

## REVIEW ARTICLE

# Cervical cancer prevention and treatment in Latin America

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Cervical cancer is a preventable disease with a known etiology (human papillomavirus), effective preventive vaccines, excellent screening methods, and a treatable pre-invasive phase. Surgery is the primary treatment for pre-invasive and early-stage disease and can safely be performed in many low-resource settings. However, cervical cancer rates remain high in many areas of Latin America. This article presents a number of evidence-based strategies being implemented to improve cervical cancer outcomes in Latin America.

**KEYWORDS**

cervical cancer, Latin America, LMICs, surgical training, telementoring

## 1 | INTRODUCTION

Cancer is one of the leading causes of death worldwide with over 17 million new cases and 8.5 million cancer-related deaths per year.<sup>1</sup> Globally, the number of deaths from cancer exceeds the number of deaths from human immunodeficiency virus (HIV), malaria, and tuberculosis combined. Global cancer rates are rising dramatically with a predicted 23.6 million new cases per year worldwide by 2030.<sup>2</sup> More than 50% of all cancer cases and 65% of related deaths occur in low and middle-income countries (LMICs), where cancer is a primary cause of early death, and the prevalence has been steadily increasing partly due to population aging, adaptation of western lifestyles, and improved control of infectious diseases.<sup>3,4</sup>

Worldwide, cervical cancer is the fourth most common cancer among women.<sup>5</sup> However, 85% of cervical cancer diagnoses and related deaths occur in women living in LMICs.<sup>6</sup> Cervical cancer is now relatively uncommon in the United States and other high-income countries due to introduction of the Papanicolaou (Pap) test coupled with the introduction of organized screening programs which together have led to a 70% decrease in cervical cancer incidence and mortality rates over the last 60 years. Cervical cancer is currently the 11th most

common cancer among women in the United States, with an incidence of 7.5 per 100 000 women and a mortality of 2.3 per 100 000 nationally between 2009 and 2013.<sup>7</sup> However, it continues to be the first or second leading cause of cancer-related death among women in many LMICs, with Latin America and the Caribbean region accounting for almost 12% of the world's cervical cancer deaths.<sup>8</sup> In Central and South America, cervical cancer incidence and mortality rates vary widely. For example, it is the leading cause of cancer-related deaths among women in French Guyana, El Salvador, and Bolivia; and in contrast, it is the sixth cause of cancer deaths among women in Chile and fourth cause in Costa Rica and Cuba.<sup>9,10</sup>

Cervical cancer is a preventable disease with excellent primary and secondary prevention strategies. Virtually all cases of cervical cancer are caused by persistent infection with high-risk types of the human papillomavirus (HPV). HPV is the most common sexually transmitted disease worldwide and approximately 80% of women and men will be infected with HPV at some point in their lifetime. The initial infection usually occurs during adolescence or early adulthood, with the majority of women clearing the infection within 18-24 months. However, in 3-5% of women, the HPV infection persists and they develop significant pre-invasive disease, and in <1% invasive cancer develops. HPV

infection is also the causative agent of other malignancies including cancer of the oropharynx, anus, penis, vulva, and vagina.

Preventive vaccines against HPV are now commercially available and have been shown to be safe and effective. The Centers for Disease Control and Prevention (CDC) in the United States recommend that the HPV vaccine be given to both boys and girls between the ages of 11 and 12 years, prior to exposure to HPV, with catch up vaccination between the ages of 13 and 26.<sup>25</sup> Unfortunately, the uptake of HPV vaccination in the United States has been poor, with less than half of eligible children completing the vaccine series. The uptake in other developed countries (Canada, Australia, UK) has been much higher (over 70%), likely due to government supported school-based programs. Many Latin American countries have also instituted HPV vaccination programs. However, economic, political, and logistical barriers in many countries have limited universal mass vaccination programs in many Latin American countries and other regions of the world.

Despite the availability of HPV vaccines, cervical cancer screening will remain necessary for the foreseeable future due to poor vaccine uptake and because the existing vaccines do not treat pre-existing HPV infections and related disease. Two to three generations of women will not benefit from the HPV vaccine as they were beyond the recommended age when the vaccines became available and/or they were already been exposed to HPV. Current approaches in developed countries for cervical cancer screening include screening with Pap and/or HPV DNA testing. Patients with abnormal results undergo colposcopy where dilute acetic acid (vinegar) is placed on the cervix and abnormal areas turn white. These areas are then biopsied and if clinically significant precursor lesions are identified, ablative (cryotherapy) or excisional procedures such as cold knife cone biopsy (CKC) or loop electrosurgical excision procedure (LEEP) are performed. LEEP and CKC involve removal of a small piece of the cervix that can be sent for pathologic diagnosis and results in removal of precancerous lesions. Although these screening and diagnosis algorithms are effective, they are expensive and require high-level infrastructure and well-trained personnel. In addition, they require three separate patient visits with communication of test results between visits. These strategies often fail in lower resource settings where there is often a lack of trained personnel, infrastructure, and pathology services. Many women in these lower resource regions therefore present with invasive disease requiring radical surgery (early stage disease) and/or combined radiation therapy and chemotherapy (locally advanced disease). Unfortunately, many women present with metastatic disease and curative treatment is no longer achievable.

