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Research Article

STUDYING THE POSSIBLE LINK OF LIFESTYLE HABITS AND CYTOKINE BIOMARKERS AMONG THE PROSTATE CANCER PATIENTS

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ABSTRACT

Objectives: Men over 50 are the main victims of prostate cancer (PCa), a non-cutaneous malignancy. It kills more than 3,000 individuals worldwide and affects more than 1.6 million people. We intended to examine the potential relationship between PCa incidence and age trends as well as PCa and cytokine levels in the current investigation.

Methods: The study was conducted between January 2019 and March 2020 and was a prospective longitudinal observational study. The study included 70 patients (n=70) with PCa who were receiving standard chemotherapy at the Gujarat Medical College Urology Service (control=20 healthy individuals). We intended to investigate the prevalence of cancer as well as lifestyle choices such as smoking and drinking.

Results: We found from the data that the subjects in the age group from 61 to 65 were more susceptible to the disease ($p<0.05$). There is no direct correlation between smoking habits and the incidence of cancer. We found the cytokines in the study also to be elevated significantly when compared to the controls ($p<0.05$). Interleukin (IL-20 and IL-4 levels were elevated to 25.67±2.132 and 45.63±3.4512, respectively, when compared to control. Il-6 and IL-10 levels were elevated to 65.43±1.654 and 12.341±2.1218, respectively, when compared to control. On the other hand, Il-17A levels were elevated to 45.33±3.121 from 16.11±1.1132 (control).

Conclusion: When combined, our findings offer the whole set of pro-inflammatory markers required for a thorough evaluation and diagnosis of PCa patients. The cytokines IL-2, 4, 6, 8, 10, and 17A may serve as indications of the progression of PCa as well as biomarkers for its pathogenesis.

Keywords: Prostate cancer, C-reactive protein, Erythrocyte sedimentation rate, Smoking, Enzyme-linked immunosorbent assay, Cytokines, Interleukins, Interleukin-2, Interleukin-10, Interleukin-17A.

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INTRODUCTION

The leading cause of cancer-related deaths in Western nations, prostate cancer (PCa) primarily affects middle-aged men between the ages of 45 and 60 [1]. Prostate biopsy and analysis, prostate-specific antigen (PSA) testing, digital rectal examination, magnetic resonance imaging, or health screening are used to diagnose PCa in many men. Family risk, race, age, obesity, and other environmental factors are risk factors for PCa. Based on both epidemiology and genetics, PCa is a diverse illness. Differences in the epidemiology of PCa in various nations are a result of the interaction of genetics, environmental factors, and societal effects, which lowers estimates of the PCa survival rate for races [2]. To determine testosterone stimulation and potential treatment options, PCa can be categorized as either androgen sensitive or androgen insensitive [3]. PCa can be treated with active surveillance, hormone therapy, radiation therapy, chemotherapy, cryotherapy, and surgery. The type of tumor, PSA level, grade and stage, and potential recurrence all influence the treatment options available to a patient. For instance, low-risk PCa is treated with radiation therapy and radical prostatectomy, a surgical procedure that removes the prostate and surrounding tissues [4]. Androgen-deprivation therapy, also known as hormonal therapy, is advised for the treatment of malignancies that have returned and spread outside the prostate [4].

PC is a non-cutaneous cancer that primarily affects men over 50. It affects over 1.6 million people and causes over 3,000 fatalities globally. According to reports, it is the fifth leading cause of cancer-related mortality and the second most frequent kind of cancer among men. With 41,532 new cases in 2020, PC was one of the most common malignancies found in India. It accounted for 5.7% of all male cancer cases, and one in 125 males was at risk of receiving a PC diagnosis. A decrease in mortality among detected cases has resulted from increasing PSA screening, which has been the primary cause of the rising incidence rate of PC in recent decades [5].

Over the past few decades, PC has consistently been the most prevalent cancer in men. Globally, 1.41 million new PC cases occurred in 2020, making up 7.3% of all cancer cases [6]. A total of 34,130 deaths and 248,530 new PC cases were reported in 2021. In addition, it is predicted that these patterns will worsen to 2.43 million additional cases and 740,000 fatalities globally by 2040. The highest occurrence rates were seen in the Caribbean, Western and Northern Europe, North America, Australia, New Zealand, and Southern Africa. At the same time, the lowest incidence rates were seen in Asia and Northern Africa [7]. Differences in diagnostic procedures are a significant factor in these disparate PC incidence rates. In the 1990s, PSA screening was introduced.

Interleukins (IL) and cancer

There are more than 40 different ILs that serve various, specific functions in humans [8]. IL signaling or production can become dysregulated, leading to cancer and/or autoimmune diseases. Designing optimal IL-containing combination therapies may yield more effective cancer therapies. ILs could potentially be used as biomarkers related to patients who would be likely to respond to a particular cancer therapy. Hence, understanding IL biology is essential to develop new diagnosis, prognosis, and therapeutic approaches to a variety of immune-related diseases [9].

