Chapter 6
Control and Prevention in Cervical Cancer

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Abstract Cervical cancer (CC) remains one of the most frequent types of neoplasia and in developing countries is the second most common cause of reported cases, after breast cancer. In Mexico, improvements have been made in defining and perfecting public policies related to this disease and, more importantly, innovative strategies aimed at increasing primary and secondary prevention have been implemented. Beginning in 1974, annual cervical cytology with referral to colposcopy was used for diagnosis and control of CC. In 1994 a histopathological registry was created, in 1996 a cancer information system set up and in 1998 the program transitioned to triennial cytology testing in women with two previous consecutive negative results. In 2007 HPV vaccination began for girls 9–12 years, and the high-risk HPV test (hrHPV) was incorporated as the primary screening test for women 35–64 years. Since 2008, regional molecular biology laboratories for hrHPV test analysis were set up, and 23 out of the 32 states currently have such a laboratory. Extending vaccination programs to include women up to 30 years old (and in some cases up to 45–50 years old) and performing at least one hrHPV test on women ≥30 years old has been proposed. Introduction of an alternative 2-dose HPV vaccination scheme with a periodicity of 6–12 months between doses is recommended for women younger than 15 years old. To improve the results of CC detection programs, it is necessary to: employ appropriate and timely triage alternatives for hrHPV-positive patients, professionalize healthcare personnel and guarantee the quality of program processes, increase screening coverage of the hrHPV test, improve information systems and use a combination of vaccination and screening to accelerate the reduction in the burden of disease associated with CC.

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6.1 Introduction

Cervical cancer (CC) is a part of the care plan for addressing central health problems around the world, especially in the least-developed countries. CC remains one of the most frequent neoplasias [1], with half a million new cases diagnosed around the world every year [2]. While in more developed regions, cases of CC may be overshadowed by cases of breast, colorectal, lung, uterine and thyroid cancer, in developing countries, CC remains the second most common cause of reported cases, right after breast cancer. By the year 2012, an adjusted rate of 15.7 cases per 100,000 was estimated for less developed countries, whereas there were 9.9 cases for every 100,000 in developed regions [2].

In all, 16% of cancer cases are attributed to an infectious agent, with a greater proportion of cancer cases attributable to infections occurring in less developed countries (22.9%). The attributable percentage varies according to the region, from 3.3% in Australia to 32.7% in Sub-Saharan Africa. It is worth mentioning that infection with *Helicobacter pylori*, Hepatitis B and C or Human Papilloma Virus (HPV) is responsible for 1.9 million cases of gastric, liver and cervical cancer around the world [3].

CC mortality is a problem that is directly related to poverty and marginalization and that affects the most vulnerable women, who live with greater disadvantages. In Mexico, the highest frequency and mortality rates are found in the southern states (Chiapas, Guerrero and Oaxaca) which present higher levels of poverty and marginalization [4]. The risk of death by CC is three-fold higher in the countryside than in urbanized areas [5].

There is currently an approximately 5% annual reduction in CC mortality rates [6]. Regarding this matter it must be mentioned that in 2006, CC stopped being the leading cause of death as a result of malignant tumors in women. It was displaced at that time by breast cancer [7]. This change can be attributed to a reduction in the birth rate and an increase in the availability of cervical cytological studies [8].

The consolidation of internationally influential research groups in addition to their work and the improvements derived from it have made it possible to offer an organized and integral social response to this problem. Because it involves fields of science and of specialized legislation, the battle against this disease is won through successive approaches that translate into, first, improvements in both diagnosis and treatment, and second, the issuing of laws and standards that contribute to better controlling the problem in terms of regulation.

For those who have closely followed the steps taken by the Mexican government regarding public health, especially over the last four decades, it is evident that although the problem may be far from solved, improvements have been made in defining and perfecting public policies related to this disease and, more importantly,

innovative strategies aimed at increasing primary and secondary prevention have been implemented among the population. These will doubtlessly yield a reduction in the number of CC cases in the near future.

A large amount of effort has been made to reduce the disparities that exist within the country and the fact that this disease severely affects more vulnerable populations. Important achievements have been made in broadening coverage and improving the quality of services available to detect and treat CC. However, it is imperative to acknowledge that there remains a need to intensify and complement the actions that have already been taken to control its spread because the persistence of this disease has serious implications for public health. Controlling CC remains an important topic on the public political agenda.

6.2 Review of the Governmental Response in Recent Years

The first steps to promote the early detection of CC were taken at the General Hospital of Mexico by the Health Secretariat (SS) in 1974. Twenty years later, the Official Mexican Normative NOM-014-SSA2–1994 was established [9], in which it was agreed that cervical cytology would be the base diagnostic test for the creation of a CC prevention and control program within the National Health System.

