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Original Article

Association between components of the metabolic syndrome and degree of cervical squamous intraepithelial lesions in Cuban women

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1. Introduction

The CC is the third neoplasm affecting the female sex worldwide, while in developing countries its incidence rate is in the first place with a high mortality and a high number of years of potential life lost (YPLL) [1]. In Cuba, it ranked fourth in incidence (2013) and fifth in mortality (2016) among the neoplasms that affect the female sex [2]. Despite the usefulness of the National Early Diagnosis Program of the CC, the morbidity and mortality due to this type of neoplasia are already high.

Persistent infection by subtypes of high oncogenic risk of human papilloma virus (HPV) is the major etiological factor for the development of SIL and CC [3]. However, the presence of this infection is a necessary but not sufficient condition for the development of cancer, since only a small proportion of infected women progress to malignant lesions. HPV is characterized by acting in a latent, subclinical and opportunistic fashion; it remains in an almost equilibrium state with the host and interacts with it, which may result in the elimination of the infection or in the persistence and progression to CC. This neoplasia is considered a multifactorial disease and different cofactors involved in the carcinogenesis process are being evaluated. Among them are environmental or exogenous factors (use of oral contraceptives, smoking, parity, co-infection with other sexually transmitted infections); viral factors (subtypes of HPV, viral load and integration) and host factors (endogenous hormones, individual genetic-immune response and nutritional deficiencies). Recently, obesity, and the metabolic alterations associated with it, have been included within host factors that could contribute to the progression to CC [4].

Since 2007, an emerging hypothesis has been proposed regarding the metabolic syndrome, or some of its components, may be important etiological factors for the development and progression of certain types of cancers and for overall cancer mortality [5]. However, there have been contradictory patterns of association due to differences in the populations studied, length of follow-up and sample size, among others. Some studies report the association of several components of metabolic syndrome, such as obesity [6], diabetes [7] and dyslipidemia [8], with an increased risk of CC.

In Cuba, there are no previous studies that define which cofactors of HPV persistence and progression to CC are present more frequently in Cuban women with premalignant lesions. The results of worldwide research related to association between the components of metabolic syndrome and CC, or its precursor lesions, are contradictory and show that they differ according to ethnic groups. The objective of this work is to determine the relationship between the components of the metabolic syndrome and the degree of SIL in a selected population of Cuban women.

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2. Materials and methods

2.1. Study design: descriptive and transversal

2.1.1. Scope

The study was carried out between January 2017 and September 2018. The women who participated in the research were eligible among those who attended the Gynecology and Obstetrics Hospital of Guanabacoa and the National Institute of Oncology and Radiobiology of Havana, for confirmation of the cytological diagnosis of cervical pathologies.

2.2. Subjects

2.2.1. Inclusion criteria

Women between 15 and 70 years of age with cytological, colposcopic and histological diagnosis of SIL who gave informed consent.

2.2.2. Exclusion criteria

Pregnant women, adolescents without the consent of their legal representative and people with mental illness.

2.2.3. Sample size

102 consecutive women were chosen, who attended the previously referred centers, 92 presented a SIL diagnosis and the remaining 10 women presented other gynecological pathologies, which were included in a control group.

2.3. Variables

2.3.1. Dependent variable

Presence of SIL that are classified as low grade (LSIL) when cervical intraepithelial neoplasia type 1 (CIN 1) is present and as high grade (HSIL) when cervical intraepithelial neoplasia type 2 and 3 (CIN 2 and 3) and carcinoma *in situ* (CIS) are present, according to the Bethesda System, 2001 [9].

2.3.2. Sociodemographic variables

Age, skin color, marital status, pathological history of diabetes mellitus and high blood pressure (HBP), obtained by applying a questionnaire.

2.3.3. Anthropometric variables

Determinations of weight (Kg), height (m), waist circumference (WC) (cm) and hip circumference (cm) were made. The measurement of WC was taken with a tape measure with the subject standing, on expiration, with the abdomen relaxed, taking as reference the midpoint between the lower edge of the last rib and the anterior superior iliac spine on each side. In cases of pendulous abdomens, measurement was made at the most prominent point of the abdomen. The circumference of the hip was taken as the maximum circumference traced on the femoral trochanters. The BMI [weight (kg)/(height (m)) ^{2}], WHR [WC (cm)/hip circumference (cm)] and WHtR [WC (cm)/height (cm)] were calculated [10]. The BMI was used for the classification of patients according to WHO [11], in the following categories: normal weight (18.5–24.9 Kg/m^2), overweight (25–29.9 kg/m^2) and obese ($\geq$30 kg/m^2). Furthermore, obesity was defined when the WC was $\geq$80.5 cm, the WHR $\geq$0.85 and the WHtR> 0.5 [11–13].