The role of ILs in the development of cancer is complex and multifaceted. Numerous ILs, such as IL-2, IL-12, and IL-15, have been studied as possible immunotherapeutic targets in the treatment of cancer [10]. The ability of T cells and NK cells to identify and destroy cancer cells can be improved by these ILs. On the other hand, it has been demonstrated that ILs such as IL-6 and IL-8 foster tumor growth, angiogenesis, and metastasis across a range of cancer types [11]. Targeting ILs may therefore result in the creation of novel cancer treatments, according to the implications of ILs in cancer. More individualized cancer therapy choices may result from the use of IL biomarkers [12]. To completely comprehend the roles of ILs in cancer and create efficient IL-based treatments, more research is necessary. A pro-tumor microenvironment can result from the action of these ILs, which are produced by cancer cells, on immune and tumor cells. In general, ILs and cancer have a complicated and situation-specific interaction [13].

According to research, pro-inflammatory cytokines may play significant roles in encouraging the growth of tumor cells, and ILs may be exceptional markers of the aggressiveness and proliferation of PCa cells [14]. According to earlier research, patients with PCa had greater levels of IL-6 [15]. Furthermore, a thorough examination and consistent viewpoints about the role of IL-1ra, IL-8, IL-16, and several other ILs in PCa are still lacking [16].

By analyzing patterns, trends, and risk factors for the disease, studies on PCa in India are important since they help create management strategies. This information can be used by clinicians and other interested parties to develop effective programs for managing diseases. In addition, this study can help identify the need for improved diagnostic processes and regional screening guidelines by increasing awareness of PC and its risk factors [17].

Here, in the current study, we planned to investigate the role of possible correlation between the incidence of PCa and age patterns, PCa and cytokines levels, and PCa and lifestyle disorders such as smoking and alcohol intake. We studied both the biochemical and molecular markers of inflammatory immune mediator expression with respect to the incidence patterns of PCa.

METHODS

Subject selection and criteria

Between January 2019 and March 2020, a total of 70 subjects suffering from PCa were enlisted from Gujarat Medical College Urology Service. The study group was grouped as control and subjects. Control (n=20) included healthy individuals with no PC but diagnosed and the subjects (n=70) included patients group with PC diagnosed and getting treated with standard treatment.

The inclusion criteria were a diagnosis of PCa (all stages) and were under the standard treatment. Exclusion criteria were subjects suffering from neuro-psychiatric disorders and acute infections. All the participants signed written consent forms, and demographic information about them including the prevailing symptoms during sample collection was recorded. Before beginning the medication, blood samples (5cc) were collected, and the separated sera were kept at 70°C in the hospital laboratory pending additional examination.

To illustrate the trends of PCa incidence patterns in different age groups among the subjects, we used differential statistics to calculate the mean, median, and standard deviation. The frequency was then evaluated as per the age group and tabulated. Control (n=20) and subjects (n=70) were evaluated in the study. To find the possible correlation between smoking and alcohol intake habits and the PCa incidence among the subjects, we collected the data during the demographic collection but with the subjects' consent. All the subjects were categorized based on "YES" or "NO." The data were sorted based on the response and a two-way analysis of variance was done to find the possible correlation between the habit and the cancer.

Blood drawn from patients and healthy controls was divided into serum and was kept at −80°C. C-reactive protein (CRP) levels in the blood were measured using specialized enzyme-linked immunosorbent assay (ELISA) kits and with a microplate reader (SpectraMax I3X Plate reader, Biorad) as directed by the manufacturer. Using conventional laboratory techniques, we determined the white blood cell (WBC) count, lymphocyte count, neutrophil count, and erythrocyte sedimentation rate (ESR) (Robonik Autora, India).

Estimation of ILs

ILs (Cat No: SEA563Hu, Cloud-Clone Corp, Iraq) levels in serum was estimated with ELISA test kit. Protocol was followed as mentioned in the instructions manual. Concentration of respective test samples was estimated using standard graph drawn with Standards. In brief, plates were impregnated with 50 µL aliquots of 100-fold diluted serum in the respective wells and incubated at room temperature (20–25°C) for 2 h. The plates were then incubated after adding 50 µL aliquots of the respective standard (5 ng/mL to 100 ng/mL) in their labelled wells. Following washing, 50 µL of biotin-conjugated respective antibodies were added to each well and kept on shaker for 1 h. About 50 µL of the HRP-conjugated avidin solution was then added and again incubated at room temperature for 30 min. Following washing, 50 µL of chromogenic substrate was added and incubated on a shaker for 20 min till the development of color. Absorbance was recorded at 450 nm using a SpectraFluor-Plus (Tecan, USA) plate reader.

Statistical analysis

All the values obtained were the mean of triplicate and expressed as value±standard deviation. Analysis was done using the Excel software package (Version 11).

RESULTS

Age and disease incidence

From the demographic data, we found significant figures in terms of the age group frequency. The mean was found to be 59.7±5.5260 and 63.46±5.97 for the control and subjects, respectively ($p<0.05$). The median was calculated to be 59.5 and 63, respectively, for the control and subjects (Fig. 1). We found from the data that the subjects in the age group from 61 to 65 to be more susceptible to the disease ($p<0.05$) with a count of 28 out of 70 (40%). This trend was followed by those in the age group of 66–70 with a count of 21 out of 70 (21%). Moreover, the count was found to be 9 out of 70 (13%) for the age group 71–75.

