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Prevalence of Human Papillomavirus Infection in Female Transplant Recipients with Normal Cytology

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Abstract

Objective: Our objective was to assess the prevalence of HPV infection in female transplant recipients with normal cytology.

Material and Methods: Cross-sectional study with a sample population of 58 patients from the gynecology outpatient clinic of a tertiary public hospital. Transplant recipients with normal Pap smear and sexually active before their surgery were included. All study patients were given a complete gynecological exam and oncotic colpocytological exam, and cervical-vaginal matter was collected to test for HPV by PCR. The resulting data on prevalence were compared to the results found in the literature. For the multivariate analysis, we used logistic regression so as to identify the factors associated with the outcome of interest.

Results: Of the 58 patients, 10 were excluded for presenting an abnormal oncotic colpocytology, and 4 for having had a hysterectomy. HPV infection prevalence was 45.5%. The most common high-risk HPV found was HPV 51. Upon comparing this result with those in the literature, we found a statistically significant difference with all of the articles that mentioned HPV infection prevalence in the general population with normal cytology. No statistical significance was found for the set of all factors in correlation with the outcome studied.

Conclusion: The importance of this high prevalence of infection is clear in terms of the risk of developing intraepithelial neoplasia and cancer of the lower genital tract in female transplant recipients.

Keywords: Transplants; Human Papillomavirus; Cervical intraepithelial neoplasia; Cervical neoplasms; Uterine cervical dysplasia

Introduction

Data from the Brazilian Organ Transplant Association show that, internationally, Brazil ranks second in terms of the number of kidney, liver and cornea transplants performed [1]. These patients will have to continuously take immunosuppressants to prevent rejection of the transplanted organ and infections or tumors may occur. Among such infections, the main one is Human Papillomavirus (HPV) infection and its related conditions, particularly cervical intraepithelial neoplasia (CIN) [2].

HPV infection is one of the most common sexually transmitted diseases and the estimated exposure of the general public varies from 70% in the U.S. to 95% in some African countries [3]. Most women in the world will likely be infected with at least one of the various types of HPV during their active sex life [3]. Persistent infection by HPV is required for the development of cervical intraepithelial neoplasia. Among women with a persistent infection, 15-30% will present with a precursor lesion for cervical cancer [3].

The types of high-risk HPV are responsible for the development of low and high-grade cervical and vaginal intraepithelial neoplasia, usual-type vulvar intraepithelial neoplasia and genital cancer [4]. It has been estimated that HPV types 16 and 18 are responsible for 70% of the cases of cervical cancer worldwide [5].

Immunosuppression due to Human Immunodeficiency Virus (HIV) has an intense effect on the natural course of HPV. The prevalence and persistence of the infection increase, in addition to a reduction in virus elimination when compared to HIV-negative patients [6]. It is believed that the same occurs under other conditions of immunosuppression. The immunological response of transplant recipients is abnormal in cases of primary HPV infection or when a latent infection is reactivated by an oncogenic virus [7].

It is known that HPV infection is widely found in the various population groups, as is variation in the frequency of the types of virus [8].

Studies have shown that oncogenic-type HPV infection is more common in transplant recipients compared to those with normal immune functions, and this may lead to an increased risk of the occurrence of precursor cancerous lesions and to cancer itself in the cervix, vagina and vulva, related to the HPV infection [9].

We found no Brazilian studies on HPV infection in the lower genital tract of female transplant recipients.

Our objective was to assess the prevalence of HPV infection in female transplant recipients with normal cytology.

Methods

This was a cross-sectional study with a sample population of 58 patients from the gynecology outpatient clinic of a tertiary public hospital. Patient selection and data collection took place from September 2013 to April 2015.

Inclusion criteria

Patients who were transplant recipients with a normal Pap smear and who were sexually active before their surgery.

Exclusion criteria

Patients with other disorders that led to immunosuppression, including HIV infection, pregnancy and other pathologies justifying the use of corticosteroids prior to their transplant. Patients who had had a total hysterectomy and those with an abnormal oncotic colpocytology were also excluded.

Study population characteristics and selection method

The sample was comprised of transplanted patients who are routinely seen at the gynecology outpatient clinic for their annual gynecology examination. These patients were invited to participate in our study (convenience sampling).

