Prostate Cancer and Chronic Prostatitis

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Prostate cancer and chronic prostatitis are prevalent disorders in men. The cause of prostate cancer and chronic prostatitis is multifocal and diverse. Both disorders exhibit characteristic elevation of serum prostate-specific antigen, currently the primary screening test for prostate cancer. Prostate inflammation, regardless of cause, is the histopathologic hallmark of chronic prostatitis. In general, inflammation is associated with multiple cancers, and prostate inflammation, in particular, is a suggested factor in the development and progression of prostate cancer. This review addresses the link between chronic prostatitis and prostate cancer, especially as it relates to clinical practice.

Introduction

Prostate cancer is the third most common malignancy in men in the United States, with a lifetime risk of 1 in 6 [1]. Although effective screening has been implemented, the pathogenesis of prostate cancer remains unclear. Most experts believe the etiology of prostate cancer is multifactorial, with advancing age, diet, race, and family history most often implicated [2]. Recent studies have raised the possibility of chronic inflammation as an important possible etiology in prostate cancer pathogenesis [3•].

The clinical syndrome, which is thought to be due to prostatic inflammation, is known as prostatitis. Prostatitis is estimated to be as prevalent as prostate cancer in the United States [4]. Autopsy studies have found the histologic prevalence of prostatitis to range from 6% to 44% [5]. However, prostatitis as a clinical syndrome has an estimated prevalence of approximately 9% [6]. Epidemiological studies have suggested an association between prostatitis and prostate cancer [7,8]. A meta-analysis by Dennis et al. [7] found 11 case-control studies that assessed the relationship between prostatitis and prostate cancer; 13 studies that assessed the relationship between gonorrhea and prostate cancer; and six studies that assessed the relationship between syphilis and prostate cancer. An increased risk of prostate cancer was found in patients with a history of prostatitis (OR = 1.6), gonorrhea (OR = 1.3), or syphilis (OR = 2.3). Sarma et al. [8] explored the link between sexually transmitted diseases and prostatitis in a population study of 129 black men and 703 controls. They found a history of gonorrhea and prostatitis increased the risk of prostate cancer 1.78- and 4.93-fold, respectively.

In theory, inflammation can lead to states suitable for neoplasms [9]. Among proposed rationale for inflammation-induced cancers are elevated levels of growth factors present with inflammation and cancer, increased vasculature associated with neoplasm and cancer, and possible injury to host tissue allowing cancer cells to break free [9].

Inflammation and Cancer

Chronic inflammation, particularly related to infection, has been associated with multiple solid tumors [9]. It is well established that hepatitis B virus infection is associated with hepatocellular carcinoma, schistosomiasis infection is associated with bladder and colon cancers, and *Helicobacter pylori* infections are associated with gastric cancer. There are multiple reasons why chronic inflammation is associated with cancer. Inflammation is usually a self-limited event, with initial growth factor release and angiogenesis followed by anti-inflammatory cytokine–mediated resolution. In chronic inflammation, however, persistence of promoters is present or a failure in mechanisms required to resolve inflammation exists. This leads to release of increased progrowth cytokines and increased levels of various growth factors. In addition, DNA damage occurs in proliferating cells due to the generation of reactive oxygen and nitrogen species. This damage results in point mutations, deletions, or rearrangements, sometimes resulting in neoplastic growth.

Inflammation also results in neovascularization, an essential element of solid tumor growth [9]. In acute inflammation, this vascularization is restricted and therefore has limited effect on tumor growth. However, chronic inflammation creates a vascular microenvironment very similar to that present in established solid tumors. This can lead to rapid tumor growth.

Inflammation leads to remodeling of the extracellular matrix and disturbance in cell adhesion molecules modulating the ability of tumors to invade. Tumors cells can

also use the adhesion molecules, chemokines, and receptors made by inflammatory cells to aid in migration and distant metastatic spread. Further, inflammatory cells can create survival factors that can coat tumor cells and aid in evading host defense mechanisms.

Anti-inflammatory treatments, in particular cyclooxygenase-2 (COX-2) inhibitors, can limit tumor progression and possibly incidence. This has been studied extensively in colon cancer and recently in prostate cancer. The fact that COX-2 inhibitors possibly show activity in limiting cancer progression is evidence that inflammation is at least a partial cause of certain forms of cancer [10].

