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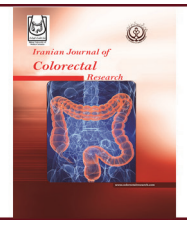

Association Between Inflammatory Bowel Disease and Prostate Cancer: Current Epidemiological Evidence and Proposed Immunological Mechanisms

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Abstract

Inflammatory bowel disease (IBD) and prostate cancer are among the most common chronic diseases affecting millions of individuals worldwide. Emerging epidemiological evidence suggests a possible association between IBD, particularly ulcerative colitis, and an increased risk of prostate cancer. However, whether this relationship reflects a causal biological effect or is influenced by surveillance bias and other confounding factors remains uncertain. This narrative review summarizes current epidemiological evidence and proposed immunological mechanisms underlying the association between IBD and prostate cancer. A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, ScienceDirect, SpringerLink, and Google Scholar for studies published between 2020 and 2026, with earlier landmark studies included when highly relevant. Current evidence suggests several biologically plausible mechanisms, including systemic cytokine-mediated inflammation, activation of the NF-κB and PI3K/AKT signaling pathways, dysregulation of the IL-23/Th17/IL-17 axis, gut microbiome dysbiosis, oxidative DNA damage, and impaired antitumor immune surveillance. Nevertheless, many of these mechanisms are primarily supported by experimental models and require further validation in human studies. Overall, the available evidence supports an association rather than a causal relationship between IBD and prostate cancer. Future prospective multicenter studies with standardized screening strategies are required to clarify the clinical significance of this association and to determine whether it should influence prostate cancer surveillance in selected patients with IBD.

Keywords: Inflammatory Bowel Diseases; Prostatic Neoplasms; Colitis, Ulcerative; Crohn Disease; Immune System Processes

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Introduction

Inflammatory bowel disease (IBD) is a group of chronic immune-mediated disorders characterized by persistent inflammation of the gastrointestinal tract, most commonly manifesting as ulcerative colitis (UC) and Crohn's disease (CD) (1). UC is a mucosal-limited condition that typically affects the rectum and extends continuously along the colon, resulting in diffuse inflammation and superficial ulcers in the inner lining. It often presents with symptoms such as bloody diarrhea, urgency, and

abdominal cramping (2). In contrast, CD is a transmural, often patchy inflammatory condition that can involve any segment of the gastrointestinal tract from the mouth to the anus, most frequently affecting the terminal ileum and colon. It is characterized by deep ulcers, strictures, fistulas, and abscesses due to full-thickness bowel wall involvement (3). Both UC and CD are relapsing–remitting disorders driven by dysregulated mucosal immunity against luminal antigens; however, they differ in anatomical distribution, depth of inflammation, and patterns of complications (4).

Prostate cancer is the second most common cancer among men worldwide (5). One contributing factor to the development of this cancer is inflammation (6). Recent scientific evidence suggests that chronic inflammation can predispose individuals to precancerous changes by inducing oxidative stress and DNA damage in prostate cells. It is estimated that approximately 20% of prostate cancer cases are associated with prior inflammation or infection of the prostate. Inflammatory cells, through the production of free radicals and growth factors, contribute to abnormal cell proliferation and tumor progression (7, 8).

IBD can extend beyond the intestinal wall into adjacent anatomical compartments. In cases of long-standing, poorly controlled disease, this may create a favorable environment for the development of malignancies in nearby organs (9). Epidemiological data robustly support an increased risk of colorectal cancer in patients with extensive or longstanding colonic involvement, particularly in UC and CD affecting the colon; this association is now well established. Additionally, several studies have reported a modestly elevated risk of smallintestinal adenocarcinoma and anal cancer in CD, especially in the presence of extensive perianal or intestinal disease (9, 10). Given the anatomical proximity of the prostate to the lower gastrointestinal tract and the shared pelvic vascular and lymphatic networks, recent epidemiological reports have suggested a potential association between IBD and an increased risk of prostate cancer, although this link remains less firmly established than the association with colorectal cancer (11, 12) .

Given the substantial number of individuals affected by these two diseases, investigating their potential association and overlap is of great importance. In this study, we aimed to review both local and global epidemiological evidence to determine whether this association and any potential overlap have been confirmed. Furthermore, we sought to explore recent studies that have investigated the mechanisms underlying this relationship from an immunological perspective.

Methods

This narrative review was conducted through a comprehensive literature search of PubMed, Scopus, Web of Science, ScienceDirect, SpringerLink, and Google Scholar. Studies published between January 2020 and June 2026 were primarily considered, while seminal studies published before 2020 were also included when they provided important background information or mechanistic evidence. Only articles published in English were selected. Searches were performed using a combination of keywords, including: “prostate cancer”, “inflammatory bowel disease”, “ulcerative colitis”, “Crohn’s disease”, and “immunological mechanisms”. Duplicate papers were removed, data were screened, irrelevant works were excluded, and full-text documents were reviewed. Inclusion criteria comprised original articles and review papers relevant to the association between IBD and prostate cancer or their underlying immunological mechanisms. Exclusion criteria included articles with inadequate, irrelevant, or insufficient information, as well as those without access to the full text.