According to this Normative, cytology would be performed on an annual basis, and the women that were diagnosed with an HPV infection would be referred to a colposcopy service. However, it was not yet known at that time that there was no treatment for cases of HPV that did not present lesions and that referring a woman with a morphological image suggesting an HPV infection to a colposcopy clinic would unnecessarily increase expenses, leading to over-diagnoses and a negative psychological impact on the patients.

In 1994, the histopathological register of malignant neoplasms was created by pathologists, hematologists, dermatologists and epidemiologists (this register would later become the cancer histopathological register). In 1996, a system was created to keep records regarding the results of cervical cytology screening activities that comprised the CC prevention and control program, which is now called the Women's cancer information system (SICAM).

Because the evidence indicates that performing a single cytology test every 3 years offers the same benefit as performing an annual test, it was decided in 1998 that triennial tests would be performed on women with two consecutive negative results for dysplasia or cancer. However, patients who tested positive for dysplasia would be subjected to a follow-up in a dysplasia clinic. After being discharged from the clinic, they would resume the triennial schedule of detection tests. At that time, the population selected for screening was women between 25 and 64 years old [10].

In 2007, the Official Mexican Normative NOM-014-SSA2–1994 was modified to improve the prevention, detection, diagnosis, treatment, control and epidemiological surveillance of CC [11]. In this norm, it was explicitly established that there was a need to privilege the detection of this disease in indigenous women and

those who reside in rural areas and marginalized urban areas. Similarly, primary and secondary prevention strategies were defined, and both the concept and the practice of counseling were introduced to the healthcare program.

The Weekly Notification System for New Cases is currently part of the System for Research and Epidemiological Surveillance. In this system, the indicators that identify cervical cancer, breast, lung and stomach cancer have been recorded by institutions in the health sector. However, the National System for Health Information gathers the data related to hospital discharges and detection activities, and consultations are granted and tests are performed using this data. Meanwhile the Epidemiological and Statistical Death Record System keeps a record of all deaths that occur in the country and the reason for death. Cancer is naturally among these causes, and also registered are the sex, age group and place of residence of each individual.

6.3 Incorporation of hrHPV as a Primary Test and Its Role as a Milestone in the Fight Against CC

It is worth mentioning that the fight against CC has increased in intensity over the last 10 years. During this same time, a new governmental initiative was issued in support of the 125 municipalities with the lowest human development index. The initiative seeks to eliminate the inequalities that prevent women from attaining access to integral health facilities and proposes the broadening of coverage and improvements in health service conditions as a way to achieve it [12]. The next year, the Health Secretariat, via the National Center for Gender Equality and Reproductive Health, undertook an integral strategy aimed at preventing CC that was called "All women, for each a prevention alternative" [13]. Within the framework of this policy, which was oriented towards improving the quality of life of women living in marginal municipalities, HPV vaccination was recommended for girls between 12 and 16 years of age, and the High-risk HPV test (hrHPV, VPHar is the abbreviation in Spanish) was recommended for women between 35 and 64 years of age. As a result, a total of 82 thousand individuals were vaccinated, and 105 thousand hrHPV tests were performed.

The use of the hrHPV test has been widely recommended as a primary screening method given that its high sensitivity makes it possible for it to identify more cases of grade II or higher intra-epithelial neoplasia (NIC 2+) than a cytological test. It was foreseen that this would result in a reduction in the number of visits to health institutions, which would, in turn, result in an increase in coverage and reliability [14–16].

Several studies have compared the sensitivity and specificity of hrHPV tests to those of cervical cytology [17–20]. The results showed that when detecting NIC 2+ cases, the hrHPV test had higher sensitivity than conventional cytology (96.1% vs. 53.0%). However, the former was also less specific (90.7% vs. 96.3%) [19]. In

Mexico, the sensitivity of the cytological test for detecting histologically confirmed NIC2/3 cases was 40.0%, while that of the hrHPV test was 93.3%. However, the specificity of the cytology assay was 97%, while that of the hrHPV test was 89.2%[20]. These results support the use of the hrHPV test as a primary screening test. This strategy can be used to improve CC prevention programs in places where cervical cytology is inadequate for detecting cancer precursor lesions.

Another advantage of the hrHPV test is that it allows the patient to collect the sample to be analyzed on her own. This is, however, recommended only when there is no qualified technician to take the cervical sample and when there are no risks related to the patient performing the sampling [21]. It is worth noting that the first studies evaluated the acceptability of vaginal self-sampling, the advantages of using this option to eventually overcome the obstacles that complicate the screening process and the suitability of using this alternative for diagnosing women with higher risk [22–24]. These studies found that its greatest advantage is that it offers the possibility of screening women who live in areas with difficult access, marginal regions, or those with other barriers against cervical screening.

