Archives of Medical Research 53 (2022) 594–602

ORIGINAL ARTICLE

Metabolic Syndrome and Prostate Cancer Risk: A Population Case-control Study

Jesús Gibran Hernández-Pérez,[a] Luisa Torres-Sánchez,[a] César Hernández-Alcaráz,[a] Lizbeth López-Carrillo,[a] Francisco Rodríguez-Covarrubias,[b] Ruth Argelia Vázquez-Salas,[a] and Marcia Galván-Portillo[a]

[a] *Instituto Nacional de Salud Pública, Cuernavaca, Morelos, México*
[b] *Departamento de Urología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México, México*

Received for publication March 15, 2022; accepted July 15, 2022 (ARCMED-D-22-00362).

Background. Metabolic syndrome (MS) with mixed dyslipidemia and prostate cancer (PC) are relevant health problems among Mexican men. However, there is no information regarding the association between MS and PC for this population.

Aim of the study. To evaluate this association in a population case-control study in Mexico City.

Methods. We analyzed the information from 394 incident PC-cases and 793 population age-matched (± 5 years) controls, identified in Mexico City (2011–2014). For cases, Gleason score at diagnosis was available. We defined MS history based on the self-report of hypertension, hypercholesterolemia, hypertriglyceridemia, and diabetes; obesity was evaluated using weight-change trajectories throughout life. In addition, the four MS-typologies described for Mexican population were used. The association between MS with PC and histological PC differentiation was evaluated using independent multivariate logistic regression models.

Results. MS history was associated with a high PC probability (OR 1.94; 95% CI 1.37–2.75). Lipid alterations, arterial hypertension, and a marked weight increase throughout life were associated with increased PC probability; however, only the marked weight increase was associated with more poorly differentiated PC (Gleason ≥8) (OR 2.79; 95% CI 1.50–5.17).

Conclusion. Like other populations, in this Mexican study, MS and some of its components were identified as potential PC risk factors. MS-lipid alteration typology seems to be relevant; however, the novelty of this approach together with the retrospective nature of this study, indicate that a prospective evaluation of the MS typologies and PC association must be performed.

Key Words: Prostate cancer, Metabolic syndrome, Weight-change trajectories, Mexico.

Introduction

Metabolic syndrome (MS) is a heterogeneous condition characterized by the presence of at least three of the following components: obesity, alteration of glucose metabolism, arterial hypertension, and dyslipidemia (1). MS produces several stress reactions, such as oxidative, inflammatory, organelle, and cell hypertrophy stresses. This leads to vicious cycles that perpetuate a state of "low-grade" chronic inflammation (2). Such condition could explain the relationship between MS and several types of cancer, including prostate cancer (PC) (3).

MS is associated with PC (OR = 1.17; 95% CI: 1.00–1.36, $p = 0.04$), mainly with high-grade PC (OR = 1.89; 95% CI: 1.50–2.38) (4). Nevertheless, individual MS-components seem to have a different contribution to

Address reprint requests to: Luisa Torres-Sánchez, Dr. Instituto Nacional de Salud Pública, Av. Universidad 655, Col. Sta. María Ahuacatitlán, 62100 Cuernavaca, Morelos, México; Phone: (+52) (777) 329 3000, ext. 3454; E-mail: ltorress@insp.mx

0188-4409/$ - see front matter.
https://doi.org/10.1016/j.arcmed.2022.07.003

prostate carcinogenesis. Obesity and hypoalphalipoproteinemia have been associated with high PC risk (5–9) meanwhile, diabetes does not seem to be associated (4,8,10,11). As far as we know, only one study has evaluated specific combinations of MS-components and their association with PC. The highest PC risk was observed among males with metabolic obesity (≥3 MS-components and a body mass index ≥30) (5).

In Mexico, PC is the most common form of cancer and the leading cause of cancer-related death (12). In addition, MS affects 50% of adult men (13), and four MS-typologies with different prevalence have been identified according to the altered MS-component: mixed dyslipidemia (40.7%); hypoalphalipoproteinemia (46.0%); hypertriglyceridemia (10.2%) and without dyslipidemia (3.1%) (13). Among males, the mixed dyslipidemia typology (altered triglycerides and HDL-C with another MS-component) is the most prevalent (43.5%) (13). Our objective was to evaluate the association between MS, MS-typologies, and each MS-component with the risk of PC and its histological differentiation grade in a case-control study carried out in Mexico City.

Methodology

Study Population

The information for this work was obtained from a population-based case-control study conducted in Mexico City between November 2011 and August 2014 (14). Participants were men between 42 and 94 years old, with at least one year of residence in Mexico City and no prior history of any other type of cancer. Briefly, cases included 402 men with an incident diagnosis of PC, histologically confirmed, who were identified at the urology department of four third level and two second-level public hospitals. Based on the reported Gleason scale at diagnosis, cases were classified as poorly- (Gleason ≥8), moderately- (Gleason = 7), and well-differentiated (Gleason ≤6).

