both vaccines have high efficacy in preventing HPV 16- and 18-related cervical precancerous lesions. (CDC, 2007, 2010, 2014; WHO, 2007). However, the prevalence of HPV 45 was higher in Africa and South/Central America and HPV 58 was higher in Eastern Asia. These subtypes showed an increase in invasive cervical cancer compared to HPV-positive women with normal cytology (De Vuyst et al., 2013; Guan et al., 2012), therefore indicating a need for development of a vaccine specific to HPV subtypes in these populations.

HPV vaccinations can be very expensive, ranging from $86–$134 for one dose in the United States (CDC, 2015). This price often is too high for most women in developing countries. To put this in perspective, 45% of people in Sub-Saharan Africa live on $1 per day, which covers essential basic needs such as food and clean water (United Nations Development Programme, 2014). Vaccine prices must dramatically decrease to enable broad access in the developing countries where high mortality rates from cervical cancer occur and high numbers of women will be infected.

Some lower-income countries with vaccine pilot programs have been able to achieve high vaccine coverage. For example, PATH, a global health nongovernmental organization, has conducted demonstration programs in India, Peru, Uganda, and Vietnam. The vaccine was delivered through school-based programs and coverage ranged from 83% in Peru to 89% in Uganda to 96% in Vietnam (LaMontagne et al., 2011). Developing more
programs reflecting socioeconomic contexts of developing countries is imperative to increasing HPV coverage.

The basis of cytology methods of screening for cervical cancer was developed by Papanicolaou (Papanicolaou & Traut, 1941) in the early 1940s and is known as the Pap smear. In developed countries, regular screening with Pap smears has been shown to effectively lower the risk for developing invasive cervical cancer by detecting precancerous changes (NCI, 2014). However, more than 80% of cervical cancers in sub-Saharan Africa are detected in later stages because of the low level of knowledge and awareness of cervical cancer in the general population and by healthcare providers (Sankaranarayanan, Budukh, & Rajkumar, 2001), as well as insufficient human and financial resources to implement effective screening programs to detect and treat precancerous lesions or early-stage cervical cancer (Forman et al., 2012; WHO, 2007). Many countries with limited resources lack the infrastructure and systems to support effective screening services and very few women are ever screened. Establishing a quality cytology-based screening program is often beyond the capability of developing countries. The high burden of cervical cancer combined with limited resources for cytology-based screening programs has led to the adoption of several screening strategies as options for developing countries (Sankaranarayanan et al., 2012; WHO, 2005).

In addition to the cost, sociocultural barriers to cytology-based screening programs in developing countries and delayed time intervals between the screening and findings of the test result in many of the screened women not returning for their test results. WHO (2014) recommends the use of Pap smears/cytology for large-scale cervical cancer screening programs if sufficient resources are available. For resource-limited countries, however, WHO (2014) recommends visual screening methods followed by cryotherapy. Studies have demonstrated that VIA is an alternative screening method in resource-limited countries.

Visual Inspection: An Alternative Screening Strategy

VILI of the cervix was the first method used for cervical cancer screening and was introduced in 1938 by Schiller. Because of its poor specificity, it was later replaced by cervical cytology. However, visual inspection methods reemerged as a screening method in low-resource settings, despite its limited specificity, because of low cost, use of readily available materials, and the immediacy of test results. VIA and VILI are not based on cytology but, rather, on the see and treat concept. Visual inspection methods are vision-based tests based on the fact that the majority of pre-invasive and invasive cervical changes are visible by the naked eye. Also called cervicoscopy, or direct visual inspection, these methods may be enhanced by low magnification (also called gynoscopy or colposcopy).

VIA is an affordable method for screening cervical cancer and has emerged as an alternative method to screen for precancerous cervical lesions or early-stage cervical cancers in developing countries (Sankaranarayanan et al., 2012; WHO, 2014). In VIA, a trained healthcare provider examines the cervix with the naked eye before and after application of acetic acid to look for acetone whitening of the tissue (acetowhite). Abnormal cervical tissue that comes into contact with the acetic acid dilution temporarily turns white in color, allowing the provider to make an immediate assessment that can be followed by immediate treatment. Programs that link screening and treatment are referred to as see-and-treat programs, or the single-visit approach.

Acetic acid is applied to the uterine cervix to discriminate abnormal epithelium from the background of normal epithelium in the transformation zone. Some providers have used cotton balls to apply acetic acid, whereas others prefer a spray bottle of acetic acid. Regardless of the application method, the amount of acetic acid should be sufficient to elicit an optimal acetowhite reaction. Administering an insufficient amount of acetic acid or misjudging the waiting time for inspection of the patient after application is one of the most frequent reasons for false-negative results. This is because it takes time for the acetic acid to interact with the epithelial cells, resulting in swelling and color change.

The results of VIA testing may be reported as VIA-negative, VIA-positive, or suspicious for cancer (Carr & Sellors, 2004; Sankaranarayanan et al., 2012) (see Table 1). Normal squamous epithelium is light pink in color and the columnar epithelium is red (see Figure 1a). In contrast to the normal epithelial cells, abnormal epithelial cells have an increased nuclear-to-cytoplasmic ratio compared with normal cells, which causes the acetowhite reaction. The degree of the acetowhite reaction is correlated with the severity of the cervical epithelial abnormality. Low-grade lesions reveal a translucent or snow-white color (see Figure 1b), whereas high-grade lesions reveal thick oyster-gray color. Finding both suspicious and positive lesions in the same patient is common (see Figure 1c).

