

Original Research Paper

Prevalence Study of Injuries Caused by Human Papillomavirus (HPV) in the Cascavel Population

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Abstract: To determine the prevalence of human Papillomavirus (HPV) infection in the population of Cascavel, Paraná, Brazil, correlating the risk factors with the infection and seeking to identify the general situation of the disease in the city. Records of patients from the Specialized Center for Infectious-Parasitic Diseases (CEDIP, Cascavel) were analyzed between 2010-2014 and clinical files of patients affected by some manifestation of HPV infection were included. Data on age, gender, sexual orientation, number of sexual partners in 12 months, history of another Sexually Transmitted Disease (STD) or presence of STD associated with clinical manifestation of HPV infection, schooling, smoking, contraceptive use and condom use. Of 2,889 records, HPV infection affected 1,189 patients (41%). The incidence of HPV infection in Cascavel is approximately 237 new cases per year, with the most common clinical manifestation of genital warts (84%). The profile of patients most affected by the manifestations of HPV was of both genders, young (42%), at the onset of sexual activity (46%), heterosexual (91%), irregular use of condoms (69%) and use of oral contraceptives (45%). HPV infection has a high prevalence in Cascavel and requires further public health measures to control the disease.

Keywords: Epidemiology, Prevalence, Papillomavirus Infections, Uterine Cervical Neoplasms, Risk Factors

Introduction

Viruses are obligate intra-cellular parasites that can only multiply within a living cell. They have complex organization and a type of nucleic acid: DNA or RNA. Viruses are capable of damaging or modifying cells because of their property of modifying the metabolic and reproductive activities of parasitized cells. Some cause cell death (cytotoxic), while others are stimulators and cause purely proliferative reactions in the cells that harbor them. Agents of this type are involved in the viral induction of neoplasms. Between two extremes of the spectrum are almost all viruses endowed with both cytotoxic and proliferative action (Kumar *et al.*, 2015).

Regarding the Human Papillomavirus (HPV), this virus is included in Papillomaviridae family and in the genus of Papillomavirus. In this genus, eight species are described, of which one is HPV (Brasil, 2006). There are more than one hundred types of Papillomavirus currently recognized, twenty of which can infect the genital tract. They are divided into two groups according to their potential for oncogenicity and those with high oncogenic

risk, when associated with other cofactors, are related with the development of intraepithelial neoplasms and invasive cancer of the uterine cervix, vulva, vagina and anal region (WHO, 2008; Kumar *et al.*, 2015)

The low-risk group includes HPV 6, 11, 42, 43 and 44, which are associated with benign infections of the genital tract such as concha acuminata and low-grade intraepithelial lesions. The high-risk group includes HPV 16, 18, 31, 33, 35, 39, 45, 46, 51, 52, 56, 58, 59 and 68, which contain oncogenes that correlate with high-grade intraepithelial lesions and carcinomas of the cervix, vulva, anus and penis (Brasil, 2006; Fedrizzi, 2011).

The viruses were enumerated in order of their discovery. The most commonly encountered types associated with cervical cancer and other cancers are HPV 16 and 18 (WHO, 2008). High-risk HPV types have the E6 and E7 genes that are associated with the immortalization and transformation of cells resulting in carcinogenesis. Specifically, the genetic code for oncoproteins of E6 and E7 manipulates cell cycle regulation, induces chromosomal abnormalities and blocks apoptosis (cell death). HPV initially infects the

basal layer of the human epithelium, causing differentiation of epithelial cells - which do not normally divide - to remain in an active cell cycle. The virus then uses the cell replication machinery in differentiation to amplify the viral genome (WHO, 2008; Nakagawa *et al.*, 2010; Dias *et al.*, 2014).

The most common malignancy related to HPV is cervical cancer. With 528,000 new cases a year, cervical cancer is the most common cancer affecting women in developing countries and the fourth most common affecting women worldwide (Vinodhini *et al.*, 2012; Ferlay *et al.*, 2015). If the incidence continues to increase in this way, the estimated incidence will be 1 million new cases per year by 2050 (WHO, 2008).

Incidence levels are highest in parts of Latin America, the Caribbean, Sub-Saharan Africa, Melanesia and parts of South Asia (WHO, 2008; Vinodhini *et al.*, 2012). Among the countries of Latin America, Brazil is considered one of the high risk areas for cervical carcinoma (Aleixo Neto, 1991).