There are many reasons for higher cervical cancer rates in low resourced and underserved regions of Latin America. These populations may be less likely to have access to cervical cancer screening due to economic, social, educational, and geographical barriers. Only Chile, Brazil, and Mexico had implemented organized screening programs as of 2008.<sup>10,11</sup> In addition, a lack of screening services may be a consequence of shortages of locally available providers trained to perform screening tests and to manage patients with abnormal findings, including performing colposcopy, cervical biopsies, and LEEP. Furthermore, geographical distance and cultural barriers play a role in access as many women with abnormal screening tests do

not receive the recommended diagnostic and treatment procedures because they are unable to travel to central healthcare facilities for the multiple necessary follow-up visits due to long the distances and high costs associated with travel.

The aim of this paper is to focus on three issues impacting cervical cancer prevention and treatment, regardless of geography, that can be addressed using evidence based strategies to reduce cervical cancer incidence and mortality rates in Latin America. These include: (1) lack of access to screening and follow-up because of limited medical/clinical infrastructure; (2) high rates of morbidity and mortality due to unsafe or unnecessary surgical procedures; and (3) lack of consistency in national cancer control plans, policies, and implementation of clinical guidelines.

## 2 | ADDRESSING CLINICAL CAPACITY

There are many models of capacity building in underserved areas based on partnerships between institutions with resources and expertise in collaboration with their counterparts in lower resource settings who often lack the specialty care to provide cancer prevention and treatment services (twinning). These collaborations aim to build capacity, strengthen health services, and improve population outcomes in the long term. They can involve two different countries and/or high and low-resource regions within one country. Previous reports have shown such collaborations to improve cancer care capacity in a variety of settings around the world including Zambia, Bangladesh, Ghana, and Nepal.<sup>12</sup> In Latin America, successful twinning programs have been reported for pediatric oncology between Nicaragua and Italy; El Salvador, Honduras, and Guatemala with the United States; as well as a partnership between St. Jude Children's Research Hospital in the United States and providers in the Amazonas region of Brazil.<sup>13</sup>

Project ECHO® (Extension for Community Healthcare Outcomes) has recently been implemented as a strategy for improving cancer care by connecting specialists in high resource areas with providers in low resource regions in order to increase clinical capacity by enabling local providers to deliver specialty care. Project ECHO® was developed in 2003 by Dr. Sanjeev Arora at the University of New Mexico (UNM) and is a powerful telementoring initiative to improve both capacity and access to specialty care for rural and underserved populations.<sup>10</sup> ECHO is a low-cost, high-impact intervention that links expert interdisciplinary specialist teams with community primary care clinicians through regularly scheduled teleECHO sessions, in which the specialists use videoconferencing to co-manage patient cases and share expertise via mentoring, guidance, feedback, and didactic education.

MD Anderson Cancer Center has adapted the Project ECHO model to educate and support local providers in the management of cervical dysplasia and invasive cervical cancer in low-resource regions of Latin America as well as along the Texas-Mexico border. This involves bi-weekly and monthly videoconferences between cervical cancer specialists at MD Anderson with providers from twelve different regions in Central and South America. The participants use

videoconferencing to co-manage patient cases, and specialists share their expertise via mentoring, guidance, feedback, and didactic education. This approach has enabled clinicians in medically underserved areas to develop the skills, confidence, and knowledge to treat patients with common, complex diseases in their own communities, thereby reducing travel costs, wait times, and avoidable complications. Project ECHO is different from telemedicine, in which the specialist assumes the care of the patient, but instead, involves telementoring, in which the community clinician retains responsibility for managing the patient, operating with increasing independence as his/her skills and self-efficacy grow. Clinicians in underserved areas learn from the specialists and from each other, and specialists learn from the community providers. This is a many-to-many approach, as opposed to the approach of traditional telemedicine.<sup>14</sup> The ECHO telementoring program is complemented by hands on training for diagnostic and therapeutic surgical procedures in the low resource areas such as colposcopy and LEEP courses held locally. In parallel, we are performing several collaborative research studies to evaluate improved methods for cervical cancer screening and treatment including low-cost mobile colposcopes, alternatives to traditional cryotherapy,<sup>15</sup> and point of care cervical dysplasia diagnostic tools such as the high-resolution microendoscopy (HRME) developed by Rice University.<sup>16</sup>

Another training program to increase capacity is the Central America Gynecologic Oncology Education Program (CONEP), a partnership with six Central American countries to train Obstetrics and Gynecology residents in the prevention and treatment of gynecologic cancers.<sup>17</sup> Since the program started in 2009, a total of seven trips involving seven volunteer gynecologic oncologists have taken place in four countries in Central America to deliver cervical cancer treatment training. Efforts for increasing clinical capacity in Latin America should be part of multi-component models requiring long term commitments from both training institutions and trainees as well as development of joint goals, accountability, and strategic planning appropriate to the resources of each country or region.