The initial search identified a total of 387 records across all databases. After removing 83 duplicate records, 304 articles remained for title and abstract screening. Of these, 215 were excluded because they were not directly relevant to the association between IBD and prostate cancer, did not address immunological mechanisms, or were not available in English. The remaining 89 articles underwent full-text assessment. During this phase, 32 articles were excluded for the following reasons: lack of full-text access (n=10), insufficient or irrelevant data (n=14), and limited methodological detail (n=8). Ultimately, 57 articles met the inclusion criteria and were included in this review.

The included articles were categorized according to study design as follows: original observational studies (cohort, case-control, and cross-sectional) (n=14), meta-analyses (n=3), systematic reviews (n=2), narrative/comprehensive reviews (n=30), animal/experimental studies (n=2), and other relevant publications (n=6). A detailed flowchart illustrating the stepwise selection process is presented in Figure 1.

Epidemiology of Inflammatory Bowel Disease

Global Scale

A comprehensive analysis of 215 studies revealed that the global burden of IBD remains substantial. The pooled prevalence of IBD was estimated at 229.7 cases per 100,000 individuals, with CD and UC accounting for 84.2 and 120.4 cases per 100,000, respectively. The global incidence of IBD was 9.7 per 100,000 person-years, including 4.0 for CD and 5.0 for UC. Regionally, the highest incidence rates of IBD and CD were observed in Oceania, at 21.3 and 12.2 per 100,000 person-years, respectively, whereas North America reported the highest incidence of UC at 9.8. In terms of prevalence, Europe demonstrated the greatest burden of IBD and UC, with rates of 348.4 and 198.6 per 100,000, respectively. Conversely,

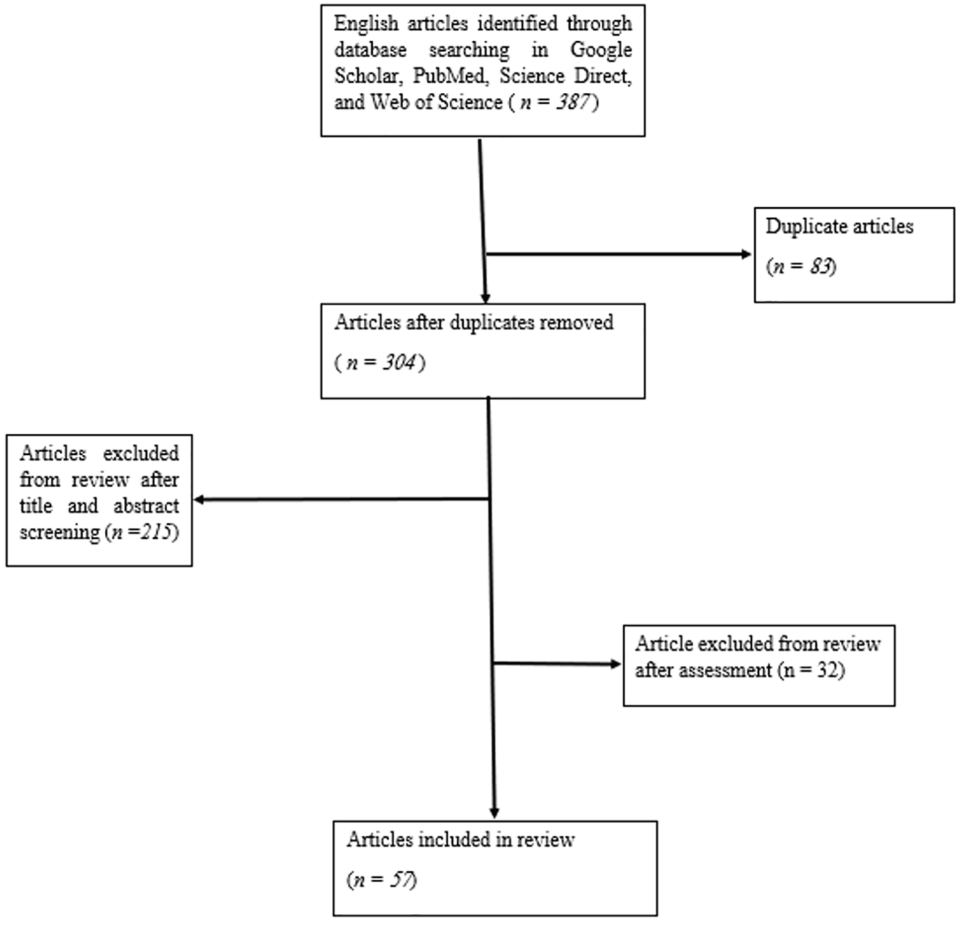

Figure 1: Flowchart of the study selection process for articles evaluating the association between inflammatory bowel disease and prostate cancer.

