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Prevalence and risk factors of HBV, HCV, and HIV infections among cervical cancer patients

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Summary

Purpose: The objective of this study was to evaluate the prevalence of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infection and coinfection in patients with cervical cancer (CC), a public health problem. *Materials and Methods:* A retrospective study of HBV, HCV, and HIV in all patients from the Brazilian National Cancer Institute diagnosed with CC between 2009 and 2012 was performed. *Results:* A total of 1,659 patients were enrolled. Eighteen women (1.5%) were positive for HIV, 17 (1.2%) for hepatitis C, and 186 (13.9%) had prior exposure to HBV virus. Coinfection with HIV and HCV was detected in 0.3%, HCV and HBV in 0.2%, and HIV and HBV in 0.6% of the cases. *Conclusion:* CC patients have a higher prevalence of HIV and HBV infection than the general population in Brazil. The results support the importance of serological evaluation of patients recently diagnosed with CC, since these diseases have a common transmission path and the prognosis of CC can be influenced.

Key words: Cervical cancer; Hepatitis B; Hepatitis C; HIV infection; Coinfection.

Introduction

Cervical cancer (CC) is a significant public health problem, representing the fourth most commonly diagnosed cancer and the fourth cause of cancer death in women worldwide [1]. In 2008, across the world, 530,000 new cases were diagnosed with 275,000 deaths, and this number is expected to increase to 410,000 by 2030 [2, 3]. Developing countries account for approximately 76-85% of CC cases [4]. In Brazil, it was estimated that there were 15,590 new cases of invasive CC in 2014 alone, which represents a rate of 15.33 cases per 100,000 women [5].

Infection by human papilloma virus (HPV) is considered a necessary factor for the development of CC, being identified in approximately 98-99.7% of cases [6]. The main route of HPV transmission is sexual – it is the most common sexually transmitted infection worldwide [7]. Factors such as multiple partners and early onset of sexual activity favour infection and transmission.

Human immunodeficiency virus (HIV) infection results in the acquired immuno-deficiency syndrome (AIDS), a condition that has spread on a global scale and reached all social classes within any community [8]. Sexual transmission is the main mode of disseminating HIV (75-85% of cases). Among women, 86.8% of the cases recorded in 2012 were due to heterosexual contact with HIV-infected people [9]. The incidence of CC in HIV-positive women is high: HIV-positive women have a 5-18 times greater risk for developing CC compared to HIV-negative women [8]. One of the reasons for HIV-infected women being at a higher risk of CC is because of the high HPV prevalence in this group, ranging from 44% to 98% and the coinfection occurs with multiple and high-risk HPV subtypes [9]. These women also have more aggressive and less responsive disease to the standard therapy [7]. Based on these data, the Centers for Disease Control and Prevention (CDC) classified CC, in HIV-infected women, as a defining disease of AIDS [7].

According to the epidemiological bulletin of the Ministry of Health in 2012, Brazil had 656,701 registered cases of AIDS - the highest infection rate among Latin American countries, corresponding to one-third of all cases in this region. In 2011, the incidence rate of AIDS in Brazil was 20.2 cases per 100,000 people, with a male to female ratio of 1.7 to 1. The UNAIDS Report on the Global AIDS Epidemic – 2013 [10] estimated 0.4% to 0.5% of HIV infection for both sexes in Brazil.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are also sexually transmitted diseases that share similar risks factors of CC. Both are highly prevalent and are associated

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with risks for both acute and chronic complications [11]. Approximately, 5% of all clinical cases of HBV infection progress to chronic disease and 20% of them will develop liver cirrhosis [8]. The Brazilian Ministry of Health estimated that in Brazil, at least 1% of the population has chronic forms of HBV [11]. Data from a Brazilian survey showed that the prevalence for anti-HBc IgG, the exposition marker for HBV, is 7.9% (95% CI: 6.6–9.2) in the Southeast Region of Brazil [12].

Infection with HCV is currently the major cause of liver cirrhosis, hepatocellular carcinoma and subsequent liver transplantation worldwide [8]. The national prevalence of HCV is not precisely known. However, there are reports that indicate a rate between 1% and 2% in the general population [13]. Data from a Brazilian survey for anti-HCV prevalence, the exposition marker for HCV, is 1.6% (95% CI: 1.1–2.2) in the Southeast Region of Brazil [12].

