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RESEARCH ARTICLE

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Serum lipids and prostate cancer

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Abstract

Background: Conflicting results are found in the literature relating serum lipids levels and prostate cancer. Some results imply a relationship between them; others contradict this association. The purpose of this study was to investigate a possible association between serum lipids levels and prostate cancer, at time of diagnosis.

Methods: We measured serum levels of total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides in 237 patients submitted to a prostate biopsy, with PSA between 2 and 10 ng/ml. Patients without cancer at biopsy were used as controls, and the others were considered as cases. No information about lipid-lowering therapy, including statins, was available neither in cases nor in controls. Cases were divided into risk groups, according to the disease severity, based on staging. Lipids levels were compared between groups, using parametric and nonparametric tests. Logistic regression analysis and odds ratios were calculated.

Results: LDL cholesterol and total cholesterol levels were lower in patients with cancer, with the difference being statistically significant for LDL cholesterol (p = 0.010) and borderline for total cholesterol (p = 0.050). No significant differences were found between the several risk groups. Odds ratios for low LDL cholesterol (<130 mg/dl) and low total cholesterol (<200 mg/dl), with prostate cancer as the outcome, were 1.983 and 1.703, respectively. There were no significant differences between cases and controls for the other lipids.

Conclusion: Lower LDL cholesterol (<130 mg/dl) and lower total cholesterol (<200 mg/dl) serum levels seem to associate with prostate cancer, at time of diagnosis.

KEYWORDS
LDL cholesterol, prostate cancer, serum lipids, total cholesterol

1 | INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men, with an estimated incidence of 1.3 million cases per year, worldwide.[1] Despite being responsible for approximately 1 in 5 diagnoses of cancer in men, there is a substantial global variation, with the odds of developing PCa being almost six times higher in developed countries, pointing to the existence of environmental or lifestyle factors.[2] With the globalization of the western lifestyle, including the adoption of diets rich in saturated fat, countries that traditionally had the lowest PCa risk have witnessed an increase in its incidence.[3] In fact, these types of diets have already been associated with an increased risk of advanced PCa,[4] and obesity was associated with a higher risk of aggressive PCa.[5]

Cholesterol makes up about one-third of the lipid content of the plasma membrane. Within the lipid bilayer, cholesterol-enriched membrane microdomains, referred as lipid rafts, modulate cell signaling.[6] Increasing evidence points to a possible role of cholesterol in PCa development, aggressiveness, and progression, through effects on inflammation and steroidogenesis.[7,8] Cholesterol was also shown to correlate with prostate-specific antigen (PSA) levels.[9] It is also thought to act as a substrate for intra-tumoral androgen biosynthesis in all stages of disease, even in metastatic castration-resistant PCa (mCRPC).[10] Adding to this evidence, an in vivo xenograft model showed an increased risk of tumor development and enhanced tumor growth in mice fed with a high content cholesterol diet,[11] while in vitro cancer progression models identified abnormalities in regulators of cholesterol metabolism.[12,13] Targeting cholesterol, through the use of statins, was also reported to decrease the risk of PCa diagnosis,[14] advanced disease, and PCa mortality.[15]

Several studies showed that higher serum total cholesterol (TC) levels were associated with increased PCa risk and high-grade disease.[16–19] However, there are conflicting findings among different studies, since an association between low TC levels and an increased risk of PCa has also been observed.[20] Some studies also reported that elevated serum levels of low-density lipoprotein-cholesterol (LDL-C) correlated with a higher risk of PCa.[14,21] An association has also been observed between nonaggressive disease, lower risk of overall PCa, and elevated serum high-density lipoprotein-cholesterol (HDL-C) levels.[21,22] Increased triglyceride (TG) serum levels have also been associated with PCa.[23]

However, the results from the published literature have been inconsistent or conflicting when analyzing associations between serum lipids levels and PCa. A recent meta-analysis, based on several prospective studies, found no association between serum levels of TC, HDL-C, or LDL-C and risk of PCa or high-grade PCa.[24] These findings call for further research to assess possible associations between serum lipids levels and PCa. Therefore, the present study aims to investigate possible associations between PCa and serum levels of TC, LDL-C, HDL-C, and TG, at time of diagnosis.

2 | MATERIAL AND METHODS

This is an observational study with patients that had a prostate biopsy scheduled for suspicion of PCa, recruited from the Urology Department of the Central Lisbon University Hospital Center (Lisbon, Portugal). This study was approved by the Research Ethics Committee of the Central Lisbon University Hospital Center (ethical approving number 360/2016), conducted in adherence to the Declaration of Helsinki, and all patients gave written informed consent.