Procedures

All study patients were given a complete gynecological exam and oncotic colpocytological exam, and cervical-vaginal matter was collected to test for HPV by PCR (polymerase chain reaction). This test was performed by the RICHET laboratory. The test used came from the Spanish company GENOMICA S.A.U. and is sold under the name CLART® (Clinical Array Technology) Human Papilloma Virus [2]. This test detects the presence of the 35 most clinically relevant types of HPV in various types of samples (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 68, 70, 71, 72, 73, 81, 82, 83, 84, 85 and 89).

Primary outcome

Prevalence of HPV infection via the collection of cervical-vaginal matter.

Secondary outcomes

HPV genotyping and distribution by age groups.

Sample size

Since this involved convenience sampling, it was not suited to calculation of the sample size.

Data collection and analysis

All of the information of interest, such as sample properties and data related to risk factors for HPV infection, were recorded on individual clinical study sheets.

The resulting data on prevalence were compared to the results found in the literature in order to determine whether our study group showed a statistically significant difference. For that purpose, we used a statistical test based on normal distribution that compares the proportion of a population with fixed values that, in the case of our study, would be given for each of the reference values found in the literature. This test has no specific name but is described in detail on page 230 of Altman [10].

For the multivariate analysis, we used logistic regression so as to identify the factors associated with the outcome of interest. The response variable was HPV infection and the explanatory variables were: age, smoking, number of children, age of onset of sexual activity, number of partners, hormone use, condom use, age at time of transplant, date of transplant, rapamycin use and prior history of sexually transmitted disease (STD). The analyses were done using the S-Plus (version 8.0) statistical application. Our result of $p<0.05$ was considered significant.

Approval by the research ethic committee

Our project was approved by the Human Subjects Research Ethics Committee of this tertiary public hospital. Study subjects signed an informed consent form and those with an abnormal oncotic colpocytology were referred for further analysis.

Results

Of the 58 patients we interviewed, 10 were excluded for presenting with an abnormal oncotic colpocytology, and 4 for having had a hysterectomy. Out of a total of 44 patients included, 41 had undergone kidney transplants and 3 had had liver transplants.

We found an HPV infection prevalence of 45.5% (20/44).

The following rates of prevalence were found for high-risk or low-risk HPV infection and multiple infections: 27.2% (12/44), 18.2% (8/44) and 13.6% (6/44).

HPV 16 was found in 2 patients (4.5%), 1 with multiple infections. HPV 18 was found in 2 cases (4.5%) of multiple infections. Other types of high-risk HPV found were: 35/51/52/53/58/59/68/70/82. The following types of low-risk HPV were found: 6/44/54/61/62/72/83/84. The most common type of high-risk HPV found was HPV 51, in 11.4% of the cases (5/44), followed by HPV 53/70 in 6.8% (3/44) and HPV 16/18/59 in 4.5% each (2/44). The most common type of low-risk HPV found was HPV 61, in 13.6% (6/44), followed by HPV 72 in 6.8% (3/44) and HPV 54 in 4.5% of the cases (2/44).

Of the 20 patients with HPV infection, 5% of the cases were under age 30 years, 35% were between 31 and 44 years and between 45 and 54 years each (7/20), and 25% were over age 55 years (5/20).

The mean age of the 44 patients included was 47.4 years (26-61 years). All the properties of the numerical and categorical variables of the sample are found in Table 1.

Variables		
Age	Mean	47.4 years
	Std. deviation	9.375
	Minimum/Maximum	26-61 years
	Median	47.5
Date of transplant	Mean	92.59 months
	Std. deviation	60.299

	Minimum/Maximum	24-270 months
	Median	77.5 months
Number of children	Mean	1.91
	Std. deviation	1.326
	Minimum/Maximum	0-6
	Median	2
Number of partners	Mean	2.77
	Std. deviation	3.22
	Minimum/Maximum	1-20
	Median	2
Age of initial sexual activity	Mean	18.55
	Std. deviation	2.807
	Minimum/Maximum	13-24
	Median	18
Age at time of Transplant	Mean	40.05
	Std. deviation	9.647
	Minimum/Maximum	20-57
	Median	40.5
Initial sexual activity before age 18	Frequency	50%
3 or more children	Frequency	31.8%
Smoking	Frequency	9.1%
Hormone use	Frequency	13.6%
History of sexually transmitted disease	Frequency	13.6%
Condom use	Frequency	29.5%
Rapamycin use	Frequency	31.8%

Table 1: Properties of the numerical and categorical variables of the sample.