Smoking, alcohol intake and disease incidence

From the data collected, we found no significant effect of smoking and alcohol habits on the cancer incidence. From the demographic data, we found 36% of them who are into smoking and the rest 64% were not into smoking (Fig. 2). We found that 27% of them are into alcohol abuse and 61% of them were not into alcohol intake. A two-way ANOVA was conducted to find the significant effect of the smoking and alcohol intake

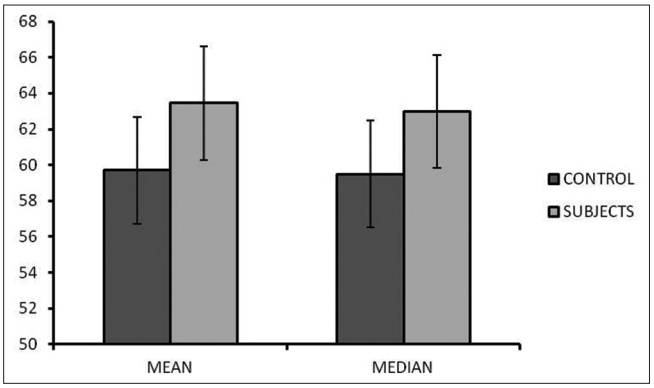

Fig. 1: Histogram showing the mean median of the control (n=20) and subjects group (n=70)

on the incidence of cancer. There was no significant effect seen between smoking and cancer incidence remembered at p<0.05 level (F[1,3]=0, p=1). There was no significant effect seen between alcohol and cancer incidence remembered at p<0.05 level (F[1,3]=81, p=0.07044).

Evaluation of blood parameters

From the hematological study, we found the parameters such as ESR, CRP, WBC, and neutrophil count to be elevated to abnormal levels when compared to control. On the other hand, the lymphocyte count got reduced significantly when compared to control (p<0.05). ESR was found to be 8.75±0.67 and 23.45±2.12, respectively, for the control and subjects. CRP was found to be 0.76±0.12 and 11.23±1.45, respectively, for the control and subjects. WBC was found to be 7.45±1.12 and 9.13 ±2.2, respectively, for the control and subjects. Neutrophil count was found to be 2325±212 and 5868±340, respectively, for the control and subjects. Lymphocyte count was found to be 2910±143 and 450±34, respectively, for the control and subjects (Table 1).

Cytokine level expression

We obtained serum samples from 70 patients and 20 healthy controls, and we analyzed the amounts of 5 general cytokines to determine the pattern of serum cytokine production in patients with PC. Patients had considerably greater levels of IL-2, IL-4, IL-6, IL-17A, and IL-10 than healthy controls.

Il-2 and IL-4 levels

We found significant results among the IL expression levels as determined by the ELISA method. The IL-2 and IL-4 levels were found to be elevated among the patient group when compared to control. IL-2 levels were elevated to 25.67±2.132 when compared to control (12.31±1.20215). Il-4 levels also followed the same pattern, where the subjects showed a rise to 45.63±3.4512 from the control (20.34±2.143726) (Fig. 3).

IL-6 and IL-10 levels

Similar pattern was seen with IL-6 and Il-10 also. The IL-6 and IL-10 levels were also found to be elevated among the patient group when compared to the control. IL-6 levels were elevated to 65.43±1.654 from control (21.34±0.9342) and IL-10 levels were found to be 12.341±2.1218 when compared to control (4.56±0.23154) (Fig. 4).

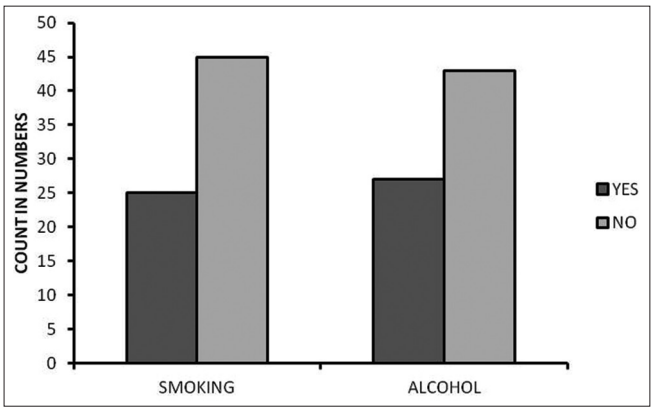

Fig. 2: Histogram showing the proportion of subjects (n=70) under the alcohol and smoking addiction

Table 1: The hematological parameters among the control (n=20) and subjects (n=70)

Parameter	Control	Subjects
ESR (mm/hr)	8.75±0.67	23.45±2.12
CRP (mg/dL)	0.76±0.12	11.23±1.45
WBC/mm^3	7.45±1.12	9.13±2.2
Neutrophil count (10^9)	2325±212	5868±340
Lymphocyte count (10^9)	2910±143	450±34

IL-17A levels

The IL-17A levels were also found to be elevated among the patient group when compared to control. Il-17A levels were elevated to 45.33±3.121 from 16.11±1.1132 (control) (Fig. 5).

DISCUSSION

The second most frequent malignancy in men worldwide is PCa. With an age-adjusted incidence rate of 29.4/100,000 population, it causes around 14.2% of new cancer cases in men [18]. PCa incidence rates are greater in North America, Europe, and Australia than in Asia and Africa. The increased frequency of screening tests in asymptomatic men or a real rise in the development of the disease could be the cause of the increasing incidence of PCa. PCa is known to be associated with old age, black ethnicity (which is particularly prevalent in some areas, like the US), and a family history of the disease [18]. However, there is not enough solid evidence to link the risk of PCa to a person's diet (including meat and dairy products), nutrition (like calcium and energy intake), physical characteristics (like height, weight, and energy expenditure), environmental factors (like exposure to chemicals and pesticides), and behavioral factors (like smoking and drinking alcohol) [19].

