RESEARCH ARTICLE

# Treatment and Follow-up of Human Papillomavirus Infected Women in a Municipality in Southern Brazil

**Joao Batista Ruggeri, Catia Millene Dell Agnolo*, Angela Andreia Franca Gravena, Marcela de Oliveira Demitto, Tiara Cristina Romeiro Lopes, Silvana Delatorre, Maria Dalva de Barros Carvalho, Marcia Edilaine Lopes Consolaro, Sandra Marisa Pelloso**

## Abstract

**Background: This study aimed toanalyze the risk behavior for cervical cancer (CC) and the human papillomavirus (HPV) prevalence and resolution among women who received care through the private healthcare network of a municipality in southern Brazil. Materials and Methods: This descriptive and retrospective study was conducted with 25 women aged 20 to 59 years who received care through the private healthcare network and were treated at a specialty clinic in the period from January to December 2012 in a municipality in Northwest Parana, Southern Brazil. Data from medical records with cytological and HPV results were used. Following treatment, these women were followed-up and reassessed after 6 months. Data were statistically analyzed using the t-test and chi-squared test at a 5% significance level. Results: The mean age of the studied women was 27.8±7.75 years old, and the majority were married, with paid employment and were non-smokers. The mean age at menarche was 13.0±0.50 years old, and the mean age at first intercourse was 17.5±1.78 years, with only 8.0% (2) initiating sexual activity at an age ≤15 years old. The majority had 1 to 2 children (60.0%), while 88.0% reported having had one sexual partner in their lifetime, and all the women were sexually active. A total of 68.0% used a hormonal contraceptive method. All the women had leukorrhea and pain and were infected by a single HPV type. Regarding the lesion grade, 80.0% showed high risk and 20.0% low risk. The most prevalent high-risk HPV strain was 16. Conclusions: These findings provide relevant information on HPV risk factors and infection, as well as the treatment and 6-month follow-up results, in economically and socially advantaged women with no traditional risk factors, corroborating previous reports that different risk factors may be described in different populations. Thus, this study reinforces the fact that even women without the traditional risk factors should undergo HPVmonitoring and assessment to determine the persistence of infection, promoting early diagnosis of the lesions presented and appropriate treatment to thus prevent the occurrence of CC.**

**Keywords:** HPV - treatment - cervical cancer - cancer screening - Brazil

*Asian Pac J Cancer Prev,* **16 (15)**, 6521-6526

## Introduction

The World Health Organization estimates that approximately 15 million new cancer cases will be annually diagnosed worldwide by 2020 (WHO, 2012). Cervical cancer (CC) is the third-most common cancer and has the fourth highest mortality rate among cancers in women worldwide (Chao et al., 2012). Although avoidable, CC affects more than 530,000 women a year, and more than 275,000 women die worldwide from this cancer. A total of 11.4% of those deaths occurred in Latin American countries (Ferlay et al., 2010). Low-income countries account for 86% of cases and 88% of deaths (Jemal et al., 2011).

In Brazil, 15,590 new CC cases were estimated in 2014 (Inca, 2014). The mortality rate is particularly high in Southern Brazil (Inca, 2014). CC is the fourth-most common type of cancer in the Southeast Region (10 cases/100,000) and is the fifth-most common cancer in the South Region (16 cases/100,000) (Inca, 2014a).The CC mortality rate recorded in the municipality of Maringa, Parana, in 2005 was 1.9 per 100,000 women (Sesa, 2005; Inca, 2008). CC is one of the most preventable and curable cancer types (approximately 100%) when diagnosed and treated early (Brasil, 2009; Brasil, 2002).

The most suitable and widely used method for the early detection of CC is the Pap smear (Inca, 2008), which reduces its morbidity and mortality (Albuquerque et al.,

*Post-Graduate Program in Health Sciences, Maringá State University, Maringá, Paraná, Programa de Pos Graduacao em Ciencias da Saude, Universidade Estadual de Maringa, Universidade Estadual de Maringa, Maringa, Brazil *For correspondence: catiaagnolo@gmail.com*

2009). An approximately 80% mortality reduction has been reported among women aged from 25 to 65 years who under go Pap smears and receive treatment for lesions with a high risk of malignancy (Brasil, 2009).

