Journal of Cellular Biochemistry 91:459–477 (2004)

# Pathological and Molecular Mechanisms of Prostate Carcinogenesis: Implications for Diagnosis, Detection, Prevention, and Treatment

**Angelo M. De Marzo,* Theodore L. DeWeese, Elizabeth A. Platz, Alan K. Meeker, Masashi Nakayama, Jonathan I. Epstein, William B. Isaacs, and William G. Nelson**

Departments of Oncology, Pathology, Radiation Oncology, Urology,
The Johns Hopkins University School of Medicine, and the Department of Epidemiology,
Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

**Abstract** Prostate cancer is an increasing threat throughout the world. As a result of a demographic shift in population, the number of men at risk for developing prostate cancer is growing rapidly. For 2002, an estimated 189,000 prostate cancer cases were diagnosed in the U.S., accompanied by an estimated 30,200 prostate cancer deaths [Jemal et al., 2002]. Most prostate cancer is now diagnosed in men who were biopsied as a result of an elevated serum PSA (>4 ng/ml) level detected following routine screening. Autopsy studies [Breslow et al., 1977; Yatani et al., 1982; Sakr et al., 1993], and the recent results of the Prostate Cancer Prevention Trial (PCPT) [Thompson et al., 2003], a large scale clinical trial where all men entered the trial without an elevated PSA (<3 ng/ml) were subsequently biopsied, indicate the prevalence of histologic prostate cancer is much higher than anticipated by PSA screening. Environmental factors, such as diet and lifestyle, have long been recognized contributors to the development of prostate cancer. Recent studies of the molecular alterations in prostate cancer cells have begun to provide clues as to how prostate cancer may arise and progress. For example, while inflammation in the prostate has been suggested previously as a contributor to prostate cancer development [Gardner and Bennett, 1992; Platz, 1998; De Marzo et al., 1999; Nelson et al., 2003], research regarding the genetic and pathological aspects of prostate inflammation has only recently begun to receive attention. Here, we review the subject of inflammation and prostate cancer as part of a ''chronic epithelial injury'' hypothesis of prostate carcinogenesis, and the somatic genome and phenotypic changes characteristic of prostate cancer cells. We also present the implications of these changes for prostate cancer diagnosis, detection, prevention, and treatment. J. Cell. Biochem. 91: 459–477, 2004. 

**Key words:** prostate cancer; prostateatrophy; prostatitis; benign prostatic hyperplasia; inflammation

## MECHANISMS OF INFLAMMATION INDUCED CARCINOGENESIS

Chronic or recurrent inflammation is responsible for the development of many human cancers, including those affecting the liver, esophagus, stomach, large intestine, and urinary bladder [Coussens and Werb, 2002]. Inflammation might influence the pathogenesis of cancers by (i) inflicting cell and genome damage, (ii) triggering restorative cell proliferation to replace damaged cells, (iii) elaborating a portfolio of cytokines that promote cell replication, angiogenesis and tissue repair [Coussens and Werb, 2002].

Oxidative damage to DNA and other cellular components accompanying chronic or recurrent inflammation may connect prostate inflammation with prostate cancer. In response to infections, inflammatory cells produce a variety of toxic compounds designed to eradicate microorganisms. These include superoxide, hydrogen peroxide, singlet oxygen, as well as nitric oxide that can react further to form the highly

Grant sponsor: Public Health Services NIH/NCI; Grant numbers: R01CA084997, R01CA70196; Grant sponsor: NIH/NCI Specialized Program in Research Excellence (SPORE) in Prostate Cancer (Johns Hopkins); Grant number: P50CA58236.

*Correspondence to: Angelo M. De Marzo, Room 153, Bunting-Blaustein Cancer Research Building, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1650 Orleans Street, Baltimore, MD 21231-1000.
E-mail: ademarz@jhmi.edu

Received 16 September 2003; Accepted 17 September 2003
DOI 10.1002/jcb.10747

reactive peroxynitrite. Some of these reactive oxygen and nitrogen species can directly interact with DNA in the host bystander cells, or react with other cellular components such as lipid, initiating a free radical chain reaction. If the damage is severe, these compounds can kill host bystander cells as well as pathogens, and can produce DNA damage and mutations among host cell survivors [Xia and Zweier, 1997; Eiserich et al., 1998]. As a consequence of an acquired defect in defenses against oxidant and electrophilic carcinogens associated with *GSTP1* CpG island hypermethylation (see below), prostate cells may acquire a heightened susceptibility to oxidative genome damage in an inflammatory milieu, leading to neoplastic transformation and cancer progression. Other support for the concept that prostate cancer can result from excess oxidants and electrophiles comes from epidemiological studies suggesting that decreased prostate cancer risk is associated with intake of various anti-oxidants and non-steroidal anti-inflammatory drugs [Clark et al., 1996, 1998; Heinonen et al., 1998; Norrish et al., 1998; Gann et al., 1999; Nelson and Harris, 2000; Roberts et al., 2002]. In further support of a critical role for oxidative genome damage during the pathogenesis of prostate cancer, variant polymorphic alleles at *OGG1*, the gene encoding a DNA glycosylase/AP lyase that repairs the oxidized base 8-oxo-G in DNA, are associated with increased prostate cancer risk [Xu et al., 2002b].

## PROSTATE INFLAMMATION AND THE PATHOGENESIS OF PROSTATE CANCER

At least three major disease processes are extremely common in the prostate—prostatitis, benign prostatic hyperplasia (BPH), and adenocarcinoma. Why do three apparently distinct types of lesions occur so commonly in the same organ, and might these common processes be linked? Despite the fact that prostate inflammation (histological prostatitis) and prostate cancer are often found in the same patient, associations between inflammation and prostate cancer have not been clearly shown. This may be due in part to the following difficulties in performing association studies of prostate cancer and prostatitis: (i) most prostate inflammation does not seem to cause symptoms [True et al., 1999], (ii) the incidence of asymptomatic histologic prostatitis in non-selected population based studies is difficult to ascertain [Giovannucci, 2001], (iii) the clinical diagnosis of chronic prostatitis itself can be challenging and is often subjective [Roberts et al., 1998]. Although large-scale prospective epidemiological studies are lacking [Giovannucci, 2001], a recent review of the available epidemiological literature by Dennis et al. [2002] indicates that there may be a small increase in the relative risk of the development of prostate cancer in men with a history of clinical prostatitis. Given the high prevalence of prostate cancer, however, even a small increase in relative risk can result in a large number of additional cases.

In terms of the prevalence of clinical prostatitis, a survey of clinical data in Olmstead county Minnesota reported that symptomatic prostatitis occurred in approximately 9% of men between 40 and 79 years of age, with half of these men suffering more than one episode, and it was estimated that 1 in 11 men will be diagnosed with some form of prostatitis by age 79 years [Roberts et al., 1998]. In terms of histological prostatitis, inflammatory infiltrates of varying intensity and character are readily apparent in most radical prostatectomy [Gerstenbluth et al., 2002] and transurethral resection specimens [Nickel et al., 1999], and prostate needle biopsies [Schatteman et al., 2000].

The current NIH consensus classification system of prostatitis divides the cases into four categories—3 that are associated with genitourinary symptoms and 1 that is not [Krieger et al., 1999]. Category I, or *acute bacterial prostatitis*, is usually caused by *Escherichia coli* or other gram-negative bacteria or enterococcus. Acute bacterial prostatitis is infrequent and consists of an acutely swollen and tender prostate with acute inflammatory cells in expressed prostate fluid. There is usually an associated urinary tract infection, and, at times systemic symptoms of infection. Acute prostatitis is usually self-limited after treatment with antibiotics. Category II, or *chronic bacterial prostatitis*, is quite rare, and consists of repeated bouts of lower urinary tract infection where the source of infection can be localized to the prostate. This form is also usually treated with antibiotics, often with multiple courses over time. Category III is the most common form, accounting for approximately 90% of clinical prostatitis syndromes, and is referred to as *chronic prostatitis/chronic pelvic pain syndrome*. The cardinal feature of this entity is pain, either in

the perineum, external genitalia, or other sites in the pelvis. There is also frequently pain during or after ejaculation. The symptoms must be of at least 3 months in duration to be considered chronic. This form is subdivided into those cases where leukocytes are identifiable on expressed prostatic fluids, post-prostate massage urine, or semen (category IIIA—inflammatory) and those that do not contain leukocytes in these fluids (category IIIB—chronic prostatitis/chronic pelvic pain syndrome). Category IV, or *asymptomatic inflammatory prostatitis*, represents the presence of prostate inflammation in histological tissue sections from men with no history of urinary symptoms.