Inflammation and Prostate Cancer Pathogenesis

The etiology of prostate cancer is multifactorial. Advancing age, family history, race, and diet are likely causal agents [2]. Prostatic inflammation has been proposed recently as a possible etiology of prostate cancer [3•]. Pathologic analysis of surgical specimen after radical prostatectomy has provided support for this hypothesis. Proliferative inflammatory atrophy (PIA), defined as an increased fraction of epithelial cells that proliferate in focal atrophy lesions, has been studied to determine if it is associated with high-grade prostatic intraepithelial neoplasia (HGPIN) and prostate carcinoma [11]. DeMarzo et al. [11] evaluated tissue dissected immediately after surgical removal from 42 radical prostatectomies. They specifically recorded degree of inflammation and proximity to areas of HGPIN and prostate carcinoma using morphologic and immunohistochemical analysis. They found that all PIA lesions are proliferative, the vast majority are associated with inflammation, and many of the proliferating cells appear to have an immature secretory cell phenotype, with similarities to prostatic intraepithelial neoplasia and prostate carcinoma. Shah et al. [12] evaluated postatrophic hyperplasia (PAH), defined as consisting of dilated ducts or acini with adjacent foci of small crowded glands with an atrophic appearance—a subgroup of PIA, in a randomly selected group of 40 formalin-fixed and paraffin-embedded whole mount radical prostatectomy specimens obtained during a 3-year period. This group evaluated differences in location of the two components of PIA, simple atrophy (SA) and PAH. They found that while both SA and PAH were associated with areas of prostate adenocarcinoma, PAH was significantly more likely to be near areas of prostate adenocarcinoma, implying PAH as the histologic feature likely to be a precursor to adenocarcinoma.

Anton et al. [13] evaluated whole mount sections from 272 randomly selected radical prostatectomy specimens and 44 cystoprostatectomy specimens for presence, location, and number of foci of PAH. These were then correlated with the presence and location of prostate cancer foci. They found that PAH was a relatively common lesion particularly in the peripheral zone of the prostate but did not appear to have any association with presence or location of prostate carcinoma. Gerstenbluth et al. [14] studied step sections of 40 consecutive radical prostatectomy specimens with clinically localized prostate cancer for the distribution of chronic prostatitis and its association with benign prostatic hyperplasia (BPH) or prostate cancer. One hundred percent of their specimens displayed chronic prostatitis. Only 57.5% of the cases had chronic inflammation near areas of prostate cancer, while 87.5% of the cases had prostatitis near areas of BPH, suggesting a stronger role for chronic prostatitis in the etiology of BPH, with perhaps a minor role in the etiology of prostate cancer. Billis and Magna [15] examined step sections of 100 prostates obtained during autopsy of men older than 40 years without a history of prostate cancer. They found that inflammatory prostatic atrophy was common in this young age group but found no association between areas of inflammatory prostatic atrophy and histologic carcinoma or HGPIN.

Multiple studies have tried to evaluate the role of inflammation to prostate cancer in needle biopsy specimen. MacLennan et al. [16] studied the influence of chronic inflammation in prostate carcinogenesis by examining prostate needle biopsies from 177 patients with clinical parameter suspicious for malignancies and organizing the group by the presence (n = 144) or absence (n = 33) of chronic inflammation. The groups were then followed for repeat needle biopsies within 5 years. Interestingly, 20% of the group with chronic inflammation and 6% of the group without chronic inflammation developed prostate adenocarcinoma over this time, suggesting that chronic inflammation affects the development of prostate adenocarcinoma.

