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ASSOCIATION BETWEEN CHRONIC INFLAMMATION AND THE DEVELOPMENT OF PROSTATE CANCER

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Abstract

Background: Chronic inflammation is gradually being identified as a risk factor of many malignancies, however, the role of this inflammation in causing prostate cancer (PCa) and the mechanism behind it are yet to be fully established. This paper sought to measure the relationship between chronic prostate inflammation and PCa progression, profile the microenvironment of inflammation, and simulate the dynamics of genomic instability driven by inflammation.Methods: A multi-stage design was used: a retrospective cohort of 1,247 men with prostate biopsies were followed over five years, a prospective case/control study with 320 PCa patients and 320 controls, and an in vitro study exposing RWPEêm1 and PNT2 cells to macrophageLTMedium over 14 days. Inflammation grading of histopathological inflammation, serum and tissue cytokines levels oxidative stress (8plessOHdG, ROS), and DNA doublenezstrand breaks (-H2AX) were measured. The firstorder kinetic modeling and logistic regression were used. Epigenetic modifications (GSTP1 methylation, MYC amplification and PTEN loss) were evaluated in proliferative inflammatory atrophy (PIA), prostate intraepithelial neoplasia (PIN) tissues and PCa tissues.Findings: A severe chronic inflammation (Grade 3 4) was linked to a 5 dieser PCa incidence of 41.2 to 53.6% and an adjusted hazard ratio of 9.87 in the highest CIBI quartile. PCa patients exhibited a dramatic increase in IL peque1b (5.15 plusieursfoit, $p<0.001$) and 8 nous OHdG \. The logistic regression model had an AUC of 0.92. Chronic inflammatory response in vitro raised the rate constant \The hypermethylation of GSTP1 rose steadily between 11.5 per cent in low grade PIA to 92.3 per cent in high grade PCa. The population attributable fraction of PCa in high CIBI was 54.2%.Conclusions: Chronic prostate inflammation facilitates the process of prostate carcinogenesis by causing oxidative DNA damage, impaired repair and progressive epigenetic changes. Chronic inflammation is an important and modifiable risk factor of aggressive PCa, with the inflammatory burden index being a strong predictor of cancer risk and upgrading. These results justify antiinflammatory methods of chemoprevention.

Keywords: Chronic inflammation, prostate cancer, oxidative DNA damage, inflammasome, proliferative inflammatory atrophy, GSTP1 hypermethylation.

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INTRODUCTION

Chronic inflammation has also been reported as a potent risk factor in the pathogenesis of many types of carcinomas, such as liver, colon, urinary bladder, and pancreatic carcinomas (Chen et al., 2019). Experimental data are becoming more strongly implicated in a close relationship between chronic inflammation over a long period and stimulation of prostate carcinogenesis (Glover et al., 2017). This connection is evidenced by the fact that proliferative inflammatory atrophy, which is a possible precursor lesion with molecular similarities to prostate intraepithelial neoplasia and known prostate cancer can be caused by prostatic inflammation (Singh et al., 2010). This hyperinflammatory microenvironment supports the occurrence of genomic instability by repeated generation of reactive oxygen and nitrogen species, cytokines and chemokines, hence affecting cellular homeostasis and enhancing the tendency to neoplastic transformation (Elkahwaji et al., 2009). It is an ongoing inflammatory state, which involves turning on pathways including NF-KB and TNF-A, and has led to ongoing tissue damage and repair cycles, which further enhances genetic changes and tumor progression (Spagnuolo, 2020). These chronic inflammatory conditions, which are frequently caused by bacterial, viral or parasitic infections, chemical irritants or non-digestible particles, create a growth-factor-rich and angiogenic factor-rich environment which can predispose tumorigenesis (Ryan and Small, 2004). Furthermore, chronic inflammation in prostate biopsies has been linked to a higher risk of PCa upgrading after radical prostatectomy, suggesting its activity in promoting more disease aggressive phenotypes (Güner et al., 2021). This interaction of continual inflammatory reactions and oxidative stress pathways thereby results in a microenvironment that supports mutagenesis and oncogenic transformation in prostatic epithelial cells (Katongole et al., 2020). In particular, the long-term oxidative stress caused by chronic inflammation may cause the damage of DNA and epigenetic changes, which may also lead to the development and progression of prostate cancer (Pérez-Gomez et al., 2023). Pro-inflammatory cytokines and growth factors usually mediate this process and define uncontrolled proliferation responses to increase cells susceptibility to mutations (Sciarra et al., 2016). These inflammatory factors may be caused by microbial infections, including some sexually transmitted infections, or by autoimmune