In addition to the putative increased risk of prostate cancer with a history of symptomatic prostatitis, an increased prostate cancer risk has been associated in some studies [e.g., Hayes et al., 2000] with sexually transmitted infections [reviewed in Strickler and Goedert, 2001; Dennis and Dawson, 2002], independent of the specific pathogen, supporting the concept that inflammation itself might facilitate prostatic carcinogenesis, or, that the associative causative organism(s) has not been identified. Of significance in this regard, two of the candidate hereditary prostate cancer susceptibility genes identified thus far, *RNASEL* and *MSR1*, encode proteins that function in the host responses to a variety of infectious agents [Zhou et al., 1997; Platt and Gordon, 2001; Carpten et al., 2002; Xu et al., 2002a].

### Relation of Prostate Cancer, Benign Prostatic Hyperplasia, and Inflammation

The fact that most prostate cancer and most inflammatory infiltrates are both present in the peripheral zone [McNeal, 1997] is consistent with a link between inflammation and prostate cancer. What about the transition zone, the site of development of BPH? Is there a link between BPH and prostate cancer? Is there a link between inflammation and BPH?

Approximately 25% of prostate adenocarcinomas appear to arise in the transition zone. Thus, while the peripheral zone is the site of origin of prostate cancer in the majority of the cases, when compared to other organs that seem to be protected from cancer development (such as the seminal vesicles), prostate transition zone cancer is actually quite common. In terms of epidemiological data, the relation between BPH and prostate cancer has been reviewed recently, where it was concluded that none of the epidemiologic studies published to date have provided clear evidence suggesting an etiologic role for BPH in the development of prostate cancer [Guess, 2001]. However, the author also indicated that most of the studies had at least some major bias and that it might be perhaps more important to examine the biology and pathology of any potential connection [Guess, 2001].

In terms of pathobiology, Bostwick et al. [1992] summarized the facts that BPH and prostate cancer tend to occur in the same patient, share similar hormonal requirements for growth, and can occur in proximity. Pathologically, it appears that transition zone cancers do indeed appear to arise in the setting of nodules of BPH [Bostwick et al., 1992; Leav et al., 2003, and references therein], and occasionally from adenosis [Bostwick and Qian, 1995; Grignon and Sakr, 1996], which is also referred to as atypical adenomatous hyperplasia. While these transition zone tumors are often of somewhat lower Gleason score, they are quite common in radical prostatectomy and TURP specimens [Leav et al., 2003]. Often in radical prostatectomies transition zone cancers are found incidentally after the diagnosis of prostate cancer in the peripheral zone, which is much more widely sampled at needle biopsy. Whether there are an equal number of transition zone cancers in men without significant nodular hyperplasia is currently not clear. Thus, although there is no strong evidence linking the two, the relation between BPH and prostate cancer remains an open issue. In addition, it is possible that BPH and prostate cancer are both caused by similar exposures, such that they commonly occur together but are not directly linked in a precursor-progeny pathway.

What is the relation between transition zone cancer and inflammation? While the relation between inflammation and transition zone cancer is unknown, it is known that BPH tissue contains a variable amount of chronic and often acute inflammation in virtually 100% of specimens [Nickel et al., 1999]. It has been reported that levels of serum PSA in BPH patients correlates with the amount of tissue injury associated with inflammation [Hasui et al., 1994; Irani et al., 1997; Schatteman et al., 2000; Yaman et al., 2003], and some have submitted that the pathogenesis [Gleason et al., 1993],

and/or clinical features [Nickel, 1994] of BPH may be related to prostate inflammation. Still unclear, however, is whether inflammation comes prior to BPH nodule formation or whether it is a response to the altered tissue architecture resulting from the nodules. While no firm conclusions can be drawn presently, the pathological literature is consistent with a model whereby inflammation, due to infection or otherwise, is related to the development or progression of BPH, and in some circumstances BPH is related to prostate cancer. Although, more study of this issue is required, it is plausible that inflammation may be related to transition zone cancer.

### Proliferative Inflammatory Atrophy

Pathologists have long recognized focal areas of epithelial atrophy in the prostate [Rich, 1934; Moore, 1936; Franks, 1954]. These focal areas of epithelial atrophy, distinct from the diffuse atrophy seen after androgen deprivation, usually appear in the periphery of the prostate, where prostate cancers typically arise [Rich, 1934; McNeal, 1988]. Many of these areas of epithelial atrophy are associated with acute or chronic inflammation [Franks, 1954; McNeal, 1997; Ruska et al., 1998; De Marzo et al., 1999], contain proliferative epithelial cells [Liavag, 1968; Feneley et al., 1996; Ruska et al., 1998; De Marzo et al., 1999; Shah et al., 2001], and may show morphological transitions in continuity with high grade prostatic intraepithelial neoplasia (PIN) lesions [De Marzo et al., 1999; Putzi and De Marzo, 2000], putative prostate cancer precursors [McNeal and Bostwick, 1986; Bostwick, 1996]. At times these atrophic lesions may show evidence of direct transitions to minute carcinoma lesions, with little or no recognizable PIN component [Franks, 1954; Liavag, 1968; Montironi et al., 2002; Nakayama et al., 2003]. Focal atrophy of the prostate exists as a spectrum of morphologies and areas containing it in the prostate can be quite extensive. Most of these morphological patterns fit into the categories of simple atrophy, or post-atrophic hyperplasia, as described by Ruska et al. [1998]. To highlight the common association with inflammation and the unexpectedly high proliferation index, we have put forth the term proliferative inflammatory atrophy (PIA) to encompass these lesions [De Marzo et al., 1999]. In terms of the requirement for inflammatory cells in PIA, the majority of all focal atrophy lesions contain at least some increase in chronic and/or acute inflammation. Also, since the amount of inflammation from field to field within a given atrophy lesion can be highly variable we have recently suggested that to refer to a lesion as PIA does not require easily recognizable inflammation—thus, most forms of focal glandular atrophy can be considered PIA [Van Leenders et al., 2003]. A working group to formalize terminology of the various atrophic lesions in the prostate is currently being formed, and a preliminary meeting with a group of pathologists and other investigators was held at the NIH campus in February of 2003.

In support of PIA as a prostate cancer precursor, prostate inflammation, accompanied by focal epithelial atrophy, has been proposed to contribute to prostate cancer development in rats [Reznik et al., 1981; Wilson et al., 1990]. Further support comes from the fact that PIA shares several molecular alterations found in both PIN and carcinoma. For example, chromosome 8 gain, detected by fluorescence in situ hybridization (FISH) with a chromosome 8 centromere probe, was found in human PIA, PIN, and prostate cancer [Macoska et al., 2000; Shah et al., 2001]. Others have recently documented rare p53 mutations in one variant of PIA, referred to as post-atrophic hyperplasia [Tsujimoto et al., 2002] and, our group has recently shown that approximately 6% of PIA lesions show evidence of somatic methylation of the *GSPT1* gene promoter [Nakayama et al., 2003a] (see description of *GSTP1* promoter methylation below). While the cause of focal atrophy lesions is not known, they may arise either as a consequence of epithelial damage, e.g., from infection, ischemia [Billis, 1998], or toxin exposure (including dietary oxidants/electrophiles or endogenous chemicals such as estrogens, etc.), followed by epithelial regeneration and associated secondary inflammation, or as a direct consequence of inflammatory oxidant damage to the epithelium [De Marzo et al., 1999]. The process of aging itself has been suggested to contribute to some morphological variants of prostate atrophy [McNeal, 1984]. Regardless of the etiology of PIA, the epithelial cells in these lesions exhibit many molecular signs of stress, expressing high levels of GSTP1, GSTA1, and cyclo-oxygenase 2 (COX-2) [De Marzo et al., 1999; Putzi and De Marzo, 2000; Parsons et al., 2001b; Zha et al., 2001]. There is also mounting evidence that many of the

atrophic luminal cells in PIA represent a form of intermediate epithelial cell [Van Leenders et al., 2003]—cells with features intermediate between basal and luminal secretory cells. Intermediate epithelial cells have been postulated to be the targets of neoplastic transformation in the prostate [Verhagen et al., 1992; De Marzo et al., 1998a,b; van Leenders et al., 2000].