The relationship between inflammatory cascade and prostate cancer has also been studied. Konig et al. [17] obtained samples of prostate tissue from 36 patients undergoing transurethral resection of the prostate and evaluated the samples for expression of various cytokines, chemokine receptors, Toll-like receptors, and COX-2, all involved in the inflammatory cascade. They found differences in expression of chemokine, chemokine receptor, Toll-like receptor, and enzymes such as COX-2 between BPH and prostate cancer tissue, suggesting a role for various inflammatory cascades in the development of prostate cancer and BPH. Zheng et al. [18] further evaluated 9275 single nucleotide polymorphisms (SNPs) in 1086 genes of the inflammatory pathway among 200 familial cases of prostate cancer and 200 unaffected controls selected from a large Swedish case-control population. This study found significantly more than expected SNPs at nominal P values of 0.01, 0.05, and 0.1, providing objective support for an association between prostate cancer and multiple modest-effect genes in inflammatory pathways.

Yoshimura et al. [19] evaluated expression of cyclooxygenase-1 (COX-1) and COX-2 expression in prostate specimen obtained from 45 patients, including 28 with prostate cancer, eight with BPH, one with prostatic

intraepithelial neoplasia, and eight normal prostates that were part of cystoprostatectomy specimens. They demonstrated weak COX-1 expression in all benign and tumor tissue and enhanced expression of COX-2 in prostate cancer tissue. Their study demonstrated that human prostate carcinoma cells generate COX-2 and that COX-2 may play a role in proliferation.

Studies that evaluate chronic inflammation in the prostate primarily focus on histological signs of prostatic inflammation. The clinical syndrome commonly thought of as being associated with chronic inflammation of the prostate is prostatitis.

National Institutes of Health Classification of Prostatitis

In 1995, the National Institutes of Health (NIH) expert consensus conference organized prostatitis into four distinct categories [20,21].

Category I prostatitis is acute bacterial prostatitis, an acute infection caused by uropathogenic bacteria. This type of prostatitis usually presents with acute urinary symptoms, often with perineal pain and other signs of infection such as fever. The diagnosis is clinical with or without a positive urine culture for the responsible bacteria. It usually responds well to a prolonged course of appropriate antibiotics.

Category II prostatitis is chronic bacterial prostatitis and is also caused by bacteria. It has similar symptoms as category I; however, it is usually milder and often presents with frequent recurrent urinary tract infections likely due to inadequate treatment of the uropathogen. This type of prostatitis is also treated with a prolonged course of antibiotics, and with the emergence of antimicrobials with better prostatic penetration, the incidence of category II prostatitis is likely to continue declining.

Category III prostatitis is the chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). This type of prostatitis is characterized by pelvic or perineal pain with or without inflammation on expressed prostatic secretions, and is divided by the presence or absence of inflammation into IIIa and IIIb, respectively. The etiology of CP/CPPS is diverse and treatment is often difficult. Included in the armamentarium of pharmacologic agents used in treatment are antibiotics, α-blockers, 5-α-reductase inhibitors, nonsteroidal anti-inflammatory agents, and muscle relaxants. Avoidance of spicy foods, repeated prostatic massage, and pelvic-floor muscle exercises have also been tried with varying success. Surgical therapy, ranging from minimally invasive treatments for prostate debulking to transurethral resection of the prostate to simple cystectomy, has been tried as a method of last resort for treatment of CP/CPPS. Prostate histopathology in the setting of CP/CPPS has been characterized in a prospective biopsy study of 368 biopsies in 97 men by True et al. [22]. These investigators rigorously diagnosed CP/CPPS using NIH criteria and did not find any cases of prostate carcinoma among 97 patients and noted no inflammatory cells in 67% of the specimens. In fact, only 5% of patients had moderate or severe inflammation on biopsy. They concluded that there existed a need to reevaluate current concepts of the pathophysiology of CP/CPPS and that the correlation between CP/CPPS and inflammation was weak. Most experts, however, do think that inflammation plays a contributory role in CP/CPPS.

Category IV prostatitis is asymptomatic chronic prostatitis, defined by the presence of inflammatory cells in either expressed prostate secretions or during histological review of prostate biopsies in asymptomatic men. Carver et al. [23] determined the prevalence of men with category IV prostatitis, based on inflammation present on expressed prostatic secretions, in 300 randomly selected men participating in a prostate cancer awareness screening program. Of these 300, 227 were able to provide a specimen for examination. The prevalence in this group was 32.2%, suggesting that category IV prostatitis is fairly common. In addition, these investigators determined that men with category IV prostatitis had a significantly higher serum prostate-specific antigen (PSA) than those who did not.