reactions, which in combination lead to the occurrence of prostatitis and, eventually, prostate cancer (Candore et al., 2010). This process is facilitated by macrophages, which are an important part of the inflammatory infiltrate, which produces the reactive oxygen and reactive nitrogen species which damage DNA and drive carcinogenesis (Josson et al., 2009). This chronic genotoxic stress which is intensified by growth factors and angiogenic factors secreted by inflammatory cells provides a fertile environment of genetic changes essential to oncogenic transformation (Dickinson & Holloway, 2013). This is supported by epidemiological reports demonstrating a correlation between chronic prostatitis and high levels of prostate specific antigen as well as a slightly higher risk of prostate cancer (Khandrika et al., 2009). Moreover, intra-prostatic inflammation may be triggered or worsened by a variety of endogenous and exogenous factors, such as diet, some chemical exposures, and an altered microbiome, thereby contributing to the DNA double-strand breaks and triggering androgen receptor activation in prostate epithelial cells (Bono et al., 2020). The exact first cause of this chronic inflammation of the prostate, however, has yet to be established, and the possible causes include pathogenic infections, cellular injury, certain dietary compositions and hormonal imbalances (Wong et al., 2008). This chronic inflammatory reaction is usually marked by the abnormal expression of enzymes like cyclooxygenase-2 and loss or loss of control of important tumor suppressors like glutathione S-transferase P1 which promotes neoplastic development and angiogenesis in the prostate tissue (Udensi and Tchounwou, 2016). This complex interplay of chronic inflammation and cellular changes forms a microenvironment that not only facilitates the development of cancer in prostate cells but also contributes to the further development and progression of prostate cancer through multiple pathways, such as epithelial-to-mesenchymal transition and the activation of inflammasomes (Sharma et al., 2025). All these intricate interactions include the IL1R-TLR-IRAK-NF-kB cascade, among many others, which play a role in metabolic reprogramming and immunosuppression in the prostatic milieu, thus providing an environment in which tumor development and progression thrive (Oseni et al., 2023). This series of events underscores the importance of chronic inflammatory events as a key, multi-dimensional factor in the initiation and progression of prostate cancer, thus revealing possible therapeutic targets in this complicated disease pathway. Particularly, the long-term inflammation is associated with epigenetic modifications,

including DNA and histone modifications, which facilitate the alteration of the expression of a variety of genes related to inflammation, thereby facilitating the occurrence of prostate cancer (Wang et al., 2019). Such epigenetic changes may involve silencing of tumor suppressor genes and activation of oncogenes, which further contribute to the neoplastic transformation (Andrés et al., 2018). This epigenomic corruption, such as GSTP1 silencing and de novo DNA methylation, in addition to telomere shortening and c-Myc activation of proliferative inflammatory atrophy lesions, sets a critical precedent to malignant progression (Nelson et al., 2013). Such molecular deviations imply that proliferative inflammatory atrophy is an important intermediate pathway in which inflammatory cues trigger genomic and epigenomic instability, which predisposes prostatic cells to ensuing carcinogenic events (Sfanos & Marzo, 2011). This idea can be justified by the facts that proliferative inflammatory atrophy is becoming a predisposing condition to prostatic intraepithelial neoplasia and prostate cancer, which are both associated with increased levels of inflammatory markers (Prakash et al., 2024; Thompson et al., 2013). As a matter of fact, it is believed that widespread inflammatory lesions, including proliferative inflammatory atrophy, can serve as a "hotbed" where prostatic intraepithelial neoplasia and invasive carcinoma may develop (Graham et al., 2024). Additional research suggests that these inflammatory mechanisms are tightly interconnected with the activation of inflammasomes, which, in turn, leads to the release of pro-inflammatory cytokines such as IL-18, IL-1β, and TNF-alpha, thereby building a tumor microenvironment, which promotes cancer development (Liang et al., 2023). This proliferative inflammatory atrophy, as it is known, is a hypothetical transition between prostatic inflammation and carcinogenesis, which can be a critical connection in the outer peripheral zones of the gland (Bahmad et al., 2021; Lai et al., 2012). Chronic inflammation in these areas has been believed to trigger proliferative inflammatory atrophy that may eventually lead to prostatic intraepithelial neoplasia and then to invasive adenocarcinoma (Packer & Maitland, 2016). Genomic instability and epigenetic changes in the proliferative inflammatory atrophy lesions, including hypermethylation of the GSTP1 gene, are further features of this transition, with a high proportion of these lesions showing it (Gharieb, 2017). They are lesions with a partial promoter hypermethylation and silencing of GSTP1, and genetic changes, including Ets fusions, P53 mutations, and centromere copy number of chromosome 8 (Graham et al., 2024). This intricate molecular

