

Chapter 17: A Global Strategy for Eliminating Cervical Cancer: Challenges and Opportunities

Silvia de Sanjosé

Striving to be focused and concrete, Silvia de Sanjosé offers a specific example to inform present and future commitments in the ongoing cancer pandemic by articulating a global strategy for eliminating cervical cancer. Cervical cancer, which is preventable, is a global public health problem. It is the fourth most common cancer, with over 600,000 new cases diagnosed every year and it is the fourth leading cause of cancer death in women worldwide. Most of these cancer cases occur in low-resource settings where women are not screened regularly. While highlighting these ongoing challenges, the author stresses the existing opportunities for prevention, screening, and vaccination.

Cervical cancer is a largely preventable disease but remains the fourth most common cancer, with over 600,000 new cases diagnosed every year.¹ Further, it is the fourth leading cause of cancer death in women worldwide.² Most of these cases occur in low-resource settings where women are not screened with practical approaches regularly. In recognition of cervical cancer as a public health problem, the World Health Organization (WHO) has set ambitious targets to scale-up effective prevention strategies as part of the Global Strategy, including 90 percent coverage of human papillomavirus (HPV) vaccination for adolescent girls,

¹ International Agency for Research on Cancer, “GLOBOCAN 2020: New Global Cancer Data,” *Union for International Cancer Control*, December 17, 2020, www.uic.org/news/globocan-2020-new-global-cancer-data.

² Jacques Ferlay, Morten Ervik, Frédéric Lam, Murielle Colombet, Les Mery, Marion Piñeros, Ariana Znaor, Isabelle Soerjomataram, and Freddie Bray, “Global Cancer Observatory: Cancer Today,” *International Agency for Research on Cancer*, 2020, goi.iarc.fr/today.

70 percent of women screened twice in their lifetime with high-performance tests by ages 35 and 45, and treatment for 90 percent of precancerous lesions.³ The strategy is based on the current knowledge of the natural history of cervical cancer and the existing prevention tools.

After years of studying the link between cervical cancer and a sexually transmitted infection, some viral types of the HPV family were recognized to play a vital role in the carcinogenic process. HPV is unequivocally linked to almost all cervical cancer cases (95 percent of cases) and a large proportion of anal cancer cases (88 percent of cases attributable to HPV).⁴ HPV is also causally associated with a varying percentage of cancers of the vulva, vagina, penis, and a subset of head and neck cancers (HNCs), particularly tonsillar cancer.⁵ Within the spectrum of HPV oncogenic types, HPV 16 is the most prevalent in all HPV-related cancer sites. HPV 16 is the most frequently detected at the population level, and it is by far the predominant type causing invasive cervical cancer worldwide (~60 percent), followed by HPV 18 (~15 percent). Moreover, HPV 16 is also involved in a more significant proportion in other body sites like anal mucosa or head and neck tumors, particularly the oropharynx.⁶ HPV 16 is considered one of the essential human carcinogens.

³ See World Health Organization, *Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem* (Geneva: World Health Organization, 2020).

⁴ Mark Schiffman, John Doorbar, Nicolas Wentzensen, Silvia de Sanjosé, Carole Fakhry, Bradley J. Monk, Margaret A. Stanley, and Silvia Franceschi, “Carcinogenic Human Papillomavirus Infection,” *Nature Reviews Disease Primers* 2 (2016): 16086, doi.org/10.1038/nrdp.2016.86.

⁵ Catherine de Martel, Damien Georges, Freddie Bray, Jacques Ferlay, and Gary M. Clifford, “Global Burden of Cancer Attributable to Infections in 2018: A Worldwide Incidence Analysis,” *Lancet Global Health* 8, no. 2 (2020): e180–e190.

⁶ Silvia de Sanjose, Beatriz Serrano, Sara Tous, Maria Alejo, Belen Lloveras, Beatriz Quiros, Omar Clavero, August Vidal, Carla Ferrandiz-Pulido, Miquel Angel Pavon, Dana Holzinger, Gordana Halec, Massimo Tommasino, Wim Quint, Michael Pawlita, Nubia Munoz, Francesc Xavier Bosch, Laia Alemany, and RIS HPV TT VVAP Head Neck study groups, “Burden of Human Papillomavirus (HPV)-Related Cancers Attributable to HPVs 6/11/16/18/31/33/45/52 and 58,” *JNCI Cancer Spectrum* 2, no. 4 (2018): doi.org/10.1093/jncics/pky045.

HPV infection is generally acquired through sexual contact, and the majority of the infections will resolve spontaneously with an adequate immune response. However, when the infection remains for an extended period, which can mean years in immunocompetent subjects, there is a disruption of the normal cell cycle inducing an abortive infection. It is this situation that increases the woman's probability of developing a pre-neoplastic lesions or invasive cancer.