Controls (n = 805) were men without a history of symptoms associated with prostate pathology (for example dysuria, hematuria, etc.) or those who reported a prior prostate-specific antigen <4 ng/mL, matched by age (± 5 years) with the cases. These males were identified in their home, through the Mexico City master sample frame used for the National Health Surveys. Initial household was randomly selected; if more than one eligible man exists, one of them was randomly chosen. If the eligible man was not present at the visit time, 3 more attempts were made to find him. If the eligible man did not agree to participate, or an eligible man was not found, then a new address was found through a systematic clockwise search. Participation rates for cases and controls were 85.9 and 87.5%, respectively. Each eligible participant received an explanation about his participation in the study and signed an informed consent form. This study was approved by the research ethics board (CI: 980) of the National Institute of Public Health and of each participant hospital

Interviews

A direct interview using a structured questionnaire was conducted to obtain information on sociodemographic characteristics (occupation, education, marital status, and birthplace), reproductive and sex life history, as well as personal pathological and PC family history. Additionally, we asked about tobacco consumption, physical activity (PA), diet, and corporal body silhouettes for different stages of life.

Trained personnel, who did not know the specific hypothesis of the study, interviewed cases at the hospital and controls at their households. The average duration of the interview was 45 min.

Components of Metabolic Syndrome (MS-components)

The history of MS-components (arterial hypertension, hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, and obesity) was evaluated by self-report. For the obesity component, we used a modified version of the Stunkard (15) weight perception scale and asked the subject to select the figure which best identified them at ages 5,10,20,30,40, and 50 years. Based on this information, we used the K-means and K-means^{++} (16) methods to identify three different life-course weight-change trajectories (Figure 1). All trajectories show a weight increase, with inflexion points at different ages. The “minor” weight-change trajectory involves normal weight across all ages, with a weight increase during adolescence. The “consistently high weight” trajectory corresponds to subjects with a consistently high weight since childhood and a scarce weight increase in adulthood. Finally, the “increased” trajectory included subjects who had large weight increases throughout their lives, reaching overweight between ages 40 and 50.

History of Metabolic Syndrome

MS was defined using two different approaches. A positive history of MS (Figure 2) was when at least three of the following conditions were present: history of diabetes, arterial hypertension, hypercholesterolemia, hypertriglyceridemia, and life-course obesity trajectories (weight-change trajectories high-consistent” or “increased”.). The second approach was based on MS-typologies, as proposed by Pedroza-Tobias A, et al. (13). Lipidic alteration typology was characterized by a history of hypertriglyceridemia and hypercholesterolemia and history of at least another MS-component. Cholesterol typology included a history of hypercholesterolemia without hypertriglyceridemia, and

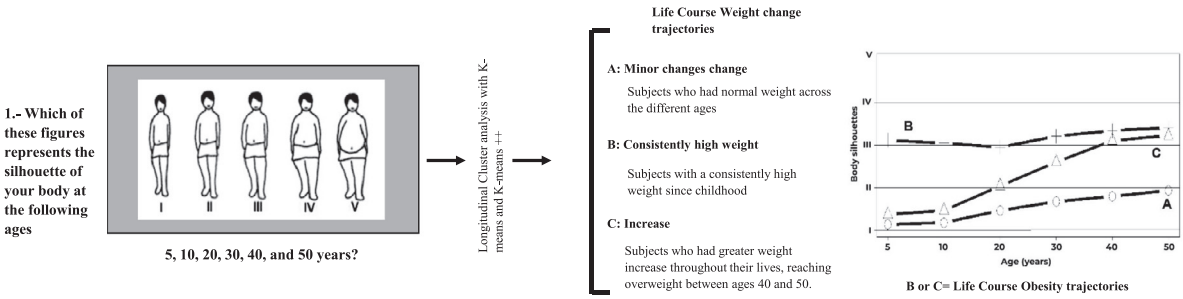

Figure 1. Identification of Life-course weight-change trajectories.

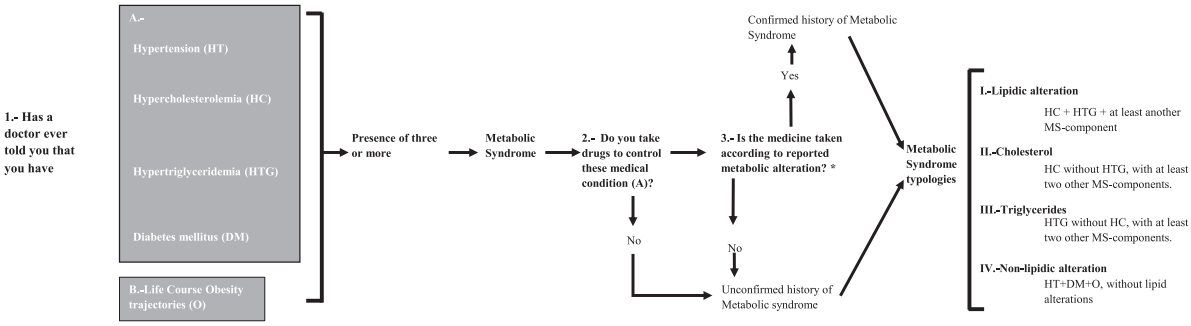

Figure 2. Definition of self-reported history of metabolic syndrome, its components, and typologies.

at least two other MS-components. Triglycerides typology, a history of hypertriglyceridemia without hypercholesterolemia, with at least two other MS-components. Finally, the non-lipidic alteration, history of diabetes, hypertension, and life-course obesity trajectories, without lipidic alterations (Figure 2). Confirmed MS-components (arterial hypertension, hypercholesterolemia, hypertriglyceridemia, and diabetes mellitus) history was considered when the reported treatment information was according to the metabolic alteration (Figure 2).