2.1 | Subjects

Patients were included from December 2017 to October 2019. All had a total PSA between 2 and 10 ng/ml (Beckman Coulter Hybritech®) and were submitted to a prostate biopsy with at least 12 cores, for clinical suspicion of PCa. We have chosen this range of PSA levels, because it corresponds to the so called diagnostic gray zone, where most of the challenges to PCa diagnosis exist, and therefore greater effort to identify associations between PCa and other laboratory findings is needed. Exclusion criteria were a previous history of PCa and several factors that could affect the PSA concentration, namely transurethral resection of the prostate, therapeutic with 5-α-reductase inhibitors and androgens, urinary tract infection, and acute bacterial prostatitis.

Blood collection and the serum lipids level measurements were done on the same day of the prostate biopsy. All biopsies were examined by the same pathologist, and the results were given with the updated Gleason grading according to the definitions of the 2014 consensus conference of the International Society of Urological Pathology.[25] Patients with high-grade intraepithelial neoplasia or atypical small acinar proliferation were considered as not having PCa. All patients with PCa were followed up until their disease was staged according to the American Joint Committee on Cancer (AJCC).[26] In a subset of 30 patients that were submitted to a radical prostatectomy, we considered the more accurate Gleason score from the surgery, instead of the score obtained at biopsy. The control group consisted of all patients without PCa at biopsy.

No information about lipid-lowering therapy, neither in PCa patients nor in controls, and particularly concerning treatment with statins, was available.

2.2 | Methods

Venous blood sampling was performed after 12 h of overnight fasting. To obtain serum samples, blood was collected in a S-Monovette® (Sarstedt AG & Co. KG, Germany) with a silicate clotting activator and polyacrylic gel. After blood collection, the samples were allowed to clot (for 30 min at room temperature) and were then centrifuged (1,500 *g*; 10 min). Within a maximum of 4 h after blood collection, lipids levels were measured using the automated Architect c16000 Clinical Chemistry Analyzer (Abbott Laboratories, Illinois, USA). Levels of TC (Ref. 7D62-21), HDL-C (Ref. 3 K33), LDL-C (Ref. 1E31-20), and TG (Ref. 7D74) were measured using an enzymatic spectrophotometric method.

2.3 | Statistical analysis

Results were expressed as mean ± SD, for variables with a normal distribution, and as median and interquartile range (IQR) for variables not normally distributed. ANOVA, Kruskal-Wallis, Student's *t* or Mann-Whitney tests were applied to identify differences between serum lipids levels in several groups of patients, depending on the normality of the variable being analyzed. Univariate binary logistic regression analysis was applied to assess possible associations between all serum lipids and PCa. Two values of TG serum levels above

500 mg/dl were considered as outliers and were removed from the statistical analysis, when evaluating TG. Odds ratio (OR) was calculated for LDL-C values under 130 mg/dl, considering LDL-C as a qualitative binary variable (LDL-C < 130 mg/dl vs. LDL-C ≥ 130 mg/dl) and PCa as the outcome. We also calculated the OR for TC as a qualitative variable (TC <200 mg/dl vs. TC ≥200 mg/dl). These cut-off values for LDL-C and TC were defined according to the Adult Treatment Panel III (ATP III) report of the National Cholesterol Education Program guidelines.[27] *p*-values <0.05 were considered as statistically significant. All statistical analyses were carried out using SPSS® Statistics, version 26 (IBM®, New York, USA).

3 | RESULTS

We evaluated 237 male patients submitted to a prostate biopsy, who fulfilled the inclusion criteria, of which 98.7% (*n* = 234) were Caucasians. Overall, patients presented a median age of 68 (IQR = 62–73) years. From all the patients enrolled, 50.2% (*n* = 119) did not have cancer (controls) and 49.8% (*n* = 118) were diagnosed with PCa (cases). The median age of controls was of 66 (IQR = 61–71) years, and cases had a median age of 69 (IQR = 63–73) years. Based on the AJCC staging system, patients with PCa were divided into 3 risk groups, according to the severity of the disease: 23.7% (*n* = 28) were classified as having low-risk disease (stages I and IIA), 52.5% (*n* = 62) high-risk disease (stages IIB and IIC), and 23.7% (*n* = 28) very high-risk disease (stages IIIB, IIIC, IVA, and IVB).

We first compared the serum lipids levels between four groups of patients: without cancer and each of the three risk groups of the disease (Table 1). When looking at TC and LDL-C, higher levels were observed in patients without cancer, but no significant difference was found when comparing all groups ($p = 0.272$ for TC and $p = 0.068$ for LDL-C). Likewise, no significant differences were found across all groups, when comparing levels of serum HDL-C ($p = 0.750$) and TG ($p = 0.696$). Considering the total Gleason score (GS), we also compared the lipids values between patients with GS<7 and GS≥7, but we found no significant differences in any of the lipids ($p = 0.578$ for TC; $p = 0.776$ for LDL-C; $p = 0.965$ for HDL-C; $p = 0.301$ for TG).