Human papillomavirus (HPV) infection is among the most common sexually transmitted diseases worldwide, both in men and women. Its incidence and prevalence are unknown because it is not a notifiable disease (Burd, 2003). HPV infection is also the main risk factor for the development of CC andhigh-grade intraepithelial lesions (Walboones et al.,1999; Schiffman et al., 2007; Lockwood et al., 2009; Kim et al., 2011) and is associated with 99.6% of cases (Lockwood-Rayermann and McIntyre, 2009). The prevalence and predominant genotypes of HPV vary between different regions (Lu-Luet al., 2012).

Several studies have reported on the incidence of HPV and its relevance for CC. However, there is as cientific gap in our region regarding the follow-upand treatment of diagnosed cases. High HPV prevalence rates have been found in several international studies. In the US, prevalence rates of 18% in Mississippi (Castle et al., 2013), 6.5% in California (women 30 years of age or older; Castle et al., 2009), and 10% in New Mexico (women 30 years of age or older; Wheeler et al., 2013) were found. In Brazilian studies, including a study conducted in Porto Alegre, recorded prevalence rates of 27% in a sample of 975 women (Nonnenmachera et al., 2002), 12.4% in Belem (Noronha et al., 2011), and 14.6% among 44 women in the Amazon (Pinto et al., 2011) were found.

Thus, this study aimed to analyze the CC prevalence and risk factors and the outcome of HPV infection following therapeutic intervention in women who received care through the private healthcare network of a municipality in Southern Brazil.

## Materials and Methods

A descriptive and retrospective study was carried out based on data from 25 women aged 20 to 59 years old who received care through the private healthcare network and were treated at a Specialty Clinic from January to December 2012 in Southern Brazil. The population consisted of all women who sought the clinic's service for Pap smear screening and had a positive result, who had complaints of pain and/or leukorrhea and who agreed to participate in the study. We excluded women who had had sex within 24 hours prior to care, had normal Pap smears, had previously had a hysterectomy, were pregnant or were undergoing treatment for gynecological lesions.

The samples for the pap smear tests were collected from the cervico vaginal region, and tests were considered normal in the absence of all the following: atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H), atypical glandular cells (AGC), low-grade (LSIL) or high-grade (HSIL) squamous intraepithelial lesion, or*in situ* (ISCC) or invasive (ICC) squamous cell cervical carcinoma.

The material collected for the histopathological examination was fixed, embedded in paraffin, and cut into thin sections using a microtome. Subsequently, the sections were fixed on slides, stained with hematoxylin-eosin (HE) and then mounted and forwarded to pathologists who performed the analysis via optical microscopy.

Ecto-and endocervical cell samples were also collected to detect HPV using the polymerase chain reaction (PCR) method and analysis of biomarkers. Positive samples for HPV DNA were typed using the restriction fragment length polymorphism (RFLP) method.

The data were analyzed and processed analytically at the Clinical Cytology Laboratories of the municipality of Maringa, Parana, Brazil.

A structured form with closed-ended questions regarding risk behavior variables was used to collect the data on risk, and the form was filled out using data from the medical records.

The sociodemographic variables measured were as follows: age (calculated in full years at the date of the interview; age group (categorized as from 20 to 29, from 30 to 39, from 40 to 49 or from 50 to 59 years); marital status (with and without a partner); paid employment (yes or no); and tobacco smoking (daily smoker or not, regardless of the number of cigarettes).

The data recorded regarding gynecological and obstetric variables were as follows: menstrual cycle (regular or irregular); time of the last preventive test (less than or more than two years); menopause (yes or no); number of sexual partners (one, more than one); prior cauterization (yes or no); personal history of cervical cancer (yes or no); family history of uterine cancer (yes or no); age at menarche (<13 or ≥13 years); age at first intercourse (<18 or ≥18); gynecological symptoms (leukorrhea, dyspareunia, itching, pain in lower abdomen, dysuria and bleeding after intercourse), which were categorized into one, two or more than two; parity (childless, 1 to 2, or more than two children); use of oral contraceptives (yes or no); and use of hormonal contraceptives (yes or no).

The data collected were compiled and processed in electronic spreadsheets, and statistical analysis was performed using the pairedt-testand chi-squared test for the difference between means of independent datasets a 5% significance level. The software package Epi Info 3.5.2 was used for the statistical analysis.

The study was approved by the Research Ethics Committee of Maringa State University (Comite de Etica em Pesquisa da Universidade Estadual de Maringa) under opinion number 464.168/2013.