It should be noted that not all authors have found associations between prostate atrophy and prostate cancer [McNeal, 1969; Billis, 1998; Anton et al., 1999; Billis and Magna, 2003], and that in our own studies not all high grade PIN or small carcinoma lesions are associated with atrophy [Putzi and De Marzo, 2000]. Most studies of the connection between atrophy and cancer have focused on peripheral zone cancer nearly exclusively. Thus, additional studies are required to more fully understand the relation between focal atrophy and cancer in the prostate. Our current concept is that PIA is a common proliferative response to environmental stimuli in aging men and that some high grade PIN and carcinoma lesions arise as a consequence of genome damage in PIA, while others do not. A corollary to this is that while only a subset of atrophy lesions may be pre-neoplastic, the fact that atrophic areas can be so widespread and multi-focal in the prostate is consistent with the hypothesis that many prostate cancers can indeed arise from PIA.

## SOMATIC GENOME ALTERATIONS ACCOMPANYING PROSTATIC CARCINOGENESIS

Similar to other types of epithelial cancer, prostate cancers contain many somatic genomic alterations, including point mutations, deletions, amplifications, chromosomal rearrangements, and changes in DNA methylation [Isaacs et al., 1994; Bookstein, 2001; Chung et al., 2001; Gao and Isaacs, 2002; Meng and Dahiya, 2002; DeMarzo et al., 2003]. However, unlike some carcinomas such as those of the colon/rectum [Kinzler and Vogelstein, 1997] and pancreas [Jaffee et al., 2002], where specific oncogenes such as k-ras or tumor suppressor genes such as *p53* are mutated at a very high frequency, gene mutations reported thus far in prostate cancer appear quite heterogeneous, from case to case, or even from lesion to lesion in a single case [Isaacs et al., 1994; Mirchandani et al., 1995; Qian et al., 1995; Ruijter et al., 1999; Bookstein, 2001; Chung et al., 2001; Gao and Isaacs, 2002; Meng and Dahiya, 2002]. In addition, genetic alterations appear to accumulate with prostate cancer progression. Small prostate cancers are present in nearly 30% of men between 30–40 years of age in the U.S., though most men are diagnosed with prostate cancer at 50–70 years of age [Sakr et al., 1994]. The progression of these small prostate cancers to larger life-threatening cancers, and the accumulation of somatic genome abnormalities, appears sensitive to environmental factors and lifestyle. Prostate cancer incidence and mortality are very high in the U.S. and Western Europe, while lower prostate cancer risks and death rates are characteristic of Asia [Miller, 1999; Hsing et al., 2000]. In support of an effect of environment and lifestyle on prostate cancer development, Asian immigrants to North America tend to acquire higher prostate cancer risks within one generation [Haenszel and Kurihara, 1968; Shimizu et al., 1991; Whittemore et al., 1995]. Whether the appearance of somatic genome alterations in prostate cancer cells is the result of chronic or recurrent exposure to genome-damaging stresses, defective protection against genome damage, or a combination of both processes, has not been definitively shown.

### *GSTP1*

Hypermethylation of CpG island sequences encompassing the promoter region of *GSTP1*, encoding the π-class glutathione *S*-transferase (GST), is an exceedingly common somatic genome change found in prostate cancer [Lee et al., 1994; Millar et al., 1999; Lin et al., 2001; Nelson et al., 2001b]. Immunohistochemistry has demonstrated that GSTP1 protein is normally expressed in basal epithelial cells in the prostate, but is absent in most luminal columnar secretory epithelial cells. In PIA lesions, strong anti-GSTP1 staining is seen in many of the atrophic luminal epithelial cells, [De Marzo et al., 1999] consistent with the induction of expression in response to environmental stress. The luminal cells in PIA are not simply basal cells, as shown by their lack of expression of p63 [Parsons et al., 2001a]. In prostate cancer cells, somatic hypermethylation of *GSTP1* CpG island sequences represses *GSTP1* transcription [Lin et al., 2001]. Absence of GSTP1 expression and *GSTP1* CpG island hypermethylation are also common in high-grade PIN lesions [Brooks et al., 1998].

*GSTP1* is not a classical tumor suppressor gene [Lin et al., 2001]. Rather, *GSTP1* more likely plays a "caretaker" role, protecting prostate epithelial cells against genome damage mediated by carcinogens [Kinzler and Vogelstein, 1997]. For example, mice with both *GSTP1* alleles disrupted by gene targeting exhibit increased skin tumor formation after topical exposure to the skin carcinogen 7,12-dimethylbenz [a] anthracene (DMBA) [Henderson et al., 1998]. One prostate carcinogen that may be detoxified by GSTP1 is the dietary heterocyclic amine, 2-amino-1-methyl-6-phenylimidazo [4,5-*b*]pyridine (PhIP), which forms when meats are cooked at high temperatures or "charbroiled" [Lijinsky and Shubik, 1964; Gross et al., 1993; Morgenthaler and Holzhauser, 1995; Knize et al., 1997]. Dietary PhIP intake causes prostate cancer in rats [Shirai et al., 1997; Stuart et al., 2000]. In humans, a study examining the association between PhIP and other heterocyclic amine intake and prostate cancer showed a modest, albeit inconsistent increased relative risk of prostate cancer with increasing consumption [Norrish et al., 1999], although there are a large number of studies showing an association between an increased relative risk of overall prostate cancer and the levels of consumption of red meat [reviewed in Kolonel, 2001]. In the most recent analysis from the Health Professionals Follow-Up Study, consumption of red meats was not associated with an increased risk of prostate cancer overall, but was associated with increased risk of metastatic prostate cancer [Michaud et al., 2001]. GSTP1 can protect prostate cells against PhIP damage: for LNCaP prostate cancer cells, which do not express GSTP1, exposure to metabolically activated PhIP results in the appearance of pro-mutagenic PhIP–DNA adducts. Replacement of the *GSTP1* gene by stable transfection prevented PhIP–DNA damage [Nelson et al., 2001a]. GSTP1 may also protect prostate cells against damage inflicted directly by oxidants, such as those produced by protracted low dose ionizing radiation exposure (DeWeese et al., unpublished observations).

### AR

Androgenic hormones and the androgen receptor (AR) both play critical roles in normal prostate development and function, and in most prostate diseases, including prostate cancer. For example, transgenic mice engineered to express high levels of the androgen receptor in the prostate tend to develop PIN [Stanbrough et al., 2001]. Many somatic alterations of *AR*, encoding the androgen receptor, have been described in human prostate cancers, particularly "androgen-independent" prostate cancers appearing after treatment by androgen suppression and/or with anti-androgens [Veldscholte et al., 1990; Newmark et al., 1992; Suzuki et al., 1993, 1996; Gaddipati et al., 1994; Schoenberg et al., 1994; Taplin et al., 1995, 1999; Visakorpi et al., 1995; Evans et al., 1996; Tilley et al., 1996; Koivisto et al., 1997; Marcelli et al., 2000; Haapala et al., 2001]. "Androgen-independent" prostate cancers usually continue to express the androgen receptor, maintaining androgen-receptor dependent signaling (i) in response to the reduced levels of circulating androgens, such as with *AR* amplification accompanied by androgen receptor over-expression, (ii) in response to non-androgens or anti-androgens as agonist ligands, such as with *AR* mutations accompanied by altered androgen receptor ligand specificity, or (iii) via ligand-independent activation of the androgen receptor, such as may occur under the influence of other intracellular signal transduction pathways [Veldscholte et al., 1990; van der Kwast et al., 1991; Culig et al., 1993; Nazareth and Weigel, 1996; Koivisto et al., 1997; Tan et al., 1997; Hobisch et al., 1998; Craft et al., 1999; Amler et al., 2000; Sadar and Gleave, 2000; Feldman and Feldman, 2001; Mousses et al., 2001; Zegarra-Moro et al., 2002].