environment of proliferative inflammatory atrophy lesions highlights their pivotal position in the pathogenesis of prostate cancer, and as a hub of genetic and epigenetic modifications induced by inflammation converging to support malignant transformation (Bardia et al., 2009). Proliferative inflammatory atrophy caused by oxidative stress in response to diverse stimuli initiates the cascade of genetic changes, such as overexpression of MYC, fusions of ETS, GSTP1 methylation, loss of PTEN, and telomere shortening, thus gradually developing into high-grade prostatic intraepithelial neoplasia and later adenocarcinoma (Fiard

METHODOLOGY

The design used in this study was a problem based, multi-phase research design to determine the causal and mechanistic relationship between chronic inflammation and prostate cancer development. The study was designed in three phases that are interwoven: retrospective cohort study to determine epidemiological correlation, a prospective caseisescontrol study to determine the inflammatory biomarkers in prostate tissues, and an experimental component in vitro to model the inflammatory microenvironment and measure oxidative stressinessinduced genomic damage. The institutional review board had approved all procedures that involved human subjects and informed consent was obtained by all subjects. The paper followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations on observational studies.

In the retrospective cohort phase, two tertiary care centers with a time span of 2010-2020 provided medical records and archived prostate biopsy specimens. The inclusion criteria were male patients with a minimum age of 45 years who had at least one prostate biopsy due to elevated prostatepletastic antigen (PSA) levels or abnormal digital rectal examination. The exclusion criteria were any previous diagnosis of any malignancy, known hereditary syndromes of prostate cancer or prior use of antiinflammatory drug (nonplesssteroidal antilezinflammatory drugs and glucocorticoids) more than three months in the last five years. One thousand two hundred and forty-seven patients were eligible. The extent of inflammation (chronic) on biopsy samples was graded using a validated histopathological grading system of the density and the extent of lymphocytic and macrophage infiltration in the stroma and in the periglandular areas. The main effect was the consequent onset of prostate cancer as dictated by the follow up biopsy or radical prostatectomy within five years of the index biopsy. The hazard

ratios were estimated using multivariable Cox proportional hazards regression to adjust the age, baseline PSA, family history, and smoking status.

During the prospective casecontrol stage, 320 new prostate cancer cases and 320 age and ethnicitymatched cancer-free controls were recruited. Transrectal ultrasoundibileoposy was performed to ensure that it was free of malignancy. Serum samples and eight core biopsy samples (six peripheral zone, two transitional zone) of each participant were obtained. ELISA was used to measure concentrations of essential inflammatory cytokines - interleukinneath6 (IL nearest6), tumor necrosis factorneathalpha (TNF nearest alpha), and interleukinneath1betrex (IL nearest1betrex). Further, reactive oxygen species (ROS) concentration in the tissues was determined by 8izontoxyoxyguanosine (8OHdG) by using high performance liquid chromatography and electrochemical method. A logistic regression function was derived to model dynamic relationship between chronic inflammatory burden and the likelihood of malignant transformation. Where PP is the probability of developing prostate cancer, II is the composite inflammatory score (a sum of zwohnerscored levels of cytokines and the concentration of ROS), and CC is a covariate vector. This equation is as follows:

$$P = \frac{1}{1 + e^{-(\beta_0 + \beta_1 I + \boldsymbol{\beta}^T \mathbf{C})}}$$

where 0 0 is the intercept, 1 1 is the coefficient of the inflammatory score and 0 - is the coefficient of covariates, such as age, PSA, and smoking. The estimates of the model parameters were made using maximum likelihood.

The experimental phase in vitro was aimed at measuring the rate of DNA double uncleavage in prevalence of chronic inflammatory conditions. Prostate epithelial cell lines of humans (RWPE żieux 1 and PNT 2) were cultured in the presence of keratinocyte serum LE and subjected to a conditioned medium containing activated macrophages (THPʒieux 1 cells in the presence of lipopolysaccharide and interferonieux 1). The cells were exposed to 14 days simulating chronic exposure. After every 48 hours fresh conditioned medium was added. On days 3, 7, 10 and 14, genomic DNA was isolated and the incidence of the doublestrand breaks was determined using the γH2AX immunofluorescence test. A firstzelvilord kinetic model was used to mathematically model the time dependence of the accumulation of DNA damage during sustained inflammatory stress. Where

D(t)D(t) is the number of breaks of the double strand per cell at time ttt (days), kdamkdam the rate constant of the damage caused by inflammatory mediators and krepkrep the firstorder repair constant. The change in damage is indicated by the net change or the change in the net damage, and this is represented by the differential equation:

$$\frac{dD}{dt} = k_{dam} - k_{rep}D(t)$$

Parameters were estimated by nonlinear least-squares fitting to the experimental data. Statistical significance was assessed using Student's t-test for paired comparisons and one-way analysis of variance (ANOVA) with Tukey's post-hoc test for multiple comparisons, with a significance threshold of $\alpha = 0.05$. All analyses were performed using R version 4.2 (R Foundation for Statistical Computing), and the study was powered at 80% to detect a 25% relative increase in cancer risk associated with high inflammatory scores.

