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Cervical cancer worldwide

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ABSTRACT

Cervical cancer is the fourth most common cancer among women globally. The burden faced by low- and middle-income countries is significantly greater than high-income countries. The disparity is a direct result of the differences in resources. Developed nations have organized vaccination and screening programs that have decreased their cervical cancer incidence. More readily available personnel and technology exists to implement appropriate treatment modalities. However, for many underdeveloped nations, the scarcity of resources and infrastructure make such preventative and treatment programs limited or even nonexistent.

Introduction/Disparity in low- and middle-income countries

Cervical cancer is a growing global burden, both for developing and industrialized nations. In 2012, cervical cancer caused an annual mortality of 266,000 and recorded 528,000 new cases.[1] It is often coined a "disease of disparity," due to the striking disproportion in incidence and mortality between low- and middle-income countries (LMIC) and the counter high-income countries (HIC). Internationally, cervical cancer is the fourth most common cancer in women. However, not

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Surprisingly, it is the LMIC who bear the weight of this statistic; where it is the second most common cancer and is responsible for approximately 85% of total new cases worldwide.[2] Most recent data suggests that cervical cancer represented 7.5% of all female cancer deaths; of those deaths, approximately 90% occurred in LMIC. Compared to HIC, LMIC have an 18-fold increase in mortality.[1] The World Health Organization (WHO) defines high risk regions to include Eastern, Southern, and Middle Africa, and Melanesia.[2] In fact, in Africa and Central America, cervical cancer is the leading cause of cancer-related deaths among women.

As a global health priority, cervical cancer control serves as an example of the substantial differences between LMIC and HIC regarding public health priority, healthcare resources and infrastructure, cultural barriers, technology, and ability to address prevention and treatment strategies. A comprehensive prevention and control strategy should include all three prevention tiers: primary prevention with human papillomavirus (HPV) vaccinations, secondary prevention where women are screened and treated, and tertiary prevention in which all identified invasive cancers are treated as necessary. The difference in age of peak HPV infection and peak of cancer incidence is two to four decades, making screening an ample area for innovation and progression toward improved disease management.[3] While vaccination programs and routine screening have been very effective in reducing cervical cancer in HIC, LMIC continue to struggle to do the same.

In order to understand the disparity of cervical cancer in LMIC, one must look no further than the challenges in implementing cervical cancer management strategies, which are multifactorial. LMIC lack the political commitment to maintain healthcare as a paramount concern in light of competing priorities such as clean water, electricity, famine, industry, or education. Current infrastructure may not exist to handle the entire scope of care needed to combat disease progression and advanced management on the national level. Moreover, successful campaigns need consistent and continued advocacy, education, and communication with the population to raise awareness. This often proves challenging when even patient accessibility may stand in the way. Reaching girls not enrolled in school for vaccinations, gaining access to populations geographically isolated for HPV testing, or transporting patients to tertiary care centers for appropriate management can be very resource-consuming. When adequate infrastructure is in place, cultural concerns such as stigmatization, religious taboos, superstition, or shame of sickness may inhibit patients from utilizing resources. Societal barriers such as poverty, illiteracy, spousal support, and distrust in the healthcare system further distance communities from access to services. Systemic underutilization in LMIC may also be attributed to the absence of general knowledge surrounding HPV and cervical cancer, lack of public health policy, need for greater awareness, underdeveloped health facilities, patients' own financial constraints, and inadequacies in professional education.[4,5]

Management strategies in low- and high-resource settings

Vaccination

HPV is the critical insulting agent for development of cervical cancer, detected in 99.7% of cases.[6] Sub-Saharan Africa has the highest global prevalence of HPV, doubling the adjusted global prevalence.[3] There is a firmly established causality between persistent infection of high risk HPV and cervical cancer. Data from industrialized countries of HPV prevalence show a lifetime probability of contracting HPV is as high as 80%-90%, the majority of which will spontaneously resolve with clinical signs or symptoms.[3] However, it is estimated that 10% of infected individuals will subsequently develop precancerous changes.[7] Although various factors have been suggested, the underlying reasons for virus clearance versus persistent infection and subsequent neoplastic transformation are still unclear. There are over 40 serotypes of HPV recognized to infect the human genitalia, 15 of which are known to be oncogenic. Serotype 16 and 18 accounts for 70% of all cervical cancers. Cancer arises as a consequence of HPV oncoproteins E6 and E7 which inactivate p53 and pRB tumor suppressors, respectively.