## Results

*Initial sample profile*

A total of 25 women with a mean age of 27.76±7.75 years participated in this study, all of whom had a partner and 76.0% had paid employment. Approximately 8.0% were tobacco smokers.

Regarding the gynecological variables, the mean age at menarche was 13.00±0.50 years and the mean age at first inter course was 17.48±1.78 years, with only 8.0% (2/25) initiating sexual activity at an age ≤15 years. Most had 1 to 2 children (60.0%), 88.0% reported having one sexual partner in their lifetime, and all the women were

sexually active at the time of data collection. A total of 68.0% used a hormonal contraceptive method-Mirena intrauterine device (IUD) (Table 1).

Regarding their gynecological symptoms at the time they sought medical care, all the women had leukorrhea and pain.

Mono infection with a single HPV type was observed in 100% of the women evaluated. Regarding lesion grade, 80.0% showed high risk lesions and 20.0% low risk.

The association between age group and lesion grade (p=0.05) and between age group and age at first intercourse (p=0.16) was non-significant, although women from 25 to 49 years of age showed an increased frequency of high-risk lesions (Table 2).

The association between the contraceptive method and lesion grade (p=0.40) was non-significant.

Table 3 shows the correspondence between the anatomic-pathological findings and the HPV types.

*Treatment*

After performing the colposcopy and biopsy, 48.0% showed dysplasia with cervical intraepithelial neoplasia (CIN) I, 48.0% showed dysplasia with CIN II, and 4.0% showed dysplasia with CIN III in the anatomic-pathological testing.

The type of treatment performed was trachelectomy with high-frequency surgery (HFS) in 100% of women.

*Evaluation after 6 months of follow-up*

Normal tests were observed in all 25 studied women with prior positive HPV results (100.0%) following treatment and repeat colposcopy with HPV testing.

**Table 1. Gynecological and Obstetric Characteristics of Women Followed-up in a Specialty Clinic. Maringa, Parana, Brazil, 2015**

| Variables | N | % |
|---|---|---|
| Age at first intercourse | | |
| ≤15 years | 2 | 8.0 |
| 16-19 years | 21 | 84.0 |
| ≥20 years | 2 | 8.0 |
| Number of lifetime sexual partners | | |
| 1 (one) | 22 | 88.0 |
| 2 (two) | 2 | 8.0 |
| 3 (three) | 1 | 4.0 |
| Current partner | | |
| Yes | 25 | 100.0 |
| No | - | - |
| Number of children | | |
| None | 8 | 32.0 |
| 1 to 2 | 15 | 60.0 |
| ≥3 | 2 | 8.0 |
| Contraceptive method | | |
| Oral contraceptive | 1 | 4.0 |
| Copper IUD* | 4 | 16.0 |
| Mirena IUD | 17 | 68.0 |
| None* | 3 | 12.0 |

*IUD= intrauterine device.

**Table 2. Lesion Grade and Age at First Intercourse, According to the Age Group of Women Followed-Upat a Obstetrics And Gynecology Private Clinic, Maringa, Parana, Brazil, 2015**

| | <25 | | 25-49 | | ≥50 | | |
|---|---|---|---|---|---|---|---|
| Age group (years) | N | % | N | % | N | % | p |
| Lesion grade | | | | | | | |
| Low risk | - | - | 4 | 80.0 | 1 | 20.0 | |
| High risk | 7 | 35.0 | 13 | 65.0 | - | - | 0.05 |
| Age at first intercourse (years) | | | | | | | |
| ≤15 | 2 | 8% | - | - | - | - | 0.16 |
| 16-19 | 4 | 19.0 | 16 | 76.2 | 1 | 4.8 | |
| ≥20 | 1 | 50.0 | 1 | 50.0 | - | - | |

**Table 3. HPV Type Distribution among the Women Followed-up According to the Severity of Their Anatomic-Pathological Findings. Maringa, Parana, Brazil, 2015**

| Type of HPV | n (%) | CIN I n (%) | CIN II n (%) | CIN III n (%) |
|---|---|---|---|---|
| High risk | | | | |
| 16 | 14 (56.0) | 6 (42.9) | 7 (70.0) | 1 (7.1) |
| 18 | 1 (4.0) | | 1 (100.0) | |
| 33 | 1 (4.0) | | 1 (100.0) | |
| 58 | 1 (4.0) | 1 (100.0) | | |
| 66 | 3 (12.0) | 1 (33.3) | 2 (66.7) | |
| Low risk | | | | |
| 6 | 2 (8.0) | 2 (100.0) | | |
| 44 | 2 (8.0) | 2 (100.0) | | |
| 57 | 1 (4.0) | | 1 (100.0) | |

*CIN=cervical intraepithelial neoplasia

## Discussion

The 6-month follow-up of these women with positive HPV tests with results after treatment is the main differential of this study, unique because, to the best of the authors' knowledge, studies addressing HPV treatment and follow-up are scarce, especially in southern Brazil, although many studies on the prevalence of HPV among women have been published worldwide.