Screening

The long latency between disease and cancer has made effective cervical cancer screening possible. In high resource settings, cervical cytological—i.e., Papanicolaou ('Pap') test—screening programs have substantially reduced mortality and incidence where it has been possible to organize and maintain them. The cytological exam of cervical cells through the microscope allows identifying the virus's harm to the human cells. The identification of these anomalies has been the subject of multiple classifications. The most recent one is the Bethesda system, where anomalies are classified as cervical intraepithelial neoplasia (CIN) grades I, II, and III. Precancer is now considered CIN2, CIN3, or CIN3. Morphological change identification suffers from observation error, particularly the lower grade lesions <CIN3. To run a high-profile screening using cytology assessment, very high levels of quality control are needed to reduce diagnosis inaccuracies. Furthermore, cervical cytology has proven challenging to expand in lower resource settings making secondary prevention a hard-to-reach outcome.⁷

Vaccination

⁷ Schiffman, Doorbar, Wentzensen, de Sanjose, Fakhry, Monk, Stanley, and Franceschi, "Carcinogenic Human Papillomavirus Infection"; Guglielmo Ronco, Joakim Dillner, K. Miriam Elfstrom, Sara Tunesi, Peter J. F. Snijders, Marc Arbyn, Henry Kitchener, Nereo Segnan, Clare Gilham, Paolo Giorgi-Rossi, Johannes Berkhof, Julian Peto, Chris J. L. M. Meijer, and International HPV screening working group, "Efficacy of HPV-Based Screening for Prevention of Invasive Cervical Cancer: Follow-up of Four European Randomised Controlled Trials," *Lancet* 383, no. 9916 (2014): 524–532.

In 2006, after years of intense research, two prophylactic vaccines became available. A bivalent vaccine (BV), covering HPV 16 and HPV 18, and the quadrivalent vaccine (QV), covering two low-risk types, HPV 6 and HPV 11, associated with benign HPV genital warts and the two most oncogenic types, HPV 16 and HPV 18. Later, the QV was expanded to add five more types (NV) that included, in addition, the HPV 31, 33, 45, 52, and 56.⁸ Recently, a new BV has also been commercialized, and a couple more are in the pipeline.

The high efficacy of these vaccines against infections, pre-neoplastic lesions, and cancer has been paramount. In girls around ages 9 to 15, using these vaccines before sexual exposure is probably the most cost-effective measure to reduce the incidence and mortality of HPV-related cancers. Vaccination of boys is also recommended, although the impact at the population levels is half of that expected when vaccinating girls.

As of December 2019, although 122 countries have implemented HPV vaccination programs in their national programs, supply, funding, and policy constrain the introduction in vaccination programs of the HPV vaccine in low and middle-income countries (LMIC). To date, only 6 percent of adolescent girls worldwide have received HPV vaccination, most of whom reside in high-income countries, and still 245 million girls were not yet eligible for vaccination in 2021. While seventy out of eighty-six high-income countries had introduced the HPV vaccines in 2019, only twenty out of eighty-one of the low, and lower-income countries had done so.⁹

⁸ Mario Poljak, “Prophylactic Human Papillomavirus Vaccination and Primary Prevention of Cervical Cancer: Issues and Challenges,” *Clinical Microbiology and Infection* 18, Suppl. 5 (2012): 64–69; Vivien D. Tsu, D. Scott LaMontagne, Phionah Atuhebwe, Paul N. Bloem, and Cathy Ndiaye, “National Implementation of HPV Vaccination Programs in Low-Resource Countries: Lessons, Challenges, and Future Prospects,” *Preventive Medicine* 144 (2021): doi.org/10.1016/j.ypmed.2020.106335; Silvia de Sanjose, Maria Brotons, D. Scott LaMontagne, and Laia Bruni, “Human Papillomavirus Vaccine Disease Impact Beyond Expectations,” *Current Opinion in Virology* 39 (2019): 16–22.

⁹ Laia Bruni, Anna Saura-Lazaro, Alexandra Montoliu, Maria Brotons, Laia Alemany, Mamadou Saliou Diallo, Oya Zeren Afsar, D. Scott LaMontagne, Liudmila Mosina, Marcela Contreras, Martha Velandia-Gonzalez, Roberta Pastore, Marta Gacic-Dobo, and Paul Bloem,

