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Association of Non-Genetic Risk Factors with Prostate Cancer in the Population of Jammu Region of J and K, India

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The rising incidence rates of prostate cancer (CAP) have become a global health disorder. It has a complex etiology and includes both potentially modifiable environmental factors and non-modifiable genetic components. In this study, we aimed to identify the potential and significant non-genetic risk factors associated with CAP in the population of Jammu and Kashmir. A total of 320 study subjects (120 clinically confirmed CAP patients and 200 healthy age-matched unrelated participants) were registered for this investigation after obtaining their prior consent. A predesigned health questionnaire and hospital-based patient history were used to collect data pertaining to clinical variables, sociodemographic characteristics, anthropometric parameters, and biochemical indices. The result revealed that diet patterns (non-vegetarianism, p=0.01), lack of physical activity (p=0.0007), dwelling (urban residents, p=0.0105), higher levels of serum LDL-cholesterol (p=<0.0001), triglyceride (p=0.01), VLDL-cholesterol (p=0.02), total cholesterol (p=0.0527), creatinine (p=0.0006), sodium (p=0.0429), urea (p=0.0006), and PSA (p=<0.0001) were significantly associated with CAP. Moreover, higher mean age (69.82±15.5), the extent/duration of diabetes mellitus (DM) (p=0.0007), lack of physical activity (p=0.0007), high intake of red meat (p=0.0005), LDL-Cholesterol (p=<0.0001) and positive family history (p=<0.0001) were found to be the most significant risk factors for CAP. The study notably identified the most significant and novel (extent/duration of diabetes and serum levels of LDL, VLDL) non-genetic risk factors associated with prostate cancer in the population of the Jammu region thus helping to target the high-risk populations and informing preventive interventions.

Keywords: Cases; Controls; Clinical Variables; Prostate cancer (CAP); Risk Factors.

According to GLOBOCAN data, prostate cancer (CAP) is the second most prevalent and fourth most aggressive neoplasm among men globally[1]. The global CAP load is projected to increase to 1.7 million new patients and 4,99,000 deaths annually past 20302 due to progressive population ageing. In India, CAP was reported to be highly prevalent and second most common in cities such as Delhi, Pune, and Kolkata, and the third dominant site of cancer in the population of Mumbai and Bangalore. Moreover, CAP falls in the top ten prominent sites of cancers in the rest

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of the Indian population[3]. In J&K, the prevalence of CAP was reported to be 6.8%[4].

The etiology of CAP is complex and multifactorial, involving the interaction of non-genetic/environmental and genetic risk factors. However, the exact etiology of CAP is not clear[5,6]. Several potential non-genetic risk factors for CAP have been identified in different populations, such as age, smoking, family history, dwelling, diet pattern, elevated cholesterol, obesity, and physical activity [7-13]. However, there is not enough data available about the potential non-genetic risk factors for CAP among the residents of Jammu and Kashmir. Moreover, the UT of J&K is the abode of heterogeneous populations in which the potential risk factors for CAP have yet to be explored. Therefore, in this study, we aimed to analyse several non-genetic/environmental risk factors linked with CAP in the population of Jammu and Kashmir.

MATERIAL AND METHODS

This was a hospital-based research investigation. The study participants comprised 120 cases with clinically confirmed CAP and 200 healthy age-matched unrelated controls) who were residents of J&K. The subjects were recruited from the outpatient department of Urology, Government Super Specialty Hospital, Jammu, and Acharya Shri Chander College of Medical Sciences and Hospital (ASCOMS) over the period of one year from 2020 to 2021. The designed study was authorised by the Institutional Ethical Committee, University of Jammu (no. RA/19/3/21), and Government Medical College, Jammu (no. IEC/GMC/Cat A/2020/155).