The HPV vaccine provides an opportunity for the primary prevention of cervical cancer by targeting the oncogenic serotypes. The concept behind prophylactic vaccinations is to achieve

high levels of neutralizing antibodies against specific oncogenic HPV serotypes that are capable of preventing cervical infection in HPV-naive individuals. Currently there are three approved vaccines to prevent HPV infection: bivalent HPV vaccine (Cervarix), quadrivalent (Gardasil), and the 9-valent formulation (Gardasil 9). All three vaccines protect against HPV serotypes 16 and 18. The quadrivalent vaccine also provides protection against HPV types 6 and 11, which can cause genital warts and low-grade cervical changes. Moreover, the 9-valent vaccine additionally targets five other high-risk HPV serotypes (31, 33, 45, 52, and 58).[8] These vaccines were first introduced to HIC in 2006 for widespread use, yet their use in LMIC has been limited.[9] It is estimated that if 70% vaccine rates could be achieved, there would be a decrease of 344,520 new cases of cervical cancer per year and avoidance of 178,182 deaths.[10] In developed countries where utilization of vaccinations is greater than 70%, there has already been a documented 38% reduction in high grade dysplasia.[11]

In efforts to combat the cervical cancer burden in LMIC, the WHO has partnered with Global Alliance for Vaccine Initiatives (GAVI), an international organization which aims to create equal access to vaccinations for children living in the world's poorest countries. The GAVI HPV program worked with vaccine manufacturers to drastically reduce the price of vaccines from over US $100 to $4.50 per dose.[12] As a member of the Global Vaccine Alliance, the WHO is working to increase access to the vaccine, with the goal of vaccinating over 30 million girls in more than 40 countries by 2020, thereby averting an estimated 900,000 deaths.[2,12] GAVI-eligible countries have the option of either the bivalent or quadrivalent vaccines with efforts to vaccinate girls aged 9 to 13 years old.

In 2012, GAVI opened applications for funding to provide support to countries interested in introducing HPV vaccination. Between 2013-2014, the GAVI HPV program supported eight projects in African countries. By 2016, GAVI funding has helped 23 countries introduce the HPV vaccine and three countries introduce nationwide immunization programs.[12,13] Over one million girls have been vaccinated with GAVI support, which is very progressive considering past decades of delay between new vaccine availability and implementation in developing countries.[14]

Screening

Cervical cancer has a long preclinical phase that can span decades without symptomatic effects on women. The role of an effective screening test is to detect precancerous lesions before it progresses to invasive cancer. With the advent of the Papanicolaou (Pap) cytology-based test in the 1940s to identify abnormal cervical cells, it became the standard screening tool adopted by many HIC. The implementation of Pap screening programs has resulted in a reduction of up to 80% in the incidence of cervical cancer among developed nations.[15] However, its utilization in many middle-income countries (MIC) have been suboptimal and in many low-income countries, even nonexistent. This disparity is largely due to the lack of resources to create effective Pap screening programs in underdeveloped communities. Successful preventative screening programs require well-organized infrastructure with skilled personnel to obtain and interpret the cytology specimens, access to clinical and laboratory materials, and financial means for implementation and sustainability.

Since complex high-quality Pap screening programs pose such great barriers, attention has turned to the development of more cost-effective screening alternatives in LMIC. The WHO issued recommendations for developed nations with sufficient resources to utilize cytology-based screening programs, whereas countries with limited resources should adopt screening methods using either HPV or visual inspection.[16] One study examined the cost-effectiveness of screening programs in 23 African nations with high burden of disease from cervical cancer. The estimation of over a ten-year interval for a cytology screening program would be less than US $10 per woman screened as opposed to US $6 per woman for a visual inspection screening model.[17] The visual inspection approach focuses on the premise of a "single-visit screen and treat."[18,19] One of the challenges of the standardized Pap model is the requirement of multiple visits in order

to be effective. It requires an initial Pap screening visit. An abnormal cytology result prompts a second visit for diagnostic testing with colposcopy and biopsy procurement. It is only with a third visit when treatment is performed. In less developed communities where access to care is already scarce and compliance can be an obstacle, such a paradigm would be economically unfeasible.

"Single-visit screen and treat" approaches have been proposed using visual inspection screening methods followed by immediate treatment with cryotherapy or cold coagulation. Visual inspection entails application of either 3%-5% acetic acid (VIA) or Lugol iodine (VILI) on the cervix with direct treatment of screen-positive cervical sites several minutes later. Compared to Pap tests, these visualization techniques have greater sensitivity but less specificity.[20,21] Given its lower cost and greater potential for large scale impact, visualization screening methods are more suitable in low-income communities.

