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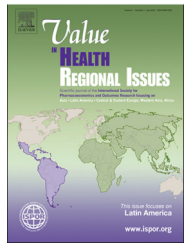

Cost-Effectiveness Study of HPV Vaccination as a Primary Prevention Strategy for Anal Cancer in HIV-Positive Men in Chile

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ABSTRACT

Background: Most anal cancers are caused by the human papilloma virus (HPV) infection. The incidence is increasing, especially in high-risk individuals such as HIV-positive men. Evidence shows that the new quadrivalent HPV vaccine reduces the rates of anal intraepithelial neoplasia among men who have sex with men. **Objective:** To determine whether vaccinating against HPV-related anal cancer is cost-effective in HIV-positive men in Chile. **Methods:** A cost-effectiveness analysis was conducted by constructing a cohort multistate life-table–based Markov model in MS Excel in which the prevention of HPV infection was expected to influence the incidence of anal cancer in HIV-positive men. The comparator was the current practice of no systematic HPV prevention. Estimates of the efficacy of the vaccine were obtained from a substudy of a larger randomized controlled trial, incidence rates from the Chilean Population Cancer Registries, mortality rates from the National Institute of Statistics, and disease costs from a cost-effectiveness report. A public health care sector perspective was applied. The outcome was measured in averted disability-adjusted life-years. The incremental cost-effectiveness ratio was calculated considering a lifetime horizon for costs and health outcomes. **Results:** The estimated incremental cost-effectiveness ratio was US $138,269/ disability-adjusted life-year (95% confidence interval $95,936–$221,862). Assuming a threshold of 3 times the gross domestic product per capita, the intervention was not cost-effective. The outcome was sensitive to the vaccine price and vaccine efficacy. **Conclusions:** HPV vaccination in HIV-positive men from a Chilean public health care sector perspective is not cost-effective.

Keywords: anal cancer, cost-effectiveness analysis, HPV, vaccines.

Introduction

Infection with human papilloma virus (HPV) has become the most common sexually transmitted infection (STI) worldwide. Although most of these infections are asymptomatic, they can result in clinically significant diseases such as cancer of the cervix, vagina, penis, oropharynx, and anus [1]. Although cervical cancer is the most common HPV-related malignancy, the incidence of other HPV-related cancers, mainly anal cancer, is increasing at an accelerating rate.

Most anal cancer cases (70%–90%) are squamous cell carcinomas (SCC) preceded by a dysplasia inflammation state known as anal intraepithelial neoplasia (AIN), in a process that is biologically similar to that leading to cervical cancer. As with cervical cancer, the main cause is infection with HPV types 16 and 18 [2]. Although there are screening techniques available to prevent AIN, there is little evidence on the effectiveness of these diagnostic tests [1] and no health system has yet implemented any. Once a case is diagnosed, the patient should be treated either with surgery or chemoradiotherapy as suggested in clinical guidelines.

The worldwide incidence of anal cancer has been increasing by 2% annually. In the United States, the incidence per 100,000 increased from 0.97 to 1.59 in men and from 1.27 to 1.84 in women during the period 1973 to 2000 [3]. In Australia, the age-adjusted annual incidence per 100,000 increased from 0.78 to 1.1 in women and almost doubled in men from 0.48 to 0.88 [4].

Data from the National AIDS Treatment Advocacy Project 2010 in the United States show that the incidence in the general population can be as low as 0.8/100,000, but it can dramatically increase to 70–144/100,000 among HIV-positive men who have sex with men (MSM) [5]. Supporting this evidence, a prospective cohort study was conducted in Seattle to evaluate the risk of contracting AIN in HIV-positive and HIV-negative MSM. The results showed that 15.2% of the HIV-positive patients developed AIN as compared with 5.4% in HIV-negative patients [6]. Palefsky et al. [7] found that HIV-positive men were 3.7 times more likely (95% confidence interval [CI] 2.6–5.7) to develop AIN than were HIV-negative men. Similar results were observed in San Francisco, where the authors suggested that the increased prevalence may be due, in part, to HIV-related immunosuppression and

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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prolonged survival after the introduction of highly active antiretroviral therapy which allowed the cancer to develop [8].

There are several risk factors that affect the incidence of anal cancer: increasing number of sexual partners, history of genital warts, history of cervical intraepithelial neoplasia type III, smoking, history of anal intercourse, immunosuppression, and HIV-positive status [9]. The presence of these risk factors not only increases the risk of HPV infection, but individuals who have them also have a lower response to disease-related treatments and develop HPV-related cancer more rapidly compared with the general population. Its highest impact, however, is observed in MSM [10], and that impact is even greater among those diagnosed with HIV [11].

The incidence and prevalence of HIV in Chile have increased since the first case was reported in 1984. Since 2005, it is mandatory to notify every diagnosed HIV case to the health authorities. As a consequence, reporting rates improved; however, an estimated 40% are still not notified. This would mean that about 40,148 people are living with HIV in Chile. Of these, 69% are males [12]. In addition, since 2005 all HIV patients are covered by the Chilean health system and hence are eligible to receive highly active antiretroviral therapy as specified in the treatment protocol guidelines. Although there is no published evidence regarding the anal cancer burden or the impact it may have as the HIV population in Chile continues to increase, there is consensus among experts regarding the higher risk observed in clinical practice. In addition, consistent with what has been reported in other countries, HPV infection is the most common STI with increased prevalence in Chile [13], which explains the high burden of disease associated with cervical cancer. This evidence led to the implementation of a vaccination policy for the prevention of HPV-related infections in 2014 when the first female cohort aged 12 years received the first vaccine dose.