We found 6 studies in the literature reporting the prevalence of HPV infection in patients with normal cytology in the general population, which are shown in Table 2.

Upon comparing our prevalence of HPV infection with the 4 articles found in the literature [11-16], there was a statistically significant difference between the value found in our study (45.5%) with all results (10.4%, 24.5%, p=0.000; p=0.000-0.00123; p=0.00123; p=0.000). Upon comparing only the prevalence of high-risk HPV infection (27.2%) as reported in the study by Berois et al. [12], we found no difference, but the result (p=0.0542) is very close to the value of p<0.05. There was no difference between the prevalences of HPV 16/18 infection found in the present study (4.5%, p=0.0962; p=0.482) and the result found in the systematic review of Ogembo et al. [11] (Table 2).

Author/Year	Population Data	HPV Prevalence in the literature	Method Used	HPV Prevalence in the present study	p
Ogembo et al. [10]	17.273	HPV 16–4.4% HPV 18–2.8%	‡	4.5% 4.5%	0.962 0.482
Berois et al. [11]	965	High-risk HPV-16.5%	‡	27.2%	0.0542
Anderson et al. [12]	5.712 Mean age-39 years	12%	PCR	45.5%	0.000
Ayres e Silva [13]	49–2.329	10.4%-24.5%	Type II hybrid capture/ PCR	45.5%	0.000-0.00123
Fernandes et al. [14]	202 women 15-64 years of age	24.5%	PCR	45.5%	0.00123
De Sanjosé et al. [15]	157.879	10.4%	‡	45.5%	0.000
‡ Not stated in the article.					

Table 2: Comparison of the prevalence of HPV infection in female transplant recipients with normal cytology found in the present study and that found in the literature on the general population.

Only one study [17] was found in the literature that reported the prevalence of HPV infection in transplant recipients with normal cytology (Table 3). That study only provides the prevalence of high-risk HPV and no statistically significant difference was found with the value determined in the present study (p=0.459) (Table 3).

Author/ Year	Population Data	HPV Prevalence in the literature	Method Used	HPV Prevalence in the present study	p
Aggarwal et al. [16]	40	32.5%	‡	27.2%	0.459
‡ Not stated in the article.					

Table 3: Comparison of the prevalence of high-risk HPV infection in female transplant recipients with normal cytology found in the present study and that found in the literature.

A multiple logistic regression was done to examine the effects of the factors studied on the occurrence of the primary outcome (Table 4).

Variable	Odds Ratio	P
Age	1.01	0.974
Prior STD	1.5	0.748

Smoking	3.48	0.463
Number of children	0.64	0.252
Age of initial sexual activity	0.81	0.205
Number of partners	0.92	0.595
Hormone use	5.87	0.126
Condom use	2.00	0.441
Date of transplant	0.99	0.898
Rapamycin use	2.42	0.261
Age at transplant	0.99	0.987

Table 4: Effects of clinical and epidemiological factors on the occurrence of HPV infection in transplant recipients using multiple logistic regression.

No statistical significance was found for the set of all factors in correlation with the outcome studied.

Discussion

We found a high prevalence of HPV infection in our group of transplant recipients. Upon comparing this result with those in the literature [13-16], we found a statistically significant difference with all of the articles that mentioned HPV infection prevalence in the general population with normal cytology. When we compared our result with the 2 articles in the literature that mention only results for high-risk HPV, we found no difference [11-12]. We also found no statistically significant difference with the one study that reported the prevalence of HPV infection in transplant recipients with no lesions [17].

HPV 51 was the high-risk HPV we most commonly found, followed by HPV 53 and 70. HPV types 16 and 18 were found in 2 patients, respectively. This result differs from what is reported in the literature [5,11]. Various meta-analyses stated that the five most prevalent types of HPV in women with or without cervical disease are 16, 18, 31, 52 and 58 [11].

