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Association of Serum Concentrations of Testosterone and Insulin with the Degree of Cervical Squamous Intraepithelial Lesions in Cuban Women

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Abstract

Cervical squamous intraepithelial lesions (SIL) and cervical cancer (CxCa) develop because of high-risk human papillomavirus (HR-HPV) infection; however, other cofactors such as endogenous hormones could contribute to the development of this neoplasia. This work aims to determine the relationship between serum concentrations of sex steroid hormones, cortisol, prolactin, and insulin and the degree of cervical squamous intraepithelial lesions in Cuban women. A descriptive and cross-sectional study was carried out at the National Institute of Oncology and Radiobiology. It included 205 women who attended a Gynecology consultation for a cytological diagnosis confirmation of SIL during 2018-2020. Blood samples were collected to determine serum concentrations of estradiol, testosterone, prolactin, cortisol, and insulin. A questionnaire about socio-demographic variables, toxic habits, and gynecological and obstetric history of the patients was applied. Were found high-grade SILs mainly in women between 36 and 45-years-old and those who had one or two births. Serum concentrations of testosterone and insulin were the only ones that showed significant differences between women who presented SIL concerning negative cytology. A 3,23- fold (CI 95% 1.55-6.73) risk of developing SIL was found when testosterone concentrations were superior to 2 nmol/L and a 2,63-fold (CI 95% 1.36-5.09) risk when the insulin concentration was greater than 12 µU/mL. The association of elevated serum concentrations of testosterone and insulin with the presence of SIL may be related to increased bioavailability of estrogens, which may cooperate with viral oncogenes in cervical carcinogenesis. Additionally, mitogenic activity of insulin and its influence on increased IGF-1 bioactivity may facilitate malignant transformation and viral survival. New research is required to determine the mechanisms involved in this process and elucidate whether there is a cooperation between both hormones during the progression to CxCa.

Keywords

Sex steroid hormones, Prolactin, Cortisol, Insulin, Cervical squamous intraepithelial lesions (SIL), Cervical cancer (Cxca)

Introduction

Cervical cancer (CxCa) is one of the most common among women worldwide. In 2020, an estimated 604,127 new cases were diagnosed, and 341,831 deaths occurred worldwide, making it the fourth location of cancer that affected the female sex in terms of incidence and mortality. The most critical situation occurred in countries with low and medium human development indices (HDI) [1]. In Cuba, CxCa ranked fourth in incidence (2017) and fifth in mortality (2020) among neoplasms that affected the female sex, according to data published in the Statistical Yearbook of Public Health, 2020 (MINSAP, 2021) [2].

CxCa develops as a consequence of a previous infection by genotypes of high oncogenic risk of the human papillomavirus (HPV-HR) [3], however, the viral infection by itself does

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not determine the fate of the infected cells. Instead, the immunological, microbial, metabolic, and hormonal microenvironment that interacts with them influences the development of premalignant lesions and progression to cancer. Through genetic integration into the host genome, HPV uses all available resources in the cell to complete its replication cycle without activating the recognition and elimination mechanisms of the immune system. To do this, it manipulates host cell signaling pathways and its microenvironment in a way that guarantees its survival and promotes cervical carcinogenesis [4,5].

Sex steroid hormones have been given an important role. An increased risk of premalignant lesions and CxCa, associated with HPV infection, has been observed among women who report oral contraceptive use for a period greater than five years, those with a high number of full-term pregnancies, and females that had their first full-term pregnancy at an age younger than 17 years [6,7]. Additionally, an association has been found between serum concentrations of testosterone and estrogens and the risk of CxCa in premenopausal and postmenopausal women [8]. The transformation zone of the uterine ectocervix is an epithelium sensitive to these hormones, which is considered the initiation site of cervical carcinogenesis [9], however, mechanisms through which these hormones contribute to cancer development are not yet completely understood.