However, this study has some limitations that must be considered. One limitation is related to the fact that different laboratories performed the tests albeit using the same method. The presence or absence of human immunodeficiency virus (HIV), which is considered a risk factor for HPV, was not assessed. Furthermore, this population is economically advantaged because the women were treated at a private practice/public-private partnership clinic, and the results obtained represent this specific population group. However, it is extremely important to study this population group because research studies on women who seek care through the Unified Health System (Sistema Unico de Saude) are more common, and such studies usually excluding this specific group. These women account for a large portion of the population and should not be disregarded when studying data on CC in the Brazilian health system.

Critical analysis of studies on the prevalence of HPV in Brazil usually focus on women utilizing the public health system. However, a screening or treatment study should also consider women who use the private or public-private partnership health care systems to provide relevant epidemiological knowledge to redirect policies on CC

control. Thus, CC surveillance actions should consider the diversity of the country according to regional context (Shiffman et al., 2007).

CC remains a public health problem throughout Latin America and is strongly associated with HPV infection (Picconi, 2013). Thus, HPV detection in women and its genotyping may contribute to reducing the morbidity and mortality from this pathology. Infection-related symptoms were detected in all 25 women treated in this study, and all underwent HPV testing and adequate treatment with 100% resolution of cases after a 6-month follow-upperiod.

HPV infection is usually associated with parity of more than 3 children, hormonal contraceptive use and tobacco smoking. The relationship between these risk factors and CCis well studied (Schuman et al., 2003; Adler, 2010; Harpes and Demars, 2014). The data from the present study found hormonal contraceptive use in 72.0% of women. However, the other risk factors were found in a reduced number of women, including parity of more than 3 children (8.0%) and tobacco smoking (8.0%).

In this study, 88.0% of the women had only had one sexual partner in their lifetime, and 100.0% had a partner at the time that the study was performed. Women younger than 25 years of age accounted for 28.0% of the sample, and 100.0% of them had high-risk HPV types. Previous reports have shown that a high number of partners in the last year and over one's lifetime, as well as young age and marital status, is a risk factor for a high prevalence of HPV (Dunne et al., 2007). The highest number of HPV cases in a study performed with women who received care through the public healthcare network of the state of Parana occurred in the age group from 20 to 24 years, followed by the age group from 15 to 19 years (Goncalves et al., 2010). Furthermore, several studies have identified a higher prevalence of HPV infection in younger women (Matos et al., 2003; Pham et al., 2003; Shin et al., 2003).

The prevalence of HPV was 41.9% in a study that included American women from 18 to 59 years of age. The populations at highest risk for HPV were identified in that same study by multivariate analysis as women with multiple sexual partners, women with lower education levels, black women and uninsured women (Shi et al., 2014). Among these related factors, only young age is a risk factor that was also found in our study, although the highest prevalence of high-risk HPV was found in the age group from 25 to 49 years (65%). Furthermore, more than 50% of sexually active people are estimated to be infected by HPV at least once in their lifetime (CDC, 2010).

In this study, 84.0% of the women initiated sexual activity under the age of 19 years old. Initiation of sexual activity under the age of 18 years is considered a risk factor for HPV infection (Harpes and Demars, 2014).

Although risk factors for HPV are well studied and proven, several researchers have shown the occurrence of differences in the exposure to risk factors for HPV infection (Martins, Thulez and Valente, 2005; Bosch et al., 2008). Therefore, an increased number of studies among specific populations is required to better assess the need for action and measures aimed at prevention.

There are more than 100 types of HPV, including more than 40 types that may infect the genital area. Most infections are usually subclinical or asymptomatic. High-risk HPV strains are the main causes of CC. Asymptomatic genital HPV infection is common and usually self-limited (CDC, 2010).

