Human papillomavirus and Brazil: Critical study of prevalence and current situation in an epidemiological investigation

Joao Do Nascimento
Case Western Reserve University

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ABSTRACT

Human papillomavirus (HPV) is one of the most prevalent sexually transmitted pathogens associated with malignancy, infecting 12% of sexually active women, worldwide. HPV is also responsible for 99.7% of cancers of the cervix. Cytology and colposcopy are the recommended diagnostic methods by the Brazilian Ministry of Health and are the most frequently used tests during routine screening exams. In this regard, the Laboratory of Pharmacogenomics and Molecular Epidemiology (LAFEM) of the State University of Santa Cruz, Ilheus/BA (Brazil), performed a critical evaluation of HPV prevalence in women in the southern region of the state of Bahia, correlating with results of meta-analysis of data shown by DataSUS. The proposal was developed in partnership with the ongoing research in the Basic Health Units and in the Family Health Program. The statistical analyses were performed using the Meta-Analyst Beta 3.13 software. We observe that the estimate of the overall prevalence of HPV infection in women in Brazil to be 36.1%. Data of scientific literature showed that, in Bahia, the prevalence is 43.9%; our study presented prevalence of 47.7%. According PCR results, in the southern region of Bahia, cervical-cancer mortality has been increasing by 2.15% per year, since 2000. The findings denote fragility of the Health System regarding HPV prevention. Furthermore, this study highlights the close relationship between diagnosis and molecular methods, observed by the increase in sensitivity and specificity when applied with cytology. In the absence of strategies for surveillance, deploying relevant public actions in control and early detection of cervical cancer remain compromised.

INTRODUCTION

The Human papillomavirus (HPV) is a DNA virus member of the papovaviridae family, whose genes are located on the positive strand of viral DNA[3, 14, 19]. This large family of viruses is capable of infecting a variety of tissues, including the cutaneous epithelium and mucosa.

Since the early 1980s, the number of clinical and laboratory research publications regarding HPV has grown considerably, as has the use of molecular epidemiology and molecular biology in HPV research[7]. These advances in research allowed the discovery of the role of HPV – primarily HPV serotypes 16 and 186, 11 – as the etiological agent of cervical cancer.

Cervical cancer is a critical public health problem as it is the second most common cancer in women worldwide[6]. Although there have been advances in its diagnosis and treatment, cervical cancer still remains an important challenge in developing countries such as Brazil, where the incidence rate is twice as high as that of developed countries. In Brazil, 17,500 new cases of cervical cancer are expected by the end of the year, 2012[9, 10, 13].

The Papanicolaou smear test is the most widely used cervical cancer

Joao Do Nascimento

João Henrique Fonseca do Nascimento is an undergraduate researcher at Case Western Reserve University, and an undergraduate in baccalaureate of Biomedicine at State University of Santa Cruz (UESC), Ilheus – Bahia, Brazil. He worked on the epidemiology and prevalence of Human Papillomavirus (HPV) in women attending a Basic Unit of Women's Health, southern Bahia (Brazil). Currently, he is in the Center for Global Health and Diseases at Case, developing research in Genetics, Molecular Biology and Epidemiology, with Dengue virus, HCV and Schistosoma mansoni, working with Dr. Ronald Blanton.

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Figure 1. Epidemiology of HPV in Brazil in 2012. The North and Midwest did not have enough data to generate reliable average values. (REGIONS: Green = North, Orange = Northeast, Yellow = Midwest, Red = Southeast, Blue = South).

Figure 2. Map of Brazil: 14 Brazilian states in blue where, from 2000 to 2011, there were no epidemiological publications on HPV available, according to the sources consulted.

screening test in the world. Organized screening programs reduces mortality due to cervical cancer. However, in developing countries, where screening programs are uncommon, the rate of death due to cervical cancer remains high. In this regard, recent studies have presented molecular diagnosticsas a great ally. Polymerase Chain Reaction (PCR) has been shown to be the most sensitive method for identifying HPV infection in clinical samples[17], and primers amplifying DNA fragments in the conserved L1 capsid antigen (L1) region have become the most widely used in clinical and epidemiological studies of HPV.

METHODS

We prospectively collected data of all women who presented themselves for routine cervical cancer screening at primary health care units (Unidades Básica de Saúde) in the Southern Region of the state of Bahia, Brazil. All women who agreed to participate provided written informed consent. Endocervical swabs were collected and sent to the Laboratory of Pharmacogenomics and Molecular Epidemiology (LAFEM) of the State University of Santa

Cruz, Ilheus, Bahia – Brazil.All samples were analyzed by the Hematoxylin and Eosin (H&E) method as well as by Nested PCR. To perform the Nested PCR, we used primers amplifying DNA fragments in the conserved L1 region.. The MY09 and MY11 primer set-mediated PCR and the GP5+ and GP6+ primer set-mediated PCR are the most frequently used amplification systems for the detection of HPV DNA in clinical samples[17].