In 2012, there were 266,000 deaths from cervical cancer (Ferlay *et al.*, 2015). Deaths from cervical cancer are estimated to increase by approximately 25% over the next 10 years. In developing countries, more than 60% of women with cervical cancer will die from late detection of the disease (WHO, 2008).

HPV infection is extremely common in the world and transmission is through sexual contact (with or without penetration). The incidence usually occurs between the ages of 16 and 20 years and may increase with increasing sexual practice. Among the risk factors for transmission include multiple sexual partners, sexual activity without a condom, coinfection with other sexually transmitted diseases including human immunodeficiency virus (HIV), social class and smoking (WHO, 2008; Ribeiro *et al.*, 2015).

Among the risk factors for the development of cancer related to HPV infection are the prolonged use of combined oral contraceptives (COCs) containing steroid hormones 17 β -estradiol (E2) and progesterone (P4) (Marks *et al.*, 2010). HPV infection is transmitted via the mucosa and has no phase in the bloodstream. Only about half of women develop serum antibodies after natural infection and the antibodies do not necessarily prevent a subsequent infection (WHO, 2008).

Starting 6 years ago, HPV vaccine was included in the Brazilian immunization calendar. After Brazil conducted its first national HPV vaccination campaign and offered the vaccine free of charge to the Unified Health System (SUS), only 48.7% of children aged 9 to 14 years in the country, the target population recommended by the World Health Organization (WHO), were immunized. Even today, there are barriers to the progress of immunization against HPV in Brazil due to the low level of population knowledge about the disease and importance of immunization, as well as resistance for fear

of possible adverse effects (De Laia Nunes *et al.*, 2015; Barbosa and Niquirilo, 2016; Leite *et al.*, 2018).

Because availability of the vaccine entails costs to the health system, there is a need for rigorous evaluation regarding the long term cost benefit of HPV vaccination. Considering the latency period of HPV, a long length of follow-up regarding development of lesions is required (Silva *et al.*, 2009; De Laia Nunes *et al.*, 2015). The overall efficacy against cervical cancer in terms of public health is still not well established. In countries where it is implemented, the vaccine has not yet provided data on incidence and mortality reduction for cervical cancer (Borsatto *et al.*, 2011).

In view of unresolved questions regarding vaccination against HPV, studies that define the prevalence and incidence of the disease by regions in Brazil are important. Therefore, this study aimed to address the prevalence of HPV in Cascavel city of Paraná, Brazil.

Methods

Study Type and Data Selection

The study was observational, retrospective, covering the period from 2010 to 2014, with quantitative and qualitative analysis of the data collected. For the sample selection, 2,889 patient records were analyzed from the Specialized Center for Infectious-Parasitic Diseases (CEDIP) in the period between 2010 and 2014, of which 1,189 were included in this study because they presented clinical manifestations of HPV infection. The final diagnosis of physicians was made by clinical examination and clinical and histopathological analyses.

The search was previously approved by the Research Ethics Committee (CEP) of the State University of the West of Paraná (UNIOESTE), under seem number 888.814 of 11/26/2014 and received authorization to collect data by the Health Department of Cascavel. The study involved the special health unit CEDIP - Specialized Center for Infectious-Parasitic Diseases, located in Cascavel, Paraná. We included all patients with HPV who were attended between 2010 and 2014 and the respective information contained in the charts analyzed and applied to the data collection instrument. The confidentiality of patient records was strictly maintained, since the reading of the medical records was carried out under supervision of the Chief Nurse and Coordinator of the establishment.

Data Collection

The relevant data in the medical records were based on the following criteria: age; gender; ethnic group; age of infection/discovery; first sexual intercourse; sexual orientation; number of sexual partners in 12 months; previous history of another Sexually Transmitted Disease

(STD) or presence of STD associated with the clinical manifestation of HPV infection; education level; smoking and drug use; use of contraceptives and condom use.

The review of studies about HPV infection was analyzed through publications indexed in the Medical Literature Analysis and Retrieval System Online (MEDLINE), accessed by PubMed; Latin American and Caribbean Literature in Health Sciences (Lilacs); and Scientific Electronic Library Online (SciELO). The investigations were carried out using the search strategy of free terms including the terms "HPV", "human papillomavirus", "prevalence" "HPV Brazil", "HPV infection", "HPV risk factors" and "cervical cancer" on the search field from May 2014 to August 2015.