Through univariate binary logistic regression analysis (Table 2), where we analyzed each lipid as a quantitative continuous variable, TC, HDL-C, and TG were not found to be predictors of overall risk of cancer. On the other hand, LDL-C was a predictor of risk of cancer, with increasing levels being associated with lower odds of cancer ($p = 0.011$).

Next, we compared the serum lipids levels between participants without (controls) and with PCa (cases), irrespective of the severity of the disease (Table 3). There were no significant differences in HDL-C or TG levels between cases and controls. Only in relation to LDL-C levels (Figure 1), we found a significant difference ($p = 0.010$) between patients without (mean =126.8 mg/dl) and with (mean = 114.9 mg/dl) PCa, although we have not found significant differences in LDL-C levels between the several risk groups (Table 1). TC serum levels (Figure 2) were also lower in PCa patients (mean = 187.5 mg/dl) than in patients without cancer (mean = 197.5 mg/dl), reaching borderline statistical significance ($p = 0.050$).

Considering these results, we calculated the OR for low TC (<200 mg/dl) and low LDL-C (<130 mg/dl), considering PCa as the outcome (Table 4).

Low TC levels (<200 mg/dl) were associated with a higher risk of overall PCa (OR = 1.703; 95% CI 1.016–2.852; $p = 0.043$). A similar association was found between low serum LDL-C levels (<130 mg/dl) and a higher risk of overall PCa (OR = 1.983; 95% CI 1.174–3.348; $p = 0.010$).

4 | DISCUSSION

Our results show that, at the time of diagnosis, patients with PCa have lower LDL-C and lower TC levels, than those without cancer. The difference is more significant for LDL-C, and these findings are corroborated by the OR calculation results. However, when comparing serum lipids levels between different risk groups of cancer patients, the differences are not significant for any of the lipids measured.

Despite most of the previous studies finding little or no evidence for an association between LDL-C and PCa risk, in a study that included 2,161 men, an association was found between elevated LDL-C levels, in men who were not statin users, and increased risk of overall PCa and aggressiveness, but these results were nonsignificant after including statin users.[21] In our study, no

TABLE 1 Serum lipids levels comparison between different groups of patients: without cancer and with different risk levels of PCa, based on the AJCC staging system

		Cancer			
Parameters	**No cancer**	**Low-risk disease**	**High-risk disease**	**Very high-risk disease**	***p*-value**
TC, mg/dl	197.5 ± 39.2	185.6 ± 36.9	187.8 ± 40.5	188.6 ± 42.0	0.272
HDL-C, mg/dl	47.0 (41.0–55.0)	46.5 (38.0–62.5)	48.0 (40.0–59.0)	46.5 ± 13.4	0.750
LDL-C, mg/dl	126.8 ± 36.1	114.1 ± 35.8	116.8 ± 34.0	111.6 ± 32.9	0.068
TG, mg/dl	98.0 (78.5–121.0)	96.6 ± 35.2	102.0 (69.0–136.0)	106.0 (73–154)	0.696

Note: Data expressed as mean ± SD or median and IQR.

p-values for the difference between means were obtained through ANOVA or Kruskal-Wallis analysis.

	TC	HDL-C	LDL-C	TG
OR[a]	0.993	1.002	0.990	1.001
95% CI[b]	0.987–1.000	0.983–1.022	0.983–0.998	0.996–1.005
p-value	0.052	0.820	0.011	0.770

[a]OR–odds ratio.

[b]95% CI–95% confidence interval.

TABLE 2 OR for all lipids, obtained through univariate binary logistic regression analysis

	TC, mg/dl	HDL, mg/dl	LDL, mg/dl	Triglycerides
No cancer	197.5 ± 39.2	47.0 (40.0–54.0)	126.8 ± 36.1	98.0 (78.5–121.0)
PCa	187.5 ± 39.7	47.0 (37.0–57.0)	114.9 ± 34.0	99.0 (73.0–136.0)
p-value	0.050	0.918	0.010	0.768

Note: Data expressed as mean ± SD or median and IQR.

p-values were obtained through Student's *t* test or Mann-Whitney tests.