2.3.4. Biochemical variables and metabolic alterations

The women included in the study underwent a blood draw at the National Institute of Endocrinology within 30 days of their recruitment in the Gynecology Consultations. Fasting blood glucose, insulin, triglycerides and HDL-c (cholesterol united to high density lipoprotein) levels were determined.

The criteria used for the analysis of metabolic disorders are a combination of the definitions of WHO [11] and the Joint Interim Statement (JIS) [14]. IGM included prediabetes (altered fasting blood glucose ($\geq$5.6 mmol/L)), diagnosed type 2 diabetes mellitus and insulin resistance (IR) determined by the homeostatic model of Mathews (HOMA-IR) that employs the following formula: fasting insulin uU/mL x fasting glucose mmol/L/22.5. For adult women, IR was defined when the HOMA-IR value was equal to or greater than 2.6; while for adolescents between 15 and 19 years it was considered a value equal to or greater than 2.52 [15,16]. The presence of dyslipidemia was defined when triglyceride levels were equal to or greater than 1.7 mmol/L or when HDL-c levels were less than 1.03 mmol/L [11].

2.4. Statistical analysis

Frequency distributions of qualitative variables, and mean and standard deviation of quantitative variables were determined. Cross-tabulations of variables related to: sociodemographic aspects (range of age, skin color and marital status); IGM (prediabetes/diabetes and IR), dyslipidemia and history of high blood pressure with the SIL grade were carried out, using the Chi square test to determine the statistical significance of the associations.

In the case of quantitative variables, the Student *t*-test was applied to compare the mean age between women with LSIL and HSIL. The Kruskal Wallis non-parametric test for independent samples was used to verify the association among WC, BMI, WHR and WHtR and the SIL grade. In all cases a level of statistical significance of 0.05 was considered. The statistical processing was carried out through the SPSS program, version 21.

2.5. Ethical aspects

This research was carried out in compliance with the regulations of the Research Ethics Committees of the National Institute of Oncology and Radiobiology, the National Institute of Endocrinology and the Gynecology and Obstetrics Hospital of Guanabacoa, based on the Declaration of Helsinki. The selected women expressed their willingness to participate in the study through informed consent.

3. Results

This study was conducted in the period of one year and seven months, from January 2017 to September 2018. We included 102 women in an age range between 17 and 69 years, whose mean age was 38.59 ± 11, 37 years. Table 1 shows the general characteristics of the women who participated in the study. Of these, 90.2% (92/102) presented SIL, of which 26.1% were LSIL and 73.9% were classified as HSIL. The mean age for women with LSIL was 32.04 ± 9.94, which differs significantly ($p = 0.001$) from that of women with HSIL, whose mean age was 40.60 ± 10.96.

The results of the association between the sociodemographic variables and the degree of the lesions show significant differences between age ranges (<35, 36–50 and > 50 years), since most of the high-grade lesions occurred in the group from 36 to 50 years old ($p = 0.006$). Regarding the skin color, significant differences were also observed, with white women being the ones that mostly presented high-grade lesions ($p = 0.046$), while no differences were found in relation to marital status ($p = 0.074$).

Table 1
Characteristics of participants in the study.