The relationship of other endogenous hormones with CxCa has been less studied. However, some studies suggest that cortisol, prolactin, and insulin could contribute to developing this neoplasm. Glucocorticoids are neuroendocrine mediators of the stress response with a demonstrated role in malignant progression, especially in solid tumors [10]. In addition, they can activate oncogenic viruses, including some types of HPV, by binding their receptors to a series of glucocorticoid response elements in the viral genome. This modifies the activity of the promoters and regulates their life cycle [11]. Prolactin is a hormone produced mainly by the anterior pituitary, although its expression has been found in other human tissues, with autocrine and paracrine effects [12]. High blood concentrations of this hormone have been associated with the development of some gynecological cancers [13]. The finding that the prolactin receptor is overexpressed in cervical cancer cells [14], and the concentration of this hormone is elevated in patients' serum [15], suggests its possible involvement in the development and progression of this type of cancer. Additionally, to the prominent role of insulin in glucose metabolism, it is added its ability to stimulate cell proliferation and inhibit apoptosis [16]. Prospective studies have shown that high insulin levels are significantly associated with obesity-related neoplasms, such as breast and endometrial cancer [17,18].

In Cuba, some studies refer to the presence of hormonal risk factors in the development of premalignant lesions and CxCa, such as oral contraceptive use and parity [19,20], however, none have addressed the connection between serum hormonal profile and precursor lesions of CxCa. This work aims to determine the relationship between serum concentrations of sex steroid hormones, cortisol, prolactin, and, insulin and the degree of cervical squamous intraepithelial lesions in Cuban women.

Materials and Methods

A descriptive and cross-sectional study was carried out from 2018 to 2020. It included 205 women between 17 and 69 years who attended the Gynecology Classification Consultation of the National Institute of Oncology and Radiobiology (INOR) of Havana to confirm the cytological diagnosis of cervical pathologies. All patients expressed their wish to participate in the study through informed consent. It excluded pregnant and adolescent patients not authorized by their legal representative.

The selected patients underwent cytological, colposcopic, and histological studies to determine the presence of SIL. According to the Bethesda System (2001) [21], it was classified as low grade (LSIL) when cervical intraepithelial neoplasia type 1 (CIN 1) was present) and high-grade (HSIL) when were detected cervical intraepithelial neoplasia type 2 and 3 (CIN 2 and 3) or carcinoma *in situ* (CIS)). Additionally, a questionnaire was applied about sociodemographic variables such as age, skin color, marital status, and toxic habits. Variables related to the gynecological and obstetric history of the patients, like the number of deliveries, oral contraceptives use, hormone replacement therapy use, and the presence of menopause, were also included in the survey. Moreover, to determine hormone concentrations, blood samples were taken between the third and fifth day of the menstrual cycle or further 30 days of inclusion in the case of peri/postmenopausal women.

Estradiol, testosterone, cortisol, and insulin determinations were performed by radioimmunoassay (RIA). At the same time, prolactin was determined by immunoradiometric analysis (IRMA) using kits of reagents from the Isotope Institute of Budapest and the company DIA source Immuno Assays S.A.

Statistical Analysis

Frequency distributions of the qualitative variables and the mean, standard deviation, and/or standard error of the mean for the quantitative ones were determined. Chi-square, Kruskal Wallis, and Mann-Whitney U tests were used to compare the variables between the different groups. The Chi-square test was also applied to estimate the relative risk (Odds ratio) and the confidence intervals (95% CI). In all cases, a statistical significance level of 0.05 was considered. Statistical processing was carried out with the SPSS program, version 21.

Ethical Aspects

This research was carried out in compliance with the regulations of the INOR Ethics Committee. Participants expressed their willingness to participate in the study through informed consent. Confidentiality of the information corresponding to each patient was ensured.

Results

In this study, the mean age was 38.20 ± 11.53 years, ranged 17 to 69 years. Of 205 participants, 161 were in the

premenopausal stage and 44 in the peri/postmenopausal stage. Table 1 shows the study group's sociodemographic variables and toxic habits according to the degree of the lesions. Statistically significant differences were observed between the mean ages since it is higher in women with HSIL than in women with LSIL or negative cytology. When performing the analysis by age range, it was observed that women between 26 and 35 years predominantly presented LSIL, while those between 36 and 45 presented HSIL. Additionally, white skin color was significantly predominant in the study group. Significant differences were not found in terms of marital status and toxic habits.