In comparing VIA to VILI, some systematic reviews suggest an even higher sensitivity of VILI compared to VIA. This is dependent on the visualization techniques employed by the healthcare provider to detect cervical color changes. With acetic acid, detection of acetowhite changes can be much more subtle than Lugol iodine solution which demonstrates unstained abnormalities more distinctly.[22,23] One study describes VILI as the more useful screening test between the two visual screening modalities with improved sensitivity but comparable specificity.[24]

Another school of thought is the introduction of self-sampling HPV tests compared to conventional tests. Though less sensitive than conventional clinician-collected tests, HPV self-sampling kits offer the promise of higher participation among women who may be difficult to reach geographically or culturally. It has the potential of decreasing societal stigma, embarrassment of testing, or implications of infidelity. However, self-sampling can pose limitations in sampling inaccuracy or failure to follow-up on results.[25]

In a systematic review comparing the different screening tools in LMIC, once in a lifetime testing with HPV had a superior sensitivity and greater reduction in cervical cancer incidence compared to VIA or cytology testing.[26] It was evident that Pap testing was the least cost-effective modality in LMIC. However, the review also cited the overall higher expense of the HPV strategy than visual inspection. Furthermore, HPV testing would likely require a two-visit approach as the test itself necessitates processing time. This burden leads to the likelihood of poorer compliance.

In LMIC, if once per lifetime screening of all women at age 35 years was performed using either the VIA one-visit or the HPV two-visit program, one study projected a decrease in lifetime cervical cancer risk by 30%. This would equate to a less than US $500 per year of life saved.[27] The development and implementation of a more affordable HPV test would make it an optimal screening tool in LMIC. By improving its cost-effectiveness and processing time, it could tangibly reduce the overwhelmingly high disease burden of cervical cancer plaguing these underdeveloped communities of the world.

Treatment

The treatment of cervical cancer is based on the International Federation of Gynecology and Obstetrics clinical staging criteria. With adequate screening programs, cervical precancerous lesions can be detected and treated early with low-expense technologies, such as cryotherapy, loop electrosurgical excision procedure, or thermocoagulation.[28] Unfortunately, with the preponderance of advanced stages of cervical cancer in LMIC, these effective low-cost methods would not be sufficient. Nearly 80% of women diagnosed with precancerous lesions in these countries go untreated.[29]

Once disease is invasive, the treatment modalities for cervical cancer become more extensive with radical surgery or chemoradiation. Thusly, with more progressive cervical cancer, it follows suit that therapy regimens also become more costly. Early stage disease can be managed surgically with cervical cone biopsy, simple or radical hysterectomy, and pelvic lymphadenectomy. With late stage disease, the recommended therapeutic options also include chemotherapy, external beam radiation, and brachytherapy. The majority of these advanced treatments hinge on a

multidisciplinary approach, requiring collaboration among gynecologic oncologists, medical oncologists, radiation oncologists, radiologists, and nursing specialists.[30] Although advanced imaging techniques such as computed tomography, magnetic resonance imaging, or positron emission tomography are not required in International Federation of Gynecology and Obstetrics staging, they can be useful adjuncts in formulating treatment plans. Moreover, the expense of such techniques may be beyond the resource scope of many LMIC.[31]

In LMIC where diagnostic resources are already scarce, patients are often plagued by late stage disease. The dearth of financial, technical and human resources make therapeutic measures exceedingly difficult. The American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network developed a practice guideline to address the management of cervical cancer for different resource settings, categorized as basic, limited, enhanced, or maximal resources. Cone biopsy is recommended in the basic setting for stage IA1 cervical cancer, whereas both cone biopsies and pelvic lymphadenopathy are recommended in the limited setting. For stage IB1 cancer patients desiring future fertility, radical trachelectomy is the preferred therapy in the enhanced and maximal-resource settings. The management of cervical cancer deviates from the standard treatment most noticeably for patients with advanced-stage disease in the basic setting.[32] In patients with locally advanced cervical cancer, neoadjuvant chemotherapy has been demonstrated to be as effective as the standard, albeit more costly concurrent chemoradiation, in terms of disease response.[33] When available, neoadjuvant chemotherapy is encouraged in LMIC for large tumors or advanced disease with the intent to reduce the tumor size for surgery. In regions where radiation therapy is unavailable for advanced stage disease, isolated simple hysterectomy with or without prior chemotherapy is the preferred management if this can be performed safely with negative margins.[32]