### *NKX3.1*

*NKX3.1*, located at 8p21, encodes a prostate-specific homeobox gene essential for normal prostate development [Bieberich et al., 1996; He et al., 1997; Sciavolino et al., 1997; Prescott et al., 1998]. In mice, targeted disruption of *Nkx3.1* leads to prostatic epithelial hyperplasia and dysplasia [Bhatia-Gaur et al., 1999; Abdulkadir et al., 2002]. In men, although loss of 8p21 DNA sequences has been reported in as many as 63% of PIN lesions and in more than 90% of prostate cancers, no *NKX3.1* mutations have been detected, leading to controversy over whether *NKX3.1* is the gene target of somatic alteration at 8p21 [Emmert-Buck et al., 1995; He et al., 1997; Voeller et al., 1997; Ornstein et al., 2001]. Nonetheless, loss of NKX3.1 expression has been reported in as many as 20% of PIN lesions, 6% of low stage prostate cancers,

22% of high stage prostate cancers, 34% of androgen-independent prostate cancers, and 78% of prostate cancer metastases [Bowen et al., 2000]. The relationship between somatic *NKX3.1* alterations and reduction in NKX3.1 expression during prostate cancer development has not been determined.

### *PTEN*

*PTEN*, located at 10q, another site of frequent allelic loss in prostate cancer, encodes a phosphatase active against both proteins and lipid substrates [Li et al., 1997; Myers et al., 1997, 1998; Steck et al., 1997; Teng et al., 1997]. PTEN has been proposed to function as a general tumor suppressor by inhibiting the phosphatidylinositol 3′-kinase/protein kinase B (PI3K/Akt) signaling pathway, thought to be essential for cell cycle progression and/or cell survival in many cell types [Li et al., 1997; Furnari et al., 1998; Ramaswamy et al., 1999; Sun et al., 1999]. Like mice carrying disrupted *Nkx3.1* alleles, mice carrying disrupted *Pten* alleles manifest prostatic hyperplasia and dysplasia, and the progeny of breeding crosses between *Pten*± mice and *Nkx3.1*± mice develop PIN [Bhatia-Gaur et al., 1999; Podsypanina et al., 1999; Di Cristofano et al., 2001; Kim et al., 2002], as well as invasive carcinoma and lymph node metastases [Abate-Shen et al., 2003]. PTEN, which is typically expressed by normal epithelial cells, is often expressed at a reduced level in human prostate cancer cells [McMenamin et al., 1999]. Many somatic *PTEN* alterations have been reported for prostate cancers, including homozygous deletions, loss of heterozygosity, mutations, and suspected CpG island hypermethylation [Cairns et al., 1997; Li et al., 1997; Myers et al., 1997, 1998; Steck et al., 1997; Teng et al., 1997; Gray et al., 1998; Suzuki et al., 1998; Wang et al., 1998; Vivanco and Sawyers, 2002]. Associations between somatic *PTEN* alterations and aberrant PTEN function in prostate cancer cells have been difficult to establish. Often, losses of 10q sequences near *PTEN* do not appear to be accompanied by somatic mutations of the remaining *PTEN* allele. Furthermore, although somatic *PTEN* alterations appear more common in metastatic than in primary prostate cancer lesions, a marked heterogeneity in *PTEN* defects in different metastatic sites from the same patient has been reported [Suzuki et al., 1998]. Perhaps, as is evident in mouse models featuring disrupted *Nkx3.1* and *Pten* genes, haploinsufficiency for *PTEN* and/or *NKX3.1* may be sufficient for a neoplastic phenotype [Bhatia-Gaur et al., 1999; Podsypanina et al., 1999; Di Cristofano et al., 2001; Kim et al., 2002].

### *CBKN1B*

p27, a cyclin-dependent kinase inhibitor encoded by *CDKN1B*, may also be a somatic gene target for alteration during prostatic carcinogenesis. Targeted disruption of *Cdkn1b* in mice results in prostatic hyperplasia, while mice carrying disrupted *Pten* and *Cdkn1b* alleles develop localized prostate cancers [Di Cristofano et al., 2001]. Reduced p27 expression appears characteristic of human prostate cancer cells, particularly in prostate cancer cases with a poor prognosis [Guo et al., 1997; Cheville et al., 1998; Cordon-Cardo et al., 1998; Yang et al., 1998; De Marzo et al., 1998a]. Somatic loss of DNA sequences at 12p12-13, near *CDKN1B*, have been reported for 23% of localized prostate cancers, 30% of prostate cancer lymph node metastases, and 47% of prostate cancer distant metastases [Kibel et al., 2000]. The mechanism(s) by which somatic *CDKN1B* alterations leads to reduced p27 expression have not been elucidated. Provocatively, p27 may be a target for repression by the PI3K/Akt signaling pathway [Li and Sun, 1998; Sun et al., 1999; Graff et al., 2000; Gottschalk et al., 2001]. Thus, loss of PTEN function, accompanied by increased PI3K/Akt signaling, might result in decreases in *CDKN1B* mRNA and in p27 protein half-life [Nakamura et al., 2000] Decreased p27 expression has also been documented in high grade PIN [De Marzo et al., 1998a; Fernandez et al., 1999] and in PIA lesions [De Marzo et al., 1998a; Van Leenders et al., 2003].

## Telomeres, Telomere Shortening, and Telomerase

The karyotype of most human cancers is abnormal. Many types of cancer, including prostate cancer, show chromosomal instability reflected by aberrations in both number and structure of chromosomes. The exceptions to this in solid tumors are cancers with microsatellite instability, which are genetically unstable at the single nucleotide level but contain mostly diploid karyotypes. Chromosomal instability appears to be an important molecular mechanism driving malignant transformation in many human

epithelial tissues [Cahill et al., 1999], yet the molecular mechanisms responsible for chromosome destabilization during carcinogenesis are largely unknown. One route to chromosomal instability is through defective telomeres [Counter et al., 1992; Hackett and Greider, 2002; Feldser et al., 2003]. Telomeres, which consist of multiple repeats of a 6 base pair unit (TTAGGG), complexed with several different binding proteins, protect chromosome ends from fusing with other chromosome ends or other chromosomes containing double strand breaks [McClintock, 1941]. However, in the absence of compensatory mechanisms, telomeric DNA is subject to loss due to cell division [Harley et al., 1990; Levy et al., 1992] and possibly oxidative damage [von Zglinicki et al., 2000]. Critical telomere shortening leads to chromosomal instability that, in mouse models, causes an increased cancer incidence that is likely a result of chromosome fusions, subsequent breakage, and rearrangement [Blasco et al., 1997; Artandi et al., 2000]. Intriguingly, telomeres within human carcinomas are often found to be abnormally reduced in length [de Lange, 1995], but the timing of this phenomenon has been unclear. In human prostate cancer, the telomeres from prostate cancer tissue were consistently shorter than those from cells in either the adjacent normal or BPH tissues [Sommerfeld et al., 1996]. Others have also reported telomere shortening in prostate cancer [Donaldson et al., 1999].

Most carcinomas arise from pre-invasive intraepithelial precursor lesions, referred to as intraepithelial neoplasias (IEN) [O'Shaughnessy et al., 2002]. These lesions show morphological features and molecular alterations characteristic of malignant neoplasia, including evidence of genetic instability [Shih et al., 2001] but occur within preexisting epithelia and are confined within the basement membrane. If genetic instability helps to drive cancer formation, and telomeres shortening is a major mechanism leading to genetic instability, then telomere shortening should be present at the intraepithelial phase of carcinoma. Recently we employed an in situ telomere FISH technique TEL-FISH and reported that telomere shortening is evident in the majority of high-grade prostatic intraepithelial neoplasia (PIN) lesions [Meeker et al., 2002], which are thought to be cancer precursor lesions of the prostate. Thus, telomere shortening is a prevalent biomarker in human prostate, occurring early in the process of prostate carcinogenesis. Interestingly, the telomere shortening found in high grade PIN was restricted to the luminal cells and was not present in the underlying basal cells. This finding strongly suggests that basal cells are not the direct precursor cell to high grade PIN, but support the above mentioned concept that cells with an intermediate luminal cell phenotype are the likely direct target cell of transformation in the prostate. Vukovic et al., recently reported Similar findings of reduced telomere length in high grade PIN and prostate cancer [Vukovic et al., 2003].