Staistical analysis

The data were analyzed according to the geometric theorem of annual growth rate for indicator analysis, pooled analysis, and analysis of variance. We used MetaAnalysis Beta version 3.13 software, developed by Tufts Medical Center and the Agency for Healthcare Research and Quality and Microsoft Excel 2010 software, developed by the Microsoft Corporation, USA.

RESULTS

During the period from July 2011 to April 2012, we performed the screening visits and the data analysis

for mortality due to cervical cancer in Brazil. Of the 195 women who participated in our study, 52 (or 26.7% of the sample) tested positive for HPV. We also observed that the sensitivity/specificity was 0.41/0.71, 0.7/0.805, and 0.909/0.783 respectively for Papanicolaou, PCR, and a combination of both methods (Fig. 4).

DISCUSSION

The data were processed obeying CI = 95% and p = 0.001. The study showed that Brazil has an average prevalence of HPV of 36.1 percent. The southern region had the highest prevalence of HPV infections and an average frequency of 43.9%. Mello and colleagues (2010) showed the southern region of Brazil to have one of the largest incidence rates of cervical cancer since the 1980s[12, 9, 20]; our results corroborate the Mello study's rates. Our study also showed that the regions of the Southeast and Northeast had average frequencies of 32.19% and 29.9%, respectively. The North and Midwest regions did not present enough data to generate reliable and significant values, with publications in the states of Amazonas[19,5] and Goias[18] only. Additionally, our study showed a strong link between HPV and gynecological neoplasms, which has been already demonstrated as well.

According to the data of the National Control Program of Cervical Cancer and DataSUS, related to statistical calculations, mortality due to cervical cancer has been increasing by 2.15% per year in Brazil – one of the largest rates of any country around the world. Despite the high rate of frequency of HPV in the Northeast, the Women's Health Program (INCA) demonstrated in 2010 that in Bahia, the ratio of the sexually active female population and the number of cytological examinations required is relatively low, reaching only 14%, one of the lowest rates in the country. The available studies only evaluated HPV-HIV co-infection, and the population samples used were women not usually seen in the routine screening exams.

The link between national HPV prevalence and the noticeable lack of data is troublesome. Fourteen Brazilian states do not present reliable or relevant data about the prevalence of the virus over the last decade (Fig. 2). Moreover, a connection can be seen between the lack of data and the high cervical cancer mortality rate of young Brazilian women – approximately 2.16% – when compared with more developed nations such as the United Kingdom, which has a mortality rate of 1.3%[2]. In the United States, 4,008 women died from cervical cancer between the years 1999 and 2008; this death toll is similar to the annual number of deaths due to cervical cancer in Brazil during the same period (Fig. 3). This emphasizes the dependence of the viral control of HPV on sufficient data.

Another point that we can infer and discuss is the women's health care in Brazil, and questions of gynecologic malignancies. In early 2012, the National Institute of Cancer (INCA) published on their website "The actions of the
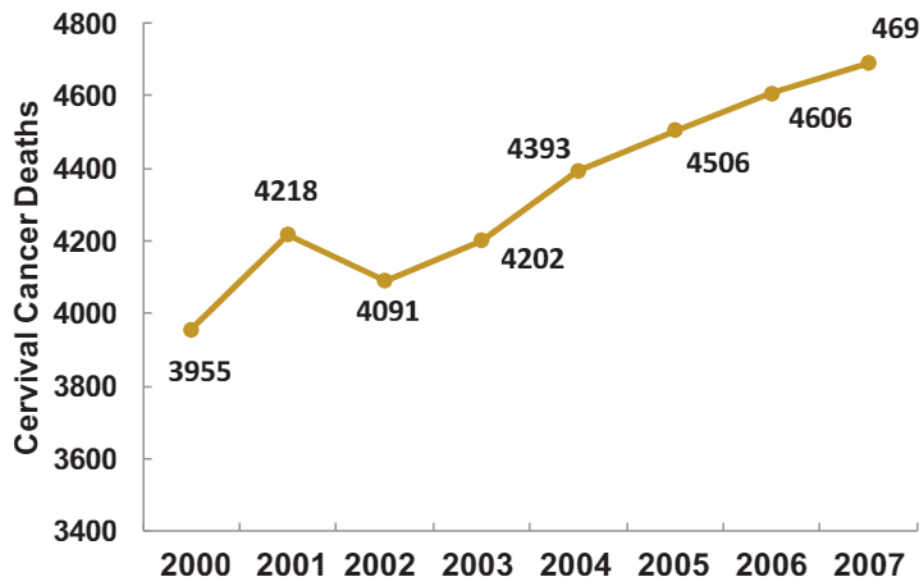
Figure 3: Deaths caused by cervical cancer during the years 2000 to 2007 in Brazil (SD = 257.9). Shows increasing rate of death of 2.156% per annum.