Compared to Western and European nations, India has comparatively lower incidence and mortality rates for PCa; nevertheless, the ratio of mortality to incidence rate is higher. In India, PCa is typically detected at an advanced stage. Interestingly, patients in India had a greater percentage of distant metastases (42.9%) than those in the USA (8.0%) and Norway (8.9%) [20]. An even greater percentage of late-stage illnesses has been documented in earlier Indian investigations. Lack of awareness, restricted access to care, and the absence of standard screening procedures could be the cause of the delayed presentation. Furthermore, delayed diagnosis may be a result of the aggressive nature of PCa in the Indian population [21].

According to the demographic data, patients between the ages of 61 and 65 were more likely to have the disease (p<0.05), with a count of 28 out of 70 (40%) in this age group. With a count of 21 out of 70 (21%), people in the 66–70 age range followed this tendency. The majority of cases of PCa occur in elderly men. There has been an increase in the number of younger males receiving diagnoses within the past 30 years. The median age at diagnosis before the PSA screening period was 70 years old. Over the previous 10 years, the median age at diagnosis was 67 [22]. Age has a significant impact on the incidence and fatality rates of PCa, with older men (over 65) having the highest incidence [23].

According to the data gathered, there is no discernible link between alcohol use and smoking and the risk of cancer. According to the demographic information, 36% of them smoke, while the remaining 64% do not. Yang *et al*. [24] revealed similar results, stating that current smokers had a considerably lower incidence of PCa, particularly in studies conducted during the era of PSA screening. Although there was no correlation between ever smoking and the risk of PCa in general analyses, there was a higher risk of PCa in the days before PSA screening. There was no correlation between prior smoking and the risk of PCa [24].

The fact that smoking is the primary risk factor for mortality in men is another explanation [25]. Before receiving a PCa diagnosis, smokers may pass away from smoking-related illnesses such as cancer, heart disease, and respiratory conditions. Cigarette smoking is responsible for 49% of cases of esophageal squamous cell carcinoma, 50% of cases of bladder cancer, the majority of cases of lung cancer, and head-and-neck cancer [26,27].

In addition, smoking was linked to a poor prognosis for patients with head-and-neck cancer and was reported to be the cause of almost 90% of lung cancer deaths [28]. Furthermore, when concentrating on a more aggressive malignancy, it is common to overlook the identification of asymptomatic PCa. Furthermore, smoking doubles or quadruples the risk of stroke and coronary heart disease, which are the two main causes

of mortality in the United States, with smoking being the primary cause of the majority of these deaths [28].

When compared to the control, we discovered that the hematological study's values, including ESR, CRP, WBC, and neutrophil count, were abnormally high. However, the number of lymphocytes was considerably lower than the control group ($p<0.05$).

In PCa, ESR can be a useful biomarker, especially for tracking the course of the disease and evaluating the effectiveness of treatment. Elevated ESR values may indicate higher inflammation and a more aggressive disease, but they are not a reliable diagnostic tool. High ESR has been linked in studies to worse survival results for men with PCa [29]. According to earlier research, CRP and ESR are thought to be prognostic inflammatory markers in PCa, and inflammation plays a significant role in the pathophysiology of this malignancy [30]. Research has indicated that persistent inflammation is linked to a number of malignancies, including those of the stomach, liver, and colon [31]. Acute and chronic inflammation can be diagnosed using two diagnostic tests for inflammation: ESR and CRP. Similar reports on WBC and neutrophils were reported by Watts *et al*. They stated that PCa mortality was linked to higher neutrophil and WBC counts [32]. Higher platelet counts have been found to positively correlate with the risk of diagnosing PCa, and higher WBC and neutrophil counts have been linked to an increased risk of dying from PCa. These findings may corroborate the theories regarding the roles that chronic inflammation and/or infection play in the initiation and/or progression of PCa [33].

Increased WBC counts may indicate inflammation, and persistent inflammation has been linked to an increased risk of PCa and other malignancies. Increases in platelet and WBC production are triggered by inflammation and infection [34]. Although it is uncertain whether chronic inflammation and/or the immune response are directly linked to PCa risk, prior research suggests that they may be related to general cancer incidence [35].

From our study, we found a significantly elevated level of all the cytokines (IL-2, IL-4, IL-6, IL-17A, and IL-10) among the subjects when compared to healthy controls. IL-2 and IL-4 have different functions in PCa that is connected to tumor growth and immunological responses [36]. While IL-4, an anti-inflammatory cytokine, can control immune responses and, in certain situations, stimulate tumor growth, IL-2, a crucial immune system component, may have an impact on tumor development by stimulating immune cells [37].

