DOI: https://doi.org/10.66984/jsmdc.v12.i01.oa.04.

Original Article

Association between High-Altitude Residence and Risk of Prostate Cancer in Misgar, Gilgit-Baltistan

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ABSTRACT

Objective: To determine the association between high-altitude residence and the risk of prostate cancer based on prostate-specific antigen density (PSAD) among residents of Gilgit-Baltistan.

Methodology: This cross-sectional analytical study was conducted at Misgar, Gilgit Baltistan, by Sharif Institute of Urology & Renal Transplant (SIURT), Sharif Medical City Hospital, Lahore, from July to December 2025, following ethical approval from the institutional review board. After meeting the selection criteria, 96 male residents of high altitude, having age ≥40 years, were enrolled using a non-probability consecutive sampling technique, irrespective of digital rectal examination (DRE) or ultrasound findings. The patients then underwent clinical evaluation, and blood samples were collected to measure their prostate-specific antigen (PSA) levels. Prostate size (ml) was measured using abdomino-pelvic ultrasound by a consultant radiologist in the nearest health facility, and PSAD was calculated. Based on PSA density, patients were categorized as having low, intermediate, and high risk of cancer. Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 26.

Results: The mean age of the patients was 59.38±11.12 years. Among patients residing at high altitude for ≥10 years, a high risk of prostate cancer based on PSA density was observed in 4(4.2%) cases, whereas among those living at high altitude for <10 years, high risk was not found in any of the patients (p <0.001). Most of the smokers, hypertensives, diabetics, and those with positive family history of prostate cancer had intermediate or high risk of prostate cancer (p <0.05). However, alcohol use showed no such association (p-value=0.18).

Conclusion: Residents living at high altitude for more than 10 years had a significantly higher risk of developing prostate cancer compared to those residing at high altitude for less than 10 years.

Keywords: *Prostate Cancer. Prostate-specific antigen. Ultrasonography. Digital rectal examination.*

INTRODUCTION

Prostate cancer is a major malignancy in men and a leading contributor to male mortality worldwide. It may present as either a localized or an advanced stage disease. Prostate cancer is classified as either androgen sensitive or androgen insensitive, reflecting its dependence on testosterone stimulation or guiding potential treatment options.[1] Globally, prostate cancer is the most common cancer among males and the prevalence and mortality increase with increasing age.[2] A high prostate-specific antigen level can be a sign of prostate cancer, but it can also be caused by non-cancerous conditions like benign prostatic hyperplasia, acute or chronic prostatitis and urinary tract infections.[3] Biopsy is the gold standard diagnostic method. Most prostate cancers are fortunately low-grade and not very aggressive.[4]

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Received: March 20, 2026; Accepted: May 7, 2026

Prostate cancer incidence varies globally, with higher rates typically found in Northern America, Australia, and Northern and Western Europe (Norway) compared with lower rates in South-Central and East/Southeast Asian countries (India, China, Thailand).[5] The incidence has been associated with older age, unhealthy diet, lack of physical activity and environmental factors. The patients usually present with lower abdominal pain, difficult micturition, hematuria, and bone pains. Most cases are localized but metastasis to bone and lymph nodes can occur in advanced cases.[6]

High-altitude residence and prostate disease, though distinct, are both linked to hypoxic conditions. To adapt to this oxygen scarcity, the body activates systemic, cellular, and molecular mechanisms. This response impacts the entire body, including the cardiovascular, respiratory, and reproductive systems. Conversely, malignant prostate tissue is associated with oxygen deprivation in the tissue microenvironment, resulting from both limited oxygen availability and elevated consumption caused by rapid cellular proliferation.[7]

Direct evidence linking high altitude to the risk of developing prostate cancer is lacking in our population, despite previous research showing the adverse impact of high altitude on other male

reproductive parameters, such as altered testosterone levels, reduced testicular volume, and decreased sperm concentration and motility.[7] To fill this gap, this study was planned and conducted among residents of a high-altitude area to generate local evidence and to make recommendations regarding screening accordingly.

