Prostate Cancer Prevention

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EXPANDED ABSTRACT

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Prostate cancer incidence and mortality vary widely in different regions of the world, with high rates of prostate cancer characteristic of the United States and Western Europe, and low rates of prostate cancer characteristic of Asia (1). This geographic variation reflects differences in lifestyle: Asian immigrants to North America face increased prostate cancer risks, especially after exposure to the Western lifestyle for 25 years or more, and Asian men born in North America have high prostate cancer risks (2–4). Diet is thought to be the key feature of Western lifestyle that fosters prostate cancer development. Consumption of animal fats has been associated with increased prostate cancer risk and intake of vitamins, fruits and vegetables has been associated with decreased prostate cancer risk (5–12). “Charred” or “well-done” meats may contain prostatic carcinogens. Male rats fed the heterocyclic aromatic amine 2-amino-1-methyl-6-phenylimidazo[4,5-β]pyridine (PhIP), a carcinogen that forms in overcooked meats, develop mutations in prostate cell DNA and prostate cancers (13,14).

Chronic (or recurrent) prostatitis also may contribute to the development of prostate cancer (15,16). About 9% of men between 40 and 79 y of age report suffering with symptomatic prostatitis, with half of these men having repeated episodes (17–19). Asymptomatic prostatitis is even more common, with inflammatory changes almost always evident in prostate tissues from prostate biopsies or radical prostatectomies. Unfortunately, the prevalence and age distribution of asymptomatic prostatitis in the United States or elsewhere is not known. Increased prostate cancer risk has been associated with sexually transmitted infections, independent of the specific pathogen, hinting that the inflammatory response to infection, rather than the infectious agent itself, might lead to prostate cancer (20–22). Also, host responses to prostate infections may underlie some familial prostate cancer clusters. Two candidate genes thought to be responsible for familial clusters of prostate cancer, RNASEL and MSR1, encode proteins with critical functions in host responses to a variety of infectious pathogens (23–26). In addition, inheritance of certain variants of OGG1, encoding an enzyme capable of repairing genome damage inflicted by inflammatory oxidants, may modify the risk of prostate cancer development (27). An inflammatory lesion in the prostate, termed proliferative inflammatory atrophy (PIA), has been proposed as a precursor to prostatic intraepithelial neoplasia (PIN) and to prostate cancer (28).

The prostate may be prone to develop cancer in the setting of dietary indiscretions and inflammation as a result of early somatic genome alterations that target genes encoding defenses against genome damage. Glutathione S-transferases (GSTs), enzymes that catalyze the conjugation of glutathione in various reactive chemical species, long have been recognized as protecting against the development of many different cancers by detoxifying carcinogens (29). GSTs, encoded by several families of genes (α, μ, π and θ), are expressed physiologically in many cell and tissue types. GSTs can be induced, via increased transcription, in most cells and tissues in response to chemical stresses and provide a critical barrier against reactive electrophiles and oxidants that threaten genomic damage (30,31). Somatic inactivation of GSTP1, encoding the human π-class GST, by CpG island hypermethylation, has been reported in >90% of prostate cancers (32,33), in >85% of liver cancers (34) and in some 30% or more of breast cancers (35,36). In the normal prostate, GSTP1 is expressed in basal epithelial cells and not in nonstressed columnar epithelial cells. GSTP1 expression is induced in PIA lesions in response to inflammatory damage (28). Loss of GSTP1 expression and GSTP1 CpG island hypermethylation appear to arise in rare PIA lesions, leading to PIN lesions and prostate cancers with defective defenses against chemical stresses (33,37,38). LNCaP prostate cancer cells that are devoid of GSTP1 suffer more genomic damage when exposed to metabolically activated PhIP, the “charred” meat carcinogen, or to reactive oxygen species, such as those produced by
activated inflammatory cells, than do LNCaP cells that have been modified genetically to express GSTP1 (39).

At this point, prostate cancer epidemiology, genetics, pathology, and molecular biology are converging on the hypothesis that prostate cancer develops as a consequence of genome damage, inflicted by reactive oxygen and nitrogen species elaborated by inflammatory cells and by ingested carcinogens likely present in red meats, in the setting of inadequate cellular defenses against reactive chemical species. Rational prostate cancer prevention strategies that might attenuate prostatic carcinogenesis include (i) administration of anti-oxidants [e.g., selenium, vitamin E, lycopene (40–42)], (ii) consumption of foods rich in carcinogen-detoxification enzyme inducers [e.g., vegetables containing sulforaphane (43)], (iii) use of anti-inflammatory drugs [e.g., targeting cyclooxygenases, nitric oxide synthases; (44)], and (iv) discovery and treatment of any infectious agents that might lead to chronic prostate inflammation.

**LITERATURE CITED**