Global Challenges

Screening and treatment programs remain essential for secondary prevention of cervical cancer for the millions of adult women who are not eligible for or will not be reached by HPV vaccination in the coming decades.¹⁰ If worldwide we manage to vaccinate 90 percent of the target girls, the addition of twice-lifetime HPV testing could considerably accelerate cervical cancer reduction and move faster towards the elimination goal.¹¹ However, implementing adequate screening strategies for the existing resources to adopting high coverage of a robust screening approach, like a molecular test to detect HPV, involves many challenges, particularly in resource-limited settings. Ideally, countries with unsuccessful screening approaches should move from cytology or visual inspection with acetic acid (VIA) to objective and reliable tests like HPV testing with validated assays. Testing for HPV by measuring the viral DNA or RNA has been expanded in many countries, particularly in high-resource settings.¹² The possibility of having low-cost HPV tests that involve minimal laboratory needs is becoming a reality. However, an

“HPV Vaccination Introduction Worldwide and WHO and UNICEF Estimates of National HPV Immunization Coverage 2010–2019,” *Preventive Medicine* 144 (2021): doi.org/10.1016/j.ypmed.2020.106399. See also personal communication from Scott LaMontagne (PATH, Center for Vaccine Innovation and Access: Policy, Access and Introduction functional area, University of Washington, Seattle, WA) and Laia Bruni at the Institut Catala d’Oncologia (ICO).

¹⁰ Silvia de Sanjosé and Francesca Holme, “What Is Needed Now for Successful Scale-up of Screening?,” *Papillomavirus Research* 7 (2019): 173–175.

¹¹ Karen Canfell, Jane J. Kim, Marc Brisson, Adam Keane, Kate T. Simms, Michael Caruana, Emily A. Burger, Dave Martin, Diep T. N. Nguyen, Elodie Benard, Stephen Sy, Catherine Regan, Melanie Drolet, Guillaume Gingras, Jean-Francois Laprise, Julie Torode, Megan A. Smith, Elena Fidarova, Dario Trapani, Freddie Bray, Andre Ilbawi, Nathalie Broutet, and Raymond Hutubessy, “Mortality Impact of Achieving WHO Cervical Cancer Elimination Targets: A Comparative Modelling Analysis in 78 Low-Income and Lower-Middle-Income Countries,” *Lancet* 395, no. 10224 (2020): 591–603.

¹² World Health Organization, *WHO Guideline for Screening and Treatment of Cervical Pre-Cancer Lesions for Cervical Cancer Prevention*, 2nd ed. (Geneva: World Health Organization, 2021).

urgent need to generate the capacity of producing the required volume of tests remains a challenge.

Prevention

Three essential elements are critical for secondary prevention of cervical cancer: self-sampling, HPV testing, and rapid treatment for those eligible. Self-sampling is key to increasing screening coverage by avoiding a gynecological exam through speculum examination. The sampling of women's vaginal cells, combined with molecular testing of oncogenic HPV types, results in a high accuracy approach to detect precancerous lesions.¹³ The inclusion of a second sequential screening test, commonly referred to as a "triage test," is an additional option to increase the specificity of a screening approach and identify women at the highest risk of developing cervical cancer who require follow-up.

WHO guidelines for screening and treating cervical precancerous lesions were updated in 2021.¹⁴ The recommendation for women in the general population is HPV testing between ages 30 and 49, with repeat screening every 5–10 years (for a minimum of twice-per lifetime screening), implemented with either an HPV test-and-treat approach or an HPV test-triage-treat approach.

In case of women living with HIV (WLHIV), the WHO recommendation is an HPV test-triage-treat approach starting at age 25 and with repeat screening every 3–5 years. Unfortunately, we still need to improve screening management among WLHIV. WLHIV have a high

¹³ Marc Arbyn, Sara B. Smith, Sarah Temin, Farhana Sultana, Philip Castle, and Collaboration on Self-Sampling and HPV Testing, "Detecting Cervical Precancer and Reaching Underscreened Women by Using HPV Testing on Self Samples: Updated Meta-Analyses," *BMJ* 363 (2018): doi.org/10.1136/bmj.k4823; David Hawkes, Marco H. T. Keung, Yanping Huang, Tracey L. McDermott, Joanne Romano, Marion Saville, and Julia M. L. Brotherton, "Self-Collection for Cervical Screening Programs: From Research to Reality," *Cancers (Basel)* 12, no. 4 (2020): doi.org/10.3390/cancers12041053; Ashwini Kamath Mulki and Mellissa Withers, "Human Papilloma Virus Self-Sampling Performance in Low-and Middle-Income Countries," *BMC Women's Health* 21, no. 1 (2021): doi.org/10.1186/s12905-020-01158-4.

¹⁴ World Health Organization, *WHO Guideline for Screening and Treatment of Cervical Pre-Cancer Lesions for Cervical Cancer Prevention*.

prevalence of HPV and are more likely to experience a persistent infection that progresses to cervical precancer. Due to the low specificity of HPV tests to rule out precancer, a second test among high-risk human papillomavirus-positive women (HR-HPV) is, therefore, necessary to determine who needs to be treated. However, an optimal strategy remains to be identified. Settings using HPV as primary screening use cervical cytology as a second test, or in LMIC, the commonest triage is VIA. VIA is a largely provider-dependent test with highly variable accuracy.