Prior to enrolment, written informed consent was obtained from all study subjects. A detailed pre-designed health questionnaire was used for data collection. All subjects were interviewed in a personal manner in the respective hospitals using the pre-designed and structured questionnaire. The questionnaire had information about socio-demographic parameters (dwelling, education level, marital status, and religion), clinical variables (age, age at diagnosis of CAP, duration of illness, family history, weight, height, haemoglobin [Hb], body mass index, blood pressure, pulse rate, urea, creatinine, sodium, potassium, uric acid, prostate-specific antigen [PSA] level, prostate weight, blood group, diabetes, hypertension, thyroid, waist-hip ratio, and family history) and behavioural parameters (diet patterns, physical activity status, vegetarian or non-vegetarian, fluid intake, tobacco consumption, alcohol consumption, and smoking habits) were examined in detail. An ordinal variable was used for assessing the lifestyle of study participants and subsequently divided into three categories, sedentary, normal, and active (yoga, walking, and workout) lifestyles.

1. Sedentary lifestyle: no time for exercise, gymming, sports activities, and physically sporty hobbies.
2. Average/Normal lifestyle: up to 40 minutes daily spent in exercise or other agile activity.
3. Active lifestyle: >40 minutes daily for leisure time, gymming, sporty activities, and rigorous agile activities.

The inclusion criteria included patients with a confirmed clinical diagnosis of CAP (classified as per World Health Organization (WHO) 2008 categorisation), patients considered eligible for intensive chemotherapy, age e" 20 years and d" 85 years, signed written informed consent, and no prior chemotherapy for prostate cancer whereas the exclusion criteria included, people with organ insufficiency, unconstrained infection, severe psychiatric or neurological condition obstructing with their ability to provide informed consent, patients with a "currently active" another malignancy in the body and known positive for HIV or any Hepatitis infection.

BMI was calculated based on height and weight as weight/height^2 (kg/m^2). Other related issues, such as frequent urination, back pain, hematuria, dysuria, and difficulty while sitting, were also noted.

Statistical analysis

Continuous variables expressed the mean and standard deviation, and the differences between the cases and controls were evaluated using the student *t*-test. The frequencies (percentages) were presented as categorical variables, and the Chi-squared test was used to assess the differences between the cases and controls. Univariate analysis identified CAP risk factors, and the results were reported as odds ratio (OR). The statistical analyses were done using SPSS Software version 26.0 (Statistical Package for Social Sciences). *P*

values <0.05 were observed as a typical indicator of statistical significance.

RESULTS AND DISCUSSION

Population-related or Socio-demographic characteristics of the study subjects

The population-related attributes of the study subjects are summarised in Table 1. Maximum research participants belonged to the Hindu religion (patients 59.7%, controls 68.3%), and the maximum disease load was reported from urban areas, which accounted for 44.3% of patients (Table 1). The majority of CAP patients were illiterate (43%) and married (patients 95% and controls 80.5%). However, the practice of consanguinity was mainly present in Muslim subjects.

Clinical variables (anthropometric, physiometric, and biochemical profiles)

Differences between the cases and controls concerning clinical variables are presented in Tables 2 and 3. CAP patients were significantly older than controls (69.82±15.5 years and 56.7±15.7 respectively) (Table 2). Likewise, the systolic and diastolic blood pressure (SBP; DBP) in cases (SBP=127.89±18.52, DBP= 89.17±10.07) were significantly higher than those in controls (SBP=124.04±7.53, DBP= 86.13±9.81). There were significant differences found between cases and controls concerning the prevalence of DM ($p<0.0001$), LDL-C ($p<0.0001$), and PSA ($p<0.0001$) levels. There was no significant between-group difference concerning uric acid, potassium levels, duration of tobacco consumption, and alcohol intake (Table 3). The difference was also observed in average weight among cases and controls (63.5±13.97 kgs and 68.314.3 kgs, respectively) (Table 2). Urea ($p=0.0006$), creatinine ($p=0.0006$), triglyceride (TG) ($p=0.0121$), duration/period of diabetes mellitus (DM) ($p=0.0007$), age of onset of diabetes mellitus (DM) ($p=0.0031$), body mass index (BMI) ($p=0.0427$), and very-low-density lipoprotein-cholesterol