National Cancer Surveillance aim to know in detail the current framework of cancer in Brazil"[9, 10]; however, despite the strong link between HPV and cervical cancers already shown, there are no official epidemiological indicators in the system of public health in Brazil on the prevalence and frequency of this virus, despite the fact that it is the second-most common sexually transmitted infection in women attending primary care units in the country.

According to the World Health Organization, more than 80% of cases of cervical cancer occur in developing countries[21] such as Brazil, and according to United Nations Population Divisions in 2009, these countries contain 82% of the population of the world. This lack of consistent results on the magnitude of infections imposes limitations on the planning of public surveillance and control[8, 15].

We also discuss in this work, aspects related to the exams and tests for the HPV diagnosis used in Brazil. The Papanicolaou smear test is the exam used in gynecological routine that allows the visualization of lesions on uterine cervix. This procedure is used as a screening test for cervical cancer, which has a strong correlation with HPV infection - 99.7% of cases of Cervical Cancer are caused by HPV infection[12]. However, a Pap smear alone is not enough to perform an efficient diagnosis; for more accurate results, molecular methods are required. We observed in out meta-analysis studies, which showed that 15.6% to 20.2% of women may have negative cytology with positive viral load[15].

These results suggest the low accuracy and efficiency of the Pap test as a method of routine care, by itself. Therefore, molecular tests are important in giving an accurate diagnosis, and also have the advantage of possibly subtyping the virus, which can result in an effective treatment that will prevent the tumor formation (Fig. 4).

We also observed that sexual and health educations represent important roles in sexual transmitted infections, as HPV. In this order to control HPV infection and consequently lower the prevalence of cervical cancer, it is necessary to improve practices in sex education. Oria and Alvez, in 2004, conducted studies in guiding adolescents and their families in the face of sexually transmitted infections and to evaluate the role of health professionals. The results were alarming, demonstrating that dialogue between parents and children about sex, contraception, and condoms is defective or, in many cases, nonexistent. Despite the increasingly publicized that HPV is the most prevalent agent of cervical cancer in the world, there is a significant weakness in health education, which is shown by the high rates of infection and of deaths linked to cervical cancer. It is crucial to invest more in practices of sexual education, to work directly on the reality of knowledge of teenagers and their families. Thus, through direct and appropriate language, myths and taboos will be broken, opening space for the modification of the current landscape of the frequency of this severe infection
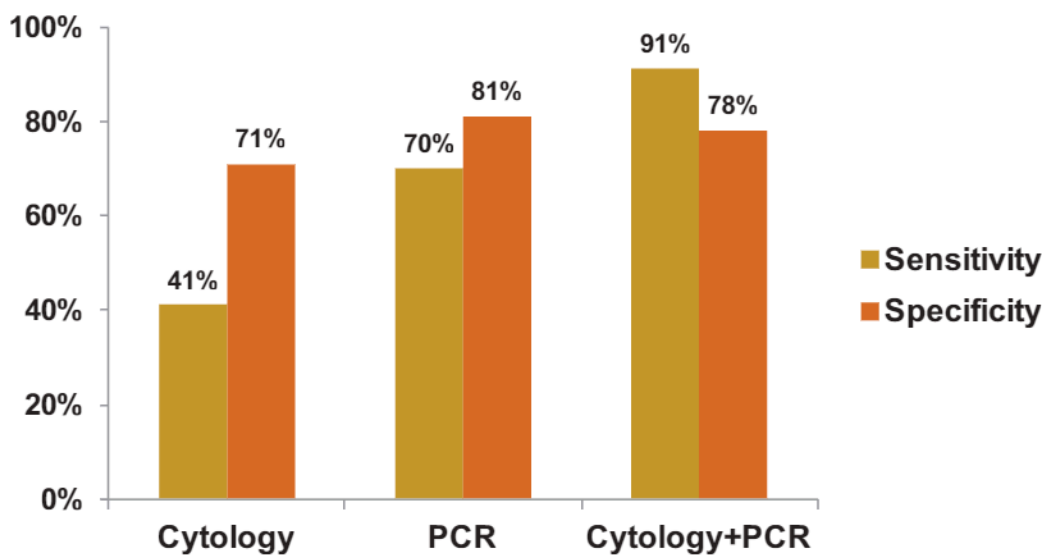
Figure 4. Evaluation of diagnostic tests for Human papillomavirus applied in the medical routine of the Brazilian public health system. In the Family Health Program of the Ministry of Health, the standard considered was hybrid capture. Analysis done by Meta-Analyst version 3.13 software.

DISCUSSIONS

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