RESULTS

Table 1 illustrates that the baseline PSA and atypical small acinar proliferation is much more common and prevalent in patients with chronic inflammation. The inflammation grades are significantly associated with increasing cancer risk and more aggressive characteristics, which is apparent in Table 2. Table 3 affirms that the levels of ILizontin 6, TNF quale, IL inventin 1, oxidative stress indicators like 8 OHdG and ROS are highly promoted among patients with prostate cancer. Table 4 measures predictive power of the inflammatory score of which odds ratio is 6.49 per unit increase. Table 5 discovers that chronic inflammation raises the rate constant kdamkdamkdam of DNA damage and decreases the capacity to repair, krepkrep. Table 6 shows a progressive progression of epigenetic lesions of normal epithelium to highnetdevgrade prostate cancer. Inflammasome activation markers strongly correlate with the grade of inflammation, as seen in Table 7. Table 8 means that preoperative inflammation is connected with a sixfold greater likelihood of pathological upgrading. Lastly, Table 9 shows that patients in the top CIBI quartile are at risk of developing prostate cancer almost ten times greater with 54 percent of the population attributable fraction.

Table 1: Baseline Characteristics of the Retrospective Cohort Stratified by Chronic Inflammation Status

Parameter	No Chronic Inflammation (n=612)	Chronic Inflammation (n=635)	P-value
Age (years)	62.4 ± 8.7	63.1 ± 9.2	0.184
Baseline PSA (ng/mL)	4.2 ± 1.8	6.7 ± 2.4	<0.001
PSA density (ng/mL²)	0.11 ± 0.04	0.18 ± 0.06	<0.001
Family history of PCa (%)	12.4	14.1	0.382
Smoking (pack-years)	14.3 ± 12.1	22.6 ± 15.3	<0.001
BMI (kg/m²)	27.1 ± 3.4	28.4 ± 3.9	0.027
IPSS score	6.2 ± 4.1	9.8 ± 5.2	<0.001
Atypical small acinar proliferation (%)	2.9	8.7	<0.001
Prostatic volume (cm³)	42.3 ± 18.4	48.9 ± 20.1	0.032

Table 2: Histopathological Inflammation Grade and Five-Year Prostate Cancer Incidence

Inflammation Grade	n	Cancer at 5 years (%)	HR (95% CI)	Adjusted HR* (95% CI)	Mean time to cancer (months)	% with Gleason ≥7	% with extraprostatic extension
Grade 0 (none)	278	8.3	1.00 (ref)	1.00 (ref)	48.2 ± 11.4	14.5	3.2
Grade 1 (mild)	341	14.9	1.82 (1.21–2.74)	1.67 (1.10–2.53)	41.7 ± 13.2	22.1	5.8
Grade 2 (moderate)	312	27.6	3.45 (2.33–5.11)	2.98 (2.01–4.42)	34.5 ± 12.8	38.4	11.2
Grade 3 (severe)	204	41.2	5.67 (3.89–8.26)	4.93 (3.34–7.28)	28.1 ± 10.5	54.2	19.7
Grade 4 (very severe)	112	53.6	7.89 (5.12–12.16)	6.71 (4.33–10.40)	22.3 ± 9.7	71.4	31.3

Table 3: Inflammatory and Oxidative Stress Biomarkers in Cases vs. Controls

Biomarker (units)	Controls (n=320)	Prostate Cancer Cases (n=320)	Fold change	P-value	AUC (95% CI)
IL-6 (pg/mL)	1.24 ± 0.47	4.89 ± 1.52	3.94	<0.001	0.87 (0.83–0.91)
TNF-α (pg/mL)	2.31 ± 0.89	7.23 ± 2.14	3.13	<0.001	0.84 (0.80–0.88)