Table 1. Population-Related Attributes of the Study Participants

Parameters	Cases(%)(n = 120)	Controls(% (n = 200)
Religion		
Hindu	72 (59.7%)	137(68.3%)
Muslim	37 (30.74%)	51 (25.6%)
Sikh	9 (7.9%)	11 (5.7%)
Christian	2 (1.66%)	1 (0.5%)
Dwelling		
Urban	53 (44.3%)	63 (31.7%)
Sub-urban	31 (25.6%)	48 (23.9%)
Rural	36 (30.1%)	89 (44.4%)
Educational Status		
Illiterate	52 (43%)	88 (44.1%)
Primary or Elementary school	21 (17.4%)	48 (23.8%)
Secondary or High school	27 (22.8%)	46 (23.1%)
Higher Education	20 (16.8%)	18 (9%)
Marital Status		
Married	95 (79.2%)	161(80.5%)
Unmarried	11 (9.16%)	22 (11%)
Widower	14 (11.66%)	17(8.5%)
Consanguinity (For married)		
Yes	4 (3.33%)	6 (3%)
No	116 (96.66%)	194 (97%)
Region		
Jammu	98 (81.6%)	181 (90.5%)
Kashmir	19 (15.8%)	18 (9%)
Other states*	3 (2.5%)	1 (0.5%)

(VLDL-C) (p=0.0212) also showed significant differences as given in (Table 3). Prostate weight was significantly higher in cases (30.06±12.6g) than in controls (27.90±2.3g).

Lifestyle and behavioural characteristics of study subjects

Data about behavioural or lifestyle factors are presented in Table 4. The diet pattern of cases

Table 2. Anthropometric variables of the study participants

Parameters	Cases(%)	Controls(%) (n = 120)	P-value (n = 200)
Age (yrs.)	69.82±15.5	56.7±15.7	<0.0001***
Average Height (in cms.)	165.1±25.7	167.64±28.3	0.4219
Average Weight (in Kgs.)	63.5±13.97	68.3±14.3	0.0036**
BMI	23.5±6.1	24.7±4.41	0.0427*
WHR	0.99±0.07	0.98±0.06	0.1765
BMR	1473.17±299.13	1470.33±287.65	0.9329

cms: centimeters; BMI: Body Mass Index; yrs: years ; WHR: Waist-Hip Ratio; Kgs: Kilograms; BMR: Basal Metabolic RateP < 0.05*, P < 0.001**, P < 0.0001***

Table 3. Clinical and metabolic variables in the study participants

Parameters	Cases(%) (n = 120)	Controls(%) (n = 200)	P-value
SBP (mmHg)	127.89±18.52	124.04±7.53	0.0096**
DBP (mmHg)	89.17±10.07	86.13±9.81	0.0083**
PR (BPM)	75.81±13.07	73.17±4.13	0.0261*
DM *(mg/dl)*	167.73±54.3	83.7±7.4	<0.0001***
TC *(mg/dl)*	176.57±25.33	170.67±16.43	0.0527*
TG *(mg/dl)*	151.23±34.32	142.77±31.32	0.0121*
HDL-C *(mg/dl)*	41.33±6.32	43.89±23.2	0.2440
LDL-C *(mg/dl)*	131.58±35.75	101.54±23.51	<0.0001***
VLDL-C *(mg/dl)*	44.67±24.47	39.32±16.78	0.0212*
Creatinine *(mg/dl)*	1.75±1	1.1±1.9	0.0006**
Sodium *(mg/dl)*	138.87±3.48	140.12±6.17	0.0429*
Potassium *(mg/dl)*	4.1±1.7	3.9±1.6	0.2912
Hemoglobin *(g/dl)*	11.7±3.7	12.6±3.1	0.0201*
Uric Acid *(mg/dl)*	5.65±1.3	5.7±1.05	0.7068
PSA level *(Free, ng/ml)*	32.55±17.6	3.9±1.9	<0.0001***
Prostate Weight *(in grams)*	30.06±12.6	27.90±2.3	0.0188*
Duration of Smoking *(years)*	24.01±13.7	19.7±17.3	0.0207*
Duration of Tobacco Consumption *(years)*	18.4±17.07	19.63±19.67	0.5701
Duration of alcohol Intake *(years)*	19.52±13.7	17.7±12.1	0.2163
Duration of HTN *(years)*	10.19±6.9	8.7±3.7	0.0125*
Age of Onset of HTN *(years)*	52.7±7.9	51.6±8.1	0.2361
Duration of DM *(years)*	9.1±8.87	6.7±3.5	0.0007**
Age of Onset of DM *(years)*	51.83±9.7	54.3±8.6	0.0031**
Group Grade	3.75±1.25	NA	NA
Gleason Score	7.3±1.7	NA	NA