Oceania exhibited the highest prevalence of CD at 173.6 per 100,000 (13).

Local Scale

In Iran, the epidemiological profile and precise prevalence of IBD have not yet been fully established. Most available data are derived from studies conducted on selected patient populations, primarily due to the absence of a comprehensive national disease registry and the historical assumption that CD is relatively rare in the country. Nevertheless, existing reports indicate a notable increase in IBD prevalence over time, rising from 4.69 per 100,000 individuals in 1990 to 40.67 per 100,000 in 2012 (14, 15).

IBD is associated with considerable morbidity and disability, particularly among young adults. The disease imposes a significant socioeconomic burden by impairing daily functioning and limiting affected individuals' ability to pursue education, employment, and personal development. Although its prevalence is relatively lower compared to other gastrointestinal disorders, the growing incidence and long-term impact of IBD underscore its growing importance as a public health concern in Iran (14).

Risk Factors

The etiology of IBD is multifactorial, involving a complex interplay among genetic susceptibility, environmental exposures, immune dysregulation, and alterations in the gut microbiota. Genetic predisposition plays a significant role, with numerous susceptibility loci—such as NOD2 and CARD9—identified, particularly in genes related to immune function and epithelial barrier integrity. However, genetic factors alone cannot fully explain the rising global incidence, highlighting the importance of environmental influences (16).

Among environmental risk factors, smoking has a differential impact, increasing the risk and severity of CD while paradoxically exerting a protective effect in UC. Dietary patterns—particularly a high intake of processed foods and saturated fats combined with low fiber consumption—have been linked to disease development through their impact on the gut microbiome and intestinal inflammation. Urbanization, antibiotic exposure, and improved hygiene conditions are also believed to contribute by altering microbial diversity, supporting the "hygiene hypothesis" (17).

Furthermore, dysbiosis of the intestinal microbiota is considered a central factor in IBD pathogenesis, leading to an abnormal immune response against commensal bacteria. Additional risk modifiers include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives,

psychological stress, and early-life exposures such as mode of delivery and breastfeeding practices. Collectively, these factors interact to trigger chronic intestinal inflammation in genetically predisposed individuals (18, 19).

Epidemiology of Prostate Cancer

Global Scale

Prostate cancer, with approximately 1.5 million identified cases, is currently one of the most prevalent malignancies threatening human health and survival. The global incidence of prostate cancer varies significantly across different ethnic groups and geographic regions. Notably, Black men exhibit the highest reported incidence rates worldwide. Among developing countries, South Africa has the highest incidence, with 65.9 cases per 100,000 population and a mortality rate of 22 per 100,000 (20, 21).

However, due to the implementation of effective screening methods based on prostate-specific antigen (PSA) testing and digital rectal examination (DRE), combined with increased public awareness in developed countries, the highest recorded incidence rates are observed in these regions. GLOBOCAN reports, based on PSA screening, indicate particularly high incidence rates in Australia (111.6 per 100,000) and the United States (97.2 per 100,000) (22).

By 2030, driven by the exponential growth of the global population and the increasing proportion of men aged over 65 years, prostate cancer is projected to reach approximately 1.7 million new cases and 499,000 deaths (22).

Local Scale

Several cross-sectional studies have been conducted in Iran. In the most recent study by Noroozi et al., a total of 49,188 prostate cancer cases were recorded in Iran between 2003 and 2016. The age-standardized incidence rate (ASIR) of prostate cancer demonstrated an increasing trend, rising from 4.46 per 100,000 population in 2003 to 18.44 per 100,000 in 2016. The highest ASIR was observed in the age group over 80 years (23).

During the study period, significant regional variations were identified across provinces. Mazandaran (29.57 per 100,000 in 2008), Isfahan (26.51 per 100,000 in 2015), and Tehran (24.47 per 100,000 in 2014) reported the highest age-standardized incidence, whereas Sistan and Baluchestan had the lowest ASIR (1.59 per 100,000) throughout the study period (23).

Although the incidence of prostate cancer in Iran remains lower than the global rate (29.4 per 100,000), the steep upward trend in incidence is highly concerning and underscores the urgent need to implement effective control and prevention programs, particularly in provinces with high incidence (24).

Risk Factors

Risk factors encompass all elements that elevate an individual's susceptibility to diseases such as cancer. Various risk factors are associated with prostate cancer; many are non-modifiable, including age and genetics, while others, such as smoking and diet, can be altered to decrease disease risk (25).

The most significant risk factor identified for prostate cancer to date is advancing age. Incidence rates are less than 1 per 100,000 in men under 50 years old, increase to approximately 100 per 100,000 in those aged 51–60 years, and exceed 500 per 100,000 in men over 60 years (20).

