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THE ROLE OF INFLAMMATION IN THE PATHOGENESIS OF PROSTATE CANCER

WILLIAM G. NELSON,*† ANGELO M. DE MARZO,‡ THEODORE L. DEWEES§
AND WILLIAM B. ISAACS

From the Brady Urological Institute and Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland

ABSTRACT

Purpose: A new hypothesis for the etiology of prostate cancer is that chronic or recurrent prostate inflammation may initiate and promote prostate cancer development.

Materials and Methods: We reviewed the current direct and indirect evidence from epidemiology, genetics, molecular biology and histopathology implicating inflammation in the pathogenesis of prostate cancer.

Results: The case for prostate inflammation as a cause of prostate cancer is compelling. Epidemiology data have correlated prostatitis and sexually transmitted infections with increased prostate cancer risk and intake of anti-inflammatory drugs and antioxidants with decreased prostate cancer risk. Genetic studies have identified *RNASEL*, encoding an interferon inducible ribonuclease, and *MSR1*, encoding subunits of the macrophage scavenger receptor, as candidate inherited susceptibility genes for familial prostate cancer. Somatic silencing of *GSTP1*, encoding a glutathione *S*-transferase capable of defending against oxidant cell and genome damage, has been found in almost all prostate cancer cases. Proliferative inflammatory atrophy lesions containing activated inflammatory cells and proliferating epithelial cells appear likely to be precursors to prostatic intraepithelial neoplasia lesions and prostatic carcinomas.

Conclusions: Emerging hints that prostate inflammation may contribute to prostatic carcinogenesis will provide opportunities for the discovery and development of new drugs and strategies for prostate cancer prevention.

KEY WORDS: prostate, prostatic neoplasms, inflammation, etiology

Although prostate cancer is a common cause of morbidity and mortality in men in the developed world, it ought to be preventable. Asian men have low prostate cancer risks while residing in Asia but they adopt higher prostate cancer risks upon immigration to North America, especially after exposure to a Western lifestyle for 25 years or more.^{1,2} What about the Western life-style causes prostate cancer? Most epidemiology studies implicate the stereotypical Western diet, rich in saturated fats and meats and poor in fruits and vegetables. Consumption of animal fats has been associated with increased prostate cancer risk and intake of antioxidants, fruits and vegetables has been associated with decreased prostate cancer risk.³⁻⁹ However, it has not been fully established whether the Western diet makes an error of commission (eg overconsumption of animal fats) and/or omission (eg under consumption of fruits and vegetables). Prostate carcinogens are present in the Western diet. Male rats fed the heterocyclic aromatic amine PhIP (2-amino-1-methyl-6-phenylimidazo[4,5- β]pyridine), a carcinogen in charred or well done meats, have mutations in prostate cell DNA and prostate cancers.^{10,11}

Recently there has been renewed interest in the role of prostatic infection and/or inflammation in the pathogenesis of prostate cancer.^{12,13} The contribution of host immune and

inflammatory responses to cancer development has been well recognized in many different human cancers. For example, independent of the etiology hepatitis and cirrhosis (eg viral infection or genetic syndromes) are major predisposing factors for hepatocarcinogenesis, especially in the setting of dietary exposure to the carcinogen aflatoxin B₁.¹⁴ We considered evidence that prostatic inflammation is the major predisposing factor for prostatic carcinogenesis.

EPIDEMIOLOGY

There are 3 major reasons the association between prostatic inflammation and prostate cancer has been difficult to test in epidemiological studies. First, although 9% of men 40 to 79 years old have symptomatic prostatitis, asymptomatic prostatitis, seen in prostate biopsies or prostate resection specimens, is almost ubiquitous in the developed world.¹⁵⁻¹⁸ Because age at onset, natural history, and incidence and prevalence in different geographic regions are unknown and difficult to ascertain, the association between asymptomatic prostatitis and prostate cancer has not been tested in population studies. A second challenge for epidemiological studies is that men with symptomatic prostatitis compared with men without prostate inflammation are more likely to seek care from a urologist, have increased serum prostate specific antigen (PSA) and undergo prostate biopsy.^{15,17} As a consequence, men with symptomatic prostatitis are more likely to have prostate cancer diagnosed, while men without prostatitis symptoms are less likely to have prostate cancer discovered even if it is present. This bias can undermine apparent associations between symptomatic prostatitis and prostate cancer in epidemiological studies. Finally, although various microbial organisms have been found to infect prostate tis-

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* Correspondence: Sidney Kimmel Comprehensive Cancer Center, CRB 151, 1650 Orleans St., Baltimore, Maryland 21231 (telephone: 410-614-1661; FAX: 410-502-9817; e-mail: bnelson@jhmi.edu).