Regarding the gynecological and obstetric variables, women with one or two deliveries significantly prevailed compared to nulliparous or those with three or more full-term pregnancies. Women who reported oral contraceptive use did not differ significantly according to the degree of lesions. Similarly, the presence or absence of menopause did not influence this variable (Table 2). None of the women participating in the study reported hormone replacement therapy use.

Table 3 and Table 4 show the serum concentrations of the hormone's estradiol, testosterone, and prolactin according to the degree of the lesions for premenopausal and peri/postmenopausal women, respectively. In both groups, significant differences were observed between the mean serum concentrations of testosterone, which increased in women with HSIL, although it did not exceed normal values for this hormone.

Insulin and cortisol serum concentrations analyses were carried out including every woman participating in the study because when comparing the means of these hormones concentrations, the distributions of insulin (p = 0.272) and cortisol (p = 0.372) concentrations were the same between menopausal categories, according to non-parametric Mann-Whitney U test. Table 5 shows the serum concentrations of insulin and cortisol according to the degree of the lesions. Mean insulin concentrations differed significantly between groups, with elevated values above the normal range in women with LSIL and HSIL as opposed to women with negative cytology.

Table 1: Relationship of sociodemographic variables and toxic habits with the degree of cervical squamous intraepithelial lesions.

		Cervical squamous intraepithelial lesions		
Sociodemographic variables	**NILM n = 60**	**Low grade n = 59**	**High grade n = 86**	**p Value**
	(M ± SD)	**(M ± SD)**	**(M ± SD)**	
Age (years)	37.90 ± 11.15	34.85 ± 11.01	40.71 ± 11.64	0.010*[a]
Age Ranges (years)	**n (%)**	**n (%)**	**n (%)**	
15-25	7 (11.9)	14 (23.7)	10 (11.6)	0.036*[b]
26-35	24 (40.7)	23 (39.0)	21 (24.4)	
36-45	11 (18.6)	9 (15.3)	27 (31.4)	
46-55	14 (23.7)	10 (16.9)	16 (18.6)	
55 and more	3 (5.1)	3 (5.1)	12 (13.9)	
Skin color	**n (%)**	**n (%)**	**n (%)**	
White	44 (73.3)	38 (64.4)	44 (51.2)	0.030*[b]
Mixed race	14 (23.4)	12 (20.3)	28 (32.6)	
Black	2 (3.3)	9 (15.3)	14 (16.2)	
Marital status	**n (%)**	**n (%)**	**n (%)**	
Single/Divorced/Widow	11 (18.3)	16 (27.1)	29 (33.7)	0.121[b]
Married/Consensual union	49 (81.7)	43 (72.9)	57 (66.3)	
Smoking	**n (%)**	**n (%)**	**n (%)**	
Yes	8 (13.3)	11 (18.6)	24 (27.9)	0.091[b]
No	52 (86.7)	48 (81.4)	62 (72.1)	
Alcohol consumption	**n (%)**	**n (%)**	**n (%)**	
Yes	8 (13.3)	6 (10.2)	17 (19.8)	0.256[b]
No	52 (86.7)	53 (89.8)	69 (80.2)	

M: Media; SD: Standard Deviation; NILM: Negative of Intraepithelial Lesion and Malignity

[a]p value estimated by Kruskal Wallis

[b]p value estimated by Chi square

Table 2: Relationship of gynecobstetric variables with the degree of cervical squamous intraepithelial lesions.

Gynecobstetric variables		Cervical squamous intraepithelial lesions		
	NILM n = 60	Low grade n = 59	High grade n = 86	P value
Number of birth	**n (%)**	**n (%)**	**n (%)**	
0	11 (18.3)	19 (32.2)	8 (9.3)	**0.007***
1-2	44 (73.3)	34 (57.6)	63 (73.3)	
≥ 3	5 (8.4)	6 (10.2)	15 (17.4)	
Oral contraceptives use	**n (%)**	**n (%)**	**n (%)**	
No	38 (63.3)	42 (71.2)	59 (68.6)	**0.643**
Yes	22 (36.7)	17 (28.8)	27 (31.4)	
Menopause	**n (%)**	**n (%)**	**n (%)**	
No	49 (81.7)	48 (81.4)	64 (74.4)	**0.474**
Yes	11 (18.3)	11(18.6)	22 (25.6)	

NILM: Negative of Intraepithelial Lesion and Malignity

*P value estimated by Chi square

Table 3: Relationships of serum concentrations of estradiol, testosterone and prolactin with the degree of cervical squamous intraepithelial lesions in premenopausic women (n = 161).