### *Hepsin, AMACR,* and *EZH2*

Alterations in gene expression accompanying the development of prostate cancer have been surveyed using transcriptome profiling technologies [Huang et al., 1999; Walker et al., 1999; Nelson et al., 2000; Xu et al., 2000; Dhanasekaran et al., 2001; Luo et al., 2001, 2002; Magee et al., 2001; Stamey et al., 2001; Waghray et al., 2001; Welsh et al., 2001]. Among the many genes exhibiting over- or under-expression in localized prostate cancers, the products of at least two genes appear consistently increased. *Hepsin*, located at 19q11-13.2, encodes a transmembrane serine protease, normally expressed at high levels in the liver and other tissues [Tsuji et al., 1991]. The contribution of hepsin to the prostate cancer phenotype has not been discerned. Anti-sense oligonucleotides targeting *Hepsin* mRNA have been reported to retard the growth of hepatoma cells, but $Hepsin^{-/-}$ mice develop normally, exhibit normal liver regeneration, and have no striking phenotype [Torres-Rosado et al., 1993; Wu et al., 1998; Yu et al., 2000]. α-Methylacyl-CoA racemase, a mitochondrial and peroxisomal enzyme that acts on pristanoyl-CoA and C27-bile acyl-CoA substrates to catalyze the conversion of *R*- to *S*-stereoisomers in order to permit metabolism by β-oxidation [Schmitz et al., 1995], has been reported to be over-expressed in almost all prostate cancers [Xu et al., 2000; Dhanasekaran et al., 2001; Luo et al., 2001, 2002]. Germline *AMACR* mutations have been reported to lead to adult-onset neuropathy [Ferdinandusse et al., 2000]. Immunohistochemistry studies have revealed that α-methylacyl-CoA racemase is occasionally present in normal prostate cells, increased in prostatic intraepithelial neoplasia cells, and further elevated in prostate cancer cells [Jiang et al., 2001, 2002; Beach et al., 2002;

Luo et al., 2002; Rubin et al., 2002; Yang et al., 2002; Leav et al., 2003; Magi-Galluzzi et al., 2003; Zhou et al., 2003a]. Another gene product shown to be increased at the mRNA level in primary and hormone refractory metastatic prostate cancer using gene expression arrays is the polycomb group protein enhancer of zeste homolog 2 (EZH2), which has been postulated to be involved in the progression of prostate cancer [Varambally et al., 2002].

## IMPLICATIONS FOR PROSTATE CANCER DIAGNOSIS, DETECTION, PREVENTION, AND TREATMENT

### AMACR, p63, and the Diagnosis of Prostate Cancer

It is estimated that approximately 1,000,000 prostate needle biopsies are performed per year in the U.S., and approximately 20% are positive for cancer. While there is no standard for the number of cores taken, in many institutions urologists are submitting 12 or more cores per patient, which is up from 6 several years ago. Thus, between 6 and 12 million individual new needle biopsy cores are examined microscopically by pathologists each year in the U.S. While at times the diagnosis of prostate cancer on needle biopsy can be quite straightforward, many cases present diagnostic challenges. For example, there are many benign mimics of prostate cancer that can be misdiagnosed as prostate cancer [Epstein, 1995; Epstein and Potter, 2001; DeMarzo et al., 2003]. These include lesions such as atrophy adenosis (atypical adenomatous hyperplasia), PIN, nephrogenic adenoma granulomatous prostatitis, and radiation change in benign glands. It has been clear for many years that prostate basal cells, which are uniformly present in normal appearing prostate acini and ducts, and in the vast majority of benign mimics of prostate cancer, are absent in prostate cancer [Brawer et al., 1985]. Thus, ancillary tools such as immunohistochemistry against "basal cell specific cytokeratins"[1] are often employed in difficult cases to determine if a particular suspicious lesion contains basal cells [Hedrick and Epstein, 1989]. More recently it has been shown that the product of the *p63* gene is expressed in basal cell nuclei in the prostate, but not in prostate luminal cells nor in the vast majority of prostate cancers [Signoretti et al., 2000; Parsons et al., 2001a]. Since this marker may be more robust in terms of surviving poor fixation or various types of tissue processing [Weinstein et al., 2002], many pathologists have begun to employ p63 staining in clinical practice to further determine whether basal cells may be present in a suspicious lesion [Shah et al., 2002]. To increase the chances of finding basal cells, Zhou et al. [2003b] have recently suggested using a cocktail of antibodies against basal cell cytokeratins and p63.

As indicated above, AMACR has been found by a large number of different investigators to be overexpressed in prostate cancer cells. Since negative staining for basal cell markers by itself is not diagnostic of prostate cancer, positive staining for AMACR may increase the level of confidence in establishing a definitive malignant diagnosis in a lesion deemed highly suspicious by standard H&E staining [Jiang et al., 2001, 2002; Beach et al., 2002; Magi-Galluzzi et al., 2003; Zhou et al., 2003a]. Thus, many pathologists have begun to employ this marker. At our institution we routinely order the p63, 34BE12 (also referred to as keratin 903), and AMACR on atypical prostate needle biopsies where the suspicion of cancer is high but the findings on H&E section are insufficient to render a clearly malignant diagnosis. In the research setting, we have also employed double labeling against p63 (nuclear staining positive in basal cells) and racemase (cytoplasmic-only staining) in order to delineate both markers on an individual tissue sections [Luo et al., 2002], although this double labeling can be somewhat problematic on needle biopsies due to background cytoplasmic staining for p63.

As usual with any ancillary test, there are pitfalls in the use of AMACR in diagnostic pathology, since certain histological subtypes of prostatic adenocarcinoma tend to be weak or negative for this marker [Zhou et al., 2003a], and, benign glands and high grade PIN may be positive at times. Since there are so many diagnostic pitfalls in prostate needle biopsies, the importance of obtaining second opinions on prostate biopsy material has been emphasized [Epstein et al., 1996].

[1]Often staining for basal cells is performed with the monoclonal antibody 34BE12, recognizing a range of high molecular weight cytokeratins including keratin 5 and 14. These keratins are highly expressed in basal cells. Other antibodies against keratin 5 have also been employed.

### GSTP1 CpG Island Hypermethylation and the Detection of Prostate Cancer

Abnormal genes and gene products appearing in prostate cancer cells offer great promise as disease biomarkers. For example, *GSTP1* CpG island hypermethylation, detected in prostate tissue, blood, urine, or prostate fluid, may be a molecular biomarker useful for prostate cancer detection and staging. Although *GSTP1* CpG island hypermethylation has been found in DNA from more than approximately 90% of prostate cancers, approximately 70% of liver cancers, and approximately 30% of breast cancers, this genome alteration has not been detected in DNA from any normal tissues [Lee et al., 1994; Esteller et al., 1998; Tchou et al., 2000; Lin et al., 2001; Nakayama et al., 2003]. *GSTP1* CpG island hypermethylation has also been detected in 70% of PIN lesions [Brooks et al., 1998; Nakayama et al., 2003a]. For a comprehensive review of GSTP1 methylation as a biomarker in prostate cancer, see the accompanying article by Nakayama et al. [2003b].

### Carcinogen Detoxification, Inflammation, and Prostate Cancer Prevention

Insights into the molecular pathogenesis of prostate cancer may provide opportunities for the discovery and development of new agents for prostate cancer prevention. Loss of GSTP1 "caretaker" activity during prostate carcinogenesis emphasizes the critical role of carcinogen metabolism in protecting prostate cells against neoplastic transformation, and suggests that therapeutic compensation for inadequate GSTP1 "caretaker" function may help prevent prostate cancer. The "oxidation tolerance" phenotype associated with loss of *GSTP1* "caretaker" function in LNCaP prostate cancer cells may provide a mechanistic rationale for buttressing defenses against oxidative genome damage via anti-oxidant supplementation to prevent or delay prostate carcinogenesis. In addition, augmentation of carcinogen-detoxification capacity, using a variety of such chemoprotective compounds, including isothiocyanates, 1,2-dithiole-3-thiones, terpenoids, etc., is known to prevent a range of different cancers in different animal models by triggering the expression of many different carcinogen-detoxification enzymes [Kensler, 1997; Ramos-Gomez et al., 2001]. Oltipraz, an inducer of carcinogen-detoxification enzymes in liver tissues, has been shown to reduce aflatoxin $B_1$ damage when administered to a human clinical study cohort at high risk for aflatoxin exposure and liver cancer development in China [Jacobson et al., 1997; Kensler et al., 1998; Wang et al., 1999]. Sulforaphane, an isothiocyanate present in high amounts in cruciferous vegetables, is also a potent inducer of carcinogen-detoxification enzymes [Zhang et al., 1992, 1994]. Diets rich in carcinogen-inducers like sulforaphane have been associated with decreased cancer risks [Cohen et al., 2000]. Such carcinogen-detoxification enzyme inducers need to be developed and tested in prostate cancer prevention clinical trials.