IL-1β (pg/mL)	0.67 ± 0.23	3.45 ± 1.08	5.15	<0.001	0.91 (0.88–0.94)
IL-8 (pg/mL)	5.43 ± 1.92	15.67 ± 4.32	2.89	<0.001	0.79 (0.74–0.84)
CRP (mg/L)	1.12 ± 0.56	4.23 ± 1.44	3.78	<0.001	0.83 (0.79–0.87)
8-OHdG (ng/mL)	0.23 ± 0.08	1.87 ± 0.61	8.13	<0.001	0.94 (0.91–0.97)
ROS (μM equivalent)	12.4 ± 4.2	58.3 ± 15.7	4.70	<0.001	0.89 (0.85–0.93)
Nitrotyrosine (μM)	0.18 ± 0.06	0.92 ± 0.29	5.11	<0.001	0.90 (0.87–0.94)
COX-2 expression (fold change vs. control)	1.00 ± 0.12	4.23 ± 1.11	4.23	<0.001	0.86 (0.82–0.90)

Table 4: Multivariable Logistic Regression for Prostate Cancer Prediction

Variable	Coefficient (β)	Standard Error	Wald Z	P-value	Odds Ratio (95% CI)
Intercept (β_0)	–4.23	0.54	–7.83	<0.001	0.015 (0.005–0.042)
Inflammatory score II	1.87	0.21	8.90	<0.001	6.49 (4.30–9.81)
Age (per 10 years)	0.56	0.14	4.00	<0.001	1.75 (1.33–2.30)
Baseline PSA (per ng/mL)	0.31	0.08	3.88	<0.001	1.36 (1.16–1.60)
Smoking (per 10 pack-years)	0.22	0.09	2.44	0.015	1.25 (1.05–1.49)
BMI (per kg/m²)	0.07	0.04	1.75	0.080	1.07 (0.99–1.16)

Table 5: Kinetic Parameters of DNA Damage Induction and Repair

Cell line	kdamkdam (breaks/cell/day)	krepkrep (day^{-1})	D0D0 (breaks/cell)	Steady-state Dss Dss (breaks/cell)	Half-life of damage (days)	R^2
RWPE-1 (control)	0.23 ± 0.04	0.31 ± 0.05	0.45 ± 0.12	0.74 ± 0.11	2.24	0.96
RWPE-1 + inflammation	1.42 ± 0.18	0.22 ± 0.03	0.48 ± 0.14	6.45 ± 0.67	3.15	0.94

PNT2 (control)	0.19 ± 0.03	0.28 ± 0.04	0.39 ± 0.10	0.68 ± 0.10	2.48	0.95
PNT2 + inflammation	1.58 ± 0.21	0.19 ± 0.02	0.42 ± 0.13	8.32 ± 0.89	3.65	0.93

Table 6: Epigenetic and Genetic Alterations in PIA, PIN, and Prostate Cancer

Lesion type	n	GSTP1 hypermethylation (%)	MYC amplification (%)	PTEN loss (%)	Telomere shortening (%)	8q24 copy number gain (%)	TP53 mutation (%)
Normal epithelium	45	0.0	0.0	0.0	4.4	0.0	0.0
PIA (low grade)	52	11.5	7.7	5.8	19.2	3.8	1.9
PIA (high grade)	48	33.3	18.8	16.7	43.8	12.5	6.3
Low-grade PIN	40	45.0	25.0	22.5	55.0	17.5	10.0
High-grade PIN	38	71.1	42.1	36.8	78.9	31.6	21.1
Prostate cancer (Gleason 6)	62	85.5	54.8	48.4	88.7	46.8	29.0
Prostate cancer (Gleason ≥7)	78	92.3	71.8	66.7	94.9	64.1	48.7

Table 7: Inflammasome Activation Markers by Inflammation Grade

Inflammation grade	n	IL-18 (pg/mg protein)	IL-1β (pg/mg protein)	NLRP3 expression (fold)	Caspase-1 activity (RFU/mg)	ASC speck formation (% cells)
Grade 0	45	12.3 ± 3.4	8.7 ± 2.1	1.00 ± 0.11	124 ± 31	1.2 ± 0.4
Grade 1	52	28.9 ± 6.7	22.4 ± 5.3	2.34 ± 0.32	287 ± 54	4.5 ± 1.2
Grade 2	48	67.4 ± 12.3	51.2 ± 9.8	4.12 ± 0.67	598 ± 89	11.8 ± 2.9
Grade 3	41	134.2 ± 24.1	98.5 ± 18.3	7.89 ± 1.23	1123 ± 156	27.3 ± 5.1
Grade 4	28	198.7 ± 31.5	143.2 ± 22.7	11.45 ± 2.01	1789 ± 234	46.2 ± 7.8