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sues, the offending pathogen is not known for many episodes of symptomatic prostatitis and for all asymptomatic prostatitis. Despite these difficulties an increase in prostate cancer risk has been correlated with symptoms of prostatitis and with sexually transmitted infections independent of the specific pathogen. These findings are consistent with the possibility that host inflammatory responses to infection rather than the infectious agent itself might lead to prostate cancer.^{19–21} In a population based case-control study prostate cancer risk was increased in men who reported a history of gonorrhea or syphilis (OR 1.6, 95% CI 1.2 to 2.1) with even further increases in risk in men reporting 3 or more episodes of gonorrhea (OR 3.3, 95% CI 1.4 to 7.8).²¹

Although an effective treatment for symptomatic or asymptomatic prostatitis is not known, several epidemiology studies have examined the effects of anti-inflammatory drugs on prostate cancer risk with somewhat mixed results. In a study of 90,100 men in the Kaiser Permanente Medical Care Program who completed a health questionnaire with information on aspirin use between 1964 and 1973 a protective effect of ingesting 6 aspirin daily was detected (OR 0.76, 95% CI 0.60 to 0.98).²² However, in the Health Professions Follow-up Study cohort of 47,882 men a trend toward a benefit of aspirin intake was only seen for metastatic prostate cancer (OR 0.73, 95% CI 0.39 to 1.38).²³ In another case-control study aspirin use correlated inversely with prostate cancer risk (OR 0.82, 95% CI 0.71 to 0.95).²⁴ A population based case-control study done in Olmsted County, Minnesota showed a protective effect of nonsteroidal anti-inflammatory drugs other than aspirin that was limited to men 60 years old and older (OR 0.4, 95% CI 0.2 to 0.8 for ages 60 to 69 years and OR 0.2, 95% CI 0.1 to 0.5 for 70 to 79 years).²⁵ Other studies have not found such a strong benefit to nonsteroidal anti-inflammatory drug use.^{24, 26, 27} A major target of nonsteroidal anti-inflammatory drugs, cyclooxygenase (COX)-2, appears to be expressed in inflammatory cells in the prostate and in proliferative inflammatory atrophy (PIA) lesions, a suspected prostate cancer precursor, but not in prostatic intraepithelial neoplasia (PIN) lesions or in prostatic carcinomas.²⁸

Intake of different antioxidants that might be expected to attenuate cell and genome damage inflicted by inflammatory oxidants (eg superoxide, nitric oxide or peroxynitrite) has consistently been found to protect against prostate cancer development. For example, several epidemiology studies have correlated low selenium with an increased risk of prostate cancer.^{29–32} In addition, a randomized, placebo controlled clinical trial of selenium supplementation for the prevention of recurrent nonmelanoma skin cancer (the Nutritional Prevention of Cancer Study) revealed a decrease in incident prostate cancers (overall RR 0.51, 95% CI 0.29 to 0.87), especially in men with low selenium at trial entry.^{7, 8, 33} Inverse correlations between vitamin E (α -tocopherol and particularly γ -tocopherol) and prostate cancer risk have also been reported.^{34–36} A randomized clinical trial of α -tocopherol and β -carotene supplementation for the prevention of lung cancer in male smokers (the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study) showed a 32% decrease in prostate cancer incidence and a 41% decrease in prostate cancer mortality in men who received α -tocopherol.^{9, 37} Consumption of vegetables containing the carotenoid lycopene and high lycopene blood levels have been associated with low prostate cancer risk.^{38, 39} Although to our knowledge no randomized clinical trials of lycopene for prostate cancer prevention have been done, a clinical trial in which men were fed tomato based pasta showed a decrease in oxidative genome damage in the prostate.⁴⁰ Finally, consumption of cruciferous vegetables containing isothiocyanates, such as the chemoprotective compound sulforaphane, has been reported to reduce prostate cancer risk.⁴ Sulforaphane can act as an antioxidant by inducing a plethora of carcinogen detoxifica-

tion enzymes via a mechanism involving the cysteine rich protein Keap1 and the transcription factor Nrf2.^{41, 42}