Variables	Control Group n = 10	Cervical squamous intraepithelial lesions	
		Low grade n = 24	High grade n = 68
	(M ± SD)	**(M ± SD)**	**(M ± SD)**
Age (years)	40,70 ± 12,36	32,04 ± 99,4	40,60 ± 10,96
Skin color	**n (%)**	**n (%)**	**n (%)**
White	10 (100)	17 (70,8)	32 (47,1)
Mixed race	0 (0)	4 (16,7)	25 (36,8)
Black	0 (0)	3 (12,5)	11 (16,1)
Marital status	**n (%)**	**n (%)**	**n (%)**
Single	1 (10,0)	8 (33,3)	23 (33,8)
Married	5 (50,0)	11 (45,8)	30 (44,1)
Unmarried couple	4 (40,0)	5 (20,9)	15 (22,1)
Diabetes mellitus history	**n (%)**	**n (%)**	**n (%)**
Yes	1 (10,0)	1 (4,2)	6 (8,8)
No	9 (90,0)	23 (95,8)	62 (91,2)
HBP history	**n (%)**	**n (%)**	**n (%)**
Yes	2 (20,0)	4 (16,7)	28 (41,2)
No	8 (80,0)	20 (83,3)	40 (58,8)
	(M ± SD)	**(M ± SD)**	**(M ± SD)**
Weight (Kg)	65,65 ± 18,80	64,22 ± 15,14	67,71 ± 14,61
Height (m)	1,59 ± 0,03	1,63 ± 0,06	1,59 ± 0,08
WC (cm))	85,7 ± 15,98	82,75 ± 10,10	90,18 ± 12,24
BMI (Kg/m^2)	26,03 ± 7,32	24,46 ± 5,19	26,76 ± 5,24
WHR	0,84 ± 0,07	0,84 ± 0,05	0,88 ± 0,16
WHtR	0,54 ± 0,09	0,51 ± 0,06	0,57 ± 0,08
	(M ± SD)	**(M ± SD)**	**(M ± SD)**
Fasting Glycaemia (mmol/L)	5,23 ± 0,70	5,25 ± 0,63	5,75 ± 1,84
Fasting Insulinemia (uU/mL)	9,64 ± 2,55	13,63 ± 8,25	14,68 ± 8,16
HOMA-IR	2,25 ± 0,75	3,36 ± 2,47	3,85 ± 3,19
Triglycerides (mmol/L)	1,19 ± 0,53	1,11 ± 0,49	1,18 ± 0,59
HDL-c (mmol/L)	1,30 ± 0,25	1,19 ± 0,23	1,20 ± 0,26

M: mean; SD: standard deviation; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to- height ratio; HOMA-IR: Insulin resistance by the homeostatic model of Mathews; HDLc: cholesterol united to high density lipoprotein.
Anthropometrics measurements and obesity indexes were obtained from 101 participants.

3.1. Components of the metabolic syndrome

3.1.1. Obesity

Table 2 shows the results of the analysis of the relationship between obesity and the degree of the lesions, taking into account both the anthropometric measures indicating the general body weight and those of central adiposity. For the analysis of obesity, the data of 101 women were taken into account, since it was not possible to record the anthropometric variables of one of them. Overweight and obesity (BMI $\geq$ 25 Kg/m^2) were present in 56.4% (57/101) of the participants in the study, however, the BMI did not show statistically significant differences with respect to the degree of the lesions ($p = 0.172$). The WC ($p = 0.006$), the WHR ($p = 0.019$) and the WHtR ($p = 0.006$) were significantly higher in the women with HSIL. In general, these last parameters, which are indicators of central adiposity, were above the normal values in the groups with LSIL and HSIL, and some of them even in the control group.

3.1.2. IGM, dyslipidemia and HBP history

Table 3 shows the results of the analysis of the IGM, which includes pre-diabetes/diabetes status and altered HOMA-IR, with respect to the degree of the injuries. A predominance of them can be observed among women with HSIL ($p = 0.024$). The factor of greatest contribution was IR ($p = 0.045$), since the presence of pre-diabetes and diabetes showed no differences among the studied groups.

Table 4 shows the results obtained when analyzing the presence of dyslipidemia in relation to the degree of lesions, which was found mostly in the group of women with HSIL ($p = 0.018$). Regarding the personal pathological history of HBP, no statistically

Table 2
Relationship among obesity expressed as BMI, WC, WHR and WHtR and degree of cervical squamous intraepithelial lesions.