Although the hrHPV test may show a clear advantage as a primary test, it is important to keep in mind that a large number of women will have a positive test because HPV infection is relatively common. This is why it is of utmost importance to have alternatives that can be used to identify the women that will require further diagnosis and confirmation, because it will reduce patient anxiety [25] and avoid both unnecessary treatments and expenses for the women with a low risk of progressing to cancer. The use of triage tests, such as the hrHPV genotyping (16/18/45), the use of the E6 protein as a marker of neoplastic progression, the use of cytology to detect morphological changes and the use of immunocytochemistry to detect markers of neoplastic progression, such as p16INK4a/Ki67, could reduce the number of required visits to health institutions, patient expenses and the anxiety that is derived from a positive detection result [26].

This is why it has been recommended that practitioners resort to triage alternatives for women with a positive hrHPV test, including the systematic collection of at least four cervical biopsies and a diagnosis by a group of pathologists. This proposition would not only reduce the number of visits to the physician but would also make the process more efficient and bring down the costs of the program. Furthermore, delaying the initial screening age by 10 years (from 25 to 35 years old) will help to reduce the incidence of this disease in young women [26].

The resources available in the fight against CC increase with time and now include the HPV vaccines, which offer protection against the HPV16 and HPV18 serotypes. Similarly, people who have become infected with these specific serotypes can be protected by these vaccines against other types of HPV and reinfection by the same serotype.

In relation to the recommendations suggesting the formulation of a vaccination policy in Mexico [27], this strategy is part of the primary prevention scheme that has been implemented since 2007 and is aimed at girls between 9 and 12 years of age. Additionally, it includes innovative proposals that could benefit older women.

Bear in mind that using vaccines for primary prevention of CC does not replace screening. On the contrary, the combination of both resources is currently one of the most promising innovations. Additionally, it has been proposed that we extend the vaccination programs to include women up to 30 years old (and in some cases up to 45–50 years old) and that we perform at least one hrHPV test on individuals who are ≥30 years old. This promising proposal, which includes a combination of resources, will extend the use of HPV vaccines and widen the use of the hrHPV test in detection programs and could thereby accelerate the reduction of CC incidence [28].

Because encouraging results have been found for combinations including both vaccination and detection methods, it is widely recommended that we broaden the screening intervals in favor of programs with a more effective cost-benefit ratio, to offer a better quality of life to women, and to reduce the burden of this disease on society as a whole. Within the framework of the recommended strategy for countries where there is a high incidence of CC, our country is currently undertaking efforts to evaluate the benefits of using a combined strategy including both vaccination and screening in women between 25 and 45 years old [29]. This has already set in motion detection programs that use the hrHPV test.

Regarding the availability of resources, a related point to consider is that since 2008, regional molecular biology laboratories have been opened in several states, and those in Puebla, Veracruz, Campeche, Guerrero and Michoacan were the first that had the means to perform the hrHPV tests. According to the most recent reports of the Health Secretary, 23 out of the 32 Mexican federal states already have a molecular biology laboratory, and there is also a reference center at the National Institute of Public Health.

6.4 Incorporation of the Vaccine Against HPV

An HPV vaccine was approved for commercial use in Mexico for the first time in 2006. Currently, 80 countries have integrated these vaccines into their national vaccination programs, and 37 more have evaluation and/or regional programs to facilitate its introduction [30].

There are three HPV vaccines today. One of them is bivalent, and this vaccine offers protection against the HPV16 and 18 serotypes. It has an AS04 adjuvant system that consists of 0.5 mg Al3+ hydrated aluminum hydroxide and 50 μg of 3-O-deacyl-4′-monophosphoryl lipid A (MPL) and is approved for use in women from 9 and older. In addition, a tetravalent vaccine also exists, with markers for HPV L1 virus-like particle (VLP) protection for types 6, 11, 16 and 18. This contains an adjuvant that contains 225 μg of amorphous aluminum hydroxyphosphate sulfate and has been approved for women from 9 to 45 years old. The use of this vaccine has also been approved in men from 9 to 26 years old [31].

The reported efficiency of this vaccine against the HPV6, 11, 16 and 18 serotypes in cases with a grade 2 or higher cervical intraepithelial neoplasia (NIC2+) is estimated to be 100% according to the FUTURE 1 and 2 studies, which were

performed on women and men between 16 and 26 years of age (95%CI 94–100) [32]. Additionally, in the sentinel cohort of Nordic countries, no NIC2+ cases have been associated with the previously mentioned serotypes [33, 34].