While elevated IL-4 levels are linked to tumor growth and hormone-refractory illness, elevated IL-2 levels in PCa may have anticancer properties. IL-2 may be engaged in endogenous defense mechanisms and may be a biomarker for PCa. Conversely, IL-4 is associated with elevated androgen expression and the activation of pathways that facilitate the growth of tumors [38]. Takeshi *et al*. [39] reported similar findings like, when comparing hormone-refractory PCa to hormone-sensitive illness, IL-4 levels are noticeably greater in the former. Elevated levels of serum PSA, a marker used in the diagnosis and surveillance of PCa, are associated with IL-4 levels. Wise *et al*. [40] also reported the elevated levels of cytokines among the PCa subjects ($p<0.01$).

IL-6 levels are generally higher in PCa, particularly when the illness progresses. Poor prognosis, metastasis, and disease progression are linked to this rise. PCa cells' autocrine and paracrine growth regulation is linked to IL-6, indicating that it contributes to the formation and spread of tumors [41]. Among males with advanced, hormone-independent PCa, serum IL-6 levels are noticeably elevated [42]. Giri *et al*. [42] confirmed the levels of IL-6, where n contrast to healthy prostatic tissue, we have demonstrated in this study that the mean IL-6 content of PCa tissues is 18 times higher. IL-6 levels were also found in rising state in patients with metastatic PCa [43]. In case of IL-10, we did notice some studies, where the levels of IL-10 are not consistent. Some studies suggest that a lower risk of PCa is linked to elevated levels of

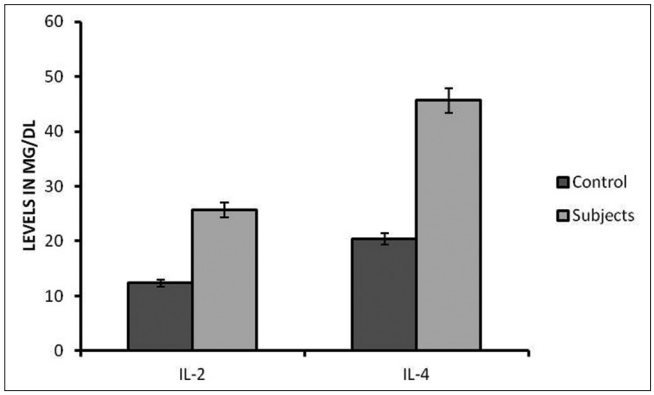

Fig. 3: Histogram drawn for the interleukin (IL-2) and IL-4 observed among the control and subjects. Experiments are done in triplicate and expressed in terms of standard deviation ($p<0.05$)

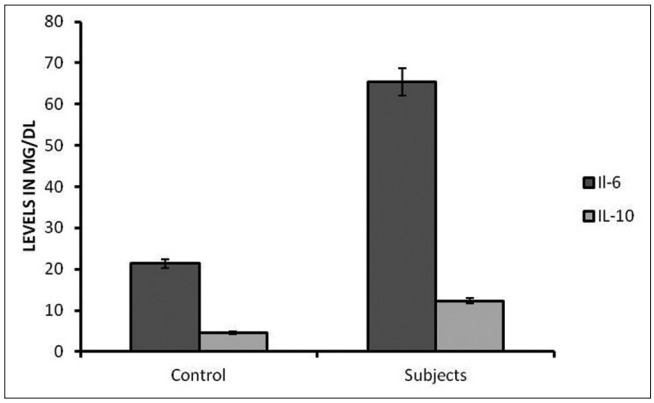

Fig. 4: Histogram drawn for the interleukin (IL-6) and IL-10 observed among the control and subjects. Experiments are done in triplicate and expressed in terms of standard deviation ($p<0.05$)

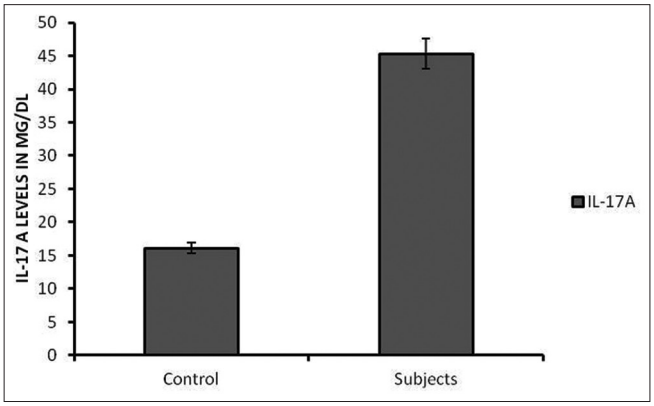

Fig. 5: Histogram drawn for the interleukin-17A observed among the control and subjects. Experiments are done in triplicate and expressed in terms of standard deviation ($p<0.05$)

the anti-inflammatory cytokine IL-10 [44]. At the same time, we found some works stating a complicated association between high IL-10 levels and worse prognoses in the setting of PCa. In addition, IL-10 can directly affect PCa cells, which may accelerate the growth and spread of the tumor [45]. Over-expression of this cytokine was found to be linked to PCa development among different populations [46,47].

A worse prognosis and more aggressive PCa are linked to elevated levels of IL-17A and IL-17RA. Tumor size and poorer prognoses are associated

with IL-17A expression, but extracapsular extension may be indicated by IL-17RA levels [48]. One important cytokine in the IL-17 family, IL-17A, has the ability to encourage tumor growth and metastasis [49,50]. Patients with PCa who have higher serum levels of IL-17A have a worse prognosis and bigger tumors. PCa is among the many tumors for which IL-17A has been demonstrated to stimulate tumor development and spread. By upregulating PD-L1 expression, elevated IL-17A levels can also lead to resistance to anti-PD-1 treatment [51]. Although some have only partially reported our results, here we present the cytokine expression levels, lifestyle choices, and cancer incidence. However, we recognize a need and intend to expand our study in a clinical context. This will help clarify the function of cytokines in PCa and any possible therapeutic ramifications.