The identification of HPV types and their assessment according to risk are mains an important topic because the presence of high-risk (oncogenic) HPV is reportedly a relevant etiological factor for the development of CC (Schiffman, 2007; CDC, 2010; Naucler et al., 2011).

Regarding types of HPV, high-risk HPV strains were reported in 80.0% of women in this study. Furthermore, high-risk HPV was reported in 55.5% (11) of patients with CIN II anatomic-pathological findings and in 40.0% (8) of patients with CIN I findings. Conversely, low-risk HPV was primarily reported in women with CIN I findings (80.0%) and in one CIN II case (20.0%).

The presence of HPV 16 (56.0%) and 3 (12.0%), followed by HPV 18, 33 and 58, with one case (4.0%) each, stood out among the high-risk HPV. HPV 6 and 44 were found in two (40.0%) women for each typology, and one case of HPV 57 (4.0%) was found among the low-risk HPV strains.

An increase in the HPV 16 prevalence was also reported in a systematic review on the prevalence of cervical infection by HPV in Brazil (Ayres and Silva, 2010).

In another Brazilian study, 18 different HPV genotypes were found, and the most prevalent genotypes were HPV 6, 11, 51, 16 and 33 (Paesi et al., 2014).

HPV 16 and 18 were the most commonly found types in South American countries, including Paraguay and Brazil, and were related to invasive CC, followed by HPV 45, 33,31, 52, 35, and 39 (Fernandes et al., 2009; Kasamatsu et al., 2012).

Conversely, a study on HPV prevalence among American women (26.8%) showed that the most prevalent HPV types were HPV 62 and 84 (each with 3.3%), 53 (2.8%), 89 (2.4%), and 61 (2.4%). HPV 16 was found in 1.5% of cases, unlike the results found in our study. The prevalence of high- and low-risk HPV types was 15.2% and 17.8%, respectively, and a high number of young women were infected by both types (Dunne et al., 2007).

These rates were 80.0% (high risk) and 20.0% (low risk) in our study. However, this fact may be explained by the exclusive inclusion of women who already had suggestive clinical symptoms (complaints).

Another study explains that the worldwide distribution and prevalence of HPV varies considerably. The differences found may be explained by the complex interaction between the different types of HPV and biological characteristics as well as the geographical location of the women studied (Wang et al., 2013).

Persistent oncogenic (high-risk) HPV infection is an important etiological factor for the development of CC (Schiffman, 2007; CDC, 2010; Naucler et al., 2011). Therefore, early detection and proper treatment may contribute to reduced national CC rates.

Trachelectomy with HFS was the treatment performed in all the women in the present study.

The treatments available following an HPV-positive screening include cryotherapy, large loop excision of

the transformation zone (HFS/LLETZ) and cold knife conization (CKC), according to the World Health Organization (WHO, 2013).

Following treatment, the women were followed-up for 6 months, and all became HPV negative. The authors of a different study performed with 217 women conducted follow-up testing, and the results showed that 91.7% (199) of the women were HPV negative after 8 months (Dimitrov et al., 2013).

In conclusion, an economically and socially advantaged population group who received care in a private practice was included in this study, which provided relevant information on the risk factors associated with HPV infection and genotypes in these women as well as on the treatment performed and the progression following a 6-month follow-up. This information is important to promote our understanding of the natural history of HPV infections in this population and may be used to develop prevention and treatment protocols.

In a country such as Brazil with a large population, a large territorial area and economic, social and cultural diversity, it is reasonable to posit that Brazilian women have different risk factors for HPV infection.

The studied population usually under goes Pap smear testing frequently and lacks the traditional risk factors for infection with HPV/CC, which certainly contributed to the low frequency of cervical lesions and the high resolution rate for HPV treatment. Thus, this study reinforces the fact that even women without traditional risk factors should undergo HPV monitoring and assessment to determine the presence of infection. They should also undergo continuous monitoring to assess the persistence of infection, promoting early diagnosis of the lesions found and adequate treatment to thus prevent the occurrence of CC.

Furthermore, a large proportion (35.0%) of the women with HPV in this study were younger than 25 years, which shows the need to improve prevention by vaccination, which is especially indicated in this population.

This study may also be used as a model for HPV/CC prevention programs in other locations with similar sociodemographic characteristics.