From a population-based point of view, the experience of Australia in 2007 with the introduction of the tetravalent vaccine, which has a coverage of about 70% in women younger than 26 years old, is a good example of the impact of this type of intervention. The sentinel event used to evaluate the effect of the vaccine was the prevalence of genital warts in a Center for Sexual Transmitted Diseases in Sydney and Melbourne. The effect of the vaccine against HPV was observed in both vaccinated women and in unvaccinated heterosexual men in the same age group. These results indicate that there is a "herd effect" in heterosexual men between 21 and 32 years of age that was not observed in homosexual men [35]. Regarding the bivalent vaccine, high efficiency was also reported for its ability to prevent HPV16 and 18 NIC2+ in women between 15 and 25 years old [36].

Additionally, women older than 25 years old are vulnerable to a new HPV infection and could therefore be vaccinated. Today, novel proposals are being considered to expand the HPV vaccination age range. It has been proposed that we vaccinate women between 25 and 45 years of age, which would provide protection to women who are not infected and protect already infected women from future reinfections [29].

Population-wide HPV vaccination programs have been recently modified at an international level. The main change consists of the introduction of an alternative 2-dose vaccination scheme with a periodicity of 6 months between doses in women younger than 15 years old. The available evidence suggests that the effect of two doses on girls between 9 and 14 years old is not less in terms of immunogenicity than the effect achieved with three doses at approximately 18–24 years of age [37]. These immunogenicity studies have also established that the size of the immune response is inversely proportional to the age at which the vaccine was first given, that giving two doses is recommended only in groups between 9 and 14 years of age and that the shortest interval between two doses should be 6 months, whereas the longest should be 12 months. This modification of the HPV vaccination scheme provides advantages, from a public health perspective. In particular, it reduces costs, provides operational benefits when there is a flexible interval between the doses (from 6 to 12 months) and allows for an increase in vaccination coverage in people older than 15 years old.

Concerning the initial schemes used with the first generation of vaccines against HPV, the Advisory Committee on Immunization Practices (ACIP) of the United States recommended using a nonavalent vaccine to continue with or complete any schemes that were initiated using any other HPV vaccine. However, it does not recommend the application of additional vaccines to already completed schemes [38]. In terms of safety, the percentage is very similar to that reported previously for the first HPV vaccines [38].

As a side note, there is a new recommendation in the 2016 ACIP (Advisory Committee on Immunization Practices) guidelines, which advises vaccinating boys and girls approximately 9 years of age when there is a history of sexual abuse

because it has been shown that there is a higher risk of HPV infection in these individuals [39]. Similarly, the Centers for Disease Control and Prevention (CDC) of the United States recommends HPV vaccination in immunosuppressed and HIV-infected women in addition to homosexual men [40].

6.5 Final Considerations

To improve the results of CC detection programs, it is necessary to identify and orchestrate triage alternatives that can improve the optimal handling of hrHPV-positive patients, professionalize the personnel who work in the screening programs, guarantee the quality of all steps that are involved and above all, establish mechanisms that make it possible to maintain follow-up of patients to guarantee their correct diagnosis.

According to the national health surveys, the preventive program coverage, which is evaluated in relation to a patient's cytological history over the previous 12 months, increased from 27.4% to 36.1% between the years 2000 and 2005 and from 36.1% to 42.8% between 2006 and 2012, when the survey was performed [41, 42].

Increasing the coverage of the hrHPV test will be an important challenge for the program in the coming years because it represents an opportunity for early detection, which translates into saved lives, the better use of resources and the availability of infrastructure to perform these tests across the country.

Information systems are fundamental to following up on the results of changes in public policies related to health. These instruments are currently facing basic problems: a lack of articulation at all levels of care can result in the numbers not matching or make it impossible to cross-reference information to increase our understanding of the problem, and a lack of access to all of the data that is collected in private medical institutions. As a consequence, we can achieve only a partial view of the problem, to the detriment of the program and the assignment of resources to attend to them.

After 10 years of intensifying the fight against CC, the greatest challenge has been recognition of this issue as a universal problem in which we consider new triage alternatives that will permit the identification of patients that require the confirmation of a positive diagnosis and timely handling of these tests. It is also recommended that the health system assume the challenge of broadening the coverage of preventive measures to facilitate the control of CC. These should use a combination of vaccination and screening to accelerate the reduction in this disease's burden.

These data indicate that it is critical that we consider governmental investment to address CC and that we prioritize related campaigns and preventive activities, such as vaccination and timely detection. This is because in the absence of the former, it is necessary to care for patients with CC when they reach advanced stages, which are associated with a much higher social cost.

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