METHODOLOGY

This cross-sectional analytical study was conducted at Misgar, Gilgit Baltistan, by Sharif Institute of Urology & Renal Transplant (SIURT), Sharif Medical City Hospital, Lahore, from July to December 2025, following ethical approval from the institutional review board (Letter No. SMDC/SMRC/342-24, 26-06-2024). A medical camp was organized in Misgar, Gilgit-Baltistan on 14th and 15th July 2025 for the purpose of data collection. The sample size of 96 was calculated using a 90% confidence level, 8% margin of error and 36.3% proportion of patients at higher risk of prostate cancer with PSA density levels greater than 0.15 ng/ml^2.[8] After obtaining informed written consent, 96 male residents of high altitude, aged ≥40 years, were enrolled using non-probability consecutive sampling, irrespective of digital rectal examination (DRE) or ultrasound findings, to ensure uniform and unbiased assessment of prostate cancer risk. The exclusion criteria included patients having prior diagnosis of prostate cancer, history of transurethral resection of the prostate and/or prostatectomy for cancer, prostatitis, acute urinary retention and intake of drugs increasing PSA levels such as betamethasone and testosterone replacement therapy.

Data regarding the history of co-morbidities & risk factors, DRE, abdomino-pelvic ultrasound and laboratory findings were recorded on a predesigned proforma. Those living at ≥2,500 meters above sea level were labelled as high-altitude residents.[7] The residents living at high altitude were divided into 2 groups (≥10 years and <10 years) on the basis of duration of high-altitude residence. The participants' digital rectal examination was done by residents of urology with minimum of 2 years of experience to assess nodularity. A firm or hard nodule on DRE was considered to be suggestive of prostate cancer.[4] Prostate size (ml) was measured using abdomino-pelvic ultrasound by a consultant radiologist in nearest health facility. A 5 ml venous blood sample was collected and sent to the laboratory for PSA levels estimation. The normal cutoff value for PSA levels is 4.0 ng/ml.[3] After obtaining PSA reports from the laboratory, PSA density (PSAD) (ng/ml^2) was calculated by using the formula as [PSA density=PSA levels (ng/ml)/prostate size (ml)].[3] Participants were classified for prostate cancer risk based on PSA density as follows: low risk for PSAD <0.10 ng/ml², intermediate risk for PSAD ≥0.10 to <0.15 ng/ml², and high risk for PSAD ≥0.15 ng/ml².[9] Those with suggestive findings on DRE and with abnormal PSA density levels were counselled on getting biopsies.

STATISTICAL ANALYSIS

Data was entered and analyzed with Statistical Package for the Social Sciences (SPSS) version 26. Continuous variables like age and PSA metrics were summarized as mean±standard deviation. Categorical variables, such as high-altitude residence status, smoking status, and other comorbidities were reported as frequencies & percentages. The association between high-altitude residence and PSA density level categories, comorbidities and digital rectal examination findings was assessed using the Chi-square and Fisher's exact test with a p-value <0.05 considered statistically significant.

RESULTS

The mean age of the participants was 59.38±11.12 years and the mean duration of residence at high altitude was 23.60±14.24 years. The mean PSA level of the study population was 5.46±3.50 ng/ml. Similarly, the mean value of PSAD of the patients was 0.16±0.07 ng/ml^2. The majority of participants (85.4%) had been living at high altitude for 10 years or more. More than half of the participants were smokers (56.3%), while only a small proportion reported alcohol use (5.2%). The prevalence of diabetes mellitus and hypertension was 9.4% and 20.8%, respectively. Additionally, 8.3% of participants reported a family history of prostate cancer.

The nodularity on digital rectal exam was exhibited by only 5(6.1%) participants of long term high-altitude residence (≥10 years). None of the high-altitude residents of less than 10 years duration had shown any abnormal findings. However, these findings were statistically insignificant (p >0.999).

Based on PSA density, 37(38.5%) out of 96 participants were categorized as having low risk, 55(57.3%) as intermediate risk, and 4(4.2%) as high risk for prostate cancer. Among those residing at high altitude for ≥10 years, the majority (55.2%) had intermediate risk of prostate cancer indicated by PSA density and only 4(4.2%) of participants were at high risk. Among those living at high altitude for <10 years, most (12.5%) had low risk, followed by

only 2 (2.1%) participants with intermediate risk of cancer. None of them had high risk of prostate cancer (p <0.001) (Table 1).