The combination of bibliographical and documentary research allowed us to collect data about the disease prevalence in the Cascavel population in the period from 2010 to 2014. Data was stored in Microsoft Excel® in sectorial worksheet, sorted by years and categorized into columns of each item of risk factors. Subsequently, the statistical analysis of the data was performed with the XLSTAT® program and the graphs constructed by Microsoft Excel® tool for graphs generation from the statistical results.

Results

Prevalence of Clinical Manifestations

Of the 2,889 records analyzed corresponding to patients seen between 2010 and 2014, 1,189 presented clinical manifestations of HPV, corresponding to 41.15% of all patients seen in a period of 5 years.

Gender

There was no statistically significant difference between genders (49% men and 51% women) and infection involved both the male and female population in an equivalent manner.

Ethnic Group

Regarding the ethnic group, the intended interpretation must be made considering the region, which despite its ethnic diversity, the majority of the population is white and brown (IBGE, 2014). Thus, 49.3% (n 375) of the sample corresponded to white individuals; 49.3% to brown; 1% to African descendants and 0.3% to the yellow population.

First Sexual Intercourse

In the data demonstrating the onset of sexual activity, 5% started between 10 and 12 years; 47% started between 13 and 15 years of age; 43% started between 16 and 18 years old and 5% were over 18 years old (Fig. 1).

Age of Infection

Regarding the age of probable HPV infection, in 41.2% of cases, it occurred between 11 and 20 years; in 40% between 21 and 30 years; in 11.2% between 31 and 40 years; in 5.4% between 41 and 50 years; in 1% between 51 and 60 and also in 1% in those older than 60 years. In 0.6% of the cases, the infection occurred in children less than 10 years old (Fig. 2).

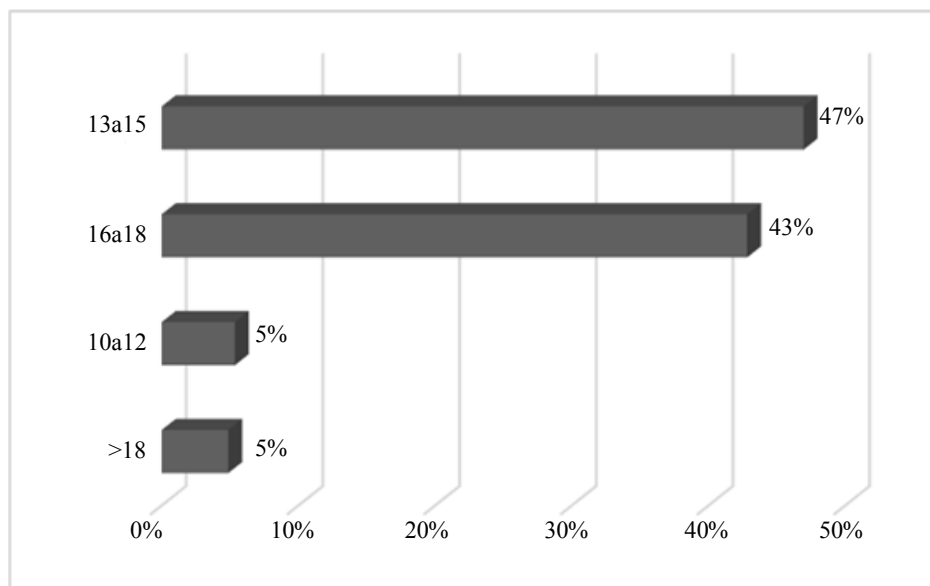


Fig. 1: Percentage of sample and age at onset of sexual activity, considering individuals infected by HPV in the city of Cascavel (PR) between the years 2010 to 2014