Surgical intervention is limited by costs of equipment and facilities, and access to skilled personnel and surgical specialists. There is a high demand for both cultivating and retaining specialists in these low-resource settings. In recent years, great emphasis has been placed on improving educational programs for surgical residents and gynecologic oncologic fellows.[34,35] A global curriculum and training program is currently being developed by the International Gynecologic Cancer Society to teach international gynecologic oncology.[36] With the different platforms of social media, video and online technology, access to training curricula is becoming more widespread in LMIC and hopefully will play a role in decreasing the gap in the disparity of care.

In addition to the current limitations in surgical services, access to radiotherapy is another significant obstacle. Radiation therapy remains a mainstay treatment for advanced cervical cancer in combination with chemotherapy. Unfortunately, the technologies of external beam radiation and brachytherapy are largely inaccessible in most underdeveloped communities, making treatment of advanced disease inadequate. Among 139 LMIC, only four met the demands for external beam radiation therapy, while only one-third of the needs were met in 80 nations, and there was no access whatsoever in the remaining 55 countries.[37] Brachytherapy is considered a mainstay radiation therapy method for cervical cancer of stage IB or greater. Strategies have been developed to adapt guidelines of The American Brachytherapy Society to accommodate the limited resources of LMIC. The recommendations include considerations of staging, treatment field, duration, dosage, applicator placement using bony landmarks instead of imaging techniques, external beam radiotherapy, and the use of concurrent chemotherapy.[38]

The goal may not always be curative for advanced stage disease; treatment for the purpose of cervical cancer control is often a more realistic option in LMIC. According to the ASCO, the highest level of care should be provided to patients whenever resources deem it possible.[31] This can include mixed methods of treatments adapted from standard practice guidelines to optimize the management of cervical cancer in patients and minimize the disease burden among LMIC.

Palliative care

A far too often overlooked element in the management of cancer patients is palliative care. Although palliative care is a human right, in resource-limited areas, services devoted to preventing and relieving suffering are commonly not of preeminent concern. An estimate of over 30 million people each year qualifies for palliative care services in LMIC, which accounts for 78% of the global need. However, in LMIC access to quality palliative care is very limited or nonexistent in the majority of cases. Worldwide, only approximately 14% of eligible patients are actually receiving palliative care.[39]

It is estimated that 34% of adults who would benefit from palliative care have cancer-related chronic disease.[39] The demand for palliative care for cervical cancer patients is also understandably higher in LMIC. This is due to the advanced stages upon diagnosis and the inadequate or inaccessible tertiary facilities to coordinate complete management. Local disease progression leading to ureteral pain, obstruction, and fistulas are often encountered prior to death from cervical cancer. Late-stage symptoms may also require physicians to perform urogenital management for tumor-directed treatment. Patients with advanced terminal disease may eventually need palliative care.

Widespread access to palliative care must first overcome multiple significant challenges. One such barrier is the lack of palliative care education amongst healthcare professionals, government policy makers, and the general public. Among clinicians, there is confusion regarding the utility, indications, or even a complete lack of knowledge about palliative care which ultimately leads to less or inadequate utilization and referrals.[40] Training on palliative care for providers is also often limited or nonexistent.[39] On a macroscopic level, palliative care is often not included in national health policies. When policy is not in place, this leads to disorganization to access, poor coordination, and lack of sustainability.[41] Furthermore, limited availability to essential opioids in LMIC is an area of focus which needs to be addressed in order to fully integrate palliative care into the healthcare system.[39,40,42] Appropriate funding and resources is the final major struggle between LMIC and adequate palliative care. In Africa, revenue for palliative care depends largely on foreign aid from both private organizations and government agencies.[40]

As palliative care has slowly evolved, it is still far from mainstream, secondary to these pivotal obstacles. In Africa, where disease burden is highest, about half the countries have no palliative care services.[40] In the majority of those African countries, palliative care is only offered in isolated tertiary facilities which are remote to the vast population.[41]

For palliative care treatments to be effective, they must be incorporated into all facets of healthcare and be easily accessible.[42] To assist in the integration of palliative care, ASCO has provided guidance on implementing palliative care to cancer patients. The consensus supports addressing palliative care with patients at the beginning stages of treatment, especially when disease-modifying interventions are not available, as in much of the LMIC.[43] Additionally, guidelines support the essential use of opioid analgesics and to ensure that the supply is readily available for these patients. ASCO guidelines also stress the necessity in training all healthcare professionals on basic palliative care skills. These include identifying the palliative care needs of patients and their families, pain management, symptomatic assessment, supportive care, and prescribing medications. As a multidisciplinary team approach, oncologists, surgeons, nurses, pharmacists, spiritual providers, psychologists, social workers, mental health professionals, and community health workers all play a role in the cumulative care of palliative care patients.

