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# EDITORIAL

## Prevention of cervical cancer in Latin America: Future challenges and opportunities

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It was not difficult to decide in 1984 that studying cervical cancer epidemiology should be a key priority when I began my research work at the Sao Paulo Branch of the Ludwig Institute for Cancer Research. At the time, Recife (the capital of the state of Pernambuco, in the Northeastern region of Brazil) had the sad distinction of boasting an incidence rate of over 100 new cases of invasive cervical cancer per 100 000 women per year.<sup>1</sup> In 1982, the Brazilian Ministry of Health published a very large tumor pathology compilation that assessed relative frequencies of cases for all cancers sites.<sup>2</sup> Cervical cancer was then the most common cancer in women in most low income states and was a close second to breast cancer in more affluent states in the south and southeast.<sup>3</sup> At the time, a new hypothesis for what caused cervical cancer was gaining momentum. Work in the early 1980's in Zur Hausen's laboratory in Heidelberg led to the identification of DNA sequences of human papillomavirus (HPV) in cervical cancer specimens,<sup>4</sup> many of which had been collected by Nubia Muñoz in her field expeditions to Northeastern Brazil. Muñoz, a Colombian pathologist with academic epidemiology training had started at the International Agency for Research on Cancer—an institution linked to the World Health Organization—a vigorous program of research that attempted to identify the cause of cervical cancer and jumpstart initiatives towards its prevention. Muñoz' voluminous contributions to the epidemiology and prevention of cervical cancer paved the way for the crowning of zur Hausen's discovery, which led him to receive the Medicine Nobel prize in 2008.\*

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\* Franco EL, Bosch FX. Proving the causal role of HPV in cervical cancer: A tale of multi-disciplinary science. In: Bosch FX, Jenkins D (eds). Human Papillomavirus: from finding the cause to preventing cervical cancer. Elsevier (in press).

Zur Hausen's findings were coherent with the observations made in 1976 by Alexander Meisels, a German cytopathologist who underwent medical training in Mexico. In his cytomorphological correlations, Meisels postulated that the koilocytotic changes in cervical cancer were the expression of a viral agent, not unlike what could be seen in genital warts.<sup>5</sup>

The contributions of Muñoz and Meisels were the earliest and most prominent by Latin American scientists<sup>‡</sup> in what has become one of the most important achievements of medicine and public health, i.e., the discovery of a virus that plays a necessary role in causing a type of cancer and the preventive strategies that stemmed from that discovery. Not surprisingly, the contributions from Latin American scientists and their studies played a prominent role in the discovery of a causal role for HPV and in the prevention-oriented research that followed. Large epidemiologic studies in Mexico, Costa Rica, Panama, Colombia, Peru, and Brazil advanced our understanding of the natural history of HPV infection and cervical carcinogenesis. Latin American countries were also major contributors to HPV vaccination trials that began in the mid-to-late 1990s.<sup>§</sup> Once they were published, these trials formed the regulatory panoply that brought publicly-funded HPV vaccination to girls and adolescent women beginning in 2007. Most Latin American countries now benefit from this major cancer prevention strategy. Challenges remain,

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‡ Although Meisels was not born in Latin America, he trained in Mexico and spent a considerable amount of time training Latin American cytopathologists. He spoke fluent Spanish and lectured extensively in Latin America.

§ Both vaccine manufacturers, Merck and GSK, established partnerships with teams in Brazil, Mexico and Costa Rica.

to be sure, but the contributions from Latin America to the fight against cervical cancer are disproportionately greater than the resources that the region and its constituent countries can afford.

It is not only on HPV vaccination that the prominence of Latin American research can be recognized. The region, particularly Mexico, Costa Rica, and Peru, has been the focal point of much research on cervical cancer screening technologies. Much of the impetus for the adoption of molecular-based HPV testing methods in cervical cancer screening originated from hard-earned scientific evidence from studies conducted in Latin America. Whether these studies stemmed from local investigator-initiated efforts or via cooperation with institutions in high income countries, the dividends were enormous. Courageous efforts by local leaders led to the pilot implementation of molecular HPV testing and self-sampling in parts of Mexico and Argentina. Much of the current thinking that led to the changes in cervical cancer screening paradigm is grounded on public health evidence from Latin American studies. Mexico, in particular, continues to advance knowledge via a large scale study of colposcopy triage methods.<sup>6</sup>

Mexico was the first Latin American country to adopt a two-dose schedule of HPV vaccination. Lessons learned from the Mexican implementation were instrumental to the recommendation by the World Health Organization of a two-dose schedule. Findings from the vaccination trial in Guanacaste, Costa Rica, supported the correctness of this policy,<sup>7</sup> which brought substantial savings to healthcare budgets worldwide. Brazil adopted a national HPV vaccination program that incorporated a technology transfer initiative. Although the benefits of such an arrangement with vaccine makers are yet to be realized, this economic experiment has great potential in the long run and may inform other financing models to be used elsewhere.

Despite the pioneering research initiatives in some countries in the region, inequalities continue to exist. Non-Governmental Organizations, such as PATH, have made major strides bringing cervical cancer prevention in partnership with local stakeholders to rural and poor communities in Central America.<sup>8</sup> Despite the gains that have been made, however, the complexity and challenges of deploying healthcare resources to countries with turbulent political landscapes and armed conflict cannot be overemphasized.

Much has been said about the opportunity to control and ultimately to eliminate cervical cancer

via a combination of high coverage HPV vaccination, improved and high-coverage screening, and prompt treatment of cases of precancerous lesions.<sup>9</sup> Concrete steps into that direction have already been made, the most important of which is to estimate the overall cost of such an initiative. A coalition of funding partners, professional stakeholders, and cancer charities has estimated the total cost to be US\$ 3.1 billion over 10 years, with a focus on countries with per capita income of less than US\$ 2 500.<sup>10</sup> Although most of the effort will have to be focused to sub-Saharan Africa, many Latin American countries would benefit from this joint initiative, once implemented.

A seldom recognized dividend from cervical cancer prevention research conducted in Latin America is personnel training. One local investigation in Brazil alone, the Ludwig-McGill Cohort Study,<sup>11</sup> generated 25 master's and doctoral theses, as well as research content for a few post-doctoral fellows. The ongoing FRIDA study<sup>6</sup> in Tlaxcala, Mexico, is another example where the frontlines of field research become indistinguishable from academia. Many graduate students have learned practical lessons and earned their degrees based on this study alone and many more will benefit as more data are added to this vast epidemiologic resource. These trainees become the next generation of a well-informed workforce, from which new leaders will emerge, all well-prepared to face the enormous challenges and to capitalize on the opportunities on the road to eliminating a type of cancer that has brought so much suffering to Latin American women and their families.

## Disclosure

I have no conflicts of interest on the topic and contents of this editorial but throughout my career I have served as occasional consultant or advisory board member to companies involved with HPV diagnostics (Qiagen, Roche, Gen-Probe, BD, Abbott), HPV vaccination (GSK, Merck), and cervical cancer screening or control (3M, Ikonisys, Cytyc). My institution has received unconditional grants from Merck and Roche to supplement publicly funded investigator-initiated studies in my unit. My entire research program has been funded by the Canadian Institutes of Health Research (CIHR), US National Institutes of Health, National Cancer Institute of Canada, Cancer Research Society, Canadian Cancer Society Research Institute, Fonds de Recherche Quebec-Santé (FRQS); salary awards: CIHR Distinguished Sci-

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