### 3 | IMPROVING CERVICAL CANCER OUTCOMES BY IMPROVING ACCESS TO SAFE SURGERY

According to the Lancet Commission on Surgery, in the absence of widely available surgical care in LMICs, case-fatality rates are high for cervical cancer which is considered a common, easily treatable condition.<sup>18</sup> Safe surgery processes, such as checklists, are not widely used in Latin America and provide an important opportunity to improve procedures and patient outcomes. In Latin America, the primary treatment for early stage cervical cancer (stage IA2-IB1 disease) is a radical hysterectomy with pelvic lymphadenectomy, which can lower quality of life and remove fertility. In addition, there are a limited number of centers with the expertise and experience to perform these radical procedures. To address this issue, MD Anderson Cancer Center in collaboration with Sister Institutions and affiliates in five Latin American countries (Colombia, Peru, Brazil, Mexico, and Argentina) is currently performing a prospective, multicenter study

(the ConCerv trial) to evaluate the feasibility and safety of performing more conservative surgery in women with early stage cervical cancer.<sup>19</sup> Patients with stage IA2-IB1 cervical cancer undergo cone biopsy or simple hysterectomy with lymphadenectomy depending on their desire for future fertility. If successful, this approach will provide the option of less radical, safer, and more widely available surgery for women with early stage cervical cancer.

For women with locally advanced disease (stage IB2-IVA), the standard therapy is chemoradiation. This includes external beam radiation therapy to the pelvis with an extended field if the para-aortic lymph nodes are involved. This treatment is given 5 days per week for ~5-6 weeks. This is followed by 2-5 internal radiation therapy treatments (brachytherapy). Concurrent chemotherapy with cisplatin is given once per week during treatment. In some regions of Latin America the wait times for this treatment are very long and in some rural and underserved areas, safe and effective radiation therapy is not available. There is a shortage of radiation therapy units due to the high cost, difficulty maintaining the machines, and lack of the significant infrastructure required. In addition, there is a lack of trained radiation oncologists, physicists, therapists, and technicians in many Latin American countries. Furthermore, it is very important for patients to complete all portions of the treatment with minimal treatment delays in order to obtain a good response. In countries with few units, there may be significant delays in starting and completing treatment because of the large number of patients requiring this treatment. Unfortunately many patients in low-resource settings receive only external beam therapy without brachytherapy, resulting in inadequate treatment and high rates of recurrence.

An alternative to chemoradiation is the use of neoadjuvant chemotherapy followed by surgery. Previous reports have shown this strategy to achieve an objective response rate of 84% and overall survival of 773% in the United States.<sup>20</sup> This strategy was also recently evaluated in the National Institute of Neoplastic Diseases (INEN) in Peru with promising preliminary results.<sup>21</sup> For these reasons, neoadjuvant chemotherapy followed by surgery should continue to be evaluated as an alternative in areas where safe and effective chemoradiation is not available.<sup>22,23</sup>

### 4 | ADDRESSING HEALTH SYSTEM DISPARITIES IN LATIN AMERICA

Primary prevention with HPV vaccination is recommended as a priority in the development of any national cancer control policies.<sup>24</sup> The National Cancer Institute Center for Global Health, along with partners in global organizations and academic institutions, facilitates discussion in development of cancer control plans with Ministries of Health around the world including in Central and South America. Furthermore, resource stratified clinical guidelines for cervical cancer prevention and treatment have been developed and published by the American Society of Clinical Oncology.<sup>23</sup> An ongoing challenge is developing strategies for successful implementation and dissemination of these guidelines in low resource regions. The Project ECHO program currently serves as a dissemination tool for advancing these guidelines.

## 5 | CONCLUSIONS

Cervical cancer is a preventable disease with very high incidence and mortality rates in low resource areas. While screening programs have reduced the burden of this disease in high resource countries, many low resource regions have ineffective screening programs and lack the infrastructure and expertise for management of patients with abnormal screening tests and invasive cancer. One such example is Uruguay, a High Income country with universal access to healthcare which has not yet seen a steep reduction of cervical cancer incidence rates due to the lack of an organized screening program. Health system strengthening strategies should be adopted and implemented by Ministries of Health, in partnership with local health care systems and NGOs to improve HPV vaccination rates, screening services, and access to these services, management of high grade dysplasia and treatment of women with cervical cancer. The use of technology for training to increase capacity and to implement low cost evidence based strategies for cervical cancer control can be complemented with strong cancer control policies and health system strengthening initiatives. North-South collaborations of institutions in developed regions working closely with colleagues in Latin America can provide support to increase clinical capacity. In addition, higher resource countries in Latin America such as Chile, Brazil, Argentina, and Uruguay can share their experiences and expertise with lower resource countries in the region.

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