Systolic Blood Pressure (SBP); Diastolic Blood pressure (DBP); Triglyceride(TG); Heartbeat/Pulse Rate (PR); Diabetes Mellitus(DM); Total Cholesterol (TC); High-Density Lipoprotein-cholesterol (HDL-C); Low-Density Lipoprotein-cholesterol (LDL-C:); Very Low-Density Lipoprotein-cholesterol(LDL-C:); Hypertension (HTN); Diabetes Mellitus (DM).*P < 0.0001***, *P < 0.001**, P < 0.05**

and controls showed a striking difference; 73.9% of CAP patients were keen on a non-vegetarian diet compared to 54.6% of controls. The prevalence of a sedentary lifestyle is higher in CAP patients (56.7%) than in controls (36.8%). Moreover, the routine of vigorous walking for a minimum of 40 minutes was higher among controls (patients 27.1% and controls 49.2%). Consumption and

Table 4. Lifestyle risk factors in the study participants

Parameters	Cases(%) (n = 120)	Controls(%) (n = 200)
Diet Pattern		
Vegetarian	31 (26.1%)	91 (45.4%)
Non Vegetarian	89 (73.9%)	109 (54.6%)
Physical Activity		
Yoga	6 (5%)	16 (7.9%)
Walk	46 (38.3%)	110 (55.3%)
Sedentary	68 (56.7%)	74 (36.8%)
High Intake of Fat, dairy, and eggs		
Yes	84 (69.8%)	105 (52.3%)
No	36 (30.2%)	95 (47.7%)
Smoking habits		
Never	37 (30.6%)	65 (32.7%)
Former	64 (53.2%)	103 (51.5%)
Current	19 (16.4%)	32 (16%)
Tobacco Chewing		
Never	61 (50.8%)	113 (56.5%)
Former	37 (30.8%)	46 (23%)
Current	22 (18.3%)	51 (25.5%)
Alcohol drinking		
Yes	77 (64.16%)	123 (61.5%)
No	43 (35.8%)	77 (38.5%)
History of HTN		
Yes	39 (32.3%)	60 (29.9%)
No	81 (67.7%)	140 (70.1%)
History of DM		
Yes	50 (41.4%)	47 (23.6%)
No	70 (58.7%)	153 (76.4%)
Family History of CAP		
Yes	42 (34.8%)	6 (3.2%)
No	71 (59.4%)	183 (91.5%)
No data	7 (5.8%)	11 (5.5%)
Clinical Stage*		
T1-T2	44 (36.7%)	NA
T3	55 (45.9%)	NA
T4	21 (17.4%)	NA
Pathological grade†		
Well differentiated (£6)	11 (9.3%)	NA
Moderate Differentiated (7)	51 (42.6%)	NA
Poor Differentiated (>7)	58 (48.1%)	NA

CAP: Prostate Cancer; HTN: Hypertension; DM: Diabetes Mellitus*CAP is staged using TNM (tumour, nodes, metastases) classification (1997-American Joint Committee for Cancer)- (T1-T2-Localized), (T3- Locally advanced), (T4- Metastatic)†Assigning a score (Gleason Score) to the biopsied tissue samples by pathologists on the basis of tissue differentiation. Two grades (Primary and secondary) combined to give the final score. (Low grade; £6- well differentiated), (Low grade; 7- moderately differentiated), (High grade; ³7- Poor differentiated).