VIA testing may give a false-negative result; however, if the entire transformation zone is visually examined, the examiner will be able to see acetone white changes in the transformation zone and well-defined borders, which are considered to be a positive result. The cervix is covered by squamous cells (on the exocervix) and glandular cells (on the endocervix). Glandular cells are constantly migrating outside the canal and undergo changes called squamous metaplasia. The region of the cervix where squamous metaplasia occurs is referred to as the transformation zone, and most cervical cancers start in the cells in the transformation zone (WHO, n.d.). Cervical abnormal cells located in the deep endocervix often are likely to be missed unless

<table>
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<th>TABLE 1. Classification of Cervical Cancer Screening</th>
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<td><strong>Category</strong></td>
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<td>VIA-negative</td>
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<td>VIA-positive</td>
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<td>Suspicious for cancer</td>
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<td>VIA—visual inspection method of screening with acetic acid</td>
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the examiner pays careful attention using special instruments, such as an endocervical speculum. Similarly, broad acetowhite epithelium can be difficult to notice because prolapsing vaginal sidewalls can hinder visualization of the entire lesion. A lateral vaginal sidewall retractor or a speculum with a sleeved condom is helpful for patients who have lax vaginal walls.

Several meta-analyses have been reported on VIA’s accuracy and performance based on large clinical trials. A systemic review of the performance of VIA in six studies involving more than 65,000 women in Burkina Faso, China, Congo, Guinea, India, Mali, Niger, Zimbabwe, and South Africa revealed that the sensitivity of VIA varied from 67%–79% and specificity ranged from 49%–86% (Sankaranarayanan, Gaffikin, Jacob, Sellors, & Robles, 2005). However, according to more recent reports from the meta-analysis, the sensitivity and specificity of VIA were as high as 92% (Sauvaget, Fayette, Muwonge, Wesley, & Sankaranarayanan, 2011).

VIA screening is shown to be an effective method to screen for cervical cancer in developing countries. A study assessing a variety of cervical cancer screening strategies in five developing countries (India, Kenya, Peru, South Africa, and Thailand) reported that a single visit for VIA screening at the age of 35 years reduced the lifetime risk of cancer by 25%–36% (Goldie et al., 2005). In addition, the relative cancer risk declined by an additional 40% with two screenings (at 35 and 40 years of age). In a randomized trial in South Africa, VIA screening followed by cryotherapy resulted in a 37% and 46% lower incidence at 6 and 12 months, compared with a control group who received a delayed assessment at 6 months (Denny et al., 2005).

A major limitation of VIA screening is the subjectivity of the test. The accuracy of VIA or VILI depends on the ability to see the cervical transformation zone, the criterion to define lesions, and the expertise of the evaluator to conduct it. Therefore, developing high-quality evidence-based training programs, providing effective supervision, and seeking continuous quality improvement are essential. Such training programs should be evidence-based, practical, accessible, culturally appropriate, and easily understandable for the intended audience (Sankaranarayanan et al., 2012).

In resource-limited settings, VIA screening, which is simple, easy to learn, and requires a minimum of infrastructure, will provide screening coverage to a larger percentage of the population than cytology. In addition, VIA training can be provided not only to physicians but also to non-physicians, including nurses and midwives, and within a short period of time (usually one to two weeks). These advantages can provide a framework to integrate VIA screening into primary healthcare services.

Conclusion

Despite the efficacy of HPV vaccines to prevent infection and the development of cervical cancer, the vaccine is often not available or affordable for women in less-developed countries. Until vaccination programs are integrated into every country’s national immunization program, the benefit of the vaccines will be limited only to the developed countries with financial resources. In resource-limited settings, cervical cancer prevention relies on secondary prevention methods. Pap smears have been shown to be effective in detecting precancerous and cancerous lesions of the cervix in the developed countries. However, because of a lack of healthcare infrastructure and human and financial resources, a high-quality cytology-based program is difficult to implement in developing countries. Alternative, cost-effective strategies that are affordable in low-resource settings are necessary, and VIA has been shown to be an effective alternative strategy for providing cervical cancer screening in low-resource settings.

VIA provides clinicians with objective criteria to use in screening for cervical cancer and precancerous lesions. Physicians or non-physician trainees, such as nurses, can rapidly increase their skills at performing the procedure, which is a strength of VIA when compared with cervical cytology that requires the knowledge of experienced pathologists. However, developing a standard training curriculum and quality standards in VIA screening is necessary to minimize the rate of false-positive results. Certification programs should be developed and only those who have successfully completed these programs should conduct VIA procedures. In addition, like the Pap smear, VIA assessments rely on subjective visual interpretation. Consistent diagnostic criteria for lesions should be developed and providers should be trained to correctly use these criteria to ensure the quality of the VIA screening and to achieve substantial gains in the prevention of cervical cancer.
Implications for Practice

- Promote primary and secondary cervical cancer prevention in developing countries.
- Increase human papillomavirus vaccination coverage by reducing vaccine price, and develop evidence-based screening training programs.
- Use visual inspection methods of screening with acetic acid and treatment with cryotherapy.

Implications for Practice and Research

VIA screening has unique advantages for nurses: it requires only a 3%–5% dilute acetic acid administered with cotton swab or a spray, and VIA can be done by non-physicians such as nurses, midwives, and paramedic workers after a short competency-based training program. Nurses can take the lead in developing evidence-based VIA screening training programs and integrate them into nursing practice in developing countries to reduce global health disparities. However, more studies are needed to compare the impact of VIA screening on the incidence of cervical cancer in other developing countries where VIA screening has not been implemented. It also is important to evaluate the effect of a standard training program on the quality of VIA screening.

References