As previously noted, African men exhibit a higher risk compared to other ethnic groups. In a UK study by Down et al., involving over 7,000 men from diverse ethnic backgrounds, African men, particularly those over 60 years old, demonstrated elevated PSA levels and a higher incidence of prostate cancer, whereas Asian men had the lowest PSA levels and incidence among the ethnic groups (26).

Family history and genetic factors also contribute to the risk of prostate cancer. Approximately 5–10% of cases are hereditary. The BRCA1 and BRCA2 genes, well established in the pathogenesis of breast cancer, may also play a role in prostate cancer, with BRCA2 having a more pronounced effect by increasing both the incidence and the earlier onset of the disease (27, 28).

Other key risk factors include obesity and dietary patterns (29). Obesity is associated with an increased risk of high-grade prostate cancer (30). Additionally, vitamin D deficiency and high dietary calcium intake have been implicated in the development of prostate cancer (31).

Association Between Inflammatory Bowel Disease and Prostate Cancer

Epidemiology

From an epidemiological perspective, the available evidence suggests a possible association between IBD and an increased risk of prostate cancer. In a systematic review by Haddad et al., nine observational studies including 205,037 men were analyzed, with most studies supporting a higher risk of prostate cancer among patients with IBD, particularly those with UC. In contrast, the evidence regarding CD was inconsistent and remains inconclusive (32).

The association was not uniform across all studies. Four studies reported an increased risk of prostate cancer in men with UC, while one study found a lower risk in this group. Only one study specifically reported an increased risk associated with CD. Additionally, a population-based study observed a reduced risk among IBD patients treated with aminosalicylates, suggesting that treatment patterns may partially influence the observed epidemiologic association (32).

Based on the meta-analysis by Zhou et al., epidemiological evidence from 18 cohort studies involving 592,853 participants indicates that IBD is associated with a modest but significant 20% increased risk of incident prostate cancer (HR=1.20). This association was primarily driven by patients with UC (HR=1.20), whereas CD showed no significant link (HR=1.03). Notably, the elevated risk was statistically significant only in European populations and was not observed in Asian or North American cohorts, suggesting potential regional differences in genetic or environmental factors (11).

Another meta-analysis showed that men with IBD have approximately a 71% higher relative risk of prostate cancer compared to the general population (RR 1.71, 95% CI 1.16–2.51), with this increased risk primarily driven by UC rather than CD. Similarly, a large prospective cohort study from the UK Biobank, involving over 218,000 men, found that IBD was associated with a 31% increased hazard of incident prostate cancer (adjusted hazard ratio [aHR] 1.31, 95% CI 1.03–1.67). Specifically, patients with UC had a 47% higher risk (aHR 1.47, 95% CI 1.11–1.95) after adjusting for confounding factors such as age, smoking status, and family history (33).

Overall, the findings suggest that UC may be associated with a higher likelihood of prostate cancer detection or occurrence, whereas the evidence for CD is less convincing. The heterogeneity among available studies, along with variations in study design, follow-up duration, and patient characteristics, limits the ability to draw definitive conclusions. Therefore, earlier prostate cancer screening may be considered for men with UC, while further well-designed epidemiological studies are needed to clarify the relationship in CD.

Pathophysiological Mechanisms

Based on the reviewed original articles and meta-analyses, several immunological and biological mechanisms have been proposed to explain the potential association between IBD and prostate cancer. First, systemic cytokine-mediated inflammation, including elevated levels of TIMP-1, CCL5, and CXCL1, promotes leukocyte trafficking from the inflamed gut to the prostate (12). Second, chronic intestinal inflammation activates pro-oncogenic NF-κB and PI3K/AKT signaling pathways, leading to oxidative stress, DNA damage, and cell cycle arrest in prostate epithelial cells (12, 34). Third, dysregulation of the IL-23/Th17/IL-17 axis impairs antitumor immunosurveillance and promotes an immunosuppressive microenvironment conducive to tumorigenesiss (35, 36). Fourth, gut microbiome dysbiosis facilitates bacterial product translocation (e.g., LPS) and alters short-chain fatty acid profiles, triggering inflammatory signaling in the prostate via the gut–prostate axis (37-39). Fifth, persistent inflammation may induce immune exhaustion characterized by increased IL-10 expression and reduced CD8+ cytotoxic T-cell activity, further compromising antitumor immunity (40-42). These mechanisms are discussed in detail in Section 6.

Immunological Mechanisms

Although multiple biological mechanisms have been proposed to explain the observed association between IBD and prostate cancer, it is important to recognize that the current evidence is heterogeneous. Some mechanisms are supported primarily by experimental animal models, whereas others are inferred from observational human studies or indirect molecular evidence. Therefore, the following mechanisms should be considered biologically plausible hypotheses rather than established causal pathways.