Variables	Cervical squamous intraepithelial lesions				p Value
	Control Group (n = 10) M ± SD	Low grade	High grade		
		CIN I (n = 24) M ± SD	CIN II (n = 44) M ± SD	CIN III (n = 23) M ± SD	
BMI	26,03 ± 7,32	24,46 ± 5,19	26,31 ± 5,49	27,61 ± 4,71	0,172
WC	85,70 ± 15,98	82,75 ± 10,10	87,52 ± 11,56	95,04 ± 12,19	0,006[a]
WHR	0,84 ± 0,07	0,84 ± 0,05	0,85 ± 0,05	0,93 ± 0,24	0,019[a]
WHtR	0,54 ± 0,09	0,51 ± 0,06	0,55 ± 0,07	0,60 ± 0,08	0,006[a]

M: average; SD: Standard deviation; CIN: cervical intraepithelial neoplasia; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to- height ratio.
[a] Value of p estimated by the Kruskal Wallis test for independent samples (this analysis was performed with n = 101).

Table 3
Relationship of impaired glucose metabolism with the degree of cervical squamous intraepithelial lesions.

Variables	Cervical squamous intraepithelial lesions				p Value
	Control Group (n = 10) n (%)	Low grade	High grade		
		CIN I (n = 24) n (%)	CIN II (n = 45) n (%)	CIN III (n = 23) n (%)	
Pre-diabetes/Diabetes					
Yes	1 (10,0)	7 (29,2)	18 (40,0)	11 (47,8)	0,164
No	9 (90,0)	17 (70,8)	27 (60,0)	12 (52,2)	
HOMA-IR > 2,6					
Yes	2 (20,0)	12 (50,0)	28 (62,2)	16 (69,6)	0,045[a]
No	8 (80,0)	12 (50,0)	17 (37,8)	7 (30,4)	
IGM					
Yes	2 (20,0)	13 (54,2)	31 (68,9)	16 (69,6)	0,024[a]
No	8 (80,0)	11 (45,8)	14 (31,1)	7 (30,4)	

CIN: Cervical intraepithelial neoplasia; HOMA-IR: Insulin resistance by the homeostatic model of Mathews; IGM: Impaired glucose metabolism (this variable includes pre-diabetes/diabetes status and HOMA-IR).
[a] Value of p estimated by the Chi square test.

Table 4
Relationship of dyslipidemia and high blood pressure with the degree of cervical squamous intraepithelial lesions.

Variables	Cervical squamous intraepithelial lesions				P Value
	Control Group (n = 10) n (%)	Low grade	High grade		
		CIN I (n = 24) n (%)	CIN II (n = 45) n (%)	CIN III (n = 23) n (%)	
Dyslipidemia					
Yes	2 (20,0)	14 (58,3)	28 (62,2)	18 (78,3)	0,018[a]
No	8 (80,0)	10 (41,7)	17 (37,8)	5 (21,7)	
HBP					
Yes	2 (20,0)	4 (16,7)	17 (37,8)	11 (47,8)	0.090
No	8 (80,0)	20 (83,3)	28 (62,2)	12 (52,2)	

CIN: Cervical intraepithelial neoplasia; HBP: High blood pressure.
[a] Value of p estimated by the Chi square test.

significant differences were observed (p = 0.090).

4. Discussion

A number of cofactors of the persistence of HPV infection and progression to CC have been studied consistently; however, very few studies have addressed the relationship between the components of the metabolic syndrome and the degree of cervical cancer precursor lesions.

According to the sociodemographic variables studied, we found that the majority of HSIL occurred in women aged between 36 and 50 years. These results are consistent with that reported in the Anuario Estadístico de Salud [2], which shows that women in the age group of 35–49 years are those with the highest rates of prevalence of CC. With regard to skin color, most of the women with HSIL were white; however, it is not possible to draw any conclusion in this regard since most of the participants had this skin color. No statistically significant associations were found between the marital status and the degree of the lesions.

BMI was elevated in more than half of the women who participated in the study, but no significant association was found with the degree of the lesions. This result differs from an investigation conducted in Mexico in which 20,236 women participated, where there was a tendency to increase the prevalence of cervical cancer in those who had a high BMI. In addition, they demonstrated a significant association between the percentage of body mass and this type of cancer [17]. The fact that there was no association between high BMI and the degree of the lesions could be explained because it is probable that abdominal obesity has more relevance in the risk of developing CC than general body weight. In our study, it was found that WC, WHR and WHtR were significantly elevated in women with HSIL. The use of BMI as a surrogate marker of energy status is less accurate than WC, WHR or WHtR [18], since the distribution of body fat varies among different individuals and its location in the abdomen is of particular interest from the clinical point of view. One of the benefits of WHtR lies in its ability to identify people with normal BMI who may have a high metabolic risk associated with central obesity, whose utility is similar or superior to the determination of WC [19].