## Authors' Contributions

JBR, AAFG, TCRL, MOD, CMDA, SD participated in the design of the study, performed the statistical analysis, conceived of the study, and participated in its design and coordination and helped to draft the manuscript. MDBC, MELC participated in its design and coordination and helped to draft the manuscript. SMP participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

## References

Adler DH (2010). The impact of HAART on HPV-related cervical disease. *Curr HIV Res*, **8**, 493-7.

Albuquerque KM, Frias PG, Andrade CLT, et al (2009). Cobertura do teste de papanicolaou e fatores associados a nao realizacao: um olhar sobre o programa de prevencao do cancer do colo do utero, Brasil. *Cad Saude Publica*, **25**, 301-9.

Ayres ARG, Silva GA (2010). Prevalencia de infeccao do colo do utero pelo HPV no Brasil: revisao sistematica. *Rev Saude Publica*, **44**, 963-74.

Bosch FX, Burchell AN, Schiffman M, et al (2008). Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. *Vaccine*, **26**, 1-16.

Brasil. Ministerio da Saude (2002). Prevencao do cancer do colo do utero-manual tecnicoprofissionais da saude. Brasilia (DF).

Brasil. Ministerio da Saude (2009). Instituto nacional de cancer (INCA). coordenacao de prevencao e vigilancia (Conprev). estimativa 2010. incidencia de cancer no Brasil. rio de janeiro (RJ).

Burd EM (2003). Human papillomavirus and cervical cancer. *Clin Microbiol Rev*, **16**, 1-17.

Castle PE, Fetterman B, Poitras N, et al (2009). Five-year experience of human papillomavirus DNA and papanicolaou test cotesting. *Obstet Gynecol*, **113**, 595-600.

Castle PE, Gage JC, Partridge EE, et al (2013). Human papillomavirur genotypes detected in clinician-collected and self-collected specimens from women living in the mississippi delta. *BMC Infectious Diseases*, 13-5.

Centers for disease control and prevention. human papillomavirus (HPV) infection. sexually transmitted diseases. treatment guidelines, 2010. Available from: http://www.cdc.gov/std/treatment/2010/hpv.htm

Chao A, Huang HJ, Lai CH (2012). Human papillomavirus research on the prevention, diagnosis, and prognosis of cervical cancer in taiwan. *Chang Gung Med J*, **35**, 297-308.

Dunne EF, Unger ER, Sternberg M, et al (2007). Prevalence of HPV Infection among females in the United States. *Jama*, **297**, 813-9.

Ferlay J, Shin HR, Bray F, et al (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, **127**, 2893-917.

Fernandes JV, Meissner R de V, de Carvalho MG, et al (2009). Prevalence of HPV infection by cervical cytologic status in Brazil. *Int J Gynecol Obstet*, **105**, 21-4.

Goncalves S, Merisio AL, Merlin JC, et al (2010). Mapeamento da incidencia do papiloma virus humano (HPV) por municipio da rede publica do estado do Parana, Brasil. *RBAC*, **42**, 197-200.

Harper DM, Demars LR (2014). Primary strategies for HPV infection and cervical cancer prevention. *Clin Obstet-Gynecol*, **57**, 256-78.

Instituto Nacional do Cancer. Brasil (2008). Ministerio da saude. instituto nacional do cancer. estimativa de cancer. Available from: www.inca.gov.br/estimativa/2008.

Instituto Nacional de Cancer Jose Alencar da Silva (2014a). Incidencia de cancer no Brasil. estimativa 2014, 2014. Available from: http://www.inca.gov.br/estimativa/2014/estimativa-24042014.pdf

Instituto Nacional de Cancer Jose Alencar da Silva (2014b). INCA e ministerio da saude apresentam estimativas de cancer para 2014 (in Portuguese). Available from: http://www2.inca.gov.br/wps/wcm/connect/agencianoticias/site±/home±/noticias/2013/inca_ministerio_saude_apresentam_estimativas_cancer_2014.

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.

Kasamatsu E, Cubilla AL, Alemany L, et al (2012). Type-specific human papillomavirus distribution in invasive cervical carcinomas in Paraguay. A study of 432 cases. *J Med Virol*, **84**, 1628-35.

Kim JY, Nam BH, Lee JA (2011). Is human papillomavirus

genotype an influencing factor on radiotherapy outcome? Ambiguity caused by an association of HPV 18 genotype and adenocarcinoma histology. *J Gynecol Oncol*, **22**, 32-8.