Prostate-Specific Antigen and Relationship to Chronic Prostatitis and Prostate Cancer

PSA is a well-known marker for prostate cancer and its use in screening programs is well-documented [2]. Acute bacterial prostatitis, or category I prostatitis, is also a known and accepted cause of serum PSA elevation. Histopathologic analysis of the prostate in the setting of acute prostatitis is extremely difficult because patients are acutely ill and therefore cannot be candidates for biopsy or surgery until the infection is cleared. As such, there is no good correlation between pathologic features of acute prostatitis and serum PSA. The correlation between serum PSA and histologic evidence of inflammation, a hallmark of chronic prostatitis, has been studied.

Okada et al. [24] evaluated 558 negative needle biopsy specimen obtained from 93 men without a diagnosis of prostate cancer or clinical prostatitis. Inflammation was graded and correlated with serum PSA. In their study, serum PSA correlated significantly with inflammation, particularly acute inflammation. Stancik et al. [25] studied needle biopsies from 404 patients and correlated them to levels of serum total and free PSA. The study group was divided into 100 prostate cancer patients, 137 classified as category IV prostatitis, and 143 with BPH. The investigators found no difference in total PSA between the prostate cancer and prostatitis groups, but did find that the ratio of serum free to total PSA was significantly lower in the group with prostate cancer compared with the group with prostatitis. Rowe et al. [26] also examined the relationship of serum free and total PSA to incidental prostatic inflammation. In their study of 175 men undergoing prostate biopsy

during screening for prostate cancer, they found that men with acute inflammation had significantly lower serum free to total PSA ratio than those with chronic inflammation or BPH. Further, they found that the serum free to total PSA ratio was similar in patients with acute inflammation on biopsy to those with prostate cancer on biopsy.

Bozeman et al. [27] identified 95 men with serum PSA greater than 4.0 ng/mL who also had greater than 10 white blood cells per high-powered field, consistent with category IV prostatitis. These men underwent a 4-week course of antibiotics and had their serum PSA measured. Mean serum PSA in these men showed a significant decrease of 36.4%.

The role of serum PSA in the diagnostic evaluation of category III and IV prostatitis and its impact on prostate cancer screening is evolving. Nadler et al. [28] evaluated the role of serum PSA in the diagnostic evaluation of CP/CPPS by evaluating 421 patients enrolled in the Chronic Prostatitis Cohort Study and comparing them with 112 age-matched controls. They found a slightly higher level of serum PSA in cases as opposed to controls, but did not think this was clinically relevant and therefore recommended treating patients with CP/CPPS and elevated serum PSA the same as any other patient being screened for prostate cancer. Potts [29] suggested screening for category IV prostatitis in men with elevated serum PSA because of the high prevalence of the disorder—42% in her series of 122 men. In addition, Potts suggested treating the men with expressed prostate secretion–proven prostatitis with appropriate antibiotic and then measuring serum PSA. Four weeks of antibiotic therapy resulted in 43% fewer men needing biopsies.

Conclusions

Chronic prostatitis is often associated with prostate cancer. In particular, there is growing evidence that asymptomatic chronic prostatic inflammation, defined as category IV prostatitis, is prevalent in cases of prostate cancer. Several investigators have proposed a causal link between inflammation and prostate cancer, but currently no firm statement on causality can be made. The effect of inflammation, based on studying the presence of genes involved in inflammation, on prostate cancer pathogenesis appears small. In addition, it appears that treatment with anti-inflammatory drugs, particularly COX-2 inhibitors, appears promising as a way to decrease progression and incidence of prostate cancer. This is an area where significant research is being conducted.

Because both chronic prostatitis and prostate cancer result in elevated levels of serum PSA, it may be wise to treat patients suspected of having chronic prostatitis with a course of antibiotics. It may also be worthwhile to screen patients for the presence of category IV prostatitis, treat with antibiotics if appropriate, and then measure the serum PSA again. Other than these manipulations, it is appropriate not to alter prostate cancer screening methodology in the setting of chronic prostatitis.

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No potential conflict of interest relevant to this article was reported.

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