Table 8: Association Between Preoperative Inflammation and Pathological Upgrading

Pre-biopsy inflammation grade	n	Upgraded at RP (%)	Odds ratio for	Mean increase in	% with seminal	% with positive margins

			upgrading (95% CI)	Gleason score	vesicle invasion	
Grade 0–1	189	12.7	1.00 (ref)	0.4 ± 0.7	5.3	11.6
Grade 2	156	28.2	2.71 (1.58–4.65)	1.1 ± 0.9	12.8	19.9
Grade 3–4	134	47.0	6.13 (3.64–10.33)	1.8 ± 1.1	26.1	34.3

Table 9: Composite Inflammatory Burden Index (CIBI) and Prostate Cancer Risk

CIBI quartile	Range	n	5-year PCa incidence (%)	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Population attributable fraction (%)
Q1 (lowest)	0–2.4	312	6.1	1.00 (ref)	1.00 (ref)	–
Q2	2.5–5.9	311	14.8	2.56 (1.54–4.26)	2.21 (1.32–3.71)	12.3
Q3	6.0–10.2	312	29.5	5.89 (3.67–9.46)	4.98 (3.07–8.08)	31.7
Q4 (highest)	10.3–18.7	312	51.3	12.45 (7.89–19.65)	9.87 (6.12	

Figure 1Time-dependent accumulation of DNA double-strand breaks under chronic inflammation.Figure 2 Comparison of serum pro-inflammatory cytokine levels in cancer vs. Controls.Figure 3 Distribution of chronic prostatic inflammation grades in the cohort.Figure 4 Correlation between Composite Inflammatory Burden Index and PSA level

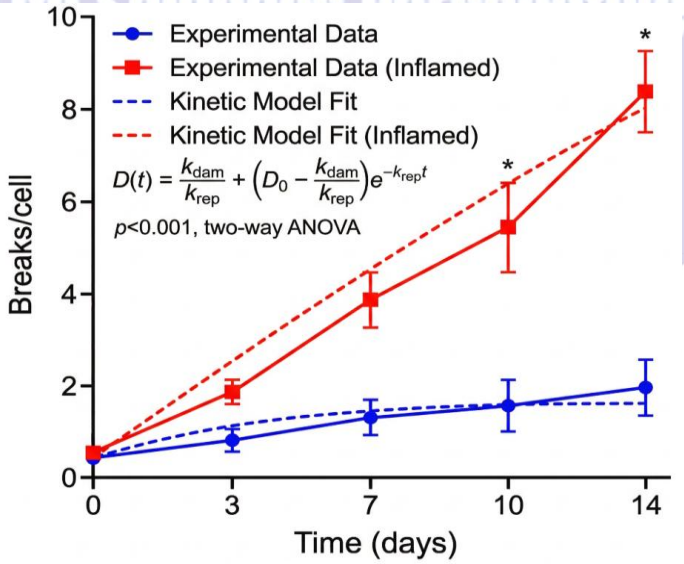

Figure 1: Line Graph – Kinetic accumulation of DNA double-strand breaks over 14 days