The comparison of comorbidities with categories of prostate cancer risk showed that smoking, hypertension, diabetes mellitus and family history of prostate cancer were significantly associated with prostate cancer risk categories based on PSAD. Most of the smokers, hypertensives, diabetics, and those with positive family history of prostate cancer were at intermediate or high risk of prostate cancer (p <0.05). However, alcohol use showed no such association (p-value=0.18) (Table 2).

DISCUSSION

Prostate cancer represents a major public health concern in Pakistan. Data from the Pakistan National Cancer Registry indicated that it is the second most prevalent cancer among males in the country. However, the prognosis is generally very good. It typically progresses slowly and is often discovered at an early, curable stage, leading to successful outcomes for the majority of patients.[10]

The mean age of our study participants was 59.38±11.12 years. Most of them (85.4%) were residents of high altitude for a duration of ≥10 years. Those residing at high altitude for ≥10 years demonstrated a high risk of prostate cancer based on PSA density in 4(4.2%) cases, while no such cases were observed among patients living at high altitude for <10 years (p <0.001). The mean PSA (5.46±3.50 ng/ml) and PSA density (0.16±0.07 ng/ml²) levels of our study population were above the normal cutoff values. Previous literature has also shown that exposure to high altitude is associated with changes in male reproductive hormones, including altered testosterone levels.[7] Serum testosterone concentrations were found to be higher among high altitude residents as compared to individuals residing at sea level, which influenced metabolic adaptation in individuals not fully acclimatized to high altitudes.[11] However, research showed that the effects of high-altitude exposure on semen quality and reproductive hormones in young men were reversible.[12] In contrast to our results, Alcantara-Zapata et al. documented cases of excessive erythrocytosis (Hb >21 g/dl) in subjects from the three highest cities in their study and levels of PSA did not increase significantly with altitude.[13]

Table 1: Association of PSA Density based Prostate Cancer risk with Duration of High-Altitude Residence

Duration of High-Altitude Residence (Years)	Risk of Cancer (on basis of PSA Density)			Total	p-value
	Low risk	Intermediate risk	High risk		
≥10	25(26%)	53(55.2%)	4(4.2%)	82(85.4%)	<0.001*
<10	12(12.5%)	2(2.1%)	0(0%)	14(14.6%)	
Total	37(38.5%)	55(57.3%)	4(4.2%)	96(100%)	

**Significant p-value*

Table 2: Association of Risk of Prostate Cancer Based on PSA Density with Risk Factors and Co-Morbidities

Risk Factors and Comorbidities		Risk of cancer (on basis of PSA Density)			Total (n=96)	p-value
		Low risk (n=37)	Intermediate risk (n=55)	High risk (n=04)		
Smoking	**Yes**	15(40.5%)	36(65.5%)	3(75%)	54(56.3%)	0.03*
	No	22(59.5%)	19(34.5%)	1(25%)	42(43.7%)	
Diabetes Mellitus	**Yes**	1(2.7%)	6(10.9%)	2(50.0%)	9(9.4%)	0.01*
	No	36(97.3%)	49(89.1%)	2(50.0%)	87(90.6%)	
Hypertension	**Yes**	4(10.8%)	14(25.5%)	2(50.0%)	20(20.8%)	0.04*
	No	33(89.2%)	41(74.5%)	2(50.0%)	76(79.2%)	
Alcohol Use	**Yes**	1(2.7%)	3(5.5%)	1(25.0%)	5(5.2%)	0.18
	No	36(97.3%)	52(94.5%)	3(75.0%)	91(94.8%)	
Family History of Prostate Cancer	**Yes**	1(2.7%)	5(9.1%)	2(50.0%)	8(8.3%)	0.006*
	No	36(97.3%)	50(90.9%)	2(50.0%)	88(91.7%)	

**Significant p-value*

Burtscher et al. also reported that incidence and mortality of cancers among males and females significantly decreased with increasing altitudes. This difference can be attributed to varied environmental and lifestyle factors like physical activity, healthy diet, smoking and use of alcohol.[14]

