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Exploring the positive association of blood lipid levels with prostate cancer risk and their relationship to pathological features in the Chinese population

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Abstract

Presently, the majority of investigations into the effects blood lipids on prostate cancer (PCa) primarily involve Western populations. Our study endeavors to investigate the impact of blood lipid levels on the risk of PCa among the Chinese population and to elucidate their potential association with the pathological characteristics of PCa. This study drew data from a dataset for early warning of PCa from the China National Population Health Science Data Center, encompassing 2624 patients who had undergone prostate biopsy. We utilized binary logistic regression to assess the ability of blood lipid levels to distinguish between PCa and non-PCa, as well as to differentiate clinically significant prostate cancer (csPCa) from non-PCa. Additionally, we assessed the ability of these lipid markers to predict whether the Gleason Grade (GG) would be upgraded or downgraded following radical prostatectomy compared to the biopsy GG. Furthermore, ordered multiclass logistic regression was employed to explore the relationship between these indicators and GG. In the Chinese population, triglycerides ($P = .004$; OR: 1.344; 95% CI: 1.201–1.503), low-density lipoprotein cholesterol ($P < .001$; OR: 1.314; 95% CI: 1.200–1.439), and apolipoprotein A1 ($P < .001$; OR: 2.451; 95% CI: 1.714–3.504) were identified as independent risk factors for predicting PCa. Additionally, triglycerides ($P = .013$; OR: 1.156; 95% CI: 1.031–1.295) and apolipoprotein A1 ($P < .001$; OR: 2.580; 95% CI: 1.809–3.680) were found to be independent risk factors for predicting csPCa. Our study demonstrated a positive association between blood lipid levels and PCa risk in the Chinese population, highlighting the potential utility of blood lipids as biomarkers for PCa. In male individuals with a familial predisposition to PCa or other recognized risk factors for PCa, the assessment of blood lipid levels can be incorporated as an auxiliary biomarker in the routine health screening protocol.

Abbreviations: ApoA1 = apolipoprotein A1, ApoB = apolipoprotein B, csPCa = clinically significant prostate cancer, GG = Gleason grade, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, NEPC = neuroendocrine prostate cancer, PCa = prostate cancer, RP = radical prostatectomy, TG = triglycerides, tPSA = total prostate-specific antigen.

Keywords: blood lipids, Gleason grade, prostate cancer, puncture biopsy

1. Introduction

Hyperlipidemia has emerged as a significant global public health concern, with a growing body of literature consistently highlighting the close correlation between these metabolic disorders and the development and progression of various malignancies.[1] Prostate cancer (PCa) is a common cancer that primarily affects older men and ranks second among all male cancers globally.[2,3] In China, the crude incidence rate of PCa is 18.61 per 100,000 people, posing a serious health threat to elderly Chinese men.[4] Numerous studies have demonstrated that the influence of blood lipids on the risk of PCa varies significantly across different ethnic groups.[5] Currently, there is a lack of large-scale studies investigating the relationship between PCa and blood lipids in the Chinese population. Therefore, the objective of our study is to investigate whether a positive correlation exists between

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The datasets generated during and/or analyzed during the current study are publicly available.

Ethical authorization for the study protocol was granted by the Institutional Ethics Committee of Wuhan Central Hospital, with the assigned Ethics Approval Number being: Hospital – City Health Commission – Ethics 2021 (52)-02. The Institutional Ethics Committee deemed it unnecessary to obtain individual informed consent given the retrospective design of the research, thereby granting an exemption consistent with ethical principles.

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lipid levels and the risk of PCa in the Chinese population, as well as to determine any potential association with pathological features of PCa.

2. Methods

2.1. Data source

The ethical authorization of our research scheme was granted by the Institutional Ethics Committee of central hospital of Wuhan (Hospital – City Health Commission – Ethics 2021 (52)-02). The Institutional Ethics Committee determined that, due to the retrospective design of the study, it was not necessary to obtain individual informed consent. Therefore, an exemption in line with ethical principles was granted. The data for this study was sourced from the patient dataset of early warning for PCa at the China National Population Health Science Data Center.[6] The inclusion criteria for participants in this study were as follows: The patient underwent a prostate biopsy; complete data for all indicators; clear diagnostic information. The exclusion criteria were: duplicate cases; excessive missing variables; no Gleason grade (GG) in pathological diagnosis. After excluding patients with unclear pathology, our study included data from 2624 patients, consisting of 1246 with PCa and 1378 without PCa. Among the PCa patients, 339 underwent radical prostatectomy (RP). The recorded data included age, total prostate-specific antigen, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), GG obtained by puncture biopsy and GG after RP. The csPCa was defined as GG greater than GG1.