Hormone		Cervical squamous intraepithelial lesions		
	NILM (n = 49) M/SE	Low grade (n = 48) M/SE	High grade (n = 64) M/SE	P value
Estradiol (pg/mL)	**65.98/7.90**	**53.78/4.70**	**65.99/7.60**	**0.249**
Testosterone (nmol/L)	**1.67/0.17**	**1.64/0.16**	**2.36/0.19**	**0.001***
Prolactin (ng/mL)	**341.03/39.73**	**301.46/24.01**	**460.24/93.98**	**0.578**

M: Media; SE: Standard Error; NILM: Negative of Intraepithelial Lesion and Malignity

*Value of p estimated by the Kruskal Wallis test for independent samples

Table 4: Relationships of serum concentrations of estradiol, testosterone and prolactin with the degree of cervical squamous intraepithelial lesions in peri/posmenopausic women (n = 44).

Hormone	NILM (n = 11) M/SE	Cervical squamous intraepithelial lesions		P value
		Low grade (n = 11) M/SE	High grade (n = 22) M/SE	
Estradiol (pg/mL)	**33.26/8.01**	**27.15/8.22**	**52.83/25.01**	**0.531**
Testosterone (nmol/L)	**0.86/0.08**	**1.42 / 0.39**	**2.38/0.48**	**0.028***
Prolactin (ng/mL)	**371.15/236.53**	**205.66/34.36**	**211.47/22.54**	**0.180**

M: Media; SE: Standard Error; NILM: Negative of Intraepithelial Lesion and Malignity

*Value of p estimated by the Kruskal Wallis test for independent samples

Table 5: Relationships of serum concentrations of cortisol and insulin with the degree of cervical squamous intraepithelial lesions (n = 205).

Hormone	NILM	Cervical squamous intraepithelial lesions		
	(n = 60) M/SE	Low grade (n = 59) M/SE	High grade (n = 86) M/SE	P value
Cortisol (nmol/L)	**334.14/19.9**	**318.89/16.5**	**353.02/16.6**	**0.483**
Insulin (uU/mL)	**11.69/0.71**	**14.31/1.03**	**14.42/0.83**	**0.028***

M: Media; SE: Standard Error; NILM: Negative of Intraepithelial Lesion and Malignity

*Value of p estimated by the Kruskal Wallis test for independent samples

Based on serum concentrations of insulin and testosterone in the whole study sample, was estimated the relative risk of developing SIL (Table 6). A 2,63-fold risk (CI 95% 1.36-5.09) of developing SIL was found when the insulin concentration was greater than 12 µU/mL, a value above the normal range; and 3.23-fold risk (CI 95% 1.55-6.73) when testosterone

Table 6: Risk estimation of developing cervical squamous intraepithelial lesions according to serum concentrations of insulin and testosterone (n = 205).

	Presence of cervical squamous intraepithelial lesions				
	Yes (n = 145)	No (n = 60)			
Hormone	n (%)	n (%)	OR	CI 95%	P value
Insulin (uU/mL)					
> 12	71 (49.0)	16 (26.7)	2.63	1.36-5.09	0,003*
Testosterone (nmol/L)					
> 2	61 (42.0)	11 (18.3)	3.23	1.55-6.73	0.001*

OR: Odds Ratio; CI: Confidence Interval

*Value of p estimated by Chi square

concentrations were more than 2 nmol/L, although in this case, it did not exceed the normal range.

Discussion

Persistent HR-HPV infection is essential for cervical carcinogenesis. Nevertheless, other factors may play a critical role in the development of precancerous lesions and their progression to CxCa. One of these is the serum hormonal profile or hormonal concentrations at the local level and their respective receptors, which could participate in the complex interaction between the virus and the host [22].