In contrast to what is known about the epidemiology of cervical cancer, there is scarce evidence regarding the present situation of anal cancer in Chile, even though both diseases share the same etiology. The only available source is the first and only cancer registry report [14]. This report presents information of all new cancer cases during the period 2003 to 2007 in a defined population that included three regions throughout the country. Even though specific information of the tumor was collected through this registry, the report does not show data regarding the stage of the disease. According to this report, the adjusted incidence rate of anal cancer in males was 0.16 per 100,000 males per year. In Chile, the diagnosis is confirmed by a specialist who will notify each case and initiate appropriate treatment. There are no local clinical guidelines available; hence, international guidelines such as those of the European Society for Medical Oncology are at present being used [15]. According to this, surgery remains the standard treatment for small well-differentiated carcinomas (T1–N0). For all other cases, chemoradiation using 5 fluorouracil and mitomycin C is the first-line treatment recommended.

In the last decade, two prophylactic HPV vaccines, one bivalent and one quadrivalent, were introduced in the market. Both showed high efficacy against genotypes 16 and 18 in women younger than 26 years previously unexposed to the virus [16]. Nevertheless, the safety and immunogenicity of these vaccines have not been tested in HIV-infected adults. Because they represent a high-risk population susceptible to HPV infection, several clinical trials are in process to establish these parameters. Some preliminary results were revealed in November 2011 in the AORTIC 7th International Conference regarding a phase II interventional study in South Africa (**Trial Registration:** clinicaltrials.gov Identifier: NCT005866339). Results showed seroconversion of HPV types 16 and 18 in both HIV-positive and HIV-negative subjects [1]. In addition, a pilot study found the quadrivalent vaccine to be safe and immunogenic in HIV-positive men. These results, however, should be treated with caution because the aim of the study was not to determine the efficacy of the vaccine in preventing HPV infection or AIN. Their clinical significance is unknown, and they have limited generalizability [17].

A cost-effectiveness analysis was conducted to provide evidence regarding the appropriateness of HPV vaccination as a primary prevention strategy of anal cancer in HIV-positive men in Chile. The health outcome was measured in averted disability-adjusted life-years (DALYs) and the costs in 2010 US dollars. Costs and benefits were measured from the perspective of the public health care system considering a lifetime horizon. With these two parameters, incremental cost-effectiveness ratios (ICERs) of HPV vaccination for the prevention of anal cancer versus the current practice of no systematic HPV prevention were calculated.

Methods

Modeling Health Outcomes and Costs

The main aim of this study was to determine the cost-effectiveness of vaccinating an HIV-positive male cohort aged 25 to 34 years for the prevention of anal cancer in Chile. This age group was considered for assessment because recent epidemiological data show that most HIV diagnoses are found to be in the age group of 20 to 29 years [18]. On the basis of prevalence data, we estimated a total of 13,396 HIV-positive men and women in the 20 to 29 years age group, in which 9243 (69%) were men. With this evidence, a cohort multistate Markov model was built in Microsoft Excel (Microsoft, Redmond, WA) to represent the natural history of anal cancer when considering an HIV-positive male cohort. Four health states were defined in this model that was governed by five types of transition states (Fig. 1). Subjects in the base health state (HIV-positive men) were considered to be initially unaffected by the disease (anal cancer) but at risk of developing anal cancer. If they were diagnosed with anal cancer (incident case), then they were at risk of dying from the disease (case fatality) or would be recovering (remission case). To ensure internal consistency between all different epidemiological data and to be able to derive some unavailable parameters (case fatality), data were fitted into the model using DisMod II (www.epigear.com). Remission rates were assumed to be zero, and we accounted for survival cases assuming them as prevalent for up to 5 years after diagnosis. The model considered that both base health state people and diseased people were at the same risk of dying from other causes (mortality case) [19]. This model calculated the effect on incidence and disease-specific mortality in subsequent years as a consequence of changes in disease incidence. Survival rates for different anal cancer stages were considered for the calculation of case fatality.

The multistate Markov model contained two separate standard life tables. The first corresponded to the reference population

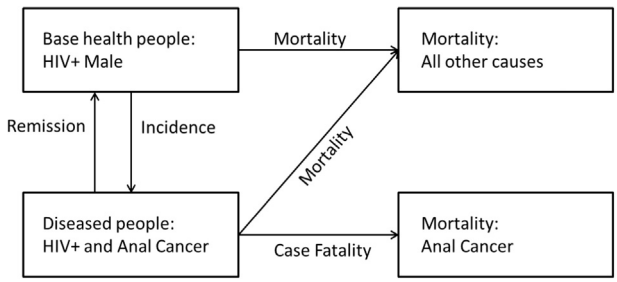

Fig. 1 – Anal cancer illness death modeling.