GENETICS

Prostate cancer has long been known to cluster in some families.⁴³ A genetic contribution to prostate cancer risk has been suggested 1) by segregation analyses and linkage studies of familial prostate cancer, which have hinted at specific prostate cancer susceptibility genes, and 2) by twin studies which, by comparing prostate cancer incidence between monozygotic and dizygotic twins, have revealed a stronger hereditary component for prostate cancer than for any other human cancer.^{44–46} What effects could prostate inflammation have on genetic susceptibility to prostate cancer? Prostate inflammation and/or infection might complicate the search for susceptibility genes. For example, exposure of many family members to an infectious agent that increases prostate cancer risk might mimic genetic predisposition. In addition, if men with a familial predilection for prostatic inflammation are more intensively screened for prostate cancer, this phenomenon might minimize the genetic contributions to prostate cancer risk by generating phenocopies or itself resemble genetic susceptibility to prostate cancer. However, if prostate inflammation and/or infection contributes to prostate cancer development, the products of some candidate prostate cancer susceptibility genes might function in host responses to infection or in host protection against cell and genome damage mediated by inflammatory oxidants.

RNASEL, which encodes a latent endoribonuclease component of an interferon inducible RNA degradation pathway activated upon viral infection, has been identified as a candidate prostate cancer susceptibility gene.^{47–49} In the first study reported variant *RNASEL* alleles Glu256X and Met1Ile encoded defective enzymes and were linked to prostate cancer in specific families.⁴⁷ In another report the variant *RNASEL* allele Arg462Gln was associated with an increased prostate cancer risk in a case-control population study (OR 1.46, 95% CI 1.09 to 1.95 for heterozygotes and OR 2.12, 95% CI 1.19 to 3.68 for homozygotes).⁵⁰ Remarkably the fraction of prostate cancer in the population studied thought attributable to the Arg462Gln *RNASEL* allele was estimated to be 0.13 (CI 0.04 to 0.21).⁵⁰ Like the Glu256X and Met1Ile *RNASEL* alleles, the Arg462Gln allele encodes a defective *RNASEL* enzyme.⁵¹ Although the precise mechanisms by which defects in an interferon inducible RNA degradation pathway might lead to prostate cancer have not been established, studies of *RnaseL*^{-/-} mice have revealed decreased interferon- α antiviral activity and deficiencies in apoptosis induction.⁵²

MSR1, which encodes subunits of a homotrimeric macrophage scavenger receptor capable of binding bacterial lipopolysaccharide and lipoteichoic acid as well as oxidized serum lipoproteins, has also been identified as a candidate prostate cancer susceptibility gene.^{53, 54} In 1 study a series of rare germline *MSR1* mutations (ie Pro36Ala, Ser41Tyr, Val113Ala, Asp174Tyr, Gly369Ser, His441Arg and Arg293X) appeared to be linked to prostate cancer susceptibility in some families at high risk for prostate cancer.⁵³ In addition, the Arg293X *MSR1* allele was detected in 2.52% of men with sporadic prostate cancer and in only 0.39% without the disease ($p = 0.047$).⁵³ In a population case-control study of black American men the Asp174Tyr *MSR1* allele was found in 6.8% with prostate cancer and only 3.6% without the disease ($p = 0.14$).⁵⁵ Other, more common *MSR1* variants may also influence prostate cancer risk.⁵⁶ In the prostate *MSR1* expression is restricted to macrophages, particularly those present at sites of prostate inflammation. Although the mechanisms by which defects in macrophage function might lead to prostate cancer have not been elucidated, *Msr-A*^{-/-} mice appear vulnerable to infection by *Listeria monocytogenes*.

genes, *Staphylococcus aureus*, *Eschericia coli* and Herpes simplex virus type 1.^{54, 57, 58}