The women's sociodemographic variables analysis included in the study showed that patients with SIL were in the age groups of 26 to 35 years and 36 to 45 years, in agreement with the ages in which premalignant lesions and CxCa occur worldwide [2]. Although most epithelial cancers increase with age, those estrogen-dependent do not share this pattern. In this case, after menopause, they rise more slowly or stop their increase, depending on the level of circulating or local estrogens. The incidence of CxCa shows growth at 45 years, followed by a plateau in Africa, Asia, and Latin America, where screening programs are imperfect. In well-screened populations, the incidence stops its increase at 30 years because early detection of SIL reduces the risk of CxCa [23].

Toxic habits, such as smoking and alcohol consumption, were present in a small percentage of the study group. Although most smokers presented HSIL, no significant differences were observed with the degree of the lesions. A study previously carried out at the INOR shows different results since the majority of smokers had an LSIL (17-18%) [24]. It is similar to another investigation in which smokers constituted 45% of those who presented mild lesions [25]. In another study carried out in the Cuban population, women who smoked or consumed alcohol had an increased risk (OR = 2.43; 95% CI = 1.11-5.32; p = 0.006) of acquiring HPV infection [26]. In a recent systematic review and meta-analysis, a significant association was found between smoking and the presence of HSIL. In the same way, a higher risk of CxCa was observed as the time of exposure to tobacco and the number of cigarettes per day increased [27].

Regarding gynecological and obstetric variables, an association was found between the number of deliveries and the presence of lesions. Women with one or two full-term pregnancies were the ones who presented HSIL, similar to another study carried out in Cuba [28]. It has been reported that women with HPV, with seven or more full-term pregnancies, have a risk of developing SIL four times greater than nulliparous women or women with fewer children [4]. This is because, during gestation, there is depression of the immune system and folate levels in the blood. In addition, the tears or erosions at the cervix constitute a gateway to HPV infection and other sexually transmitted infections (STIs) [26]. In Cuba, however, a notable decrease in fertility has been observed since the 1970s [29]. In 2021, the birth rate was 8.9‰, and the total fertility rate was 1.45 [30]. Taking these indicators into account, it is understandable that the increased risk of HSIL has not been associated with such a high number of pregnancies in any of the studies carried out on the Cuban population.

In this study, no significant differences were observed in serum estradiol concentrations between women with precursor lesions of CxCa and those with negative cytology, regardless of menopausal stage. Similar results were obtained by other researchers, who attributed their inability to detect this association to a decrease in the number of cases by separating them according to their menopausal stage. Moreover, using a simple blood sample at a point in time does not allow the characterization of the female hormonal environment, which is very complex. Endogenous hormone levels vary in response to factors such as changes in body weight, age, use of exogenous hormones, and during the menstrual cycle [31].

Most of the estrogens in women are formed in the ovaries, adipose tissue, and adrenal glands [32,33]. At the onset of menopause, estrogen production decreases significantly, and most estradiol is formed by the extragonadal conversion of testosterone by aromatase [34]. Estradiol can also be synthesized in tissues from estrone sulfate, which is converted to estrone by the enzyme estrone sulfatase, which can be converted to estradiol by 17β-hydroxy-steroid dehydrogenase type 1 (17β-HSD1) [35].

In the study conducted by Salazar, et al., no correlation was found between the degree of the SILs and estradiol

levels [36]. Serum estradiol concentrations are probably not the most representative of the relationship of estrogens with the presence of SIL and CxCa. It has been suggested that increased conversion of androstenedione to estrone by aromatization and eventually to 16-α hydroxy estrone could be a risk factor for CxCa due to proliferation promotion. It has been observed that increased levels of estrone are associated with an escalation in the degree of SIL, although the studies carried out have only been done in women with an average age of 20 years and require confirmation [37], since this is the way that it is present predominantly in perimenopausal women [32].