Abdominal obesity is related to hypertension, insulin resistance and dyslipidemia, among other health problems, such as low-grade chronic systemic inflammation that allows the establishment of a protumorigenic environment. In addition, it facilitates the establishment of states known as dysglycaemics that comprise varying degrees of IGM [20].

In a recent study in the Cuban population, a positive correlation was found among WC and glycaemia, insulinemia, uric acid and HOMA-IR index values. WC was the variable with the greatest predictive power of dysglycaemia, with a cut-off point of 80.5 cm in women [12]. Our results show that the central adiposity, fundamentally expressed by the WC, was above the normal values in the control group and in those with LSIL and HSIL, although this elevation was more marked in the group with HSIL. In Cuba, according to data from national surveys of risk factors for non-communicable diseases, overweight and obesity has a higher prevalence in females, as well as the deposit of fat around the waist [21]. These data, together with the previously cited studies, show that abdominal obesity is very prevalent in the Cuban female population, which could constitutes an early risk factor in the process of cervical carcinogenesis, since it is present from the lower grade lesions. Our results are consistent with other authors who have stated that obesity in adults increases the risk of thyroid, ovary, esophagus, cervix, pancreas and prostate cancer [22].

With respect to IGM, their presence was significantly associated

with HSIL. Among them, the IR was the component of greatest contribution to this association. There are studies that demonstrate the connection of the IR with the development and progression of various types of cancer, including CC [23]. However, the behavior of this variable differs in different populations. In another investigation, it was found that participants with IR had a greater frequency of endometrial, ovarian and pre/postmenopausal breast cancer [24].

Dyslipidemia also showed a statistically significant association with presence of HSIL in this group of women. The relationship of the lipid profile with cancer is controversial, the variability of this in blood plasma could be due to factors linked to individual life habits such as nutritional status, BMI, alcohol consumption and physical activity [25]. However, some studies argue that a high concentration of triglycerides and a low concentration of HDL-c in blood are related to an increased risk of progression to cancer, including CC. However, other studies are needed on the molecular changes in lipid metabolism in patients with this neoplasm, as well as on the enzymes, genes and receptors involved, to decide if it plays any role in the diagnosis and/or prognosis of the disease [26]. On the other hand, in our work the history of HBP showed no statistically significant association with the degree of the lesions. There are some references in the literature in this sense, where they found an association among the presence of obesity, hypertension and high levels of triglycerides with an increased risk of CC [27,28]. However, in these studies they perform direct measurement of blood pressure, in addition to recording the cases that receive treatment due to a previous diagnosis of hypertension.

The potential mechanisms through which the components of the metabolic syndrome promote the development of cancer include the stimulation of insulin-like growth factor 1 (IGF1) by hyperinsulinemia, and the generation of reactive species of oxygen (ROS) due to the increase in the concentration of glucose and triglycerides in blood [27]. Similarly, excess adipose tissue involves an altered secretion of adipocytokines, including leptin and adiponectin. The first regulates energy homeostasis and the second increases the sensitivity of insulin in other tissues [29]. The union of this phenomenon with the increased production of proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) leads to chronic inflammation, which has been recognized as a state that favors the initiation and progression of malignant tumors [30].

4.1. Study limitations

This study was carried out with a small sample size, so the results not show the behavior of these factors in the general population of Cuban women, with precursory lesions of cervical cancer. In addition, no blood pressure measurements were taken, only the history of HBP reported by the study participants was taken into account, which makes it difficult to compare our results with other similar investigations.

4.2. Conclusions

The results of our study suggest that some components of the metabolic syndrome, such as central adiposity, IGM and dyslipidemia, which were predominantly present in women with HSIL, could contribute to progression to CC, taking into account the dynamic interaction that is established between the HPV and the host. This work constitutes the first Cuban study of comorbidities in women at risk of developing CC. These are modifiable risk factors, so these results create the basis for the design of prevention strategies that allow the treatment and/or modification of the lifestyles of women at risk.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.02.011.

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