Systemic Cytokine-Mediated Inflammation and Leukocyte Trafficking to the Prostate

Chronic IBD is characterized by a sustained systemic elevation of pro-inflammatory cytokines that extend beyond the intestinal environment and actively regulate leukocyte trafficking to extraintestinal sites.

Desai et al. demonstrated that men with IBD exhibit significantly higher infiltration of T and B lymphocyte within prostate tumors compared to non-IBD controls. This study examines the systemic impact of IBD on the prostate microenvironment, specifically testing the hypothesis of an immunological connection between these conditions. Clinical analysis of prostatectomy specimens revealed that patients with IBD have significantly higher infiltration of CD4+, CD8+, and CD20+ lymphocytes within their prostate tumors compared to non-IBD controls, suggesting that chronic gut inflammation may actively reshape the prostatic immune landscape (12).

To determine the underlying mechanism, the researchers utilized a murine model of chronic colitis to observe the effects of intestinal inflammation on distal prostatic tissues. The study demonstrated that chronic colitis triggers a significant infiltration of CD45+ leukocytes and CD8+ T lymphocytes into the prostate, confirming that systemic inflammatory signaling—rather than direct chemical toxicity—drives this prostatic immune response (12).

Furthermore, the study identified the upregulation of specific pro-inflammatory cytokines, including TIMP-1, CCL5, and CXCL1, within the prostates of mice afflicted with colitis. These findings suggest that soluble inflammatory mediators serve as critical orchestrators in the recruitment and retention of immune cells, ultimately fostering a pro-tumorigenic microenvironment that may explain the observed clinical association between IBD and prostate cancer (12).

In a mouse model of chemically induced colitis, Kura et al. demonstrated that systemic inflammation resulting from dextran sulfate sodium-induced UC

(DSS-UC) or prostate cancer promotes the trafficking of Grl+ myeloid leukocytes to the normal prostate via inflammatory cytokines. This process leads to histological alterations resembling proliferative inflammatory atrophy. Notably, DSS-induced colitis proved more severe in prostate cancer-bearing mice and triggered colorectal cancer development even in the absence of azoxymethane administration (43).

Conversely, colonic inflammation in prostate cancer-naïve mice induced the accumulation of Grl+ cells within the prostate. Immunohistochemical profiling revealed enrichment of these cells in areas of active colitis and colonic tumors, providing evidence for a bidirectional link between systemic inflammation and prostate-colorectal carcinogenesis (43).

Collectively, these mechanisms illustrate how systemic cytokine dysregulation in IBD may directly regulate leukocyte trafficking dynamics, enabling the recruitment and accumulation of immune cells within the prostate.

Activation of Pro-Oncogenic NF-κB and PI3K/AKT Signaling Pathways

NF-κB is widely recognized as a master regulator of inflammatory gene expression and has a well-established role in the initiation and progression of prostate cancer (44). Beyond its classical function in immune signaling, aberrant activation of NF-κB in prostate epithelial cells contributes to tumorigenesis by promoting cell survival through the upregulation of anti-apoptotic proteins such as Bcl-2 and surviving (45). In addition, NF-κB has been strongly implicated in the acquisition of metastatic traits in prostate cancer cells. It enhances epithelial–mesenchymal transition (EMT), increases the expression of matrix metalloproteinases (MMPs), and facilitates tumor invasion and dissemination to distant organs, particularly bone (46). Recent studies have further demonstrated that NF-κB signaling interacts with androgen receptor (AR) pathways, creating a complex regulatory network that sustains tumor growth even under androgen-deprived conditions. This crosstalk is particularly relevant in the development of castration resistant prostate cancer (CRPC), where NF-κB activity remains elevated despite androgen suppression therapies (47, 48).

AKT directly phosphorylates IKKα, thereby establishing a functional link between PI3K/AKT signaling and NF-κB activation, which plays a crucial role in prostate cancer progression (49). This interaction is particularly significant in PTEN-deficient prostate cancer cells, where the loss of PTEN leads to constitutive activation of the PI3K/AKT pathway, resulting in persistent NF-κB signaling (50). The AKT/mTOR/NF κB axis contributes to tumor growth by promoting cell proliferation, inhibiting apoptosis, and enhancing metabolic adaptation under stress conditions. Moreover, this signaling network supports disease progression by facilitating resistance to conventional therapies, including androgen deprivation, and by promoting a more aggressive and invasive phenotype (51, 52).

IBD, dysregulated NF-κB signaling in the intestinal epithelium drives excessive production of proinflammatory cytokines, including IL-1β, IL-6, and TNF-α. These cytokines enter the systemic circulation and activate NF-κB pathways in distant organs, such as the prostate. This is supported by studies using a murine colitis model, which demonstrate that chronic colitis activates pro-oncogenic AKT and NF-κB signaling, leading to oxidative stress, DNA damage, and cell cycle arrest in prostate epithelial cells (12, 34).