CONCLUSION

We discovered noteworthy numbers for the frequency of each age group using the demographic data. With a count of 28 out of 70 (40%), we discovered that the patients in the 61–65 age group were more prone to the disease ($p<0.05$). According to the data gathered, there is no discernible link between alcohol use and smoking and the risk of cancer. However, there was no discernible relationship between alcohol use, smoking habits, and cancer incidence. From our study, we found that the patients' levels of IL-2, IL-4, IL-6, IL-17A, and IL-10 were significantly higher than those of healthy controls. The ELISA approach revealed significant differences in the levels of IL expression. When compared to the control group, the sick group's IL-2 and IL-4 levels were shown to be higher. This would validate the robust correlation between PCa and ILs. In conclusion, this study clarifies the potential of ILs as markers in PCa. To ascertain the function and potential use of both markers in PCa, more research is necessary, ideally with a control group and long-term results.

AUTHOR'S CONTRIBUTION

Study, design, and implementation (Author 1, 2, 3); manuscript editing and evaluation: (Author 1, 2, 3, 4).

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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REFERENCES

1. Chen J, Zhang D, Yan W, Yang D, Shen B. Translational bioinformatics for diagnostic and prognostic prediction of prostate cancer in the next-generation sequencing era. Biomed Res Int. 2013;2013:901578. doi: 10.1155/2013/901578, PMID 23957008
2. Termini D, Den Hartogh DJ, Jaglanian A, Tsiani E. Curcumin against prostate cancer: Current evidence. Biomolecules. 2020;10(11):1536. doi: 10.3390/biom10111536, PMID 33182828
3. Cittadini A, Isidori AM, Salzano A. Testosterone therapy and cardiovascular diseases. Cardiovasc Res. 2022;118(9):2039-57. doi: 10.1093/cvr/cvab241, PMID 34293112
4. Takayama KI. Splicing factors have an essential role in prostate cancer progression and androgen receptor signaling. Biomolecules. 2019;9(4):131. doi: 10.3390/biom9040131, PMID 30939845
5. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, *et al*. Cancer statistics, 2020: Report from national cancer registry programme, India. JCO Glob Oncol. 2020;6:1063-75. doi: 10.1200/GO.20.00122, PMID 32673076
6. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. doi: 10.3322/caac.21660, PMID 33538338
7. Pernar CH, Ebot EM, Wilson KM, Mucci LA. The epidemiology of prostate cancer. Cold Spring Harb Perspect Med. 2018;8(12):a030361. doi: 10.1101/cshperspect.a030361, PMID 29311132
8. Bhardwaj P, Au CM, Benito-Martin A, Ladumor H, Oshchepkova S, Moges R, *et al*. Estrogens and breast cancer: Mechanisms involved in obesity-related development, growth and progression. J Steroid Biochem Mol Biol. 2019;189:161-70. doi: 10.1016/j.jsbmb.2019.03.002, PMID 30851382
9. Ramis-Zaldivar JE, Gonzalez-Farre B, Nicolae A, Pack S, Clot G, Nadeu F, *et al*. MAPK and JAK-STAT pathways dysregulation in plasmablastic lymphoma. Haematologica. 2021;106(10):2682-93. doi: 10.3324/haematol.2020.271957, PMID 33951889
10. Ugge H, Downer MK, Carlsson J, Bowden M, Davidsson S, Mucci LA, *et al*. Circulating inflammation markers and prostate cancer. Prostate. 2019;79(11):1338-46. doi: 10.1002/pros.23842, PMID 31212389
11. Toriola AT, Laukkanen JA, Kurl S, Nyyssönen K, Ronkainen K, Kauhanen J. Prediagnostic circulating markers of inflammation and risk of prostate cancer. Int J Cancer. 2013;133(12):2961-7. doi: 10.1002/ijc.28313, PMID 23754532
12. Garrido MM, Ribeiro RM, Krüger K, Pinheiro LC, Guimarães JT, Holdenrieder S. Are proinflammatory cytokines relevant for the diagnosis of prostate cancer? Anticancer Res. 2021;41(6):3067-73. doi: 10.21873/anticanres.15090, PMID 34083299