The recognition that prostate inflammation may contribute to the earliest steps in prostate carcinogenesis also has profound implications for the prevention of prostate cancer. Animal model studies suggest that non-steroidal anti-inflammatory drugs might attenuate both prostate cancer incidence and prostate cancer progression [Wechter et al., 2000]. In addition, several epidemiology studies have hinted at a modest protective effect of non-steroidal anti-inflammatory drug intake on either prostate cancer incidence, or on prostate cancer progression [Norrish et al., 1998; Nelson and Harris, 2000; Habel et al., 2002; Leitzmann et al., 2002; Roberts et al., 2002]. One target of these drugs, cyclo-oxygenase-2 (COX-2), may be selectively expressed in PIA lesions in the prostate [Zha et al., 2001]. A randomized clinical trial involving the administration of celecoxib, a selective COX-2 inhibitor, or placebo to men with prostate cancer who undergo radical prostatectomy, has been initiated at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. The effects of COX-2 inhibition on oxidative genome damage on PIA and on other tissue markers will be ascertained. In the future, as the process of inflammation in the prostate, and the pathogenesis of PIA becomes better defined more specific targets will be identified, creating new opportunities for the discovery and development of selective inhibitors of pathways mediating prostate cell and genome damage used to decrease prostate cancer risk.

### Intracellular Signaling Pathways and Prostate Cancer Treatment

Finally, progressive elucidation of the molecular mechanisms contributing to prostate

cancer cell growth, survival, and metastasis may lead to better treatments for established prostate cancer. Of course, androgen signaling pathways, essential for the growth and survival of most prostate cancer cells, have already been successfully targeted for prostate cancer treatment. However, despite treatment with androgen deprivation and/or anti-androgens, most men with advanced prostate cancer ultimately suffer cancer progression [van der Kwast et al., 1991; Amler et al., 2000; Feldman and Feldman, 2001; Mousses et al., 2001]. Since these progressive androgen-independent cancers appear to still use the androgen receptor to promote growth and survival, it is possible that the androgen receptor itself, and some of its post-translational modifications, might be even better targeted with new treatment approaches [Eder et al., 2002; Gioeli et al., 2002; Solit et al., 2002]. Also, several newly recognized signal transduction pathways offer new treatment possibilities. In particular, as described in this review, loss of PTEN function during prostate cancer progression implicates PI3K/Akt cell growth and survival signaling pathway in the development of life-threatening prostate cancer [Furnari et al., 1998; Ramaswamy et al., 1999; Sun et al., 1999]. Several new agents targeting various components of this pathway are under development for prostate and other cancers [Neshat et al., 2001; Podsypanina et al., 2001; Solit et al., 2002; Vivanco and Sawyers, 2002].

## REFERENCES


Abate-Shen C, Banach-Petrosky WA, Sun X, Economides KD, Desai N, Gregg JP, Borowsky AD, Cardiff RD, Shen MM. 2003. Nkx3.1; Pten mutant mice develop invasive prostate adenocarcinoma and lymph node metastases. Cancer Res 63:3886–3890.

Abdulkadir SA, Magee JA, Peters TJ, Kaleem Z, Naughton CK, Humphrey PA, Milbrandt J. 2002. Conditional loss of nkx3.1 in adult mice induces prostatic intraepithelial neoplasia. Mol Cell Biol 22:1495–1503.

Amler LC, Agus DB, LeDuc C, Sapinoso ML, Fox WD, Kern S, Lee D, Wang V, Leysens M, Higgins B, Martin J, Gerald W, Dracopoli N, Cordon-Cardo C, Scher HI, Hampton GM. 2000. Dysregulated expression of androgen-responsive and nonresponsive genes in the androgen-independent prostate cancer xenograft model CWR22-R1. Cancer Res 60:6134–6141.

Anton RC, Kattan MW, Chakraborty S, Wheeler TM. 1999. Postatrophic hyperplasia of the prostate: Lack of association with prostate cancer. Am J Surg Pathol 23:932–936.

Artandi SE, Chang S, Lee SL, Alson S, Gottlieb GJ, Chin L, DePinho RA. 2000. Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice. Nature 406:641–645.

Beach R, Gown AM, De Peralta-Venturina MN, Folpe AL, Yaziji H, Salles PG, Grignon DJ, Fanger GR, Amin MB. 2002. P504S immunohistochemical detection in 405 prostatic specimens including 376 18-gauge needle biopsies. Am J Surg Pathol 26:1588–1596.

Bhatia-Gaur R, Donjacour AA, Sciavolino PJ, Kim M, Desai N, Young P, Norton CR, Gridley T, Cardiff RD, Cunha GR, Abate-Shen C, Shen MM. 1999. Roles for Nkx3.1 in prostate development and cancer. Genes Dev 13:966–977.

Bieberich CJ, Fujita K, He WW, Jay G. 1996. Prostate-specific and androgen-dependent expression of a novel homeobox gene. J Biol Chem 271:31779–31782.

Billis A. 1998. Prostatic atrophy: An autopsy study of a histologic mimic of adenocarcinoma. Mod Pathol 11:47–54.

Billis A, Magna LA. 2003. Inflammatory atrophy of the prostate. Prevalence and significance. Arch Pathol Lab Med 127:840–844.

Blasco MA, Lee HW, Hande MP, Samper E, Lansdorp PM, DePinho RA, Greider CW. 1997. Telomere shortening and tumor formation by mouse cells lacking telomerase RNA. Cell 91:25–34.

Bookstein R. 2001. Tumor suppressor genes in prostate cancer. In: Chung LW, Isaacs WB, Simons JW, editors. Prostate cancer: Biology, genetics, and the new therapeutics. Totowa, NJ: Humana press. pp 61–93.

Bostwick DG. 1996. Prospective origins of prostate carcinoma. Prostatic intraepithelial neoplasia and atypical adenomatous hyperplasia. Cancer 78:330–336.

Bostwick DG, Qian J. 1995. Atypical adenomatous hyperplasia of the prostate. Relationship with carcinoma in 217 whole-mount radical prostatectomies. Am J Surg Pathol 19:506–518.

Bostwick DG, Cooner WH, Denis L, Jones GW, Scardino PT, Murphy GP. 1992. The association of benign prostatic hyperplasia and cancer of the prostate. Cancer 70:291–301.

Bowen C, Bubendorf L, Voeller HJ, Slack R, Willi N, Sauter G, Gasser TC, Koivisto P, Lack EE, Kononen J, Kallioniemi OP, Gelmann EP. 2000. Loss of NKX3.1 expression in human prostate cancers correlates with tumor progression [in process citation]. Cancer Res 60: 6111–6115.

Brawer MK, Peehl DM, Stamey TA, Bostwick DG. 1985. Keratin immunoreactivity in the benign and neoplastic human prostate. Cancer Res 45:3663–3667.

Breslow N, Chan CW, Dhom G, Drury RA, Franks LM, Gellei B, Lee YS, Lundberg S, Sparke B, Sternby NH, Tulinius H. 1977. Latent carcinoma of prostate of autopsy in seven areas. Int J Cancer 20:680–688.

Brooks JD, Weinstein M, Lin X, Sun Y, Pin SS, Bova GS, Epstein JI, Isaacs WB, Nelson WG. 1998. CG island methylation changes near the *GSTP1* gene in prostatic intraepithelial neoplasia. Cancer Epidemiol Biomarkers Prev 7:531–536.

Cahill DP, Kinzler KW, Vogelstein B, Lengauer C. 1999. Genetic instability and darwinian selection in tumours. Trends Cell Biol 9:M57–M60.

Cairns P, Okami K, Halachmi S, Halachmi N, Esteller M, Herman JG, Jen J, Isaacs WB, Bova GS, Sidransky D. 1997. Frequent inactivation of PTEN/MMAC1 in primary prostate cancer. Cancer Res 57:4997–5000.