Moreover, IBD-associated systemic inflammation promotes prostate cancer progression by maintaining a proinflammatory microenvironment, enhancing tumor immune cell infiltration, and contributing to therapeutic resistance, as observed in mouse models of chronic colitis and human cohorts with an increased risk of prostate cancer.

The IL-23/Th17/IL-17 Axis and Impaired Immunosurveillance

The IL-23/Th17/IL-17 axis has a central role in the immunopathology of IBD, driving the persistent mucosal inflammation characteristic of both CD and UC. In this pathway, IL-23, produced by antigen-presenting cells, supports the expansion and survival of Th17 cells, which in turn release IL-17 and other inflammatory mediators. These mediators intensify neutrophil recruitment, promote chemokine production, and sustain tissue injury. Although Th17 responses are normally important for mucosal defense, their prolonged activation in IBD shifts this response from protective to harmful, contributing to epithelial damage, barrier dysfunction, and a self-perpetuating inflammatory environment (35, 53).

Dysregulation of the IL-23/Th17/IL-17 axis may contribute to impaired intestinal immunosurveillance, thereby sustaining chronic inflammation and disrupting mucosal immune homeostasis. Under normal conditions, immunosurveillance maintains tolerance, clears damaged cells, and regulates microbial interactions. However, chronic IL-23-driven inflammation disrupts this balance and weakens local immune control. Consequently, the mucosa becomes less effective at resolving inflammation (54).

Consequently, impaired immune surveillance may reduce the efficiency of eliminating transformed cells, providing a biologically plausible explanation for the observed epidemiological association between chronic IBD and malignancy. However, direct evidence in prostate tissue remains limited. A large study identified the IL-23/Th17/IL-17 axis as a key mechanistic link between immune-mediated diseases such as UC and extraintestinal cancers, including prostate cancer. Overactivation of IL-12

and IL-23 signaling in IBD drives aberrant Th1 and Th17 immune responses (36).

The IL-23/Th17/IL-17 axis reduces mucosal barrier function and, critically, suppresses cytotoxic T-cell–mediated antitumor immune surveillance. In IBD, the balance between Th17 and regulatory T (Treg) cells is disrupted: Th17 cell activity is enhanced, while Treg cell function is compromised, resulting in chronic inflammation that promotes tumorigenesis. Th17 cells exhibit remarkable plasticity and can promote tumor progression through IL-17-driven recruitment of neutrophils and myeloid-derived suppressor cells (MDSCs), thereby fostering angiogenesis and immune evasion. Paradoxically, Tregs in the setting of intestinal dysbiosis can also promote tumorigenesis by limiting IL-2 availability, which enhances Th17 development at the expense of IFNγ-producing antitumor responses (36).

Oxidative Stress and Genomic Instability

Experimental studies suggest that chronic colitis may promote oxidative stress in the prostate, resulting in increased production of reactive oxygen species (ROS) and oxidative DNA damage. However, it remains uncertain whether this mechanism operates similarly in humans. This oxidative stress can induce point mutations, epigenetic alterations, and genomic instability in prostate epithelial cells, creating a pre-neoplastic state analogous to proliferative inflammatory atrophy (PIA) lesions, which are considered putative precursors to prostate cancer (43, 55).

Evidence from experimental animal models supports this hypothesis. Desai et al. found that mice with chronic colitis exhibited significantly greater prostatic oxidative stress and DNA damage, and that prostate epithelial cells had undergone cell cycle arrest, a hallmark of the DNA damage response (12).

Gut Microbiome Dysbiosis and the Gut-Prostate Axis

IBD is characterized by significant intestinal dysbiosis, which contributes to prostate carcinogenesis through several immune-mediated pathways.

Increased intestinal permeability, commonly known as “leaky gut,” allows the translocation of bacterial products, particularly lipopolysaccharide (LPS), into the systemic circulation, where they can initiate inflammatory signaling in distant tissues. Zhong et al. demonstrated that gut dysbiosis characterized by an enrichment of Proteobacteria led to elevated intratumoral LPS levels, which promoted prostate cancer progression through the NF-κB–IL-6–STAT3 axis (37).

Microbiome-derived short-chain fatty acids (SCFAs) may influence prostatic carcinogenesis by modulating immune signaling and cellular growth pathways. By upregulating Toll-like receptors and promoting M2 macrophage polarization, SCFAs can enhance IGF-1 signaling and activate the MAPK and PI3K pathways, thereby fostering a pro-tumorigenic prostatic microenvironment characterized by chronic immune activation, altered stromal support, and increased cellular proliferation (38).

Pathway enrichment analyses indicate that gut dysbiosis may contribute to disease progression by activating multiple interrelated inflammatory and immune-regulatory networks. In particular, bacterial pathogen signaling and the intestinal immune network involved in IgA production are closely associated with increased expression of key inflammatory mediators, including MCP-1, IL-1β, and CXCL1. These mediators can enhance immune cell recruitment and sustain both mucosal and systemic inflammation, while also triggering downstream signaling cascades including JAK/STAT, NF-κB, and PI3K/Akt/mTOR. Together, these pathways create a self-reinforcing inflammatory environment that may promote epithelial injury, disrupt immune homeostasis, and facilitate the progression of chronic disease (39).