2.2. Statistical methods

The SPSS statistical software (version 26.0) (Chicago) was utilized for conducting statistical analyses. The measurement data adhering to the normal distribution pattern were denoted utilizing "mean (SD)" notation, and the intergroup comparisons were executed through the employment of Student's *t*-test method. Concurrently, the measurement data exhibiting skewness distribution characteristics were articulated in the form of *M (Q1, Q3)*, and the intergroup comparisons applied the Mann–Whitney *U* test for their assessment.

We utilized binary logistic regression to assess the ability of blood lipid levels to distinguish between PCa and non-PCa, as well as to differentiate csPCa from non-PCa. Additionally, we assessed the ability of these lipid markers to predict whether the GG would be upgraded or downgraded following RP compared to the biopsy GG. Owing to the limited number of variables, they were all incorporated into the multivariable binary logistic regression analysis when investigating the relationships between lipid levels and PCa, csPCa, GG upgrading following radical RP, and GG downgrading after RP. Given the established association between age and lipid levels, age was also included in the analysis. Multivariable binary logistic regression can minimize the impact of confounding factors.[7] However, for the sake of result robustness, if both age and lipid levels were identified as independent risk factors, we would assess multicollinearity using the variance inflation factor. Additionally, the ordered multinomial logistic regression was used to explore the correlation between lipid levels and GG. Statistical significance was determined with a P-value < .05.

3. Results

3.1. Baseline characteristics of patients

In this study, a cohort of 2624 patients were analyzed, with demographic and baseline data detailed in Table 1. Of these, 1246 were diagnosed with PCa while 1378 were non-PCa cases. In the PCa group, the levels of age, total prostate-specific antigen, TG, LDL-C, ApoA1 and ApoB were significantly higher than those in the non-PCa group ($P < .05$). Among the 339 patients who underwent RP, 122 patients (36.0%) experienced a postoperative GG upgrade, 62 patients (18.3%) experienced a GG downgrade, while 155 patients (45.7%) maintained their original GG classification. Table 2 presents the distribution of GG following prostate biopsy and following RP for the 339 patients.

3.2. Multivariable logistic regression Analysis of predictive factors of PCa and csPCa

In predicting PCa, multivariable logistic regression analysis identified TG ($P = .004$; OR: 1.344; 95% CI: 1.201–1.503), LDL-C ($P < .001$; OR: 1.314; 95% CI: 1.200–1.439), and ApoA1 ($P < .001$; OR: 2.451; 95% CI: 1.714–3.504) were identified as independent risk factors (Table 3). In terms of discriminating between csPCa and non-csPCa, TG ($P = .013$; OR: 1.156; 95% CI: 1.031–1.295) and ApoA1 ($P < .001$; OR: 2.580; 95% CI: 1.809–3.680) were found to be independent risk factors (Table 4).

3.3. Multivariable logistic regression analysis of predictive factors of GG upgrade and downgrade after RP

Multivariable logistic regression results showed that age, TG, HDL-C, LDL-C, ApoA1 and ApoB were not predictive factors for GG upgrade and downgrade after RP (Table 5).

Table 1

Comparison of baseline characteristics between PCa and non-PCa patients.

Characteristics	PCa (n = 1246)	Non-PCa (n = 1378)	*t/z*	*P*-value
Age [mean (SD), yr]	71.87 (7.78)	69.09 (7.07)	4.411	<.001*
tPSA [*M (Q1, Q3),* ng/mL]	8.55 (3.34, 21.35)	4.78 (2.15, 9.95)	9.803	<.001†
TG [*M (Q1, Q3),* mmol/L]	1.21 (0.87, 1.69)	1.08 (0.82, 1.48)	4.532	<.001†
HDL-C [mean (SD), mmol/L]	1.18 (0.32)	1.17 (0.311)	1.426	.154*
LDL-C [mean (SD), mmol/L]	2.82 (0.77)	2.639 (0.72)	5.898	<.001*
ApoA1 [mean (SD), g/L]	1.29 (0.25)	1.24 (0.25)	5.192	<.001*
ApoB [mean (SD), g/L]	0.90 (0.22)	0.86 (0.21)	5.421	<.001*

ApoA1 = apolipoprotein A1, ApoB = apolipoprotein B, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, PCa = prostate cancer, TG = triglycerides, tPSA = total prostate-specific antigen.