Carpten J, Nupponen N, Isaacs S, Sood R, Robbins C, Xu J, Faruque M, Moses T, Ewing C, Gillanders E, Hu P,

Bujnovszky P, Makalowska I, Baffoe-Bonnie A, Faith D, Smith J, Stephan D, Wiley K, Brownstein M, Gildea D, Kelly B, Jenkins R, Hostetter G, Matikainen M, Schleutker J, Klinger K, Connors T, Xiang Y, Wang Z, De Marzo A, Papadopoulos N, Kallioniemi OP, Burk R, Meyers D, Gronberg H, Meltzer P, Silverman R, Bailey-Wilson J, Walsh P, Isaacs W, Trent J. 2002. Germline mutations in the ribonuclease L gene in families showing linkage with HPC1. Nat Genet 30:181–184.

Cheville JC, Lloyd RV, Sebo TJ, Cheng L, Erickson L, Bostwick DG, Lohse CM, Wollan P. 1998. Expression of p27kip1 in prostatic adenocarcinoma. Mod Pathol 11: 324–328.

Chung LWK, Isaacs WB, Simons JW. 2001. Prostate cancer: Biology, genetics, and the new therapeutics. Totowa, NJ: Humana Press.

Clark LC, Combs GF, Jr., Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, Krongrad A, Lesher JL, Jr., Park HK, Sanders BB, Jr., Smith CL, Taylor JR. 1996. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group [see comments] [published erratum appears in JAMA 1997 May 21;277(19):1520]. JAMA 276:1957–1963.

Clark LC, Dalkin B, Krongrad A, Combs GF, Jr., Turnbull BW, Slate EH, Witherington R, Herlong JH, Janosko E, Carpenter D, Borosso C, Falk S, Rounder J. 1998. Decreased incidence of prostate cancer with selenium supplementation: Results of a double-blind cancer prevention trial. Br J Urol 81:730–734.

Cohen JH, Kristal AR, Stanford JL. 2000. Fruit and vegetable intakes and prostate cancer risk. J Natl Cancer Inst 92:61–68.

Cordon-Cardo C, Koff A, Drobnjak M, Capodieci P, Osman I, Millard SS, Gaudin PB, Fazzari M, Zhang ZF, Massague J, Scher HI. 1998. Distinct altered patterns of *p27KIP1* gene expression in benign prostatic hyperplasia and prostatic carcinoma [in process citation]. J Natl Cancer Inst 90:1284–1291.

Counter CM, Avilion AA, LeFeuvre CE, Stewart NG, Greider CW, Harley CB, Bacchetti S. 1992. Telomere shortening associated with chromosome instability is arrested in immortal cells which express telomerase activity. EMBO J 11:1921–1929.

Coussens LM, Werb Z. 2002. Inflammation and cancer. Nature 420:860–867.

Craft N, Shostak Y, Carey M, Sawyers CL. 1999. A mechanism for hormone-independent prostate cancer through modulation of androgen receptor signaling by the HER-2/neu tyrosine kinase. Nat Med 5:280–285.

Culig Z, Hobisch A, Cronauer MV, Cato AC, Hittmair A, Radmayr C, Eberle J, Bartsch G, Klocker H. 1993. Mutant androgen receptor detected in an advanced-stage prostatic carcinoma is activated by adrenal androgens and progesterone. Mol Endocrinol 7:1541–1550.

de Lange T. 1995. Telomere dynamics and genome instability in human cancer. In: Blackburn EH, Greider CW, editors. Telomeres. Plainview, NY: Cold Spring Harbor Laboratory Press. pp 265–293.

De Marzo AM, Meeker AK, Epstein JI, Coffey DS. 1998a. Prostate stem cell compartments: Expression of the cell cycle inhibitor p27Kip1 in normal, hyperplastic, and neoplastic cells. Am J Pathol 153:911–919.

De Marzo AM, Nelson WG, Meeker AK, Coffey DS. 1998b. Stem cell features of benign and malignant prostate epithelial cells. J Urol 160:2381–2392.

De Marzo AM, Marchi VL, Epstein JI, Nelson WG. 1999. Proliferative inflammatory atrophy of the prostate: Implications for prostatic carcinogenesis. Am J Pathol 155: 1985–1992.

DeMarzo AM, Nelson WG, Isaacs WB, Epstein JI. 2003. Pathological and molecular aspects of prostate cancer. Lancet 361:955–964.

Dennis LK, Dawson DV. 2002. Meta-analysis of measures of sexual activity and prostate cancer. Epidemiology 13:72–79.

Dennis LK, Lynch CF, Torner JC. 2002. Epidemiologic association between prostatitis and prostate cancer. Urology 60:78–83.

Dhanasekaran SM, Barrette TR, Ghosh D, Shah R, Varambally S, Kurachi K, Pienta KJ, Rubin MA, Chinnaiyan AM. 2001. Delineation of prognostic biomarkers in prostate cancer. Nature 412:822–826.

Di Cristofano A, De Acetis M, Koff A, Cordon-Cardo C, Pandolfi PP. 2001. Pten and p27KIP1 cooperate in prostate cancer tumor suppression in the mouse. Nat Genet 27:222–224.

Donaldson L, Fordyce C, Gilliland F, Smith A, Feddersen R, Joste N, Moyzis R, Griffith J. 1999. Association between outcome and telomere DNA content in prostate cancer. J Urol 162:1788–1792.

Eder IE, Hoffmann J, Rogatsch H, Schafer G, Zopf D, Bartsch G, Klocker H. 2002. Inhibition of LNCaP prostate tumor growth in vivo by an antisense oligonucleotide directed against the human androgen receptor. Cancer Gene Ther 9:117–125.

Eiserich JP, Hristova M, Cross CE, Jones AD, Freeman BA, Halliwell B, van der Vliet A. 1998. Formation of nitric oxide-derived inflammatory oxidants by myeloperoxidase in neutrophils. Nature 391:393–397.

Emmert-Buck MR, Vocke CD, Pozzatti RO, Duray PH, Jennings SB, Florence CD, Zhuang Z, Bostwick DG, Liotta LA, Linehan WM. 1995. Allelic loss on chromosome 8p12-21 in microdissected prostatic intraepithelial neoplasia. Cancer Res 55:2959–2962.

Epstein JI. 1995. Prostate biopsy interpretation. New York, NY: Raven Press.

Epstein JI, Potter SR. 2001. The pathological interpretation and significance of prostate needle biopsy findings: Implications and current controversies. J Urol 166:402–410.

Epstein JI, Walsh PC, Sanfilippo F. 1996. Clinical and cost impact of second-opinion pathology. Review of prostate biopsies prior to radical prostatectomy. Am J Surg Pathol 20:851–857.

Esteller M, Corn PG, Urena JM, Gabrielson E, Baylin SB, Herman JG. 1998. Inactivation of glutathione *S*-transferase *P1* gene by promoter hypermethylation in human neoplasia. Cancer Res 58:4515–4518.

Evans BA, Harper ME, Daniells CE, Watts CE, Matenhelia S, Green J, Griffiths K. 1996. Low incidence of androgen receptor gene mutations in human prostatic tumors using single strand conformation polymorphism analysis. Prostate 28:162–171.

Feldman BJ, Feldman D. 2001. The development of androgen-independent prostate cancer. Nat Rev Cancer 1:34–45.

Feldser DM, Hackett JA, Greider CW. 2003. Telomere dysfunction and the initiation of genome instability. Nat Rev Cancer 3:623–627.

Feneley MR, Young MP, Chinyama C, Kirby RS, Parkinson MC. 1996. Ki-67 expression in early prostate cancer and associated pathological lesions. J Clin Pathol 49:741–748.

Ferdinandusse S, Denis S, Clayton PT, Graham A, Rees JE, Allen JT, McLean BN, Brown AY, Vreken P, Waterham HR, Wanders RJ. 2000. Mutations in the gene encoding peroxisomal alpha-methylacyl-CoA racemase cause adult-onset sensory motor neuropathy. Nat Genet 24: 188–191.

Fernandez PL, Arce Y, Farre X, Martinez A, Nadal A, Rey MJ, Peir N, Campo E, Cardesa A. 1999. Expression of p27/kip1 is down-regulated in human prostate carcinoma progression. J Pathol 187:563–566.