The aberrant fecal microbiome seen in UC, together with the close anatomical relationship between the colon and prostate, may help explain why UC, but not CD, is more specifically associated with an increased risk of prostate cancer. In this context, persistent colonic dysbiosis may promote both local and systemic inflammatory signaling, alter microbial metabolite profiles, and facilitate crosstalk along the gut–prostate axis, ultimately creating a microenvironment that favors prostatic neoplasia (56, 57).

Despite increasing interest in the gut–prostate axis, direct clinical evidence linking specific microbial signatures to prostate cancer development in patients with IBD is currently limited.

Chronic Inflammation-Induced Immune Exhaustion

Sustained intestinal inflammation can activate compensatory anti-inflammatory programs that reduce tissue injury but may also impair antitumor immunosurveillance. In chronic IBD, spatial transcriptomics studies have shown increased IL-10 expression by lamina propria IgA+ plasma cells and CD163+ macrophages, together with reduced CD8+ intraepithelial T cells and lower granzyme B expression. These changes reflect a shift from cytotoxic immune activity toward immune suppression. Although such adaptations are protective within the inflamed gut, they may also induce a broader immunosuppressive state that weakens the body’s ability to detect and eliminate nascent tumor cells, including those in the prostate (40).

This immune remodeling may be especially relevant in the context of the gut–prostate axis, where persistent intestinal inflammation can influence systemic cytokine balance, immune cell function, and tissue-specific surveillance (41). Over time, the dominance of IL-10–mediated suppression and

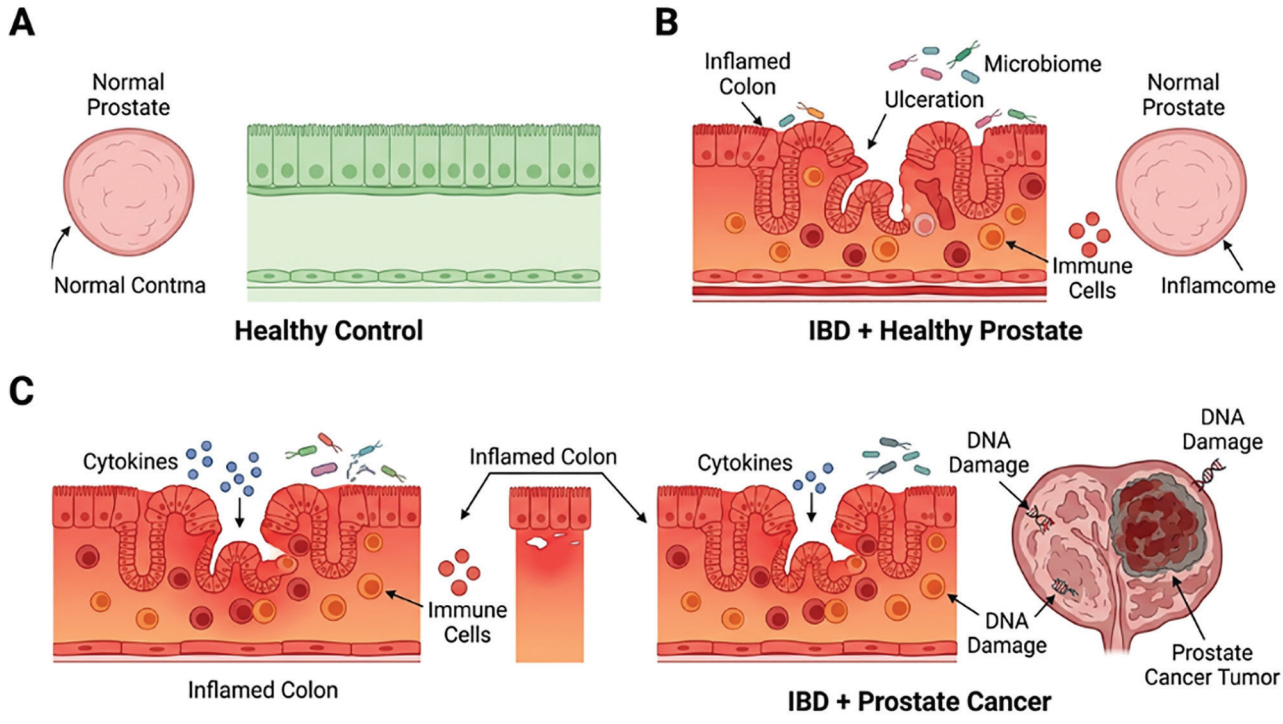

Figure 2: Schematic comparison of colonic and prostate pathology. In Healthy controls (A), IBD with a healthy prostate (B), and IBD with prostate cancer (C).

reduced cytotoxic T-cell activity may allow early malignant clones to evade immune clearance more effectively. Thus, mechanisms that initially function to contain intestinal damage may paradoxically contribute to a permissive environment for tumor development beyond the gut (41, 42).