TABLE 3 Serum lipid level comparison between patients with and without PCa

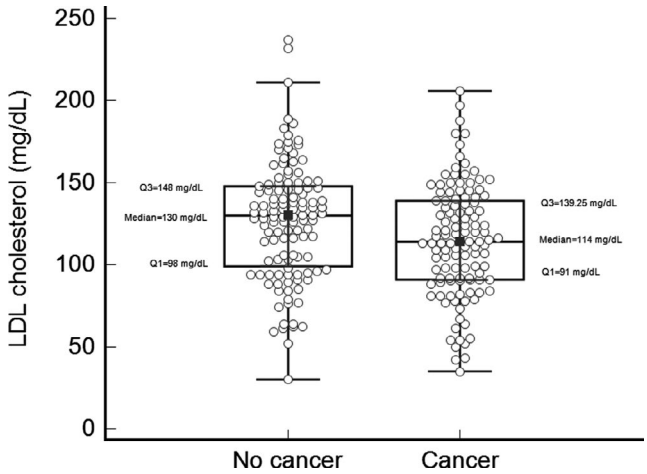

FIGURE 1 Distribution of LDL-C serum levels between controls (no cancer) and cases (cancer). Q1, first quartile; Q3, third quartile

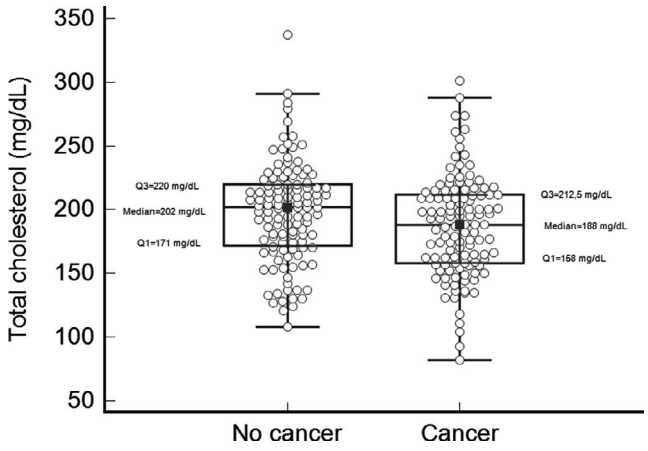

FIGURE 2 Distribution of TC serum levels between controls (no cancer) and cases (cancer). Q1, first quartile; Q3, third quartile

				Overall prostate cancer risk	
	Total, *n* (%)	No cancer, *n* (%)	PCa, *n* (%)	OR[a] (95% CI[b])	*p*-value
TC serum levels					
High (≥200 mg/dl)	108 (45.6)	62 (26.2)	46 (19.4)	-	-
Low (<200 mg/dl)	129 (54.4)	57 (24.1)	72 (30.4)	1.703 (1.016–2.852)	0.043
LDL serum levels					
High (≥130 mg/dl)	100 (42.2)	60 (25.3)	40 (16.9)	-	-
Low (<130 mg/dl)	137 (57.8)	59 (24.9)	78 (32.9)	1.983 (1.174–3.348)	0.010

[a]OR–odds ratio.

[b]95% CI–95% confidence interval.

TABLE 4 Number of patients with elevated and low TC and LDL-C levels, divided according to the outcome (PCa), and respective OR values

information was available about statin use by the patients. In a different study, an increased risk of overall PCa was found in the highest two quartiles of LDL-C levels and an increased risk of high-grade PCa in the highest quartile.[14] In opposition to these findings, our results point to an association between lower LDL-C and overall PCa. In cancer patients, one study demonstrated that HDL-C levels are more affected than LDL-C levels in malignant tumor development, leading to decreasing levels of TC.[28] Although our results do not confirm this association, it is true that during periods of rapid cell growth and development, LDL particles provide cholesterol to most peripheral tissues through the LDL receptor.[29] Furthermore, many studies where several cancer tissues and cells were analyzed, revealed an overexpression of specific cellular components of cholesterol transport and the LDL receptor.[30] This increased activity of the LDL receptor may explain the lower LDL levels seen in PCa patients with a corresponding decrease in TC levels.

Our study has some limitations. Besides the small number of participants, variables were not adjusted for factors such as body mass index, statin usage, age, family history of PCa, digital rectal examination findings, lower urinary tract symptoms, alcohol use, and smoking habits. One important limitation is that we did not have any information about lipid-lowering therapy, particularly statins. Actually, several studies have shown a possible benefit of statins in patients with different types of cancer,[31] including PCa.[32] Moreover, this was not a cohort study, where lipid levels would have been monitored before PCa developed. So, we could not assess lipid levels as risk factors for PCa, but only the association between lipid serum levels and PCa at the time of cancer diagnosis. Due to this fact, we cannot evaluate a possible causal relationship between serum lipids and PCa.

In summary, our results suggest that lower LDL-C levels (<130 mg/dl) and lower TC levels (<200 mg/dl) are associated with PCa, at the time of diagnosis. These findings should be further studied and corroborated in a larger sample of men submitted to prostate biopsy, to better characterize the role of serum lipids in PCa.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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