Other Covariables

History of Tobacco Consumption and Physical Activity. Tobacco consumption and leisure-time PA were also evaluated using patterns. For the former (17), pattern A included men who reported low intensity (Median: 4 cigarettes/d, duration 35 years) but constant tobacco consumption throughout their lifespan. Pattern B was found in men with initially low-intensity tobacco consumption followed by a sustained increase after 30 years old (Median: 15.5 cigarettes/d, duration 48 years).

PA evaluation was based on the frequency of moderate and vigorous leisure-time PA (3–6 or more metabolic equivalents [METs]) during three different life stages (15–18,19–29, and >30 years), as well as time invested (h/d/year). With this information, we estimated (METs/h/week/year) for each stage and three individual PA patterns were identified. Low, moderate, and high consistent PA throughout life (18). Finally, never smoker and no PA were the reference categories.

Dietary Inflammatory Index

The dietary inflammatory index was estimated from information collected using a validated semi-quantitative food frequency questionnaire that included 127 foods. The three years before diagnosis or interview were the reference for cases and controls, respectively (19). The index was adjusted for energy and categorized based on the tertiles distribution among controls; the reference category was the lowest tertile.

Due to implausible energy intake values (<800 or >4,500 calories) 8 cases and 11 controls were excluded. Additionally, we excluded one control who did not have information on body silhouette perception. The final sample included 394 cases and 793 controls.

Statistical Analysis

MS, MS-components history and other characteristics of cases and controls were compared using χ^2 or Fisher exact test.

The association with PC and histological PC-differentiation grade were estimated, using unconditional logistic regression models by each independent variable. a) History of MS; b) history of MS-typologies, and c) history of each MS-component. As potential confounders, we included age at diagnosis or interview, education, family history of first-degree PC, personal history of sexually transmitted diseases, dietary inflammatory index, leisure-time PA, and smoking history. The models corresponding to each MS-component were also adjusted by the other components. However, the arterial hypertension model was

not adjusted by hypercholesterolemia and the hypercholesterolemia/hypertriglyceridemia models were not adjusted by diabetes. The goodness of fit of the models was evaluated using a Pearson χ^2 statistical test and multicollinearity test.

Sensitivity Analysis

To evaluate the impact of a possible misclassification error derived from the self-reported MS-components, we run the final regression model with only those subjects with a confirmed history of MS–components.

The weight-change trajectories were estimated with R-studio software, version 1.2.5001. The remaining analysis was carried out using Stata 14.0 software.

Results

The average age at diagnosis for cases was like the controls' age at the time of interview (67.69 ± 8.39 vs. 66.94 ± 8.94 years; $p = 0.17$). At diagnosis, around 73% of cases were classified as moderately- (Gleason 7) or poorly differentiated (Gleason ≥8).

Compared to controls, a higher proportion of cases were born in the central-eastern region and had at least a bachelor's degree. Family history of first-degree PC, as well as personal history of sexually transmitted diseases, was significantly greater among cases. Also, controls reported greater leisure-time PA throughout their lifespan (Table 1).

Table 2 shows the association between MS, MS-typologies, and MS-components with PC. History of MS was two times greater (OR 2.15; 95% CI 1.56–2.96) among PC cases; this association remained even after adjusting by confounders (OR 1.94; 95% CI 1.37–2.75). Mainly MS-lipid alteration (OR 1.85; 95% CI 1.17–2.94) and cholesterol (OR 3.97; 95% CI 1.38–11.39) typologies were associated with greater PC odds. The MS-components mainly associated with PC were a history of arterial hypertension (OR 1.93; 95% CI 1.44–2.58), hypercholesterolemia (OR 1.69; 95% CI 1.14–2.50), and an increased weight-change trajectory throughout their lives (OR 1.67; 95% CI 1.17–2.40). Assuming an equal MS-components contribution, the PC possibilities (OR 1.37; 95% CI 1.21–1.56) increased by 37% for each increase of an MS-component (Table 2). Concerning PC-histological differentiation (Table 3), only the increased weight-change trajectory was associated with poorly differentiated PC (OR 2.79; 95% CI 1.50–5.17). History of diabetes was not associated with PC or histological PC differentiation.

The prevalence of confirmed history of MS was low (Table 4), mainly as consequence of the low confirmed history of hypercholesterolemia (3.7%), and hypertriglyceridemia (4.8%). However, the association between hypercholesterolemia history and PC remained in the same direction (OR 1.21; 95% CI 0.65–2.26) and the association with hypertension history did not change.

Discussion

In Mexico, MS seems to be a risk factor for PC; but some differences by MS-typologies could exist. Lipidic alterations and cholesterol were the main typologies associated with greater PC odds. History of arterial hypertension, hypercholesterolemia, and a weight increase since childhood and up to adulthood were the individual MS-components associated with PC. The increased weight-change trajectory was the only MS-component associated with greater odds of poorly differentiated PC at diagnosis.

It is difficult to compare our results with other studies because our MS and MS-components evaluation was retrospective and based on self-report. However, our findings are congruent with a large prospective study, with better confounding control, that shows the risk of PC increases by 20% in men with MS (5). Also, our results are comparable to a nested case-control study, where MS was associated with almost three times higher risk of PC (20).

MS-typologies are a recent proposal for Mexican population to characterize MS (13), which has not been used to evaluate the association between MS and PC. Nevertheless, in a previous study that considered a MS definition with and without hypercholesterolemia, a significant association with PC (four times greater) was only observed when hypercholesterolemia was included in the MS definition (8).

Like prior studies (7,8), we found that PC risk was 37% higher for every increase in the number of affected MS-components. Nevertheless, when four or more components were affected, we observed a small decrease, probably because of the limited number of participants under such conditions or because each MS-component likely contributes to PC risk in different ways. The main MS-components associated with PC were history of arterial hypertension (5,9–11) and hypercholesterolemia (5,7,8), both reported in previous studies.

Contrary to our results, in a meta-analysis, the authors concluded that MS is associated with a greater risk of poorly differentiated (Gleason ≥8) PC (4). High heterogeneity was observed between the studies, probably due to the diversity of designs (five retrospective studies and a prospective one), differences in the prevalence of MS-components affected, or the mixture of outcomes. At least two of the included studies evaluated the risk of biochemical recurrence and not the Gleason scale at diagnosis.

The association between weight increase over the patient's lifespan and a poorly differentiated PC is consistent with advanced PC and fatal PC risk increase, associated with obesity and abdominal obesity (21). Only one prospective study with health professionals in the United States has used body shape trajectories to evaluate the association between adiposity and advanced PC risk. Cases

Table 1. Selected characteristics of Mexican men. Prostate cancer cases and population controls.

Characteristics	Cases $n = 394$ (%)	Controls $n = 793$ (%)	*p-value*[a]
Birthplace[b]			
Mexico City	200 (51.1)	521 (65.9)	<0.001
South	30 (7.7)	53 (6.7)	
Central-western	36 (9.2)	60 (7.6)	
Central-eastern	90 (23.0)	118 (14.9)	
North	16 (4.1)	19 (2.4)	
East	19 (4.9)	20 (2.5)	
Education			
Elementary school or less	177 (44.9)	358 (45.2)	<0.001
Junior high school	66 (16.7)	199 (25.1)	
High school	70 (17.8)	143 (18.0)	
Bachelor's degree or higher	81 (20.6)	93 (11.7)	
Marital status			
United vs. Non-united	304 (77.2)	635 (80.1)	0.244
Family history of first-degree PC			
Yes vs. No	41 (10.4)	20 (2.5)	<0.001
Personal history of sexually transmitted diseases			
Yes vs. No	105 (26.7)	87 (10.9)	<0.001
Dietary inflammatory index (%)			
Low	134 (34.0)	259 (32.7)	0.879
Middle	132 (33.5)	267 (33.7)	
High	128 (32.5)	267 (33.7)	
Physical activity pattern[c]			
None	58 (14.7)	74 (9.3)	<0.001
Low	215 (54.6)	524 (66.1)	
Moderate	96 (24.4)	138 (17.4)	
High	25 (6.3)	57 (7.2)	
Smoking pattern[d]			
Never smoker	128 (32.5)	260 (32.8)	0.420
A	228 (57.9)	474 (59.8)	
B	38 (9.6)	59 (7.4)	

[a] χ^2 test;
[b] Mexico City: Only Ciudad de México; South: Campeche, Chiapas, Guerrero, Oaxaca, Quintana Roo, and Yucatán. Central-western: Aguascalientes, Colima, Guanajuato, Jalisco, and Michoacán. Central-eastern: Hidalgo; Estado de México, Morelos, Puebla, Querétaro, and Tlaxcala. North: Chihuahua, Coahuila, Durango, San Luis Potosí, Zacatecas, Baja California, Baja California Sur, Sinaloa, Sonora, Nayarit, Nuevo León, and Tamaulipas. East: Veracruz y Tabasco;
[c] Low, a consistently low physical activity throughout life; Moderate, moderated physical activity throughout life; and High, high, and consistent physical activity throughout life;
[d] Pattern A: men who reported low intensity but constant tobacco consumption throughout life. Pattern B: males with initially low intensity tobacco consumption followed by a sustained increase after 30 years old.

reported in that study as never smoker who were lean in early life and experienced a moderate increase in body shape showed only a marginally higher risk of advanced prostate cancer (22).

In addition to the chronic inflammation mechanisms involved in prostate carcinogenesis (2), other mechanisms, mainly hormonal, may explain the association between MS and PC. High cholesterol concentrations are related to high testosterone levels, increased cell proliferation, and alteration of the membrane's organization, which have been associated with increased PC risk (23). Adiposity promotes a testosterone/estrogen imbalance, which has been related to PC-aggressiveness and is also associated with high concentrations of type 1 insulin-like growth factor, which promotes the proliferation of PC cells independently from androgens (24). In addition, arterial hypertension seems to be related to increased androgenic production, a consequence of an alteration in the sympathetic system (25).

Our results must be interpreted with caution because this is a retrospective study where the MS-components history was evaluated by self-report. Since the interviewers and participants did not know the hypothesis of the study, it is unlikely that our results are a consequence of a differential measurement error. However, we do not reject the possibility of a non-differential misclassification error, particularly related to hypercholesterolemia and hypertriglyceridemia history. Compared with the medical records, the reproducibility of the self-report for both conditions are 0.36. For diabetes and arterial hypertension, reproducibility is 0.90 and 0.68, respectively (26). A similar situation could have occurred in relation to the self-reported medi-

Table 2. Association between metabolic syndrome (MS), typologies, and its components with prostate cancer (PC) in Mexican men.

Characteristics	ControlsControls	Prostate cancer		
	$n = 793$ (%)	Cases $n = 394$ (%)	OR[a] (95%CI)	OR[b] (95%CI)
Metabolic Syndrome				
Yes[c]	94 (11.9)	89 (22.6)	**2.15 (1.56–2.96)**	**1.94 (1.37–2.75)**
No	699 (88.1)	305 (77.4)	1.00	1.00
MS-Typologies[d]				
Lipidic alteration	49 (6.2)	47 (11.9)	**2.21 (1.45–3.69)**	**1.85 (1.17–2.94)**
Cholesterol	6 (0.8)	11 (2.8)	**4.14 (1.52–11.32)**	**3.97 (1.38–11.39)**
Triglycerides	7 (0.9)	5 (1.3)	1.63 (0.52–5.18)	1.74 (0.51–5.91)
Non-lipidic alteration	32 (4.0)	26 (6.6)	**1.81 (1.06–3.10)**	1.74 (0.97–3.12)
No	699 (88.1)	305 (77.4)	1.00	1.00
MS-Components (Yes vs. No)				
Hypertension	192 (24.2)	154 (39.1)	**1.98 (1.52–2.58)**	**1.93[e] (1.44–2.58)**
Hypercholesterolemia	70 (8.8)	73 (18.6)	**2.39 (1.68–3.41)**	**1.69[f] (1.14–2.50)**
Hypertriglyceridemia	76 (9.6)	61 (15.5)	**1.76 (1.23–2.53)**	1.40[f] (0.94–2.10)
Weight-change trajectories[g]				
Increased	352 (44.4)	200 (50.8)	**1.57 (1.13–2.18)**	**1.67[h] (1.17–2.40)**
Consistently high weight	254 (32.0)	127 (32.2)	1.38 (0.97–1.97)	1.39 (0.95–2.04)
Minor change	187 (23.6)	67 (17.0)	1.00	1.00
Diabetes	152 (19.2)	83 (21.1)	1.11 (0.82–1.50)	0.97[i] (0.70–1.36)
MS-Components affected				
Continuous	-	-	**1.44 (1.27–1.62)**	**1.37 (1.21–1.56)**
1	427 (53.8)	162 (41.1)	1.51 (0.94–2.4)	1.38 (0.84–2.27)
2	172 (21.7)	118 (29.9)	**2.71 (1.65–4.46)**	**2.40 (1.43–4.06)**
3	59 (7.44)	61 (15.5)	**4.08 (2.31–7.19)**	**3.42 (1.88–6.24)**
4	27 (3.4)	23 (5.8)	**3.4 (1.67–6.90)**	**2.93 (1.37–6.24)**
5	8 (1.0)	5 (1.3)	2.47 (0.74–8.21)	1.61 (0.43–5.94)

[a]Adjusted by age at interview;
[b]Adjusted by age at interview, birthplace, education, family history of first-degree PC, history of sexually transmitted diseases, energy-adjusted dietary inflammatory index, life-course physical activity and smoking patterns;
[c]History of at least three out of five MS-components;
[d]Lipidic alteration: history of hypertriglyceridemia and hypercholesterolemia with history of at least another MS-component. Cholesterol: hypercholesterolemia without hypertriglyceridemia, with at least two other MS-components. Triglycerides: hypertriglyceridemia without hypercholesterolemia, with at least two other MS-components. Non-lipidic alteration: diabetes, hypertension, and life-course obesity trajectories, without lipidic alterations;
[e]Additionally adjusted by history of diabetes, hypertriglyceridemia, and weight-change trajectories;
[f]Additionally, adjusted by antecedent of hypertension, and weight-change trajectories;
[g]Weight-change trajectories: Minor: subjects with weight increase during adolescence that maintained a normal weight. Consistently high weight: subjects with a consistently high weight since childhood. Increased: subjects who had greater weight increase throughout their lives, reaching overweight between ages 40 and 50;
[h]Additionally, adjusted by antecedent of hypercholesterolemia, hhypertriglyceridemia, and hypertension
[i]Additionally adjusted by history of hypercholesterolemia, hypertriglyceridemia, arterial hypertension, and weight-change trajectories. Text in bold denotes statistical significance.

cation. Previous report from Japan suggests among males with not high education level a good validity for regular medication of hypertension, diabetes mellitus, but not for dyslipidemias (27). This may explain why the association with hypertriglyceridemia changed direction when only subjects with coherent pharmacological treatment were analyzed. The association maintained the same direction for hypercholesterolemia, but it was not statistically significant.

Central and abdominal obesity lead to different inflammatory effects, however, we decided not to use body mass index and waist circumference as adiposity measures because both measurements could be affected by PC condition. A better temporal relationship between body composition and PC could be obtained with weight-change trajectories. These trajectories were estimated using body silhouettes, which have a sensitivity >0.80 for the detection of obesity and overweight (28). However, a longitudinal study that considered different ages (from 5–20 years) (29) indicated that the figures underestimate the corresponding body mass index, mostly for the oldest. Due to the epidemiological design used in this study, we cannot correlate body silhouettes and body mass index at early life stages, but the correlation at the time of the interview or diagnosis suggests that the underestimation was similar in cases (0.55) and controls (0.54), and the impact on the estimators would tend towards the null value.

It is worth noting that our results are unlikely to be a consequence of selection bias because the participation

Table 3. Association between metabolic syndrome (MS) and its components with histological prostate cancer (PC) differentiation in Mexican men.

Characteristics	Controls	Gleason ≤6		Gleason 7		Gleason≥8	
		Cases	OR[a] (95%CI)	Cases	OR[a] (95%CI)	Cases	OR[a] (95% CI)
	n = 793 (%)	*n* = 102		*n* = 140		*n* = 134	
Metabolic Syndrome[b]							
Yes	94 (11.9)	25 (24.5)	**2.11 (1.22–3.64)**	34 (24.3)	**2.04 (1.27–3.29)**	25 (18.7)	1.43 (0.83–2.46)
No	699 (88.1)	77 (75.5)	1.00	106 (75.7)	1.00	109 (81.3)	1.00
MS-Components (Yes vs. No)							
Hypertension[c]	192 (24.2)	38 (37.2)	**1.86 (1.13–3.04)**	65 (46.4)	**2.67 (1.77–4.04)**	46 (34.3)	**1.69 (1.07–2.66)**
Hypercholesterolemia[d]	70 (8.8)	22 (21.6)	**2.12 (1.17–3.86)**	25 (18.0)	1.54 (0.90–2.66)	21 (15.7)	1.30 (0.71–2.37)
Hypertriglyceridemia[d]	76 (9.6)	19 (18.6)	**1.84 (0.99–3.43)**	18 (12.9)	0.96 (0.53–1.76)	21 (15.7)	1.39 (0.76–2.53)
Weight-change trajectories[e]							
Increased	352 (44.4)	55 (53.9)	**1.91 (1.03–3.55)**	57 (40.7)	1.25 (0.74–2.14)	78 (58.2)	**2.79 (1.50–5.17)**
Consistently high weight	254 (32.0)	29 (28.4)	1.26 (0.65–2.46)	56 (40.0)	1.48 (0.86–2.53)	37 (27.6)	1.62 (0.84–3.15)
Minor change	187 (23.6)	18 (17.6)	1.00	27 (19.3)	1.00	19 (14.2)	1.00
Diabetes[f]	152 (19.2)	18 (17.6)	0.82 (0.46–1.52)	30 (21.4)	0.95 (0.58–1.55)	29 (21.6)	1.05 (0.63–1.79)

[a]Adjusted by age at interview, birth place, education, first-degree familiar history of PC, history of sexually transmitted diseases, energy-adjusted dietary inflammatory index, life-course physical activity and smoking patterns;
[b]At least three out of five MS components;
[c]Additionally, adjusted by history of diabetes, hypertriglyceridemia, and weight change trajectories;
[d]Additionally, adjusted by history of arterial hypertension, and weight-change trajectories;
[e]Additionally, adjusted by history of hypercholesterolemia, hypertriglyceridemia, and arterial hypertension;
[f]Additionally, adjusted by history of hypercholesterolemia, hypertriglyceridemia, arterial hypertension, and weight-change trajectories.Text in bold denotes statistical significance

Table 4. Association between confirmed history of metabolic syndrome (MS) and its components with prostate cancer (PC) in Mexican men.

Characteristics	ControlsCases	Prostate cancer		
		Cases	OR[a] 95% CI	OR[b] 95% CI
	n = 793 (%)	*n* = 394		
Metabolic Syndrome				
Yes	67 (8.4)	35 (8.9)	1.03 (0.67–21.59)	0.85 (0.54–1.38)
No	726 (91.6)	359 (91.1)	1.00	1.0
MS-Components (Yes vs. No)				
Hypertension[c]	173 (21.8)	137 (34.8)	**1.88 (1.44–2.47)**	**1.99 (1.47–2.68)**
Hypercholesterolemia[d]	29 (3.7)	23 (5.8)	1.63 (0.93–2.86)	1.21 (0.65–2.26
Hypertriglyceridemia[d]	38 (4.8)	14 (3.6)	0.73 (0.39–1.36)	**0.49** (0.25–0.96)
Weight-change trajectories[e]				
Increased	352 (44.4)	200 (50.8)	**1.57 (1.13–2.18)**	**1.63 (1.14–2.33)**
Consistently high weight	254 (32.0)	127 (32.2)	1.38 (0.97–1.97)	1.43 (0.97–2.09)
Minor change	187 (23.6)	67 (17.0)	1.00	1.00
Diabetes[f]	140 (17.6)	66 (16.7)	0.93 (0.67–1.28)	0.88 (0.62–1.26)
MS-Components affected				
Continuous	-	-	**1.29 (1.12–1.49)**	**1.27 (1.09–1.48)**
1	456 (57.5)	198 (50.2)	**1.55 (1.01–2.38)**	1.55 (0.99–2.45)
2	155 (19.5)	129 (32.7)	**2.94 (1.86–4.66)**	**3.13 (1.92–5.10)**
3	51 (6.4)	29 (7.4)	**2.00 (1.10–3.67)**	1.69 (0.88–3.25)
4	16 (2.0)	6 (1.5)	1.64 (0.58–4.66)	1.50 (0.49–4.59)

[a]Adjusted by age at interview;
[b]Adjusted by age at interview, birthplace, education, first-degree familiar history of PC, history of sexually transmitted diseases, energy-adjusted dietary inflammatory index, life-course physical activity, and smoking patterns;
[c]Additionally, adjusted by history of diabetes, hypertriglyceridemia, and weight-change trajectories;
[d]Additionally, adjusted by history of arterial hypertension, and weight-change trajectories;
[e]Additionally, adjusted by history of hypercholesterolemia, hypertriglyceridemia, and arterial hypertension;
[f]Additionally, adjusted by history of hypercholesterolemia, hypertriglyceridemia, arterial hypertension, and weight-change trajectories. Text in bold denotes statistical significance.

rates for cases and controls were high. In Mexico, there is not a national cancer registry that would allow to ensure the representativeness of our cases. However, the frequency of cases with Gleason ≥7 in our study is like that reported in the available limited reports (30). Regarding the controls' representativeness, it is difficult to compare our MS prevalence. As far as we know, there is none previous study that used self-report MS components for identifying MS history. Nevertheless, the prevalence of diagnosed diabetes mellitus (22.9 vs. 19.2%) and hypertension (27.9 vs. 24.2%) in our controls were like that observed in the National Health Survey 2012 for Mexico City male residents between 43 and 94 years old (31). Likewise, our prevalence of the MS-typology without lipid alterations in our controls was the same as that reported previously (4.1 vs. 4.0%) (13).

Finally, we do not rule out the possibility of residual confounding. Alcohol consumption has been associated with higher PC (32), but we did not have information on it. Another limitation was imposed by our sample size, which did not permit us to evaluate whether MS-typologies are differentially associated with histological PC differentiation.

Despite the retrospective nature of this first study with Mexican men, our results reaffirm the potential association between of MS and PC. MS is a heterogeneous condition and prospective studies using MS-typologies would be recommendable to test this hypothesis. According to the MS prevalence among our controls and that reported previously, (13) between 11 and 33% of PC cases in Mexico City could be attributed to MS. MS is a risk factor for other chronic degenerative diseases and susceptible to primary prevention. In addition, men diagnosed with MS could be subjected to PC early detection strategies.

Conflict of Interest

The authors declare that they do not have competing interests.

Acknowledgements

We are thankful to all participants and hospitals: Hospital General de México, Instituto Nacional de Cancerología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Hospital de Oncología del Centro Médico Siglo XXI, Hospital General Regional No.1 "Dr. Carlos McGregor Sánchez Navarro", and Hospital Regional "Adolfo López Mateos", for their collaboration in the development of this study. This study was supported by the National Council of Science and Technology of Mexico (CONACYT) under funding numbers 140482 and 272810. Additionally, JGHP received a scholarship from CONACYT (Grant number: 711947). The funding source had no role in the study design, collection, analysis, and interpretation of data, as well as in the writing of the report, and in the decision to submit the article for publication.

References

1. Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech 2009;2:231–237.
2. Monteiro R, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. Mediators Inflamm 2010;2010:289645.
3. Uzunlulu M, Telci Caklili O, Oguz A. Association between Metabolic Syndrome and Cancer. Ann Nutr Metab 2016;68:173–179.
4. Gacci M, Russo GI, De Nunzio C, et al. Meta-analysis of metabolic syndrome and prostate cancer. Prostate Cancer Prostatic Dis 2017;20:146–155.
5. Kim JW, Ahn ST, Oh MM, et al. Incidence of Prostate Cancer according to Metabolic Health Status: a Nationwide Cohort Study. J Korean Med Sci 2019;34:e49–e59.
6. Yoo S, Oh S, Park J, et al. Effects of metabolic syndrome on the prevalence of prostate cancer: historical cohort study using the national health insurance service database. J Cancer Res Clin Oncol 2019;145:775–780.
7. Zhang JQ, Geng H, Ma M, et al. Metabolic Syndrome Components are Associated with Increased Prostate Cancer Risk. Med Sci Monit 2015;21:2387–2396.
8. Pelucchi C, Serraino D, Negri E, et al. The metabolic syndrome and risk of prostate cancer in Italy. Ann Epidemiol 2011;21:835–841.
9. Beebe-Dimmer JL, Dunn RL, Sarma AV, et al. Features of the metabolic syndrome and prostate cancer in African-American men. Cancer 2007;109:875–881.
10. Wallner LP, Morgenstern H, McGree ME, et al. The effects of metabolic conditions on prostate cancer incidence over 15 years of follow-up: results from the Olmsted County Study. BJU Int 2011;107:929–935.
11. Grundmark B, Garmo H, Loda M, et al. The metabolic syndrome and the risk of prostate cancer under competing risks of death from other causes. Cancer Epidemiol Biomarkers Prev 2010;19:2088–2096.
12. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2018;144:1941–1953.
13. Pedroza-Tobias A, Trejo-Valdivia B, Sanchez-Romero LM, et al. Classification of metabolic syndrome according to lipid alterations: analysis from the Mexican National Health and Nutrition Survey 2006. BMC Public Health 2014;14:1056.
14. Vázquez-Salas RA, Torres-Sánchez L, López-Carrillo L, et al. History of gonorrhea and prostate cancer in a population-based case-control study in Mexico. Cancer Epidemiol 2016;40:95–101.
15. Stunkard AJ, Sørensen T, Schulsinger F. Use of the Danish Adoption Register for the study of obesity and thinness. Res Publ Assoc Res Nerv Ment Dis 1983;60:115–120.
16. Genolini C, Alacoque X, Sentenac M, et al. kml and kml3d : R Packages to Cluster Longitudinal Data. J Stat Softw 2015;65:1–34.
17. Jiménez-Mendoza E, Vázquez-Salas RA, Barrientos-Gutierrez T, et al. Smoking and prostate cancer: a life course analysis. BMC Cancer 2018;18:160.
18. Vázquez-Salas RA, Torres-Sánchez L, Galván-Portillo M, et al. Association between life-course leisure-time physical activity and prostate cancer. Salud Publica Mex 2022;64:169–178.
19. Vázquez-Salas RA, Shivappa N, Galván-Portillo M, et al. Dietary inflammatory index and prostate cancer risk in a case-control study in Mexico. Br J Nutr 2016;116:1945–1953.
20. Tuohimaa P, Tenkanen L, Syvälä H, et al. Interaction of factors related to the metabolic syndrome and vitamin D on risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2007;16:302–307.

21. Perez-Cornago A, Appleby PN, Pischon T, et al. Tall height and obesity are associated with an increased risk of aggressive prostate cancer: results from the EPIC cohort study. BMC Med 2017;15:115.
22. Song M, Willett WC, Hu FB, et al. Trajectory of body shape across the lifespan and cancer risk. Int J Cancer 2016;138:2383–2395.
23. Pelton K, Freeman MR, Solomon KR. Cholesterol and prostate cancer. Curr Opin Pharmacol 2012;12:751–759.
24. Freedland SJ, Platz EA. Obesity and Prostate Cancer: Making Sense out of Apparently Conflicting Data. Epidemiol Rev 2007;29:88–97.
25. Gann PH, Daviglus ML, Dyer AR, et al. Heart rate and prostate cancer mortality: results of a prospective analysis. Cancer Epidemiol Biomarkers Prev 1995;4:611–616.
26. Ye F, Moon DH, Carpenter WR, et al. Comparison of Patient Report and Medical Records of Comorbidities. JAMA Oncol 2017;3:1035–1042.
27. Matsumoto M, Harada S, Iida M, et al. Validity Assessment of Self-reported Medication Use for Hypertension, Diabetes, and Dyslipidemia in a Pharmacoepidemiologic Study by Comparison With Health Insurance Claims. J Epidemiol 2021;31:495–502.
28. Kaufer-Horwitz M, Martínez J, Goti-Rodríguez LM, et al. Association between measured BMI and self-perceived body size in Mexican adults. Ann Hum Biol 2006;33:536–545.
29. Must A, Willett WC, Dietz WH. Remote recall of childhood height, weight, and body build by elderly subjects. Am J Epidemiol 1993;138:56–64.
30. Cayetano-Alcaraz AA, Ramírez-Rivera JA, Sotomayor de Zavaleta M, et al. Características de los casos incidentes de cáncer de próstata en los últimos 5 años en un hospital de tercer nivel en México. Rev Mex Urol 2016;76:76–80.
31. Gutiérrez JP, Rivera-Dommarco J, Shamah-Levy T, et al. Encuesta Nacional de Salud y Nutrición 2012. Resultados nacionales. 2a ed. Cuernavaca: Instituto Nacional de Salud Pública (MX); 2012.
32. Zhao J, Stockwell T, Roemer A, et al. Is alcohol consumption a risk factor for prostate cancer? A systematic review and meta-analysis. BMC Cancer 2016;16:845.