Estradiol and estrone can reach premalignant lesions or tumors and their microenvironment by blood circulation or local production. Estradiol can even accumulate inside tumor cells due to increased activity of the cytochrome P450 aromatase (CYP19A1), which converts androstenedione and testosterone into estradiol [38]. Estradiol levels have been observed to be increased in the tumor microenvironment while present at standard concentrations in blood plasma. Estradiol is distributed in the cytoplasm of transformed cervical keratinocytes. However, in infiltrating immune cells and the stroma it is distributed in both the cytoplasm and the nucleus [39,40].

Estrogens have been widely related to the development of CxCa. In studies with transgenic mice that express the viral oncoproteins E6/E7 of HPV 16, cancer only developed when exposed to this hormone [41]. In human tissues showed an increase in the expression of the estrogen receptor (ER) with the progression of the disease. These confirm the importance of this hormone in the evolution of this pathology [42]. The action of estrogens in females is exerted in an endocrine, paracrine, or intracrine manner through the classic ERs (ERα and ERβ) and by the G-protein coupled estrogen receptor (GPER) [43,44]. Estrogens can regulate the expression of E6 and E7 oncogenes in SiHa cells because HPV 16 contains estrogen response element (ERE)-like sequences in the promoter region, and nuclear ERs can bind to them [45]. Additionally, these viral oncogenic proteins of HPV 16/18 in SiHa and HeLa cells significantly increase the protein expression of ERα, ERβ, and GPER, suggesting that the mutual regulation between estrogens and viral oncogenes may cooperate in the cervical carcinogenesis process [46].

It has recently been described that ERα expression decreased during the progression to CxCa, both at the mRNA and protein levels. However, ERα expression was maintained within the stroma. This expression occurred mainly in cancer-associated fibroblasts, which can promote tumor growth through estrogen-dependent paracrine signaling pathways. The mechanisms involved in this action include enhancing cell proliferation, angiogenesis, metabolism, epithelial-mesenchymal transition, migration of epithelial cells, and inflammation induced by HPV [34,47]. ERα expression in stromal cells had already been observed in the normal cervix without increased estradiol plasma concentrations in premenopausal women [48]. In the same way, the expression of ERα was also described in more than 50% of the microenvironment cells, which indicates that local production of this hormone occurs in regional tissues [49].

Given the gradual loss of ERα expression through the progression of precursor lesions to CxCa, it is likely that initially, estradiol acts through the classical genomic pathway, and with the decrease of ERα in transformed cells, it uses the genomic pathway non-classical or non-genomic. Furthermore, estradiol promotes an anti-inflammatory microenvironment, which regulates the immune response and should contribute to the success of cervical carcinogenesis [50]. However, the role of estrogens and their receptors in human CxCa requires new research to be understood entirely.

Concerning testosterone, the other sex steroid hormone evaluated in this study, significant differences were found in its serum concentration between the groups with HSIL and negative cytology. The same behavior was observed in premenopausal and peri/postmenopausal women, although testosterone concentration did not exceed the normal range in any case. Values greater than 2 nmol/L corresponded to a more than threefold increase in the risk of developing SIL. These results are in agreement with those reported in the European Prospective Investigation into Cancer and Nutrition (EPIC), which showed for the first time an association between free testosterone and invasive cervical carcinoma (ICC) in premenopausal women (OR 5.6 95% CI: 1.50-20.1), whereas in postmenopausal women found an association when testosterone exceeds 1.67 nmol/L (OR 3.14 95% CI: 1.21-9.37). It differs from our study because they did not find an association of this hormone with the presence of CIN 3 [7].

A study on the genetic regulation of testosterone levels found that high testosterone concentrations in women are related to an increased risk of developing cancer, such as breast and endometrial cancer [51]. The positive association between serum androgen concentrations and breast cancer risk has been confirmed in some studies [52,53]. However, most evaluated circulating testosterone levels being metabolized to estrogens [54]. The effects of testosterone on mammary cell proliferation are closely related to the expression and activity of 5α-reductase and aromatase enzymes. Therefore, this evidence does not fully reflect the hormone concentration within mammary tissue. The fact that testosterone is one of the precursors of estrogen synthesis is a doubtful factor in determining the role of androgen concentration in breast carcinogenesis and other cancer sites in women, such as the cervix. It is necessary to measure the levels of steroid hormones at the tissue level to establish the differences between serum and local hormone concentrations [55,56], and thus obtain valuable data on susceptibility to them.