Despite their shared sexual health risk factors, few studies evaluated the prevalence of HPV, HIV, HBV and HCV coinfection and because the biological characteristics of these viruses are quite distinct, the outcome of coinfection by these agents is unpredictable [14].

The objective of this study was to investigate the prevalence and risk factors for infection of hepatitis B, C or HIV in a cohort of patients diagnosed with CC in a tertiary specialized center in Brazil.

Materials and Methods

A retrospective study of HBV, HCV, and HIV infections was carried out. All patients diagnosed with CC between October 2009 and December 2012 were considered in the cohort. Information on anti-HBV, HCV and HIV antibody, and patient data were retrospectively obtained by chart review at Brazilian National Cancer Institute (*Hospital do Câncer II*), which is a tertiary cancer care referral center in Rio de Janeiro, Brazil, specialized in treating gynecological cancer.

The antibody to hepatitis B core antigen (anti-HBc IgG antibody) was performed using enzyme-linked immunosorbent assay (ELISA) method. A positive test was considered as a marker of previous exposition to HBV. HCV antibodies were detected by a third-generation enzyme immunoassay and positive or indeterminate HCV tests were confirmed by third-generation recombinant immunoblot assay (RIBA). For the purposes of this analysis, patients were considered HCV positive if they tested positive on both platforms. Two tests were used to detect HIV: ELISA for screening and Western Blot for confirmation.

Demographic and clinical characteristics were summarized as medians and interquartile range (IQR) for continuous variables and as frequencies and percentages for categorical variables. The variables studied were: age at cancer diagnosis, sexarche, years of schooling, skin color/ethnicity, marital status, lifetime number of sexual partners, use of illicit drugs and HBV current or past infection, and HCV and HIV positivity. The overall prevalence of HBV current or past infection, HCV and HIV positivity among the study population was calculated with 95% CI. The association between the demographic, clinical and behavioral variables and prevalence of HBV current or past infection, and HCV and HIV markers was evaluated using the Chi-square test. All tests were two-sided and *p*-values less than 0.05 were considered statistically significant. Multivariate logistic regression analyses were used to identify the independent predictors of these infection markers. The variables with a p-value < 0.15 on univariate analysis were included in a stepwise multiple logistic regression model. The ratio of the observed prevalence of CC patients with anti-HBc IgG, anti-HCV, and HIV antibody to the prevalence observed in the Brazilian population was assessed. Data on the prevalence of HBV current or past infection and HCV infection in Brazil [15, 16] were taken from a nationwide cross-sectional survey of prevalence of hepatitis A, B, and C infection, which covered all Brazilian macro-regions from 2005 to 2009, representing individuals living in all 26 state capitals and the Federal District. For this study purpose, the authors used the prevalence estimated to the Southeast Region of the country (the same Region where the HCII/INCA is located) to the general population (males and females) from 20- to 69-years-old. The prevalence of hepatitis B and C antibodies was 7.9% (95% CI: 6.6–9.2) and 1.6% (95% CI: 1.1–2.2), respectively. The adult HIV estimated prevalence for the years covered by this study was taken from the UNAIDS Report on the Global AIDS Epidemic – 2013 [10]. For the years 2000-2012 the estimates for both sexes ranged from 0.4% (low estimate) to 0.5% (high estimate); the median value (0.45%) was considered for comparison in this study. All statistical analyses were performed using the SPSS version 21.0 software package (São Paulo, Brazil).

This study was approved by the Ethics in Human Research Committee of INCA, Rio de Janeiro, Brazil, and conducted in ac-

Table 1. — *Population characteristics and prevalence of HBV, HCV, and HIV antibodies in 1,659 women with CC.*