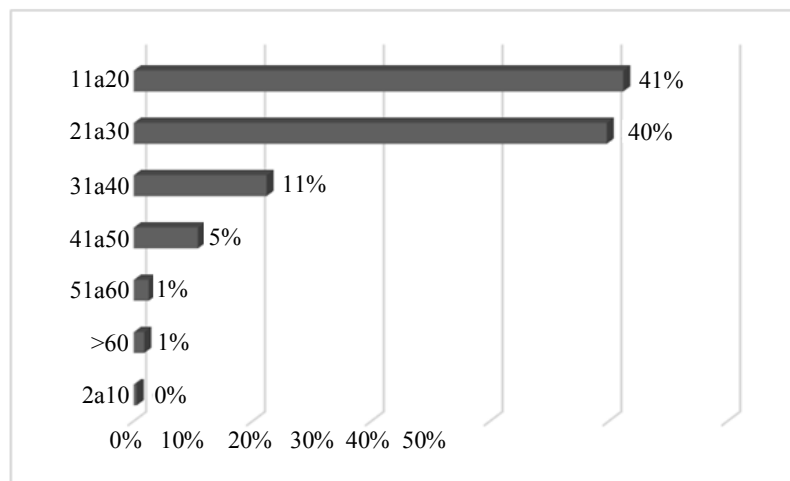


Fig. 2: Percentage of the likely age of HPV infection in the city of Cascavel (PR) between the years 2010 to 2014 for both genders

Education

Regarding schooling, 39.5% of the respondents studied high school; 18% studied until incomplete high school; 16.48% studied incomplete elementary school; 11.4% studied the complete elementary school. 8.75% of the sample represented individuals with incomplete higher education and 4.84% with complete higher education. Individuals without schooling corresponded to the lowest value of the sample, being 0.93% of the total.

Sexual Orientation

Data on sexual orientation showed that 91% of the patients declared themselves to be heterosexual, 7% declared themselves to be homosexual; 1% bisexual and 1% does not apply (data concerning children). This information should be interpreted with caution, since the group of people who declare themselves with sexual orientations other than heterosexuals are, in general, a minority.

Number of Partners in 12 Months

Regarding the number of partners that each patient reported in 12 months, 47.5% reported having had a single sexual partner in 12 months; 32% reported having sex with more than 2 sex partners per year; 18.2% reported 2 partners per year and 2% reported abstinence from sexual activity in the last 12 months.

Clinical Manifestation

The most frequent form of clinical manifestation was genital condyloma representing 84.6% of the patient sample. Cervical Intraepithelial Neoplasms (CIN) of degree I or II were found in 5.21%, genital papules were detected in 4.12% and 2.94% were asymptomatic at the time of consultation. About 2% of patients had other manifestations such as flat condyloma, plaque or genital

spot, while 1% of the patients with any clinical manifestation of HPV had oral lesions, with sites varying between tongue, oropharynx, palate and lip border. Genital carcinomas were found in 0.58% of patients (Fig. 3).

Associated STDs

The main STDs associated were syphilis (40%); genital herpes (33.3%); gonorrhea (31.1%); and other diseases (26%). Associated diseases, those affecting the genital tract and not necessarily sexually transmitted, have been excluded.

Also in this category, information was obtained regarding the association of HPV infection with other STDs. It was verified that 78.3% of the patients were not infected with another disease and 21.7% had a history of or association with other STDs. Of the 21.7% with coinfection, 64% had one STD associated with HPV infection, 7% had 2 STDs associated with infection, 19% had an STD history, 2% had more than 2 STDs associated with the infection and 1% had a STD history at some time in life and STD associated with HPV infection.

Smoking

The category "smoking" was divided into "no" and "yes", with subdivision of "yes" to identify the frequency of the habit. Of the patients with HPV, 51% smoked from 11 to 20 cigarettes per day, 28% from 5 to 10 cigarettes/day, 12% less than 5 cigarettes/day and 8% more than 20 cigarettes/day. We should consider in this data that there is a reduction in HPV incidence in individuals who smoke more than 20 cigarettes per day, showing a possible tendency to reduce infection in patients who smoke more frequently. Among the 24.3% of smokers, more detailed information showed the following: smoking alone (63%), former smokers (4%), smoking and current drug users (19%) and smoking and former drug users (12%).