Androgen receptor (AR) expression has also been reported to decrease during progression from normal epithelium, the appearance of SIL, and CxCa [57]. Additionally, aromatase expression has not been detected in normal cervical tissue or epithelium with SIL. However, similar to what occurs in breast cancer [22], an increased expression of this enzyme in cervical squamous cell carcinoma occurs, which allows us to infer that there is a local conversion of testosterone to estradiol in tumor cells. It has been observed that aromatase

is distributed in the same way as estradiol in the cytoplasm, the nucleus of tumor cells, and the microenvironment [38]. Therefore, the increased expression of aromatase in the transformation zone of the squamocolumnar epithelium of the cervix, highly sensitive to estrogen, could be a potential factor in the progression of cervical carcinogenesis [58].

The regulatory mechanisms and biological effects resulting from the loss of ERα and AR are not fully understood. Recently, overexpression of mi-R-130a-3p was described in CxCa compared to normal cervical tissue. This miRNA was able to bind to non-coding regions located towards the 3' end of the mRNA of the ESR1 gene and similar sequences to the AR gene. It suggests that this miRNA is a mediator in the progression to CxCa by negative regulation of the expression of these receptors. mi-R-130a-3p may contribute to the development of CxCa and may be a candidate for targeted therapy in patients with this type of neoplasia [59].

In this study, no significant associations were found between serum concentrations of Prl and cortisol with the degree of SIL. Some authors have described that the concentration of Prl was elevated in the serum of patients with CxCa [13]. However, recent research identified that some cancer biomarkers usually detected in serum/plasma, such as the hormone Prl, are elevated in the cervicovaginal microenvironment of patients with CxCa, but not in patients with SIL or healthy controls [60], like those that make up our study group. It has been shown that the Prl receptor (PrlR) increases its expression as the severity of SIL increases [12] and it has been suggested that there is a differential signaling of the Prl-PrlR axis between premalignant stages and CxCa. The results obtained in this investigation do not allow us to corroborate this statement since only the serum concentrations of these hormones were analyzed in patients with premalignant lesions.

Some studies do not refer to a relationship between adverse life events such as divorce, the death of a close relative, or lack of social support and the risk of developing CxCa precursor lesions [61,62]. Nevertheless, other researchers have shown an association between psychosocial stress, cortisol levels, and the risk of HR-HPV infection, suggesting that this hormone may be related to cervical carcinogenesis [63,64]. Moreover, systemic use of glucocorticoids could increase the risk for HR-HPV persistence (OR, 2.04; 95% CI, 1.16-3.56) [65]. However, there are still contradictions between experimental and clinical studies on the involvement of glucocorticoids in the development of CxCa [66].

The results showed elevated insulin concentrations in women with SIL compared to negative cytology. Raised concentrations were observed both in women with LSIL and HSIL. Serum concentrations greater than 12 uU/mL of insulin corresponded to a a more than twofold increased risk of developing SIL. In a previous pilot study with smaller sample size, insulin resistance was observed in 50% of women with LSIL and 62-69% of those with HSIL. In that study, overweight and obesity were present in 56.4% of the participants, but no significant differences were obtained between body mass index (BMI) and the degree of lesions. However, representative rates of abdominal obesity were significantly elevated in women with HSIL [67]. Little research has been done on hyperinsulinemia, obesity, premalignant lesions, and CxCa. In a study carried out in India in women diagnosed with SIL, they found that the concentrations of C-peptide, a known marker of endogenous insulin secretion, decreased significantly in the group diagnosed with SIL compared to the control group. However, in this research work, most of the participants with premalignant lesions (96.7%) were not obese since they had a BMI of less than 27 Kg/m^2 [68].