Table 5. Univariate association examination of various non-genetic risk factors for CAP

Parameters	Cases(%) (n=120)	Controls(%) (n = 200)	Odds Ratio (95% CI)	P-value	Z-statistics
Dwelling					
Urban	84(44.3%)	111 (31.7%)	1.87 (1.15 –3.02)	0.0105*	2.559
Rural	31(25.6%)	48 (23.9%)			
Diet Pattern					
Non Vegetarian	89(73.9%)	109 (54.6%)	2.39 (1.46-3.93)	0.0005**	3.46
Vegetarian	31 (26.1%)	91 (45.4%)			
Physical Activity					
No	68 (56.7%)	74 (36.8%)	2.26 (1.40-3.53)	0.0007**	3.401
Yes	52 (5%)	126 (63%)			
High Intake of Fat, dairy, and eggs					
Yes	84 (69.8%)	105 (52.3%)	2.11 (1.3 – 3.40)	0.0022*	3.057
No	36(30.2%)	95 (47.7%)			
Family History of CAP					
Yes	42 (34.8%)	6 (3.2%)	18.04(7.34-44.29)	<0.0001***	6.312
No	71 (59.4%)	183 (91.5%)			
No data	7 (5.8%)	11 (5.5%)			
Diabetes					
Yes	50 (41.4%)	47 (23.6%)	2.32 (1.42 –3.78)	0.0007**	3.386
No	70 (58.7%)	153 (76.4%)			

CAP: Prostate Cancer
P < 0.0001***,P < 0.001**, P < 0.05*

high intake of fats were more prevalent in cases (69.8%) than in controls (52.3%). The prevalence of smoking between-group differences showed no statistical significance. However, the duration of smoking was significantly longer among cases (24.01±13.7) compared to controls (19.7±17.3; p=0.0207). A greater proportion of patients consumed alcohol than controls (64.16% and 61.5%, respectively). Most CAP patients had elevated cholesterol (48.6%) compared to controls (39.6%). CAP patients had a higher prevalence of comorbid conditions such as hypertension (patients 32.3%, controls 29.9%) and diabetes (patients 41.4%, controls 23.6%). Positive family history of hypertension, diabetes mellitus, and CAP were identified as risk factors for prostate cancer (Table 4). Moreover, the majority of the cases had >3 (3.75±1.25) grade prostate cancer (TNM classification) and >7 (7.3±1.7) Gleason score, which depicts the level of tissue differentiation in prostate cancer.

The findings of the logistic regression analysis are presented in Table 5. In the population of the Jammu region of J&K, there is a significant link found between prostate cancer and several factors, including residential settings, dietary habits, lack of physical activity, high intake of fats, dairy, and eggs, and a family history of CAP and diabetes.

DISCUSSION

As per recent GLOBOCAN data, there were an estimated 1,414,259 cases of prostate cancer worldwide in 2020, which makes the prostate the second-most common and fourth-most aggressive neoplasm among men worldwide[1]. In addition, International Agency for Research on Cancer (IARC), in its 2020 cancer statistics, reported that out of 19.3 million newly diagnosed cancers among both sexes, prostate cancer is classified as the third most frequently occurring cancer (accounting for 7.1% of the overall cases)[14]. Prostate cancer is estimated to be the seventh most common cancer in males accounting for 4.75% of subjects in the Jammu region[15]. Owing to the high load of CAP patients in J&K[16], identifying the anthropometric, behavioural, biochemical,

and socio-demographic risk factors for CAP in the population of Jammu and Kashmir is a crucial imperative. In this research investigation, various potential non-genetic risk factors such as age, family history, HTN, smoking, diabetes, alcohol intake, lifestyle, dietary pattern, etc.) were assessed, and comparisons were drawn with other studies from all over the globe.