Genetic epidemiology studies have implicated several polymorphic variant alleles of genes encoding oxidant defense enzymes and of genes encoding inflammatory cytokines in prostate cancer risk. In a case-control study done in the clinical trial cohort from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, the Ala16Val allele of *MnSOD*, encoding a mitochondrial enzyme that protects cells against oxidative damage was associated with an increased prostate cancer risk (OR 1.72, 95% CI 0.96 to 3.08 for Ala16Val homozygotes).⁵⁹ In another case-control study several variants of *hOGG1*, encoding an enzyme that repairs oxidative genome damage, were associated with increased prostate cancer risks.⁶⁰ The increased prostate cancer risk associated with 1 of the *hOGG1* variant alleles, Ser362Cys, was confirmed in an independent case-control study (OR 2.1, 95% CI 1.2 to 3.8).⁶¹ Single nucleotide polymorphisms in the promoter regions of genes encoding interleukin-8, vascular endothelial growth factor and interleukin-10 have been reported to influence prostate cancer risk.⁶² Additional studies of polymorphic variants of other genes participating in host immunity and prostate cancer risk are underway.

MOLECULAR PATHOGENESIS

The key features of the molecular pathogenesis of prostate cancer that hint at a role for prostatic inflammation in prostatic carcinogenesis are the somatic inactivation of *GSTP1*, the gene encoding the π -class glutathione S-transferase (GST) and the strong possibility that PIA lesions are prostate cancer precursors.^{13, 63, 64} GSTs, which are enzymes that catalyze the conjugation of the chemical scavenger glutathione to various reactive chemical species, including oxidants, have long been recognized to protect against cancer development. The loss of *GSTP1* expression, attributable to silencing of *GSTP1* transcription accompanying somatic CpG island hypermethylation, almost always accompanies prostate cancer development and the mechanism by which the *GSTP1* CpG island is selectively targeted for de novo hypermethylation has not been established.⁶³ In normal prostate tissues *GSTP1* tends to be expressed by basal epithelial cells and not by columnar secretory cells. However, *GSTP1* expression is typically induced to high levels at sites of prostatic inflammation and the loss of *GSTP1* expression is characteristic of PIN lesions and prostatic carcinomas.^{63, 64} The consequences of this loss of *GSTP1* function are likely to be inadequate defenses against chemical carcinogenesis. For example, LNCaP prostate cancer cells, which do not express *GSTP1*, accumulate more genome damage when exposed to metabolically activated PhIP, a carcinogen present in charred or well done meats, than LNCaP cells in which *GSTP1* expression has been restored by genetic means.⁶⁵ Similarly in preliminary studies when compared to LNCaP cells genetically modified to express *GSTP1*, LNCaP cells also accumulated more oxidative genome damage when exposed to prolonged oxidative stress (DeWeese, T. L. and Nelson, W. G., unpublished data). Finally, mice carrying disrupted *Gstp1/2* genes have increased numbers of skin tumors after topical treatment with the carcinogen 7,12 dimethylbenz[a]anthracene.⁶⁶

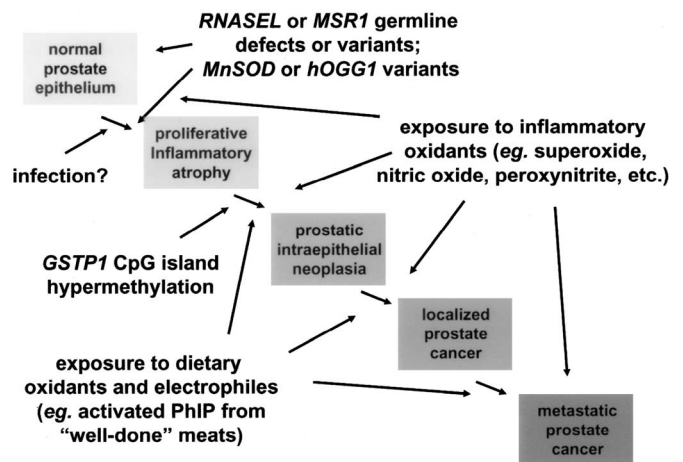
The term PIA designates focal prostate lesions that are characteristically composed of atrophic but proliferating prostatic epithelial cells and are often located near activated inflammatory cells.⁶⁴ PIA cells typically show many signs of stress, including the induction of *GSTP1*, *GSTA1* and *COX-2* expression, as well as features of cells thought to be intermediates in differentiation between basal epithelial cells and columnar epithelial cells.^{28, 64, 67, 68} Accumulating evidence suggests that PIA lesions may be precursors to prostate cancer. PIA lesions are often located directly adjacent to PIN lesions and to prostatic carcinomas.^{64, 69} *TP53* mutations,