	Value*
Age, years	
Median	50.3
Interquartile range	40.7-60.6
Histology, n (%)	
Squamous cell carcinoma	1303 (78.5)
Others	356 (21.5)
Grade, n (%)	
Grade 1	128 (7.7)
Grade 2	960 (57.9)
Grade 3	308 (18.6)
Unknown	263 (15.9)
FIGO Stage, n (%)	
IA1 – IA2	56 (3.4)
IB1	234 (14.1)
IB2	94 (5.7)
IIA	17 (1.0)
IIB	363 (21.9)
IIIA	10 (0.6)
IIIB	538 (32.4)
IVA	54 (3.3)
IVB	18 (1.1)
Unknown	274 (16.6)
	1077 (64.9)
HBV, n (%)	
Anti-HBc IgG Positive	186 (13.9)
HCV, n (%)	
Anti-HCV Positive	17 (1.2)
HIV, n (%)	
Anti-HIV Positive	18 (1.5)

* *Totals may vary due to missing values.*

Table 2. — *Independent predictors of HBV, HCV, and HIV infection among CC patients.*

	HR	95% CI	*p*-value
Anti-HBc IgG positive			
Age ≥ 50 yrs *vs*. < 50 yrs	2.713	1.8-4.1	<0.001
Sexarche < 16 yrs *vs*. ≥ 18 yrs	2.091	1.3-3.4	0.003
Skin color non-white *vs*. white	1.673	1.1-2.5	0.011
Anti-HCV positive			
Age ≥ 50 yrs *vs*. < 50 yrs	4.957	1.3-18.6	0.017
Skin color non-white *vs*. white	11.697	1.5-90.6	0.019
Lifetime number of sexual partners ≥ 3 *vs*. < 3	4.387	1.2-16.4	0.028
Anti-HIV positive			
Lifetime number of sexual partners ≥ 3 *vs*. < 3	5.659	1.2-26.9	0.029

HR = hazard Ratio; 95% CI= 95% confidence interval.

Table 3. — *Ratio of the prevalence of anti-HBc IgG, anti HCV, and HIV antibody observed in cervical cancer patients and the estimated prevalence in the Brazilian population*

	Prevalence in this study % (95% CI)	Prevalence in Brazil % (95 %CI)	Prevalence ratio
Anti-HBc IgG positive	13.9 (12.1–15.9)	7.9 (6.6–9.2)	1.8
Anti-HCV positive	1.2 (0.7–1.9)	1.6 (1.1–2.2)	0.8
Anti-HIV positive	1.5 (0.9–2.3)	0.45	3.3

cordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Results

A total of 1,659 women with CC were enrolled in this study. Patient characteristics are listed in Table 1. The median age at the time of CC diagnosis was 50.3 years (interquartile range, 40.7 to 60.6 years), the most frequent histology was squamous cell carcinoma (SCC) 78.5%, followed by adenocarcinoma and adenosquamous carcinoma (21.5%); most of them were grade 2 (57.9%).

Considering FIGO stage, 1,077 patients (64.9%) were diagnosed as IB2 to IVA (locally advanced disease), 18 patients (1.1%) as IVB (metastatic disease), and 289 patients (17.9%) as IA to IB1 (initial disease).

Ten patients (0.8%) had evidence of persistent HBV infection (indicated by reactivity to HBsAg), 17 (1.0%) had a positive anti-HBe test, 17 (1.0%) a positive HBeAg test and one patient (0.1%) had a positive anti-HBc IgM test (serological marker for recent HBV infection). The anti-HBs antibody was positive in 102 (6.1%) cases. Overall, within the cohort, 186 (13.9%) had evidence of a previous exposure to HBV.

Eighteen women (1.5%) carried HIV infection, 17 (1.2%) HCV and HIV, and HCV coinfection were detected in 0.3%, HCV and HBV in 0.2% and HIV and HBV in 0.6% of the tested group.

According to the univariate analysis, patients with a positive anti-HBc test were more likely to be older than 50 years ($p < 0.001$), to have had their first sexual intercourse in an age lower than 16 years ($p < 0.05$), to be illiterate or semilliterate ($p < 0.001$), to be non-white ($p < 0.001$). The marital status, the lifetime number or sexual partners, and the use of illicit drugs were characteristics not associated with a positive anti-HBc test ($p > 0.05$ for all comparisons). Patients with a positive anti-HCV test were also more likely to be non-white ($p < 0.05$); living without a partner ($p < 0.001$), to be younger than 50 years ($p < 0.01$), and have less than eight years of schooling. The sexarche, the number or sexual partners, and the use of illicit drugs were characteristics not associated with a positive anti-HCV ($p > 0.05$ for all comparisons). Finally, patients with a positive test for HIV were more likely to live without a partner ($p < 0.05$), to have had three or more sexual partners during the lifetime ($p < 0.05$), and to have used illicit drugs ($p < 0.05$). The age, sexarche, years of schooling, and skin color were not associated with a positive anti-HIV test ($p > 0.05$).