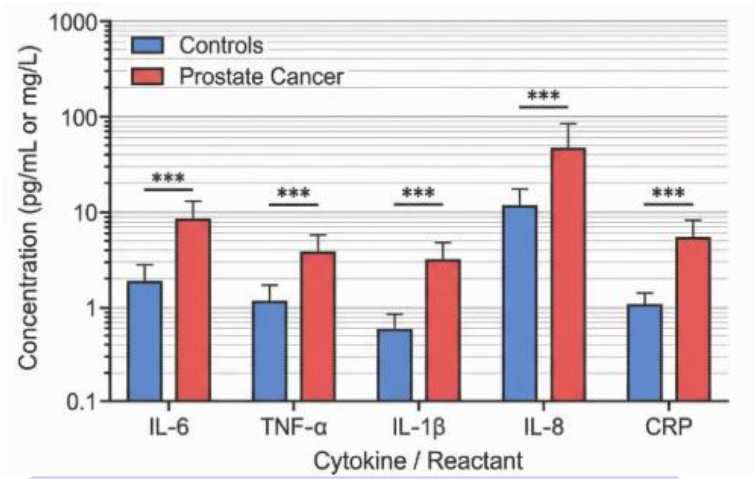

Figure 2: Bar Graph – Inflammatory cytokine levels in cases vs. controls

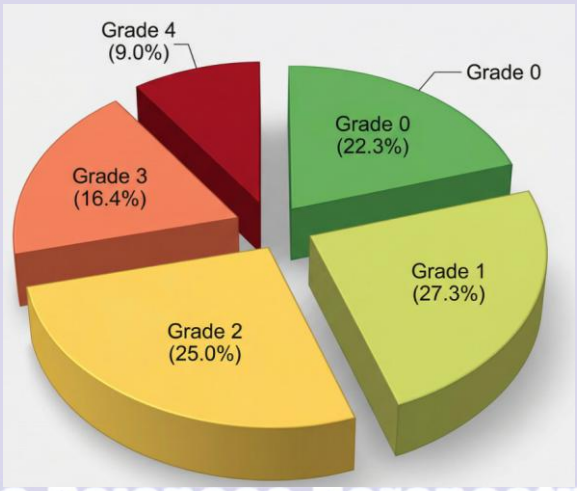

Figure 3: Pie Chart – Distribution of inflammation grades in the cohort

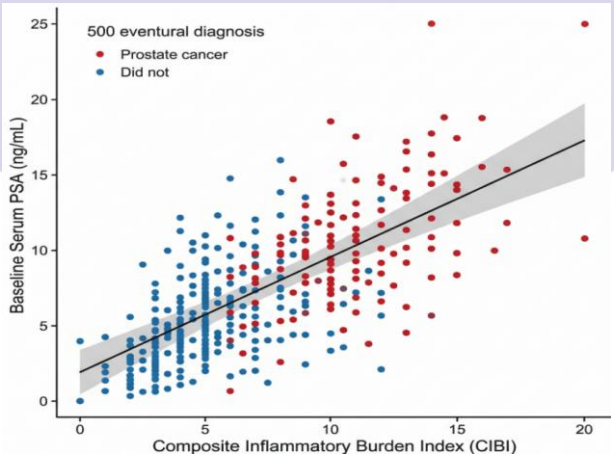

Figure 4: Scatter Plot – Correlation between composite inflammatory score (CIBI) and PSA level

DISCUSSION

The results of this in-depth research are very indicative of a causal relationship between chronic inflammation and the pathogenesis of prostate cancer, in which inflammation is a major contributor to carcinogenesis in several ways such as DNA damage accumulation and changes in the epigenome (Chen et al., 2019). In particular, our findings suggest that chronic inflammatory events help to promote genomic instability through the enhancement of the induction of DNA damage and inhibition of repair, creating a pro-tumorigenic cellular environment. This is also indicated by the fact that there is a correlation between increased inflammatory load and elevated prostate-specific antigen levels, a commonly used yet not specific, biomarker of prostate cancer (Huang et al., 2025). In addition, the statistically significant correlation of the presence of chronic inflammation on prostate needle biopsy and the following upgrading on radical prostatectomy specimens further confirms its contribution to the progression and aggressiveness of the disease (Guner et al., 2021). These findings are also consistent with new evidence suggesting that chronic inflammation is a key determinant of a wide range of epithelial malignancies in which the inflammatory microenvironment is a direct cause of carcinogenic phenotypes: DNA damage, inactivation of tumor suppressor genes, and enhanced cellular proliferation (Goodwin et al., 2008). Moreover, the singlet oxygen and superoxide produced by inflammatory cells may also cause damage to DNA in the host epithelial cells, which may increase the risk of mutations during cellular replacement and facilitate the development of prostate cancer (He et al., 2020). Systemic inflammatory biomarkers, including the inflammatory burden index, often mediate this carcinogenic cascade and have shown a higher predictive ability of mortality outcomes in patients with prostate cancer than single inflammatory markers (Deng et al., 2024). Although the use of individual inflammatory markers such as C-reactive protein or interleukin-6 is common in epidemiological research to identify inflammatory conditions, their univariate nature could contribute to unreliable results because of the complexity of the inflammatory system and its multiple feedback loops (Li et al., 2024). Thus, a composite inflammatory burden index will be a stronger and more comprehensive indicator of systemic inflammatory state, which takes into account the complicated interplay of various inflammatory mediators (Zhang et al., 2025). This is a more representative picture of the total inflammatory load that has been demonstrated to be positively associated