* Student's *t*-test.

† Mann-Whitney *U* test.

3.4. Ordered multiclass logistic regression for GG prediction

The results of ordered multiclass logistic regression showed that age, TG, HDL-C, LDL-C, ApoA1 and ApoB were not predictors of GG (Table 6).

4. Discussion

The incidence of PCa is increasing annually in the Chinese population, and early detection and diagnosis are crucial for its treatment. Currently, early screening for PCa relies mainly on PSA. Developing new and inexpensive biomarkers could aid in the diagnosis.[8,9] In our study, we uncovered a compelling relationship between blood lipids and the risk of PCa within a Chinese cohort. Our findings demonstrate a positive correlation between elevated levels of TG, LDL-C, and ApoA1 with the risk of PCa. Furthermore, both TG and ApoA1 exhibited a positive association with the risk of csPCa. Our findings suggest a substantial link between lipid abnormalities and PCa, highlighting the potential of blood lipids as biomarkers for PCa.

Extensive research has elucidated the impact of ApoA1on PCa. Some studies have demonstrated a significant upregulation of APOA1 in primary PCa.[10] In addition, from androgen-dependent PCa to castration-resistant PCa and neuroendocrine PCa (NEPC) stages, the expression of APOA1 consistently shows an increasing trend, suggesting that APOA1 may be a molecular marker closely associated with PCa progression.[11] Furthermore, the expression of APOA1 has been shown to positively correlate with the loss of multiple tumor suppressor genes, such as *PTEN*, *RB1*, and *TP53*, as well as the absence of the NEPC repressor gene *REST*, reinforcing its potential role in the development of PCa.[11] Future research should endeavor to explore the interactions between APOA1 and other key genes to unveil its mechanism of action, thereby providing novel targets and strategies for the diagnosis and treatment of PCa.

Our study demonstrates a positive correlation between TG levels and PCa risk. However, the mechanistic basis for TG level elevation in relation to increased PCa risk remains undefined. Research suggests that TG residues may trigger cancer by activating cellular signaling pathways, such as the MEK/ERK and Akt pathways.[12] These pathways are closely related to cell growth, proliferation, apoptosis, and lipid biosynthesis. High concentrations of TG is also associated with the development of insulin resistance and an increase in insulin-like growth factor-1, while simultaneously leading to an increase in reactive oxygen species and oxidative stress levels.[13] All these factors have a significant correlation with the occurrence and development of PCa. The aforementioned study emphasizes the potential role of TG and their metabolic derivatives in promoting carcinogenesis, with a particular focus on PCa. Understanding these mechanisms could pave the way for new therapeutic strategies and preventive measures targeting these specific pathways. In order to identify whether the increase of TG level is a risk factor of PCa or the result of tumor metabolism, Zhu[14] employed a Mendelian randomization study to establish a robust causal link between TG levels and PCa risk. As for LDL-C, Jung et al[15] revealed that LDL-C drives PCa cell proliferation, migration, and invasion by activating the JAK1/JAK2/STAT3 pathway, thereby upregulating oncogenic proteins, which may elucidate its role as a risk factor for both PCa and csPCa. Moreover, retrospective studies have consistently demonstrated that statin use in men is linked to a reduced PCa risk, lending credence to the current findings.[16]

Table 2

Distribution of GG following prostate biopsy and RP.

	GG of puncture biopsy					
GG after RP	**1**	**2**	**3**	**4**	**5**	**Total**
1	35	12	4	3	1	55
2	36	43	14	6	5	104
3	20	21	35	6	7	89
4	2	8	11	13	4	38
5	2	5	7	10	29	53
Total	95	89	71	38	46	339

GG = Gleason grade, RP = radical prostatectomy.

Table 3

Binary logistic regression for predicting PCa.