which are present in some 20% of prostate cancer cases, have been detected in as many as 5.3% of PIA lesions.^{70, 71} Gain in DNA sequences at the chromosome 8 centromere, which is present in some 6% of prostate cancer cases, has been found in 4% of PIA lesions.⁷² Finally, *GSTP1* CpG island hypermethylation, which is present in greater than 90% of prostate cancer cases, has been found in 6.3% of PIA lesions.⁷³ The tendency for the loss of *GSTP1* function to mark the transition between PIA lesions and PIN lesions (with *GSTP1* CpG island hypermethylation present in at least 70%) is consistent with the possibility that compromised defenses against inflammatory oxidants may initiate prostatic carcinogenesis.¹³ Provocatively the pathogenesis of gastric cancer, which is known to be triggered by chronic infection with *Helicobacter pylori*, is also characterized by chronic inflammation, inflammatory damage to the epithelium, and subsequent epithelial atrophy (often accompanied by intestinal metaplasia) and dysplasia.^{74, 75} In this chronic inflammatory state repeat epithelial damage and regeneration occur in the setting of exposure to reactive oxygen and nitrogen species elaborated by inflammatory cells, increasing the propensity for neoplastic transformation.⁷⁴

CONCLUSIONS

When considered together, evidence from prostate cancer epidemiology, genetics and molecular pathogenesis converge on the hypothesis that prostate inflammation and/or infection may be a cause of prostate cancer (see figure). Prostatitis and sexually transmitted infections, intake of antiinflammatory drugs and antioxidants, variant alleles of genes encoding determinants of host responses to infections, such as *RNASEL* and *MSR1*, and of host protection against oxidative damage, such as *MnSOD* and *hOGG1*, appear to influence the risk of prostate cancer. The appearance of PIA lesions with subsequent somatic inactivation of *GSTP1*, encoding a defense against carcinogenic genome damage, characteristically accompanies prostatic carcinogenesis. To test fully this new hypothesis several critical questions remain to be answered. Do geographic differences in the age specific incidence of prostatic inflammation explain geographic differences in prostate cancer incidence and mortality? Various infectious organisms are known to infect the prostate, cause prostate inflammation and/or increase serum PSA, including *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *E. coli* and other bacteria as well as a number of viruses.⁷⁶⁻⁷⁹ Is

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Prostate cancer pathogenesis. Contributions of genetics (*RNASEL*, *MSR1*, *MnSOD* and *hOGG1*), epidemiology (infection, inflammatory oxidants, and dietary oxidants and electrophiles) and somatic genome alterations (*GSTP1* CpG island hypermethylation) are shown driving neoplastic transformation and malignant progression through PIA and PIN to localized and metastatic prostate cancer.

there a specific etiological infectious agent responsible for chronic persistent prostatitis that leads to prostate cancer? Transcriptome profiling studies of mRNAs expressed in the prostates of rats fed high beef fat diets have revealed an induction of genes associated with inflammation.⁸⁰ Do dietary practices influence the extent or intensity of prostatic inflammation? If these issues can be resolved, there are potentially profound implications for the prevention and treatment of prostate cancer.

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DISCUSSION

Dr. Edward P. Gelmann. Is there any evidence that the COX pathway influences DNA methylation? You have a pathway with subtle changes in methylation. There is some correlation of expression in methylation with androgen receptors in vitro and estrogen receptors in vivo but what is the evidence that the methylated genes that you are looking at have in fact altered protein expression?

Dr. William G. Nelson. The ones that we have identified definitely do. At this point most of the studies reported about methylation do not deal with the mechanism of gene expression. In the GST- π gene (*GSTP1*) every prostate cancer that we are aware of that has at least 1 unmethylated allele expresses a lot of the enzyme.