Lockwood-Rayermann S, McIntyre SJ (2009). Understanding HPV disease and prevention: a guide for school nurses. *J Sch Nurs*, **25**, 261-9.

Lu-Lu S, Qiong J, Hui L, et al (2012). Population-based study on the prevalence of and risk factors for human papillomavirus infection in qujing of Yunnan province, Southwest China. *Virol J*, **8**, 153.

Martins LFL, Thuler LCS, et al (2005). Cobertura do exame de Papanicolaou no Brasil e seusfatoresdeterminantes: umarevisaosistematica da literatura. *Rev Bras Ginecol Obstet*, **27**, 485-92.

Matos E, Loria D, Amestoy GM, et al (2003). Prevalence of human papillomavirus infection among women in Concordia, Argentina: a population-based study. *Sex Transm Dis*, **30**, 593-9.

Naucler P, Mabota da Costa F, da Costa JL, et al (2011). Human papillomavirus type-specific risk of cervical cancer in a population with high human immunodeficiency virus prevalence: case-control study. *J Gen Virol*, **92**, 2784-91.

Nonnenmachera B, Breitenbacha V, Villab LL, et al (2002). Identificacao do papilomavirushumanoporbiologia molecular em mulheres assintomaticas. *Rev Saude Publica*, **36**, 95-100.

Noronha VL, Cruz EM, Pinho CN, et al (2011). Papilomavirus humano (HPV) em mulheres submetidas a rastreamento para cancer de cervice uterina, Belem-Para-Brasil. *DST-J bras Doencas Sex Transm*, **23**, 5-11.

Paesi S, Correa L, Tregnago MC, et al (2014). Human papillomavirus among women with atypical squamous cells of undetermined significance in southern Brazil. *Int J Gynecol Obstetrics*. 2014. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25257569.

Pham TH, Nguyen TH, Herrero R, et al (2003). Human papillomavirus infection among women in South and North Vietnam. *Int J Cancer*, **104**, 213-20.

Picconi MA (2013). Deteccion de virus papilloma humano enla prevencion del cancer cervico-uterino. *Medicina*, **73**, 585-96.

Pinto DS, Fuzii HT, Quaresma JAS (2011). Prevalencia de infeccao genital pelo HPV em populacoes urbana e rural da amazonia oriental Brasileira. Cad. *SaudePublica*, **27**, 769-78.

Schiffman M (2007). Integration of human papillomavirus vaccination, cytology and human papillomavirus testing. *Cancer*, **111**, 145-53.

Schiffman M, Castle PE, Jeronimo J, et al (2007). Human papillomavirus and cervical cancer. *Lancet*, **370**, 890-907.

Schuman P, Ohmit SE, Klein RS, et al (2003) HIV epidemiology research study (HERS) group: longitudinal study of cervical squamous intraepithelial lesions in human immunodeficiency virus (HIV)-seropositive and at-risk HIV-seronegative women. *J Infect Dis*, **188**, 128-36.

Sesa (2005). Secretaria de saude do estado do parana. coeficiente de mortalidadeporneoplasiasmalignaspor100 mil, porRegionais de Saude,Municipios de Residencia, Parana, Available from: http://www.saude.pr.gov.br/

Shi R, Devarakonda S, Liu L, et al (2014). Factors associated with human papillomavirus infection among adult females in the United States, NHANES 2007-2010. *BMC Res Notes*, **7**, 544-51.

Shin HR, Lee DH, Herrero R, et al (2003). Prevalence of human papillomavirus infection in women in Busan, South Korea. *Int J Cancer*, **103**, 413-21.

Walboomers JM, Jacobs MV, Manos MM, et al (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*, **189**, 12-9.

Wang X, Gu D, Lou B, et al (2013). Hospital-based prevalence of high-risk cervical HPV types infecting the general population and female sex workers in Huzhou, China. *Int J Gynecol Obstet*, **120**, 37-41.

Wheeler CM, Hunt WC, Cuzick J, et al (2013). A population-based study of HPV genotype prevalence in the United States: baseline measures prior tomass HPV vaccination. *Int J Cancer*, **132**, 198-207.

World Health Organization (2012). International agency for research on cancer. Globocan. Available from: http://globocan.iarc.fr/

World Health Organization (2013). Who guidelines for screening and treatment pre cancerous lesions for cervical cancer prevention, Available from: http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf