

ARTICULO DE INVESTIGACIÓN

FACTORES DE RIESGO CARDIOVASCULAR EN PACIENTES CON CÁNCER DE PRÓSTATA DE UNA UNIDAD DE CARDIO-ONCOLOGÍA

CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH PROSTATE CANCER OF A CARDIO-ONCOLOGY UNIT

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RESUMEN:

Antecedentes: La enfermedad cardiovascular es la principal causa de mortalidad en cáncer de próstata (CaP). El diagnóstico y manejo de factores de riesgo (FR) en estos pacientes representa una oportunidad para optimizar la supervivencia. **Objetivo:** evaluar la presencia de FR cardiovascular en CaP con y sin metástasis ósea de una Unidad de Cardio-Oncología. **Método:** estudio observacional, descriptivo de FR como peso, hipertensión arterial (HAS), diabetes, tabaquismo y dislipidemia. **Resultados:** se analizaron 420 pacientes con CaP, 74 metastásicos. La edad promedio fue 70 años. El sobrepeso (44,3%) fue el FR más frecuente, seguido de HAS (34,5%), dislipidemia (19,8%), tabaquismo (16%) y diabetes (9,5%). La HAS y la diabetes tuvieron mayor frecuencia en CaP y metástasis ósea en comparación con los no metastásicos. Hubo diferencia significativa entre tabaquismo y dislipidemia, los metastásicos fuman menos, pero tienen mayor hipercolesterolemia. La presencia de 3 o más

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FR predominó en metastásicos (31,1%) vs no metastásicos (15,9%) con diferencia significativa ($p < 0,001$). **Conclusión:** Los sujetos con CaP al momento del diagnóstico tienen con mayor frecuencia sobrepeso e HAS. Los pacientes con CaP y metástasis ósea tienen tres o más FR en comparación con los no metastásicos. La población de riesgo debe continuar control cardiovascular en una unidad de Cardio-Oncología.

PALABRAS CLAVE: Hipertensión Arterial, Obesidad, Tabaquismo, Cáncer de Próstata.

ABSTRACT:

Background: Cardiovascular disease has become the main cause of mortality in prostate cancer. Diagnosing and management of risk factors in these patients represent an opportunity to optimize survival outcomes. **Objective:** to evaluate the presence of cardiovascular risk factors in prostate cancer with and without bone metastasis from a Cardio-Oncology Unit. **Method:** observational, descriptive study on weight, hypertension, diabetes, smoking, and dyslipidemia. **Results:** 420 patients with prostate cancer were analyzed, and seventy-four had bone metastasis. The average age was 70 years. The most frequent risk factor was overweight (44.3%), hypertension (34.5%); diabetes 9.5%, smoking (16%) and Dyslipidemia (19.8%). Hypertension and diabetes were the most common in prostate cancer and bone metastasis compared with non-metastatic. A significant association was found between smoking and dyslipidemia; patients with metastasis smoke less but have greater hypercholesterolemia. The presence of three or more risk factors predominated in metastatic patients (31.1%) than in non-metastatic (15.9%) with a significant difference ($p < 0.001$). **Conclusion:** Subjects with prostate cancer at the time of diagnosis are more frequently overweight and have hypertension. Patients with prostate cancer and bone metastasis more regularly have three or more factors compared with non-metastatic. The at-risk population should continue cardiovascular control in a Cardio-Oncology unit.

KEYWORDS: Hypertension, Obesity, Smoking, Prostate Cancer.

INTRODUCTION

After cardiovascular diseases (CVD), cancer is the second leading cause of death worldwide (9.6 million), and in men, prostate cancer (PCa) is the second most frequent, according to GLOBOCAN in 2018, 1,276,106 new cases were reported, of which 358,989 died (3.8% of all cancer deaths), 66% of these deaths being in people over 65 years of age (1). Since the 1990s, cancer survival worldwide has increased considerably. In the United States, during the 1970s only 68% of patients with PCa survived and currently more than 90% survive 15 years, thanks to early diagnosis and new therapeutic alternatives (2). Various studies such as that of Zaorsky showed that survivors have a higher incidence of cardiovascular events, with CVD being the second cause of death in PCa (3).

Death from CVD in patients with PCa occurs basically because these patients at the time of oncological diagnosis already have cardiovascular risk factors (CVRF) or are carriers of heart disease, as observed in the study by Liu, where 24.61% were hypertensive, 11.49% diabetic, 5.89% had ischemic coronary artery disease (ICD) and 1.99% were dyslipidemic (4); these patients prioritize the disease and oncological treatment, frequently abandoning cardiological

controls and treatments. The second reason is that hormone therapy for PCa relies on androgen deprivation therapy (ADT), which favors the development of metabolic syndrome, heart failure and ICD, especially in patients with CVRF (5).

CVDs are caused by RFs, and failure to detect them early can lead to a poor prognosis for patients and even death. Multiple clinical studies have shown that in patients with PCa, CVRFs are underestimated and undertreated. In the Lova Sun study of 90,494 patients with PCa, only 68.1% received a comprehensive evaluation for CVRF and 54.1% had uncontrolled CVRF; of these, 29.6% did not receive risk-reducing medication (6).

The present study aims to determine and analyze the presence of the main CVRF (obesity, SAH, diabetes, smoking and dyslipidemia) in subjects with PCa with and without bone metastasis.

MATERIALS AND METHODS

Retrospective study of patients with PCa, who attended the Cardio-Oncology Unit of our institution due to surgical risk during the period between 2019 and 2020. Data were collected on age, body mass index, blood pressure, diabetes, tobacco use and elevated cholesterol, in patients with

PCa with and without metastasis. Weight parameters according to the World Health Organization (WHO) (7), were used, the 2017 American College of Cardiology / American Heart Association guidelines for blood pressure classification (8), a fasting blood glucose equal to or greater than 126 mg/dL was a diagnostic criterion for type 2 diabetes mellitus and dyslipidemia when total cholesterol was greater than 200 mg/dL.

Statistical analysis: A descriptive analysis was performed using frequencies and percentages; the results are shown in frequency tables and contingency tables. Possible associations between qualitative variables were assessed using the Chi-square test, applying Yates' correction or Fisher's exact test when appropriate, or grouping categories to meet the test's assumptions. A p-value <0.05 was considered statistically significant. The statistical software R was used.

RESULTS

A total of 420 patients diagnosed with PCa were analyzed. The average age was 70 years, with the highest percentage being in the 70-79 age group (40%) (Table 1).

Overweight was the most common CVRF, accounting for 44.3% of cases, while obesity was third. The second

most common CVRF was SAH (34.5%), diabetes was found in 9.5% of cases, 16.0% were smokers, and 19.8% had dyslipidemia.

In the PCa group, 74 patients had metastases (Table 2). No significant differences were found between PCa cases with and without metastases by age. Overweight predominated in both patients with and without metastases, followed by obesity. Regarding SAH, the group of patients with PCa and metastases had a higher percentage of hypertension (40.5%) than the group without metastases (33.2%), although this was not statistically significant. Regarding diabetes, there was no significant difference between the two groups. A significant association was observed between smoking and dyslipidemia; patients with metastases smoked less and had higher dyslipidemia.

Table 3 shows that patients with PCa and bone metastasis had 3 or more risk factors more frequently than the group without metastasis, with a significant difference.

DISCUSSION

Chronic diseases such as CVD and cancer generate high treatment costs, so prevention is the best tool for their control and eradication. These two clinical entities have several RFs in common, so if we want to address

these diseases and reduce their morbidity and mortality, it is first necessary to understand the prevalence of these factors (9, 10).

PCa is the most prevalent cancer in more than half of the world's countries and the most common in Latin America. However, the mortality rate from PCa has decreased considerably, so this indicator reflects progress in the fight against this cancer. Between 1950 and 1970, PCa mortality was stable, and during the 1990s, these figures decreased significantly (37%). This led to an epidemiological shift, with PCa patients dying from cardiovascular disease. The European Association of Urology guidelines report that cardiovascular mortality now surpasses PCa as the most common cause of death in these patients. Therefore, the importance of this study is to understand the frequency of CVRFs in patients with PCa and to address these risks to reduce mortality.

The results of this study are consistent with other reports. The older the patient, the greater the risk of PCa. In patients over 65 years of age, the prevalence of PCa was 66% (11). In this observational study, three-quarters of the patients were in the 60 to 79 age group, and then gradually declined. The fact that this is an older population with unfavorable lifestyles

meant that at the time of PCa diagnosis, the patient already had CVD or was a carrier of one or more CVRFs.

The prevalence of overweight/obesity worldwide has increased in recent decades. According to the WHO, in 2016 there were more than 1.9 billion overweight subjects (39%) and more than 650 million with obesity (13%) (12); in the Americas, 58% of its inhabitants are overweight/obese (360 million) (13); in the Peruvian population it is also a frequent clinical condition, and in the present study, overweight is the first CVRF; however, it is important to highlight that it is a preventable and avoidable factor.

Obesity is a condition that promotes the development of various diseases such as diabetes, SAH, ischemic heart disease, but it is also related to cancer (after tobacco, obesity is the most frequent risk factor for solid tumors), multiple studies have demonstrated the connection between obesity and breast neoplasms, colon, pancreas, among others. The mechanisms are given by hyperinsulinemia, adiponectins, interleukins, tumor necrosis factor, which produce a chronic inflammatory state and free radicals, among others. Regarding PCa, an association with obesity has been observed both in aggressiveness, and progression as well as in mortality (14). In our study it

can be observed that PCa predominated in subjects with overweight and mild obesity, which agrees with other researchers, where although it is a frequent variable in Latin America, its mentioned metabolic effects establish a causality.

SAH is a clinical condition and a very frequent CVRF worldwide (35%) that increases with age and in various clinical trials it has been reported that it is one of the most common comorbidities in patients with cancer (37%). SAH is a public health problem given its high prevalence worldwide; in 1980 there were around 691 million hypertensive patients, in 2012 it reached one billion and it is expected that in 2030 there will be 1.5 billion hypertensive patients if preventive health measures are not taken (15). Various meta-analyses establish an increased risk of kidney cancer in SAH, while other relationships remain to be established, such as colon cancer, melanoma or prostate cancer (16).

The prevalence of SAH in Peru according to the Tornasol II study is 27.3% (17), however, in the present study it is 34.5%, taking into account that our population is older. If patients with metastatic disease are evaluated compared to non-metastatic patients, the difference is greater, but does not reach a significant value, probably due to the sample size of our study. The tendency would be that the disease is

greater, the hypertension is greater; our results are in agreement with some observations of Pai or Tulinius, however, others deny it. In the study by Häggström, it was shown that there was no relationship between SAH and PCa, but it was established that there was an increased risk of death (18).

Several researchers such as Wallner (19) have reported that hypertensive men are 1.5 times more likely to develop PCa than non-hypertensive men, the pathophysiology of SAH is very broad and complex (20), in the case of PCa androgens, which have a role in the genesis of this type of cancer, increase the reabsorption of sodium and water through the Renin Angiotensin Aldosterone system, producing SAH. In mice treated with Angiotensin II receptor blockers a reduction in prostate tumor volume was observed, while the administration of angiotensin II increases the viability of prostate tumor cells (21). These observations have not yet been validated.

Regarding diabetes mellitus, in 1932 Wilson et al. described that patients with diabetes developed cancer more frequently; this observation was corroborated by other researchers; however, a causal relationship and pathophysiological mechanisms have not been established, although both hyperinsulinemia and insulin resistance play a fundamental role in

these two diseases, even more so after it was discovered that tumor cells have insulin receptors. The presence of diabetes in our study was within the average prevalence of this metabolic disease.

In smoking, the results of clinical studies are inconclusive and very modest, however, it is known that tobacco is one of the main preventable CVRF in cancer, including PCa, which is a hormone-dependent tumor, and the effect of tobacco on sexual hormone bioavailability is established. Both estradiol and testosterone participate in the growth of prostate tumors (22). Our results show that the number of smokers is lower than the prevalence of the Peruvian population in general, this may be because with age the tendency is to quit smoking; when smoking is compared between patients with and without metastases, a significant difference was found, due to a higher percentage of smokers in the group without metastases than in the group with metastases (17.9% versus 6.8%, respectively) (23).

A relationship between dyslipidemia and PCa has not yet been established. Several publications, such as the Health Professionals Follow-up Study and Prostate Cancer Prevention Trial, the Alpha Tocopherol Beta Carotene Cancer Prevention Study, and the REDUCE Study, have shown that higher total cholesterol levels increase the risk of advanced PCa. A first

mechanism is that androgens are derived from cholesterol, and that alterations in lipid metabolism influence androgen levels. Likewise, the use of statins for hypercholesterolemia has been analyzed in several clinical studies and is believed to be associated with a reduced risk of some types of cancer, such as prostate cancer (2). In our study, hypercholesterolemia occurred in one in five subjects.

Androgen deprivation therapy (ADT) for PCa is the primary therapeutic regimen and has been shown to reduce mortality, but it is associated with metabolic adverse effects that increase the risk of fatal and non-fatal cardiovascular events. ADT causes sarcopenic obesity, increases insulin resistance and diabetes, and SAH, and also promotes lipid metabolism disorders. All of this contributes to metabolic syndrome, which can lead to sudden death, fatal and non-fatal myocardial infarction, and stroke, among others.

Therefore, failure to recognize or treat CVRF in patients with PCa may represent a major clinical failure that jeopardizes the survival of these patients.

CONCLUSION

Patients with PCa at diagnosis have CVRF, with overweight being the most common, followed by SAH; Patients

with PCa and bone metastasis more frequently have three or more factors compared with non-metastatic patients.

It is recommended that educational interventions on CVRF be carried out in these patients through Cardio-Oncology Units with the aim of reducing their mortality.

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Table 1. Distribution of risk factors according to characteristics

	NM Prostate (%)
	N=420
Age, years	
Average (min-max)	70 (46-91)
Age groups	
<60	46 (11)
60-69	149 (35.5)
70-79	168 (40)
80-89	56 (13.3)
≥90	1 (0.2)

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Weight: BMI	
Normal	108 (25.7)
Overweight	186 (44.3)
Mild Obesity	107 (25.5)
Moderate Obesity	16 (3.8)
Severe Obesity	3 (0.7)
Hypertensive	
Yes	145 (34.5)
No	275 (65.5)
Diabetes	
Yes	40 (9.5)
No	380 (90.5)
Smoking	
Yes	67 (16.0)
No	353 (84.0)
Dyslipidemia	
Yes	83 (19.8)
No	337 (80.2)

Table 2. Risk Factors according to metastasis

	With metastasis (%) N=74	Without metastasis (%) N=346	p
Age, years			
Average (min-max)	69.7 (51-91)	70.1 (46-89)	0.754
Age groups			
<60	10 (13.5)	36 (10.4)	
60-69	23 (31.1)	126 (36.4)	
70-79	30 (40.5)	138 (39.9)	
80-89	10 (13.5)	46 (13.3)	

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≥90	1 (1.4)	0 (0.0)	0.222
BMI			
Normal	10 (13.5)	98 (28.3)	0.029
Overweight	39 (52.5)	147 (42.5)	
Obesity	25 (33.8)	101 (29.2)	
Hypertensive			
Yes	30 (40.5)	115 (33.2)	0.287
No	44 (59.5)	231 (66.8)	
Diabetes			
Yes	9 (12.2)	31 (9.0)	0.526
No	65 (87.8)	315 (91.0)	
Smoking			
Yes	5 (6.8)	62 (17.9)	0.027
No	69 (93.2)	284 (82.1)	
Dyslipidemia			
Yes	25 (33.8)	58 (16.8)	0.001
No	49 (66.2)	288 (83.2%)	

Table 3. Distribution of patients by number of risk factors according to metastasis.

	Metastasis (%)		p
	Yeah N=74	No N=346	
No. of factors			
None	16 (21.6)	51 (14.7)	ns
1	13 (17.6)	131 (37.9)	ns
2	22 (29.7)	109 (31.5)	ns
3 or more	23 (31.1)	55 (15.9)	<0.001

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