Dr. Mark A. Rubin. What do you think is the time course between the actual insult and PIA? Also, do you think that PIA progresses from normal tissue to high grade PIN or could PIA and high grade PIN be on different pathways?

Dr. William Nelson. I do not have a sense for how far careful morphology can take us. When you look at these lesions, some of them are overtly inflamed, some have the appearance of chronic scarring and others look sort of burned out. The number 1 thing that we would love to know is what one of these lesions looks like during its life span.

Doctor Rubin. Your data appear to show that a lot of PIA lesions are necessary to get to PIN, or you have a subset of men with PIA that is going to PIN or PIA leads to a totally different cancer.

Dr. William Nelson. I wonder if those PIA lesions containing cells with larger nuclei with nucleoli and some clearing of the cytoplasm might be in transition. If they are, how could we show that? It appears that they might already have some *GSTP1* methylation. However, there is a technical issue about how easy it is to see that in the frozen section used for laser capture.

Dr. Joel B. Nelson. My clinical observation is that clinical prostatitis is not a common event in the history of men with prostate cancer. However, I think that the development of clinical prostatitis may actually be the response that prevents progression to cancer.

Dr. William Nelson. I have been very interested in some of the longitudinal data for PSA. If PSA in a man is above the median at age 40 years, he is almost certain to get prostate cancer. What is driving PSA at age 40 years? It is difficult for me to believe that the tiny cancers we can now screen for are the answer. Is it inflammation? If so, most of it has to be asymptomatic because these men have no symptoms. Is inflammation in the causal pathway, sort of like cholesterol? Are we doing something helpful if we treat men and lower the PSA value? The only thing about prostatitis that is useful for the symptomatic syndrome is the possibility that an anti-inflammatory agent might treat that syndrome. I think that there would be a lot of pharmaceutical interest in selling that product. If it sold well, there would be a greater chance of doing a clinical study to find out if it changed the risk of prostate cancer.

Dr. Laurence Klotz. There seems to be a lack of any real evidence of a dose-response phenomenon between clinical infection and prostate cancer. If the association exists, you would expect patients with acute infection or a history of recurrent infections to be at higher risk. A relative risk of 1.5 is really not enough to conclude that this is a serious risk factor, unlike the link between human papillomavirus infection and cervical cancer, for example. How do you address this apparent lack of any kind of real dose-response phenomenon between the severity of infection and the risk of cancer?

Dr. William Nelson. If inflammation in the peripheral zone of the prostate is effectively asymptomatic, the clinical syndrome is just the presence of inflammation and has nothing to do with prostate cancer. In that case, I do not know how we would monitor it other than possibly looking at PSA levels in young men when there is inflammation that changes the architecture of the gland. We are currently looking at the blood of young men who had a sexually transmitted disease to see if the infection elevated PSA levels.

Dr. Philip W. Kantoff. How would you go about choosing pathological end points in a trial designed to evaluate a potential chemopreventive agent? The finasteride trial showed us how difficult that is to do. In a short-term trial most of the men who have cancer at the end of the trial had cancer when they were enrolled. You are stuck with that inescapable reality.

Doctor Rubin. You have the inflammation/antioxidant hypothesis and 20 agents that could affect those pathways. How are you going to model that for an 18,000 patient study?

Dr. William Nelson. I think that you could imagine a presurgical model in which you could define end points that you believe are in the causal pathway of the disease to reduce oxidative damage and inflammation in the prostate. Since chemoprevention implies using an agent in half a million men each year, the safety data become paramount. You need a trial with 20,000 men, which is actually more cost-effective than several small trials.

Doctor Rubin. Safety aside, end points are important. Would it be a reduction in PIA?

Dr. William Nelson. End points would be reductions in PIA, inflammation and DNA damage plus the appropriate proximate target.

Dr. Howard Sandler. Can you put the finasteride trial into the context of your previous discussion?

Dr. William Nelson. If you look at androgen in men over time, the levels do not rise as they get older and develop prostate cancer. If anything, androgen levels fall with age. In dog models for benign prostate hyperplasia keeping androgen levels from falling prevented benign prostatic hyperplasia. The idea that androgen excess drives the disease is not based on anything other than a couple of animal models.

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

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