CAP is deemed a disease of the elderly as the age of >60 years is a well-known risk factor for this disease[17,18]. The higher mean age of cases in our study is consistent with previous studies[18-20]. In the present study, positive family history was a significant risk factor for CAP which is also consistent with other studies[20-22]. In an earlier study, men with a positive family history of CAP compared to those without a family history showed a 1.5 to 4 times higher risk of prostate cancer [23]. In urban areas, people are more aware and educated and have greater access to healthcare facilities. Nonetheless, CAP is generally perceived as a disease of urban dwellings. A lower prevalence of CAP in rural areas than in urban areas was also reported by a maximum number of epidemiological studies conducted in India by the present investigation[3].

Obesity (BMI>25) and high intake of red meat, fats, and dairy products are considered substantial risk factors for CAP[8,24-28]. In the present investigation, a high-fat diet and red meat consumption were associated with CAP risk, and the results are consistent with other studies[29]. Sonoda et al. (2004) also reported that the risk of CAP is positively correlated and associated with the consumption of red meat. The present study also showed a direct link between obesity and CAP, which aligns with another study that showed higher BMI (obese men) and taller height were positively associated with lethal CAP[30-32].

Smoking and alcohol intake were found to be nonsignificant in this study. The findings are inconsistent with a previous study[33,34]. However, in the present investigation, the duration of smoking was associated with CAP. Many other studies have also reported a positive association between the duration of smoking and the risk of developing prostate cancer[35-38].

A physically active lifestyle reduces the risk of fat-associated abnormalities, hypertension (HT), and diabetes mellitus (DM), and the present investigation also revealed that regular physical activity reduces substantially reduces the risk of CAP. These findings are in accordance with another study by Friedenreich and Thune, 2001 who found an inverse association between a physically active lifestyle and CAP risk[39,40]. The results are also consistent with the findings of Torti and Matheson (2004), who reported that exercise and normally active lifestyles reduced 10-30% the average risk of developing CAP[41]. A higher regularity of lazy/ sedentary lifestyle is observed in the cases, while the controls showed a higher frequency of regular workouts in the style of yoga and walking. The present study also reported a substantial association of diabetes mellitus with CAP as a more significant proportion of participants in the cases had diabetes compared to the control group. The findings are consistent with other studies[42-44]. However, the results are inconsistent and at odds with the findings reported by another study[45].

CONCLUSION

The present study was the first approach for carrying out a non-genetic risk factor analysis for prostate cancer in the population of the Jammu region of J&K, India. Many non-genetic factors were for the first time identified as potential risk factors in the inhabitants of the Jammu region, such as higher levels of serum low-density lipoprotein-cholesterol ($p=<0.0001$) and very low-density lipoprotein-cholesterol ($p=0.02$). Similarly, the extent/duration of diabetes in the population of the Jammu region was also reported for the first time as a potential and significant risk factor for CAP.

Moreover, factors such as age, family history, lack of active lifestyles, and non-vegetarian diet were also identified as significant risk factors for CAP in the inhabitants of J&K. Additionally, patients with CAP had higher serum levels of LDL, VLDL, and TG, and low levels of HDL, indicating that increased intake of fat and red meat are potent risk factors for CAP. A better lifestyle and regular physical activity were found to have a protective effect against CAP. Our findings will be helpful for both health professionals and the general public. The results help inform preventive interventions and target high-risk populations for CAP screening.

Limitations

Some limitations of our study should be considered while interpreting the results. The cases were enrolled from only two medical college hospitals in Jammu City. This may limit the generalizability of our findings. Moreover, our results may have been affected by selection bias.

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Conflict of Interest

The authors declare no conflict of Interest.

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