Table 2 shows the multivariate analysis of the independent predictors of HBV (age higher than 50 years, first sexual intercourse in an age lower than 18 years, and non-white patients), HCV (age lower than 50 years, non-white patients and more than three sexual partners during their lifetime), and HIV (more than three sexual partners during their lifetime) infection among CC patients.

The prevalence of anti-HBc IgG, anti-HCV, and HIV antibodies in this study with CC patients was compared to the estimated prevalence in the Brazilian population (Table 3). Previous contact with HBV and HIV infection was higher in the current cohort; the prevalence ratio was 1.8 and 3.3, respectively.

Discussion

To date and to the best of the authors' knowledge, this is the first study in a tertiary center specialized in the treatment of gynaecological cancer evaluating a cohort of patients recently diagnosed with CC and the prevalence of HIV and HBV and HCV.

HPV infection is sexually transmitted and may lead to CC. Many HPV infected women are also coinfected with other viruses [8], reinforcing the importance of testing for HIV, HBV, and HBC if the patient is not aware of her serology status when a CC is diagnosed. At HCII/INCA, after formal consent, CC patients are tested for HIV and hepatitis as routine clinical practice.

Women infected with HIV are at least 5-18 times more likely to be diagnosed with CC, which is considered by CDC an AIDS-defining disease [17]. The HIV infection weakens the immune system and reduces the body's ability to fight infections, resulting in a high risk of active HPV coinfection that may lead to CC [9]. In the current cohort an independent predictor of HIV infection among CC patients was more than three sexual partners during their lifetime that can be easily explained once the sexual contact with an infected partner is one important route for HIV and the most important one for HPV transmission. In addition, the HIV infection prevalence in this analysis is 3.3 times higher than the estimated prevalence in the Brazilian population.

HBV and HCV are transmitted through mucosal contact with infected blood or body fluids including sex with an infected partner in a number of cases [8]. The first sexual intercourse in an age lower than 18 years and non-white patients were independent predictor factors for HBV infection in this CC cohort. The higher time for sexual exposure to the virus and unfortunately the low education level for non-white patients in Brazil [18] can explain the higher rates of infection in this subpopulation. Compared to the estimated prevalence in the Brazilian population, HBV infection prevalence in this analysis is almost two times higher. The number of sexual partners during their lifetime and the non-white skin color were independent predictor factors for HCV infection and are also explained by the sexual route of transmission and the education level of non-white people. The HCV prevalence in the CC cohort is the same as the estimated for the Brazilian population.

The number of coinfected patients (HIV-HCV, HCV-HBV, and HIV-HBV) in this cohort is far lower (0.3%, 0.2%, and 0.6%, respectively) than the number described by the US CDC (25%, 10%, and 10%, respectively) [19]. This is probably explained by the differences in the present populations. In Brazil the authors of this study concentrated on a female population who had sex with men. In contrast, other published data indicate that coinfection is higher between people who inject drugs and men who have sex with men.

The retrospective nature of this study raises the possibility of bias once some data were missing on the medical charts and because some patients were not tested for HIV or HBV and HCV according to physicians' discretion, or because the patient did not consent for serology. In addition, the authors did not evaluate HPV status in this study to determine if these viral infections segregated with a particular genotype of HPV. Instead, they used the diagnosis of CC as evidence for prior HPV infection, which is supported by the literature.

The presented results support serology tests indicating that routine screening for HIV, HBV, and HCV is reasonable, especially for women newly diagnosed with cervical cancer. In addition, it highlights that vaccination against HPV may not be sufficient. Instead, it should be part of a global strategy for sexual health that emphasizes safer sex practices and the value of limiting the number of sexual partners.

The natural course of each of these viral infections can be affected by potential interactions between such agents and, as the biological characteristics of these viruses are very distinct, the result of their coinfection is unpredictable [14]. Therefore, more studies and strategies are required to reduce the transmission of those diseases, which have high costs for society and the healthcare system [16].

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