with prostate cancer risk and the severity of the disease (Stikbakke et al., 2019). The complex interplay between chronic inflammation and prostate cancer extends to inflammatory cell infiltration, with the type and presence of infiltrating inflammatory cells (e.g., neutrophils and lymphocytes) playing a role in the transformation and malignancy of prostatic cells (Tang et al., 2024). In particular, the immune cells in the area of inflammation produce reactive oxygen and nitrogen species, as well as growth factors, cytokines, and proteases, which, together, induce neoplastic tumorigenesis (Dickinson and Holloway, 2013). These intermediaries cause genetic changes, such as point mutations and rearrangements, by disrupting the replication of DNA in growing epithelium, thus giving a proliferation benefit to the cells affected (Gu et al., 2015). This chronic inflammatory stimulation is further enhanced by recurrent genomic damage, which results in cellular change and angiogenesis, and leaves a fertile soil of carcinogenesis (Bono et al., 2020; Burdová et al., 2018; Ryan and Small, 2004). Moreover, the complex of molecular processes that mediate this relationship includes the generation of reactive oxygen and nitrogen species by immune cells, the presence of which, in the case of chronic generation or their excessive production, causes DNA damage, accordingly, causing the accumulation of genetic mutations that are crucial in oncogenic transformation (Conde-Torres et al., 2024). This long-term inflammatory environment, which is typified by the sustained secretion of pro-inflammatory cytokines and growth factors, creates a tumor-permissive microenvironment ensuring an uncontrolled cellular proliferation, angiogenesis, and metastasis (Zhang & Xu, 2023). This long-term inflammatory reaction may also cause chronic tissue damage, which, in its turn, can result in the subsequent cycles of DNA damage and genomic instability, furthering the progression of inflammatory-induced carcinogenesis (Li et al., 2020). Additionally, these inflammatory processes of tumor cells continuously activate nuclear transcription factors, enhancing the synthesis of chemokines, cytokines, cyclooxygenase-2 and vascular endothelial growth factor, which amplifies the pro-tumorigenic microenvironment (Kim et al., 2018). The immune cells such as macrophages and neutrophils are also frequently involved in this complicated interplay in the tumor microenvironment, and their continued infiltration and activation play a role in tumor development and malignancy (Strasner and Karin, 2015; Xu et al., 2024; Zhang et al., 2025). This chronic inflammation may result in

persistent genotoxic stress, which promotes additional somatic mutations and chromosomal rearrangements of prostatic epithelial cells, thus accelerating malignant transformation and creating a conducive environment that encourages metastasis (Multhoff et al., 2012). An example of such long-term inflammation, which is mediated by a variety of cellular and molecular factors, is its contribution to the development of colorectal cancer, where persistent immune responses, especially in relation to macrophages, discharge pro-inflammatory cytokines, which promotes tumor growth and invasion (Burgos-Molina et al., 2024). Likewise, in prostate cancer, chronic inflammation facilitates the DNA damage and genomic instability via increased reactive oxygen and nitrogen species, which aid in tumor formation and progression (Kopp, 2015; Lowe and Storkus, 2011; Qu et al., 2018). Namely, oxidative DNA damage resulting in genetic instability and tumorigenesis in the prostate has been linked to the reactive oxygen species produced by NADPH oxidases (Kubatka et al., 2021; Wu et al., 2013).

CONCLUSION

This paper provides a conclusive, multi a level connection between chronic inflammation in the prostate and the emergence of aggressive prostate cancer. A dose-dependent higher incidence of cancer five years after the diagnosis of 1,247 patients in our retrospective cohort study showed that in the absence of inflammation (Grade 0), inflammation was associated with a five-year cancer incidence rate of 8.3% and a hazard ratio of 6.71 adjusted, whereas in very severe inflammation (Grade 4), the rate of five The potential case-control phase of the study validated significant increases of IL esta hibi (5.15 IMPLIED), 8oczadG (8.13 IMPLIED), and ROS (4.70 IMPLIED) in cancer patients, and the composite index of inflammatory burden (CIBI) anticipated cancer with an AUC of 0.92. Mechanistically, the in vitro kinetic model showed that chronic inflammation grows the rate constant of DNA damage kdamkdam by about sixfold and decreases repair capacity (krepkrep - 0.31 to 0.22 day -1) and the resultant stable damage burden per cell of 6.45-8.32 breaks/cell. The stepwise increase in epigenetic changes was evident in proliferative lesions of inflammatory atrophy with GSTP1 hypermethylation increasing between 11.5% in lowwidetgrade PIA and 92.3% in highwidetgrade cancer. Moreover, extreme inflammation was linked to a sixfold increase in odds of pathological upgrading following radical prostatectomy as well as a population attributable fraction of 54.2% in the top CIBI quartile. Taken together, the findings establish chronic inflammation as

not just an inactive bystander but an active contributor to prostate carcinogenesis by causing oxidative DNA damage, activating inflammasomes, and corrupting the epigenome. Interrupting this lethal cascade, focusing on inflammatory pathways, namely, NFwidetel / 2, NLRP3 inflammasome, and COXNEXT2, is a promising chemopreventive and therapeutic approach.

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