Characteristics	OR	95% CI	*P*-value
Age	1.024	0.998 to 1.050	.076
TG	1.344	1.201 to 1.503	.004
HDL-C	1.205	0.933 to 1.558	.155
LDL-C	1.314	1.200 to 1.439	<.001
ApoA1	2.451	1.714 to 3.504	<.001
ApoB	0.879	0.340 to 2.271	.790

ApoA1 = apolipoprotein A1, ApoB = apolipoprotein B, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides.

Table 4

Binary logistic regression for predicting csPCa.

Characteristics	OR	95% CI	*P*-value
Age	1.270	0.977 to 1.651	.074
TG	1.156	1.031 to 1.295	.013
HDL-C	1.396	0.562 to 3.452	.474
LDL-C	1.095	0.840 to 1.428	.573
ApoA1	2.580	1.809 to 3.680	<.001
ApoB	1.648	0.633 to 4.291	.306

ApoA1 = apolipoprotein A1, ApoB = apolipoprotein B, csPCa = clinically significant prostate cancer, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides.

Table 5

Binary logistic regression for predicting GG upgrade and downgrade after RP.

	GG downgrade			GG upgrade		
Characteristics	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age	1.085	0.891 to 1.251	.515	1.053	0.897 to 1.157	.285
TG	0.960	0.864 to 1.346	.812	0.816	0.518 to 1.284	.379
HDL-C	2.392	0.971 to 4.062	.063	1.856	0.579 to 3.612	.534
LDL-C	1.168	0.852 to 1.601	.334	0.788	0.527 to 1.180	.248
ApoA1	1.009	0.969 to 1.051	.674	1.023	0.995 to 1.051	.115
ApoB	0.973	0.901 to 1.052	.496	0.934	0.848 to 1.029	.168

ApoA1 = apolipoprotein A1, ApoB = apolipoprotein B, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides.

Table 6

Ordered multiclass logistic regression for predicting GG.

Characteristics	OR	95% CI	*P*-value
Age	1.012	0.997 to 1.026	.122
TG	1.004	0.846 to 1.150	.952
HDL-C	1.153	0.762 to 1.745	.511
LDL-C	1.016	0.873 to 1.182	.370
ApoA1	1.056	0.556 to 1.886	.940
ApoB	1.013	0.952 to 1.077	.689

ApoA1 = apolipoprotein A1, ApoB = apolipoprotein B, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides.

Prostate cancer is characterized by its multi-focal growth and considerable heterogeneity.[17] Prostate biopsy, fundamentally a sampling process, may yield specimens that do not comprehensively represent the histological features of the entire tumor mass. Post-RP GG upgrade could lead to patients missing out on optimal treatment, while GG downgrade may result in patients receiving excessive treatment. In order to significantly reduce this kind of risk, it is very important to find the risk factors of GG upgrade or downgrade after RP. However, our results showed that the blood lipid levels in the Chinese population was not a predictor of GG upgrade or downgrade after RP. Additionally, the results from the ordinal multiclass logistic regression indicate that there is no significant statistical association between lipid levels and GG.

Our study also has some limitations. First, as this is a retrospective study, there are some missing data and biases. Future multicenter, large-sample prospective studies are needed to validate the conclusions. Second, due to database limitations, the time interval between RP and biopsy cannot be determined. If the interval between RP and biopsy is too long, the occurrence of GG upgrading after RP may be related to disease progression. Finally, according to previous literature reports, the number of biopsy needles used during the biopsy is a risk factor for GG upgrading after RP.[18] However, the dataset used in this study does not show the number of biopsy needles, making it impossible to exclude biases caused by different numbers of biopsy needles. Therefore, in future studies, samples with an interval of more than 3 months between RP and biopsy can be excluded, and patients with different numbers of biopsy needles can be categorized when studying GG upgrading after RP, to maximize the rigor of the study.

5. Conclusions

Our research revealed a positive correlation between blood lipids and the risk of PCa in the Chinese population, emphasizing the potential of blood lipids as biomarkers for PCa. However, blood lipid levels were not predictive of GG levels or changes in GG after RP. Overall, lipid levels can be included as auxiliary biomarkers in routine health monitoring for men with a family history of PCa or other known PCa risk factors.

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Author contributions

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