Some studies reported a second peak in HPV infection after menopause [8,16,18,19]. The present study also found this renewed increase in HPV infection after age 55 years. However, the mean age of the patients in our sample was 40.05 years and the small number of patients under age 30 years (1 case) may represent a bias in this result.

There are very few studies in the literature worldwide that deal with transplant recipients. Most of the studies on transplant recipients, including those with a small sample size, report a greater prevalence of HPV infection, cervical intraepithelial neoplasia and a higher risk of cancer in the lower genital tract [20,21]. We found no Brazilian data in the literature on HPV infection in transplant recipients. The only study we found on transplant recipients with normal cytology was conducted in India, had a small sample size and only reported the prevalence of high-risk oncogenic HPV infection [17].

The present study also has its limitations. Our results are based on a small sample size. The patients studied were older than those generally found in the literature, with a mean age of 40.5 years. It is known that HPV infection is usually transmitted at the onset of sexual activity, meaning in adolescents or young adults, the age groups in which one finds the greatest prevalence of infection [6]. Since this was a cross-sectional study, it also did not allow us to differentiate between incident or persistent HPV infections.

Historically, there are various risk factors related to the increased risk of HPV infection, including age, early onset of sexual activity, multiparity, multiple partners, a history of STD, smoking, hormonal contraceptive use and immunosuppression [18]. Onset of sexual activity before age 18 years was found in half of the patients. Some studies report that the determining factor for elevated risk in this age group is due to the fact that these patients have abnormal metaplasia of the cervix, which favors HPV infection [19-21].

No statistical correlation was found with any of the risk factors related to HPV infection and its persistence as mentioned above. We also found no correlation between patient age, age at time of transplant, rapamycin use or time of transplant and HPV infection. We thus believe that immunosuppression may be considered the determinant factor in the prevalence of infection in this group of patients. Chronic immunosuppression is acknowledged to be one of the main risk factors for infection by, and the persistence of, the HPV virus and, consequently, for the development of HPV-induced lower genital tract lesions [22,23].

We believe that transplant recipients are at higher risk for developing cancer, including cancer of the cervix, than the general population due to their extended immunosuppressant therapy [24].

In the present study, 31.8% of the patients use rapamycin as part of their immunosuppressant therapy.

The mammalian target rapamycin inhibitors (also known as sirolimus and everolimus) are newer immunosuppressants and, unlike other immunosuppressants, seem to reduce the chances of developing cancer while maintaining their immunosuppressant effect. This is still a subject of controversy in the literature. More studies are needed to confirm this effect of rapamycin in reducing the likelihood of cancer occurring, as well as when it is used in combination with other immunosuppressants [25].

The Ministry of Health recommends that screening begin at age 25 and, after 2 normal annual examinations, be continued every 3 years until age 64. In cases of immunosuppressed patients, screening should start after the onset of sexual activity, be done at six-month intervals in the first year and, if the results are normal, be continued annually as long as immunosuppression is maintained [26]. The result found in this study confirms the value of the variant screening scheme for transplant recipients as recommended by the Ministry of Health and emphasizes the importance of appropriate follow up in these patients.

Our knowledge of the prevalence of the various types of HPV is extremely relevant in order to analyze the effect of immunization for HPV, especially for types other than 16 and 18. The relatively high frequency of genotypes other than those for which vaccinations are given should be taken into consideration in evaluating vaccination programs.

Additional studies should be conducted to broaden our knowledge of the prevalence of HPV infection in this group of patients.

Conclusion

We found a high prevalence of HPV infection of 45.5% in transplant recipients with normal cytology. HPV 51 was the type with high oncogenic risk we encountered most frequently.

Despite our small sample size and the above-mentioned limitations, the importance of this high prevalence of infection is clear in terms of the risk of developing intraepithelial neoplasia and cancer of the lower genital tract in female transplant recipients.

New studies should be conducted to enhance our knowledge of the prevalence and frequency of the various types of HPV, of the correlation of the risk factors with HPV infection and its persistence and, consequently, with their effect on the development of HPV-induced lesions in the lower genital tract of female transplant patients.

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