Conclusion/Moving forward

The disparity in cervical cancer incidence and prevalence between HIC and LMIC is a direct result of the differences in resource availability (Table 1). With the development of more cost-effective methods for prevention, screening, and treatment, positive change can be achieved in LMIC. There is resounding evidence over the last few decades from developed countries that reductions in both morbidity and mortality from cervical cancer can be realized with the installation of well-organized programs. It is paramount that similar paradigms be created in LMIC to

Table 1
Current status of cervical cancer and its management in low- and high-resource settings.

	Low-resource settings	High-resource settings
Incidence and death	85%	15%
Vaccination	Girls (ages 9-13)	Boys and girls (ages 11-26)
Screening	HPV screening VIA (lowest resource settings)	HPV screening Pap and HPV co-testing
Treatment	Early (IA2, IB1, IIA1): radical hysterectomy + pelvic lymphadenectomy or concurrent chemoradiation or neoadjuvant chemotherapy followed by radical hysterectomy + pelvic lymphadenectomy	Early (IA2, IB1, IIA1): radical hysterectomy + pelvic lymphadenectomy or concurrent chemoradiation
	Locally advanced: concurrent chemoradiation or neoadjuvant chemotherapy followed by radical hysterectomy + pelvic lymphadenectomy	Locally advanced: concurrent chemoradiation
Palliative care	Development is needed; Pain control is basic human rights	Palliative care is widely offered to terminally ill patients

decrease the burden of disease. Using economical practicality and innovation, we have a responsibility to tackle this global problem and eliminate that disparity. With the vaccines we have engineered, the screening and diagnostic tests we have established, and the treatments we have developed, cervical cancer is certainly a preventable disease. Advanced stages of cervical cancer are those we should not have to encounter in the future.

By utilizing resources created by organizations such as GAVI, our global society can work toward a goal of worldwide HPV vaccination to curtail the development of cervical cancer. With the well-established higher incidence of HPV and cervical cancer in LMIC, the urgency for efficient preventative screening tools is palpable. Focus should be placed on the development of a test that is cost-effective and accessible to a breadth of women. The current HPV-DNA-based assay is the conventional screening tool used by HIC, but rarely accessible to LMIC due to its high cost and requirement of more sophisticated testing platforms. Recently, a new point-of-care test, known as the *care*HPV test by Qiagen could be a possible alternative assay that can be optimized for LMIC. It is a simplified version of its more expensive counterpart, Diagene Hybrid Capture 2 assay with a more modest testing platform. The battery-operated test requires processing time of only 2.5 hours by trained staff using only a small bench work-space. Unlike the Hybrid Capture 2 assay, it has a longer shelf-life and does not require running water to perform the test.[44] Based on the resource-stratified guidelines of the National Comprehensive Cancer Network and ASCO, the objective is to improve patient survival from cervical cancer. In addition, screening and early treatment is essential to make such guidelines successful. Implementation of appropriate treatment early with surgery can prevent disease progression that would warrant the use of the more costly modalities of chemoradiation or brachytherapy for curative results.

All the potential solutions for improving the prevention and management of cervical cancer in LMIC hinge on two critical factors for success: the allocation of resources and the distribution of knowledge. Governing bodies and health institutions need to realize the urgency in reallocating funds and developing programs to curtail the problem. By investing in cost-effective vaccinations and preventative screening programs, the financial burden will be significantly less than combating the exponential costs of managing advanced disease in growing populations. The skill and knowledge among healthcare providers and trained personnel are needed to disseminate these preventative practices and treatment programs.

As the fourth most common cancer among women worldwide, cervical cancer is a global problem that necessitates a global effort. Solving this crisis will require a multifaceted approach from world leaders, policymakers, health specialists, and philanthropic organizations. Progress

has been made with vaccinations, new screening tools, and cost-effective treatment plans, but there is still a long road ahead of us, and it is far from over.

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