13. Stark JR, Li H, Kraft P, Kurth T, Giovannucci EL, Stampfer MJ, *et al*. Circulating prediagnostic interleukin-6 and C-reactive protein and prostate cancer incidence and mortality. Int J Cancer. 2009;124(11):2683-9. doi: 10.1002/ijc.24241, PMID 19189403
14. Parekh DJ, Ankerst DP, Baillargeon J, Higgins B, Platz EA, Troyer D, *et al*. Assessment of 54 biomarkers for biopsy-detectable prostate cancer. Cancer Epidemiol Biomarkers Prev. 2007;16(10):1966-72. doi: 10.1158/1055-9965.EPI-07-0302, PMID 17932343
15. Roumeguère T, Legrand F, Rassy EE, Kaitouni MI, Albisinni S, Rousseau A, *et al*. A prospective clinical study of the implications of IL-8 in the diagnosis, aggressiveness and prognosis of prostate cancer. Future Sci OA. 2018;4(2):FSO266. doi: 10.4155/fsoa-2017-0084, PMID 29379640
16. Xu S, Hu Y, Zhang L, Yue S, Zhang L, Liang C. Association of cytokine gene polymorphisms with prostate cancer risk from a study in central China. Contrast Media Mol Imaging. 2022;2022:1259009. doi: 10.1155/2022/1259009, PMID 36034203
17. Li BH, Yan SY, Luo LS, Zeng XT, Wang YB, Wang XH. Ten interleukins and risk of prostate cancer. Front Oncol. 2023;13(13):1108633. doi: 10.3389/fonc.2023.1108633, PMID 36733309, PMCID PMC9887118
18. Hsing AW, Devesa SS. Trends and patterns of prostate cancer: What do they suggest? Epidemiol Rev. 2001;23(1):3-13. doi: 10.1093/oxfordjournals.epirev.a000792, PMID 11588851
19. Eapen RS, Herlemann A, Washington SL, 3rd, Cooperberg MR. Impact of the United States preventive services task force 'D' recommendation on prostate cancer screening and staging. Curr Opin Urol. 2017;27(3):205-9. doi: 10.1097/MOU.0000000000000383, PMID 28221220
20. Sailo SL, Sailo LP, Stonewann VC. Clinicopathological profile of prostate cancer patients: A 10 years retrospective study from a tertiary care centre, North East India. J Clin Diagn Res. 2022;16:PC7-10. doi: 10.7860/JCDR/2022/57485.17161
21. Hariharan K, Padmanabha V. Demography and disease characteristics of prostate cancer in India. Indian J Urol. 2016;32(2):103-8. doi: 10.4103/0970-1591.174774, PMID 27127351
22. Brawley OW. Trends in prostate cancer in the United States. J Natl Cancer Inst Monogr. 2012;2012(45):152-6. doi: 10.1093/jncimonographs/lgs035, PMID 23271766, PMCID PMC3540881
23. Rawla P. Epidemiology of prostate cancer. World J Oncol. 2019;10(2):63-89. doi: 10.14740/wjon1191, PMID 31068988, PMCID PMC6497009
24. Yang X, Chen H, Zhang S, Chen X, Sheng Y, Pang J. Association of cigarette smoking habits with the risk of prostate cancer: A systematic review and meta-analysis. BMC Public Health. 2023;23(1):1150. doi: 10.1186/s12889-023-16085-w, PMID 37316851
25. De Nunzio C, Tema G, Trucchi A, Cicione A, Sica A, Lombardo R, *et al*. Smoking reduces PSA accuracy for detection of prostate cancer: Results from an Italian cross-sectional study. Minerva Urol Nefrol. 2019;71(6):583-9. doi: 10.23736/S0393-2249.19.03360-5, PMID 31144489
26. Sturgis EM, Wei Q, Spitz MR. Descriptive epidemiology and risk factors for head and neck cancer. Semin Oncol. 2004;31(6):726-33. doi: 10.1053/j.seminoncol.2004.09.013, PMID 15599850
27. Karam-Hage M, Cinciripini PM, Gritz ER. Tobacco use and cessation for cancer survivors: An overview for clinicians. CA Cancer J Clin. 2014;64(4):272-90. doi: 10.3322/caac.21231, PMID 24817674
28. Foerster B, Pozo C, Abufaraj M, Mari A, Kimura S, D'Andrea D, *et al*. Association of smoking status with recurrence, metastasis, and mortality among patients with localized prostate cancer undergoing prostatectomy or radiotherapy: A systematic review and meta-analysis.