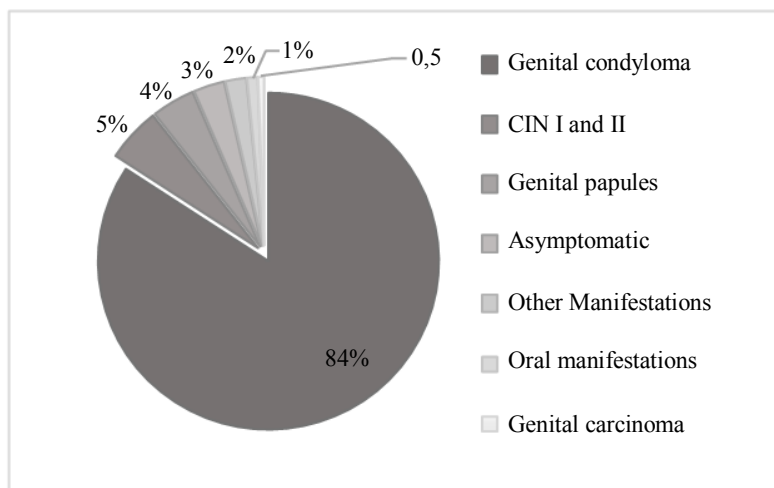


Fig. 3: Percentage of clinical manifestations of HPV infection in the city of Cascavel (PR) between the years 2010 to 2014

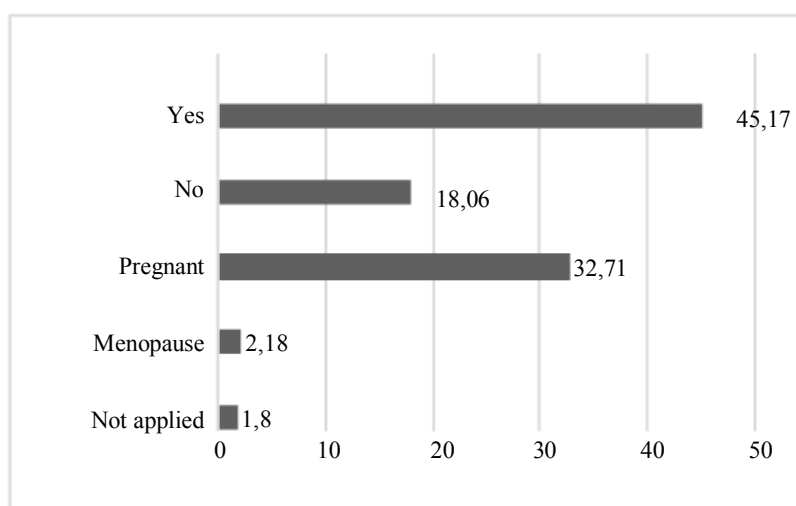


Fig. 4: Percentage of use of oral contraceptives by women affected by HPV

Oral Contraceptives Use

Regarding the percentage of women who use oral contraceptives, the findings revealed that 45.1% of the women declared themselves to be using contraceptive medication; 32.7% were pregnant at the time of the consultation; 18% do not use contraceptive drugs; 2.18% of the women presented in menopause and 1.80% did not apply to this category (children or women who had a hysterectomy procedure) (Fig. 4). For the "Yes" answer, it was divided into "Yes and continuous use" subcategories (16%) and "Yes non-continuous use" (40%).

Condoms Use

Condom use was found in 69% of patients reporting irregular use and 29% reporting regular use of this contraceptive method.

As an additional result to what was initially proposed as specific research objectives, in addition to the categories already exposed, data were collected regarding the civil status of infected patients with the following results: 69% single; 27.7% married; 2.41% divorced and 0.70% widowed. When separated by gender, HPV infection is present in 77.8% of single men and in 57.44% in single women. In married men the infection rate was 20.5% and in married women the rate was 37.3%. The lowest proportions were in divorced and widowed men (0.8% and 0.7%), which was lower than the rate in divorced and widowed women (7.8% and 1.2%).

Incidence of Disease/Year

Regarding the distribution of cases per year, there was no statistically relevant difference between 2010 and 2014. The average found was 237.8 new cases per year

in the established period. This corresponds to 0.07% of the total population in the city, which has 309,259 inhabitants, according to IBGE (2014).

Discussion

The recognition of the medical importance of HPV infection has increased gradually over the years. As has been reported in the literature, clinical manifestations of the disease have been known since antiquity, but causal factors have been unknown for centuries (Oriol, 1971; Garfield, 1988). In the last decades, not only the different types of HPV have been discovered but also the potential for oncogenicity, being subdivided into a group of high oncogenic risk and low oncogenic risk (WHO, 2008). In global studies, high-risk HPV is shown to be present in the normal cytology of many women and in these women associated cofactors may induce carcinogenesis (Bruni *et al.*, 2010; Kumar *et al.*, 2015).