More than half of our participants were smokers (56.3%) and only 5.2% were alcoholics. Most of the smokers, hypertensives, diabetics and those with positive family history of prostate cancer were at intermediate or high risk of prostate cancer ($p < 0.05$). However, alcohol use showed no such association. Raphael et al. also found no statistically significant relationship between cigarette smoking, alcohol consumption, and the risk of prostate cancer.[15] However, another study found that healthier lifestyles, such as reduced smoking and alcohol consumption, showed an opposite association for prostate cancer, where a higher lifestyle index was linked with a slightly increased risk [hazard ratio (HR) 1.04, 95% confidence interval (CI):1.01-1.08], possibly due to greater screening and detection among individuals with healthier lifestyles.[16] A meta-analysis reported that cardiometabolic diseases like hypertension and diabetes significantly influenced the risk of aggressive prostate cancer.[17] Patients with a family history of prostate cancer also demonstrated a significantly higher risk of developing prostate cancer in a study [Relative Risk (RR)=1.25, 95% CI:1.16-1.35, $p < 0.001$].[18]

In our study, 38.5% males were at low risk as their PSAD levels were below the cut-off value of 0.10 ng/ml^2. Those (57.3%) with PSAD between 0.10 to 0.15 ng/ml^2 were at intermediate risk of prostate cancer. Only 4.2% were at high risk where PSAD was $\geq$0.15 ng/ml^2. Park et al. showed that prostate cancer risk increased among those with high PSAD ($\geq$0.218 ng/ml^2) as compared to those with lower PSAD [odds ratio=3.51; 95% CI:1.306 - 9.415]. The use of PSAD levels to determine risk of prostate cancer had additional benefits of reduction in missed diagnosis and unnecessary biopsies.[19] Nazir et al. also reported that PSA levels were non-specific for prostate cancer. However, PSAD levels were independent predictors of clinically significant prostate cancer and those patients with PSAD below 0.10 ng/ml^2 had a significantly low likelihood of getting clinically significant prostate cancer.[20] Similarly, Girometti et al. revealed that PSAD threshold of 0.10 ng/ml^2 demonstrated greater clinical utility in stratifying prostate cancer risk.[21] Maeda-Minami et al. observed that even PSA levels above a specific high value posed a threat for malignancy and mitigating these PSA levels could prove an effective preventive strategy.[22]

CONCLUSION

Residents living at high altitude for more than 10 years had a significantly higher risk of developing prostate cancer compared to those residing at high altitude for less than 10 years. Therefore, males residing at high altitude for longer durations should undergo periodic screening to facilitate early detection and timely management of prostate cancer.

LIMITATIONS & RECOMMENDATIONS

The cross-sectional design, small sample size, and use of a non-probability sampling technique are key limitations, as they restrict the generalizability of the findings to the broader population. Additionally, risk assessment was based solely on prostate-specific antigen density (PSAD) and was not validated through biopsy. Another limitation is the absence of previously published studies exploring the direct relationship between high-altitude residence and prostate cancer risk using PSAD, which constrained comparison with existing literature. Future studies with longitudinal follow-up, larger sample sizes, and probability-based sampling methods are recommended to validate and strengthen these results.

Conflict of interest: None.
Source of funding: None.

Authors' Contributions:
M.R.Z: Conceptualization, Supervision, study design, supervision, final approval of the manuscript
M.H: Data collection, clinical assessment, manuscript drafting.
A.H: Methodology, data interpretation, manuscript editing.
B.S: Statistical analysis, data interpretation.
F.H: Data collection, literature review.
M.H: Data acquisition, patient coordination.
E.H: Data analysis, manuscript proofreading.
A.B: literature review, manuscript review.

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How to cite: *Zaki MR, Hussain M, Haider A, Sattar B, Haider F, Hamza M, et al. Association between high-altitude residence and risk of prostate cancer in Misgar, Gilgit-Baltistan. JSMDC. 2026; 12(01):21-25. doi:https://doi.org/10.66984/jsmdc.v12.i01.oa.04.*