JAMA Oncol. 2018;4(7):953-61. doi: 10.1001/jamaoncol.2018.1071, PMID 29800115
29. Johansson JE, Sigurdsson T, Holmberg L, Bergström R. Erythrocyte sedimentation rate as a tumor marker in human prostatic cancer. An analysis of prognostic factors in 300 population-based consecutive cases. Cancer. 1992;70(6):1556-63. doi: 10.1002/1097-0142(19920915)70:6<1556:aid-cncr2820700619>3.0.co;2-i, PMID 1516006
30. Eklund CM, Tammela TL, Schleutker J, Hurme M. C-reactive protein haplotype is associated with high PSA as a marker of metastatic prostate cancer but not with overall cancer risk. Br J Cancer. 2009;100(12):1846-51. doi: 10.1038/sj.bjc.6605081, PMID 19436291
31. Platz EA, De Marzo AM. Epidemiology of inflammation and prostate cancer. J Urol. 2004;171(2 Pt 2):S36-40. doi: 10.1097/01.ju.0000108131.43160.77, PMID 14713751
32. Watts EL, Perez-Cornago A, Kothari J, Allen NE, Travis RC, Key TJ. Hematologic markers and prostate cancer risk: A prospective analysis in UK Biobank. Cancer Epidemiol Biomarkers Prev. 2020;29(8):1615-26. doi: 10.1158/1055-9965.EPI-19-1525, PMID 32457180
33. Caini S, Gandini S, Dudas M, Bremer V, Severi E, Gherasim A. Sexually transmitted infections and prostate cancer risk: A systematic review and meta-analysis. Cancer Epidemiol. 2014;38(4):329-38. doi: 10.1016/j.canep.2014.06.002, PMID 24986642
34. Ghoshal K, Bhattacharyya M. Overview of platelet physiology: Its hemostatic and nonhemostatic role in disease pathogenesis. ScientificWorldJournal. 2014;2014:781857. doi: 10.1155/2014/781857, PMID 24729754
35. Doat S, Marous M, Rebillard X, Trétarre B, Lamy PJ, Soares P, *et al*. Prostatitis, other genitourinary infections and prostate cancer risk: Influence of non-steroidal anti-inflammatory drugs? Results from the EPICAP study. Int J Cancer. 2018;143(7):1644-51. doi: 10.1002/ijc.31565, PMID 29696626
36. Jiang T, Zhou C, Ren S. Role of IL-2 in cancer immunotherapy. Oncoimmunology. 2016;5(6):e1163462. doi: 10.1080/2162402X.2016.1163462, PMID 27471638
37. Chen R, Liu L, Chen H, Xing C, Zhang T, Pang Y, *et al*. Evaluation of the clinical application value of cytokine expression profiles in the differential diagnosis of prostate cancer. Cancer Immunol Immunother. 2024;73(8):139. doi: 10.1007/s00262-024-03723-4, PMID 38833027
38. Mao C, Ding Y, Xu N. A double-edged sword role of cytokines in prostate cancer immunotherapy. Front Oncol. 2021 Nov 16;11:688489. doi: 10.3389/fonc.2021.688489, PMID 34868907
39. Takeshi U, Sadar MD, Suzuki H, Akakura K, Sakamoto S, Shimbo M, *et al*. Interleukin-4 in patients with prostate cancer. Anticancer Res. 2005;25(6C):4595-8. PMID 16334148
40. Wise GJ, Marella VK, Talluri G, Shirazian D. Cytokine variations in patients with hormone treated prostate cancer. J Urol. 2000;164(3 Pt 1):722-5. doi: 10.1097/00005392-200009010-00024, PMID 10953133
41. Nguyen DP, Li J, Tewari AK. Inflammation and prostate cancer: The role of interleukin 6 (IL-6). BJU Int. 2014 Jun;113(6):986-92. doi: 10.1111/bju.12452, PMID 24053309
42. Giri D, Ozen M, Ittmann M. Interleukin-6 is an autocrine growth factor in human prostate cancer. Am J Pathol. 2001 Dec;159(6):2159-65. doi: 10.1016/S0002-9440(10)63067-2, PMID 11733366
43. Lou W, Ni Z, Dyer K, Tweardy DJ, Gao AC. Interleukin-6 induces prostate cancer cell growth accompanied by activation of stat3 signaling pathway. Prostate. 2000 Feb 15;42(3):239-42. doi: 10.1002/(sici)1097-0045(20000215)42:3<239:aid-pros10>3.0.co;2-g, PMID 10639195
44. Thomas CE, Bauer DC, Yuan JM, Cauley JA. Circulating IL-10 is associated with reduced risk of prostate cancer in a prospective cohort of elderly men: The MrOS study. Cancer Causes Control. 2023 Jan;34(1):59-68. doi: 10.1007/s10552-022-01639-x, PMID 36239865
45. Ouyang W, O'Garra A. IL-10 family cytokines IL-10 and IL-22: From basic science to clinical translation. Immunity. 2019;50(4):871-91. doi: 10.1016/j.immuni.2019.03.020, PMID 30995504
46. Chen KY, Chien WC, Liao JM, Tsai CW, Chang WS, Su CH, *et al*. Contribution of interleukin-10 genotype to triple negative breast cancer risk. Anticancer Res. 2021;41(5):2451-7. doi: 10.21873/anticanres.15020, PMID 33952470
47. Al-janaby MS, Al-ani MQ, Rasheed MN. Relationship between some immunological factors and type 2 diabetes mellitus in Iraqi patients. Asian J Pharm Clin Res. 2018 Jun;11(6):489-92. doi: 10.22159/ajpcr.2018.v11i6.25881
48. Elbaz FK, Aly HF, Khalil WK, Ali GH, Booles HF. *Haematococcus pluvialis* extract promoting the recovery of memory impairment in Alzheimer's rats: Anti-inflammatory and antiapoptotic effects. Asian J Pharm Clin Res. 2016 Dec;9(9):171-7. doi: 10.22159/ajpcr.2016.v9s3.14715
49. Singh A, Jaiswal V, Bisht S. Advances in cocrystals of anticancer agents: Formulation strategies and therapeutic implications. Int J Pharm Pharm Sci. 2024 Jun;16(6):27-32. doi: 10.22159/ijpps.2024v16i6.51044
50. Kiełb P, Kaczorowski M, Kowalczyk K, Piotrowska A, Nowak Ł, Krajewski W, *et al*. Role of IL-17A and IL-17RA in prostate cancer with lymph nodes metastasis: Expression patterns and clinical significance. Cancers (Basel). 2023 Sep 15;15(18):4578. doi: 10.3390/cancers15184578, PMID 37760548
51. Na G, Ge S, Ying Z, Moustafa AA, Dongxia G, Zongbing Y. Interleukin-17 promotes migration and invasion of human cancer cells through upregulation of MTA1 expression. Front Oncol. 2019;9:546.