Furthermore, WLHIV have a high level of recurrences, as high as 30 percent.¹⁵ Although managing HIV infection with antiretrovirals is essential for a good immune response, the fact that WLHIV that are regular users of antiretroviral therapy (ARV) maintain high levels of detectable HPV infections suggests an immune impairment not fully restored amid viral treatment. Most guidelines recommend initiating ARV as soon as HIV is diagnosed to sustain, as much as possible, a sound immune system.

Our team is working on a combined screening strategy for LMIC among women aged 30–49 years old. The age restriction targets precancerous lesions that will be easily managed with no surgery-based treatments. The proposed primary screening test is a self-sampling approach for oncogenic HPV DNA testing with genotype identification. HPV-negative women have a low-level risk of having a precancer or cancer and therefore can go back to screening in five or ten years.

For those women with a positive test, the risk of precancer is classified by the oncogenicity of the HPV type detected. HPV-positive women undergo a gynecological visit. An image is taken and ranked through a well-

¹⁵ Michael H. Chung, Hugo De Vuyst, Sharon A. Greene, Nelly R. Mugo, Troy D. Querec, Evans Nyongesa-Malava, Anthony Cagle, Samah R. Sakr, Stanley Luchters, Marleen Temmerman, Elizabeth R. Unger, and Christine J. McGrath, “Human Papillomavirus Persistence and Association with Recurrent Cervical Intraepithelial Neoplasia after Cryotherapy vs Loop Electrosurgical Excision Procedure among HIVPositive Women: A Secondary Analysis of a Randomized Clinical Trial,” *JAMA Oncology* 7, no. 10 (2021): 1514–1520.

validated artificial intelligence (AI) algorithm.¹⁶ Combining the HPV genotype and the image evaluation provides an excellent stratification of the women's risk. This stratification will direct the management of the patient. Either treat her, follow up with her, or send her home. There are indications that this strategy can be helpful irrespective of HIV status, can be low cost, and can be performed by trained health workers. Combined with ablative approaches, managing can be completed in one single visit for most patients when lesions are visible and not too large. Referral for surgical methods would then be restricted to fewer women.

Conclusion

We need to increase vaccination coverage among girls, hoping that a one-dose vaccine will provide good enough efficacy against cervical cancer. Self-sampling using an HPV test may be the only path to reach every woman at least twice in their lifetime. However, it remains necessary to have availability of HPV tests at an affordable cost. Visual inspection of the cervix with acetic acid is being downgraded as a correct approach to screening. However, the complement with automated technology using AI approaches may increase the performance considerably, although we are still under a period of active research.

Furthermore, all the presented strategies consider minimizing crowded spaces and unnecessary physical exams when the world is being impacted by the COVID pandemic.¹⁷ Managing precancerous lesions with thermal ablation has improved the accomplishment of treatment compared to the

¹⁶ Kanan T. Desai, Brian Befano, Zhiyun Xue, Helen Kelly, Nicole G. Campos, Didem Egemen, Julia C. Gage, Ana-Cecilia Rodriguez, Vikrant Sahasrabudhe, David Levitz, Paul Pearlman, Jose Jeronimo, Sameer Antani, Mark Schiffman, and Silvia de Sanjose, "The Development of 'Automated Visual Evaluation' for Cervical Cancer Screening: The Promise and Challenges in Adapting Deep-Learning for Clinical Testing," *International Journal of Cancer* (2021): doi.org/10.1002/ijc.33879.

¹⁷ Nicolas Wentzensen, Megan A. Clarke, and Rebecca B. Perkins, "Impact of COVID-19 on Cervical Cancer Screening: Challenges and Opportunities to Improving Resilience and Reduce Disparities," *Preventive Medicine* 151 (2021): doi.org/10.1016/j.ypmed.2021.106596.

use of cryotherapy at an equal efficacy. Finally, we need to explore more accurate approaches to screen and manage WLHIV, considering this population's high rates of treatment failures.

Silvia de Sanjosé, M.D., Ph.D., works with the Division of Cancer Epidemiology and Genetics of the National Cancer Institute, National Institutes of Health, in Rockville, MD, and ISGlobal (Institute of Global Health) in Barcelona, Spain. She has over thirty years of expertise in epidemiology of human papilloma virus (HPV) and related cancers. She served as the President of the International Papilloma Virus Society (2015–2018) and has been Co-Chair of the Cape Town, Sydney, and Barcelona (virtual) conferences of the inactivated poliovirus vaccines (IPVs). She is an affiliated professor at the Department of Epidemiology of the University of Washington in Seattle.