In relation to risk factors, the results of this sample showed similar involvement of HPV infection in both genders. In the literature, we find information compatible with this result. The study of Araujo (2013), reports that HPV has a high prevalence in both genders. Another study by Giuliano *et al.* (2010), reveals that men are more affected, probably because they have a longer active sexual life than women and a greater number of genital sites that contribute to the infection. Men who report irregular condom use also have a higher risk of infection and transmission compared to men who report regular condom use (Giuliano *et al.*, 2010). The findings of our investigation show that most of the infected individuals do not regularly use condoms (69%) coinciding with results reported in the literature.

Regarding the age of probable infection, the highest rate (41%) was found in young individuals between 11 and 20 years with a second peak (40%) in individuals between 21 and 30 years and a third peak (11%) in adults from 31 to 40 years. One report demonstrated a bimodal curve in the statistical analysis of the age of infection, with the first peak at the young age soon after initiation of sexual activities and an incidence in mature adult patients with a mean age of 45 years (Bruni *et al.*, 2010). Thus the age of initial HPV infection in our patient cohort differs somewhat from the age of infection in other populations reported in the medical literature.

The data from this research also demonstrate that the probable infection of the individuals occurred soon after the first sexual contact. The most prevalent age of onset of sexual activity is between 13 and 15 years of age (47%), followed by 16 to 18 (43%). When compared to the age of probable infection, which includes ages between 11 and 30 years (81%), the results complement and reinforce the conclusion of Ribeiro *et al.* (2015), which states that infection occurs in the early years after

initiation of sexual activity. According to previous research, it is considered that the earlier the onset of puberty, the longer the sexual activity time during the life and the greater the increase of the sexual practice with multiple partners the greater the exposure to the disease (WHO, 2008; Giuliano *et al.*, 2010). Therefore, further studies are needed to determine the mean age of sexual activity and the mean age of individuals with multiple sexual partners and to find the age group most exposed to HPV infection.

In the case of other STDs in association with the clinical manifestations of HPV, it was found that most infected patients did not present associated STD at the time of diagnosis (78%), while the smallest part had at least one STD associated with the infection by HPV (21.7%). We can infer from this result that the majority of people treated at CEDIP have only HPV infection without coinfection or history of another STD.

In contrast to the data of this research, it was verified in the study of Bruniet *al.* (2010), that coinfection with other STDs probably contribute to the risk of infection and/or the development of clinical manifestations of HPV. The most frequently associated HPV-associated STDs in the CEDIP survey were syphilis, herpes and gonorrhea. It is interesting to note that, historically, HPV was an unknown cause of genital warts, but for a long time warts were considered part of the clinical manifestations of syphilis and of gonorrhea (Garfield, 1988). It is demonstrated, therefore, that the association of HPV and syphilis or gonorrhea has been quite common for centuries and today, we can still verify the frequent association of these diseases with HPV infection.

Regarding the use of oral contraceptives, 45% of the infected women use this method and 18% do not use any. Another aspect that draws attention, in the data collected in the CEDIP, is that 32% of the women were pregnant concomitantly to the appearance of clinical manifestations of the infection. The higher prevalence of infection that is present in women who use oral contraceptives and in pregnant women has been demonstrated in previous studies (Moreno *et al.*, 2002; Ragin *et al.*, 2009; Salcedo *et al.*, 2015). These studies describe the immunosuppressive role of hormones present in oral contraceptives and the hormones produced during pregnancy. In addition, the presence of steroid hormone receptors present in HPV 16 may stimulate the expression of the E6 and E7 genes, suggesting a hormonal activation effect for HPV replication. We must consider, however, the possibility that this data relates to the fact that women who make exclusive use of oral contraceptives for birth control may not make use of the physical barrier of condoms to prevent STD's.

As regards pregnancy, this is characterized as a state in which the immune system is physiologically suppressed, because there is significant amount of circulating steroid hormones. These observations suggest that the temporary altered state of immunity and increased levels of steroid hormones during pregnancy may have an effect on HPV replication (De Sanjosé *et al.*, 2007; Salcedo *et al.*, 2015). However, it should also be considered that CEDIP receives a large volume of referrals regarding pregnant women during prenatal exams. Therefore, the high percentage of pregnant women infected with HPV and treated at CEDIP may be a reflection of the medical follow-up of these women in the UBS.