Some works demonstrate the connection of insulin resistance, which leads to compensatory hyperinsulinemia, with the development of various types of cancer, including breast, ovarian, endometrial, and CxCa [69]. There are although contradictory results, the balance favors the existence of a positive association between hyperinsulinemia and cancer risk. The conventional theory places insulin resistance as the initial cause and hyperinsulinemia as a consequence. However, some clinical observations question whether this paradigm is applicable in all cases. Basal hyperinsulinemia has been documented to precede insulin resistance, obesity, and hyperglycemia [70,71]. Further research is required to test the hypothesis that hyperinsulinemia drives the onset of chronic diseases such as diabetes, obesity, and cancer [72].

Unlike carcinogens that induce malignant transformation through genetic changes in cellular DNA, insulin is a mitogenic agent that promotes cell growth. The interaction of this hormone with the insulin receptor (INSR) activates the mitogen-activated protein kinase (MAPK) signaling pathway, which stimulates cell proliferation and inhibits apoptosis but has no metabolic effects. Both of these activities link insulin to an increased risk of malignant transformation. Additionally, insulin promotes the activation of the phosphatidyl-inositol-3 kinase (PI3K) pathway, which is linked to its metabolic effects, such as the introduction of glucose into cells through the transporter protein GLUT4, for its subsequent degradation and obtaining of cellular energy [73].

Additionally, insulin can interact with insulin-like growth factor family receptors 1 and 2 (IGF1R and IGF2R) and with hybrid IGFR/INSR receptors due to its structural similarity with their native ligands (IGF- 1 and 2) [74]. In addition, insulin can increase IGF1 bioactivity by decreasing the synthesis of its binding proteins [75]. Activation of IGF1R by insulin has robust effects on cell proliferation and survival [76]. The IGF- 1 pathway is used by HPV for cell transformation, and it is involved in both premalignant lesions and CxCa [69,77]. Research has also associated polymorphism in the P1 promoter of IGF1 with the risk of CxCa [78].

Our results showed that in the group of women with SIL, the only hormones that showed significant differences in serum concentrations were insulin and testosterone, concerning women with negative cytology. Different mechanisms show the relationship of insulin with sex hormones. The insulin-sex hormone axis provokes increased ovarian androgen production and peripheral aromatase activity [79]. Moreover, hyperinsulinemia decreases the production of sex hormone-binding globulin (SHBG), probably

because of direct suppression of its synthesis in the liver. In this way, it can increase the bioavailability of testosterone and free estrogens, which favors the development of hormone-dependent neoplasms such as the breast, endometrium [71], and, probably, CxCa.

Recently, it was shown for the first time that human pancreatic islets could locally activate androgens and estrogens by converting circulating testosterone. This action occurs in the ß cell, where testosterone acts as a prohormone, requiring conversion to dihydrotestosterone (DHT) by type 1 5-α-reductase or to 17-β-estradiol by aromatase to activate AR and ER, respectively. It is considered an intracrine pathway of sex hormone action on β cells to stimulate glucose-promoted insulin secretion [80].

In hormone-dependent cancers such as breast and prostate cancer, an intracellular interaction between the sex steroid hormone receptor and IGF pathways has been observed, resulting in increased synthesis of IGF1 and IGF1R [77]. HPVs have to maintain cell integrity, probably by harnessing and/or inducing pathways that are involved in normal cell survival. There is strong evidence that the IGF axis is manipulated by this virus to support the process of immortalization and malignant transformation [81]. To verify whether insulin and sex steroid hormones cooperate on the development of HPV-associated cancers, like CxCa, additional research is required.

Study limitations are that no measurements were made of the local concentrations of the hormones or the expression of their specific receptors. It restricts the analysis of the results by not taking into account all the elements that participate in this complex interaction between the hormonal profile of the host and the HPV, which leads to the development of premalignant lesions and CxCa.

The association of elevated serum concentrations of testosterone and insulin with the presence of SIL may be related to increased bioavailability of estrogens, which may cooperate with viral oncogenes in cervical carcinogenesis. Adittionaly, mitogenic activity of insulin and its influence on increased IGF-1 bioactivity may facilitate malignant transformation and viral survival. New research is required to determine the mechanisms involved in this process and elucidate whether there is a cooperation between both hormones during the progression to CxCa.

Conflicts of Interest

The authors declare not to have any interest conflicts.

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