Notably, a Mendelian randomization study did not support a direct causal genetic link, suggesting that these mechanisms may reflect shared environmental and immunological pathways rather than a simple causal chain (35). Figure 2 illustrates three conditions. Healthy controls (A) show a normal colon and prostate. In IBD with a healthy prostate (B), the colon is inflamed, but the prostate is normal. In IBD with prostate cancer (C), colonic inflammation is present alongside a prostatic tumor, representing the combined pathology.

Limitations and Future Perspectives

Despite growing epidemiological evidence suggesting an association between IBD and prostate cancer, establishing a causal relationship remains limited due to several methodological and biological uncertainties.

Methodological Limitations. Most available data come from observational studies, which are inherently susceptible to detection bias. Patients with IBD undergo more frequent medical surveillance, including routine blood tests, abdominal imaging, and specialist visits, potentially increasing the likelihood of PSA testing and biopsy compared to the general population. Consequently, the observed higher incidence of prostate cancer in IBD cohorts may partly reflect increased diagnostic intensity rather than a true biological risk. Additionally, heterogeneity across studies in IBD subtype classification (UC versus CD), disease activity assessment, follow-up duration, and adjustment for confounders (such as age, smoking, obesity, family history, and PSA screening practices) limits the comparability of findings and precludes robust meta-analytic estimates. The consistently stronger association reported for UC remains unexplained and may reflect differences in inflammatory burden, treatment regimens, or underlying genetic susceptibility.

Mechanistic Gaps. Preclinical models have identified plausible biological pathways linking chronic intestinal inflammation to prostatic carcinogenesis, including systemic cytokine signaling (IL-6, TNF-α), chemokine-mediated immune cell trafficking, activation of NF-κB and PI3K/AKT pathways, oxidative DNA damage, and gut dysbiosis. However, these mechanisms have not been robustly validated in human tissues. Animal models typically employ acute or chemically induced colitis, which does not fully replicate the relapsing-remitting course of human IBD over decades. Furthermore, the prostate harbors a unique androgen-sensitive immune microenvironment that remains underexplored in the context of extraintestinal inflammation.

Future Research Priorities. To address these limitations, prospective cohort studies with standardized screening protocols and longitudinal biospecimen collection, including serial blood, stool, and ideally prostatic fluid, are urgently needed, especially in Iran. Such resources would enable investigation into whether rising faecal calprotectin levels, serum cytokines, or specific microbial

signatures precede the diagnosis of prostate cancer. Paired shotgun metagenomic analyses of the gut–prostate axis, coupled with single-cell RNA sequencing and spatial transcriptomics of prostatic tissue from well-phenotyped IBD patients, could clarify which immune populations, such as, Th17 cells, exhausted CD8+ T cells, or myeloid-derived suppressor cells, distinguish benign inflammatory infiltrates from pre-malignant field effects. Finally, the potential modifying effects of IBD-directed therapies, including anti-TNF agents, vedolizumab, JAK inhibitors, and integrin antagonists, on prostate cancer risk remain entirely uncharacterized, representing a critical knowledge gap for clinical risk stratification and pharmacovigilance.

Conclusion

The findings of this review indicate a biologically plausible and epidemiologically supported association between IBD, particularly UC, and an enhanced risk of prostate cancer. This association is primarily mediated through systemic inflammation, activation of oncogenic signaling pathways, gut dysbiosis, and impaired immune surveillance. From a clinical perspective, these results suggest that clinicians, especially gastroenterologists and urologists, should consider more vigilant prostate cancer monitoring in male patients with long-standing or poorly controlled UC. This may include earlier initiation of PSA screening and lower thresholds for urological referral in this population. At the public health level, healthcare policymakers in Iran should prioritize establishing a national IBD registry and integrating it with cancer surveillance systems to enable region-specific risk assessment. However, given the current lack of Iranian-specific prospective data and the presence of detection bias in existing studies, routine population-wide screening cannot yet be recommended. Instead, targeted screening strategies for high-risk IBD subgroups, especially those with extensive colonic involvement, prolonged disease duration, or exposure to immunosuppressive therapies, appear to be the most pragmatic approach until further local evidence becomes available.

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Data Availability Statement

This study did not generate any new data.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Authors' Contribution

Zhila Sheikhi designed and supervised the study; Sayyid Ali Hosseini and Bagher Soleimani contributed to data collection and writing the draft of the manuscript; Sayyid Ali Hosseini made Figure 1. Zhila Sheikhi and Bagher Soleimani revised the manuscript; all authors approved the final version.

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