Among the clinical manifestations found in this study there was a higher frequency of condylomata acuminata (84%). At the other extreme, 1% of all HPV-infected patients had oral lesions such as condylomata acuminata and 0.58% had carcinomas. Historically, oral cancer affects adults over 40 years with harmful habits such as smoking and alcoholism. However, recent epidemiological studies have shown an increased incidence of oral cancer in young adults concomitantly with reports of the presence of HPV in cancerous lesions (De Sanjosé *et al.*, 2007; Araujo, 2013; Egawa *et al.*, 2015). In addition to the harmful habits, the association of oncogenic type HPV is also reported as a contributing factor to the genetic mutation of p53 in cells, which can trigger malignant reactions resulting from inactivation of tumor suppressor genes and defects in cell cycle and scheduled death (De Sanjosé *et al.*, 2007; Araujo, 2013; Egawa *et al.*, 2015).

According to one study, smoking contributes mainly to cancer lesions of the oropharyngeal and stomatognathic system but not to genital malignancy (Araujo, 2013). Regarding the results, the majority of the patients with HPV genital manifestations were not smokers (75%). In our study, 51% of patients smoke 10 to 20 cigarettes a day, but when evaluating infected patients who smoke more than 20 cigarettes per day, they are only 8%. The low percentage of those infected who smoke more than 20 cigarettes per day may be misleading to consider that those who smoke more cigarettes would be less likely to be infected than those who smoke less frequently. It is also worth noting that the data revealed a higher proportion of smokers than of drug users.

With regard to education level, most infected patients reached high school level. From this information, there was a tendency, in the CEDIP patients, for a medium-level training profile. However, due to the limitation of this research, which had only one special health unit as a sample, these data are not enough to infer that people with higher education are less affected. In additional information, it was found that among single people, there are more infected men (77.8%) compared to infected

single women (54.44%). However, this proportion is reversed when comparing married men (20.5%) with married women (37.3%), with a difference of 16.8%. The proportion of divorced women and widows is also higher when compared to men.

This research does not allow certain generalizations considering its limitation to a special health unit. In addition, data from medical charts were collected from 2010 to 2014, so it does not cover all the patients who were seen in that period of time. Records created prior to the 2010 period but that had the incidence or recurrence of HPV in the period from 2010 to 2014 were not included. Therefore, in order to carry out a prevalence survey with the aim of locating Cascavel in a broad way, it is necessary to have as coverage all the health units of the city, both public and private.

The data found in this study on the prevalence of HPV infection was 41% of patients seen at CEDIP in the period 2010-2014 and the rate of new cases in the city reflects the slow progress of immunization against HPV in Brazil. Lack of knowledge about the disease and the importance of immunization directly affects the progress of public prevention policies in the population (De Laia Nunes *et al.*, 2015; Barbosa and Niquirilo, 2016; Leite *et al.*, 2018). Overall effectiveness against cervical cancer in terms of public health has not yet been well established, as HPV vaccine does not replace disease screening programs (Pap smears). In the countries where it is implemented, studies on vaccination have not yet promoted data on reduction of incidence and mortality from cervical cancer (Borsatto *et al.*, 2011).

Conclusion

This study analyzed the clinical characteristics of HPV infection in a city of Brazil over a five year period. The study population reflects the high rate of HPV infection and the need for increased education and prevention efforts including vaccination against HPV. With further education and vaccination campaigns it is hoped that we can achieve the future eradication of the disease.

Author's Contributions

Giulia Rechia Vasconcellos da Rosa: Contributed to the conceptualization, writing the original draft, collecting data, reviewing and editing.

Talita Rechia Vasconcellos da Rosa: Contributed to writing the original draft, reviewing, translating and editing.

Competing Interest

The authors declare that they have no competing interests.

Ethics

The aims and objectives of the study was discussed with Nurse Chief and Coordinator Josana Dranka of Center for Infectious-Parasitic Diseases (CEDIP). Ethical clearance of Ethics Committee and permission to undertake the study were obtained from these stakeholders.

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