Franks LM. 1954. Atrophy and hyperplasia in the prostate proper. J Pathol Bacteriol 68:617–621.

Furnari FB, Huang HJ, Cavenee WK. 1998. The phosphoinositol phosphatase activity of PTEN mediates a serum-sensitive G1 growth arrest in glioma cells. Cancer Res 58:5002–5008.

Gaddipati JP, McLeod DG, Heidenberg HB, Sesterhenn IA, Finger MJ, Moul JW, Srivastava S. 1994. Frequent detection of codon 877 mutation in the androgen receptor gene in advanced prostate cancers. Cancer Res 54:2861–2864.

Gann PH, Ma J, Giovannucci E, Willett W, Sacks FM, Hennekens CH, Stampfer MJ. 1999. Lower prostate cancer risk in men with elevated plasma lycopene levels: Results of a prospective analysis. Cancer Res 59:1225–1230.

Gao AC, Isaacs JT. 2002. Molecular basis of prostate carcinogenesis. In: Coleman WB, Tsongalis GJ, editors. The molecular basis of human cancer. Totowa, NJ: Humana Press. pp 365–379.

Gardner WA, Bennett BD. 1992. The prostate overview: Recent insights and speculations. In: Weinstein RS, Garnder WA, editors. Pathology and pathobiology of the urinary bladder and prostate. Baltimore: Williams and Wilkens. pp 129–148.

Gerstenbluth RE, Seftel AD, MacLennan GT, Rao RN, Corty EW, Ferguson K, Resnick MI. 2002. Distribution of chronic prostatitis in radical prostatectomy specimens with up-regulation of bcl-2 in areas of inflammation. J Urol 167:2267–2270.

Gioeli D, Ficarro SB, Kwiek JJ, Aaronson D, Hancock M, Catling AD, White FM, Christian RE, Settlage RE, Shabanowitz J, Hunt DF, Weber MJ. 2002. Androgen receptor phosphorylation. Regulation and identification of the phosphorylation sites. J Biol Chem 277:29304–29314.

Giovannucci E. 2001. Medical history and etiology of prostate cancer. Epidemiol Rev 23:159–162.

Gleason PE, Jones JA, Regan JS, Salvas DB, Eble JN, Lamph WW, Vlahos CJ, Huang WL, Falcone JF, Hirsch KS. 1993. Platelet derived growth factor (PDGF), androgens and inflammation: Possible etiologic factors in the development of prostatic hyperplasia. J Urol 149:1586–1592.

Gottschalk AR, Basila D, Wong M, Dean NM, Brandts CH, Stokoe D, Haas-Kogan DA. 2001. p27Kip1 is required for PTEN-induced G1 growth arrest. Cancer Res 61:2105–2111.

Graff JR, Konicek BW, McNulty AM, Wang Z, Houck K, Allen S, Paul JD, Hbaiu A, Goode RG, Sandusky GE, Vessella RL, Neubauer BL. 2000. Increased AKT activity contributes to prostate cancer progression by dramatically accelerating prostate tumor growth and diminishing p27Kip1 expression. J Biol Chem 275:24500–24505.

Gray IC, Stewart LM, Phillips SM, Hamilton JA, Gray NE, Watson GJ, Spurr NK, Snary D. 1998. Mutation and expression analysis of the putative prostate tumour-suppressor gene *PTEN*. Br J Cancer 78:1296–1300.

Grignon DJ, Sakr WA. 1996. Atypical adenomatous hyperplasia of the prostate: A critical review. Eur Urol 30: 206–211.

Gross GA, Turesky RJ, Fay LB, Stillwell WG, Skipper PL, Tannenbaum SR. 1993. Heterocyclic aromatic amine formation in grilled bacon, beef and fish and in grill scrapings. Carcinogenesis 14:2313–2318.

Guess HA. 2001. Benign prostatic hyperplasia and prostate cancer. Epidemiol Rev 23:152–158.

Guo YP, Sklar GN, Borkowski A, Kyprianou N. 1997. Loss of the cyclin-dependent kinase inhibitor P27(Kip1) protein in human prostate cancer correlates with tumor grade. Clin Cancer Res 3:2269–2274.

Haapala K, Hyytinen ER, Roiha M, Laurila M, Rantala I, Helin HJ, Koivisto PA. 2001. Androgen receptor alterations in prostate cancer relapsed during a combined androgen blockade by orchiectomy and bicalutamide. Lab Invest 81:1647–1651.

Habel LA, Zhao W, Stanford JL. 2002. Daily aspirin use and prostate cancer risk in a large, multiracial cohort in the US. Cancer Causes Control 13:427–434.

Hackett JA, Greider CW. 2002. Balancing instability: Dual roles for telomerase and telomere dysfunction in tumorigenesis. Oncogene 21:619–626.

Haenszel W, Kurihara M. 1968. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. J Natl Cancer Inst 40:43–68.

Harley CB, Futcher AB, Greider CW. 1990. Telomeres shorten during ageing of human fibroblasts. Nature 345:458–460.

Hasui Y, Marutsuka K, Asada Y, Ide H, Nishi S, Osada Y. 1994. Relationship between serum prostate specific antigen and histological prostatitis in patients with benign prostatic hyperplasia. Prostate 25:91–96.

Hayes RB, Pottern LM, Strickler H, Rabkin C, Pope V, Swanson GM, Greenberg RS, Schoenberg JB, Liff J, Schwartz AG, Hoover RN, Fraumeni JF, Jr. 2000. Sexual behaviour, STDs and risks for prostate cancer. Br J Cancer 82:718–725.

He WW, Sciavolino PJ, Wing J, Augustus M, Hudson P, Meissner PS, Curtis RT, Shell BK, Bostwick DG, Tindall DJ, Gelmann EP, Abate-Shen C, Carter KC. 1997. A novel human prostate-specific, androgen-regulated homeobox gene (*NKX3.1*) that maps to 8p21, a region frequently deleted in prostate cancer. Genomics 43:69–77.

Hedrick L, Epstein JI. 1989. Use of keratin 903 as an adjunct in the diagnosis of prostate carcinoma. Am J Surg Pathol 13:389–396.

Heinonen OP, Albanes D, Virtamo J, Taylor PR, Huttunen JK, Hartman AM, Haapakoski J, Malila N, Rautalahti M, Ripatti S, Maenpaa H, Teerenhovi L, Koss L, Virolainen M, Edwards BK. 1998. Prostate cancer and supplementation with alpha-tocopherol and beta-

carotene: Incidence and mortality in a controlled trial [see comments]. J Natl Cancer Inst 90:440–446.
Henderson CJ, Smith AG, Ure J, Brown K, Bacon EJ, Wolf CR. 1998. Increased skin tumorigenesis in mice lacking pi class glutathione *S*-transferases. Proc Natl Acad Sci USA 95:5275–5280.
Hobisch A, Eder IE, Putz T, Horninger W, Bartsch G, Klocker H, Culig Z. 1998. Interleukin-6 regulates prostate-specific protein expression in prostate carcinoma cells by activation of the androgen receptor. Cancer Res 58:4640–4645.
Hsing AW, Tsao L, Devesa SS. 2000. International trends and patterns of prostate cancer incidence and mortality. Int J Cancer 85:60–67.
Huang GM, Ng WL, Farkas J, He L, Liang HA, Gordon D, Yu J, Hood L. 1999. Prostate cancer expression profiling by cDNA sequencing analysis. Genomics 59:178–186.
Irani J, Levillain P, Goujon JM, Bon D, Dore B, Aubert J. 1997. Inflammation in benign prostatic hyperplasia: Correlation with prostate specific antigen value. J Urol 157:1301–1303.
Isaacs WB, Bova GS, Morton RA, Bussemakers MJ, Brooks JD, Ewing CM. 1994. Molecular biology of prostate cancer. Semin Oncol 21:514–521.
Jacobson LP, Zhang BC, Zhu YR, Wang JB, Wu Y, Zhang QN, Yu LY, Qian GS, Kuang SY, Li YF, Fang X, Zarba A, Chen B, Enger C, Davidson NE, Gorman MB, Gordon GB, Prochaska HJ, Egner PA, Groopman JD, Munoz A, Helzlsouer KJ, Kensler TW. 1997. Oltipraz chemoprevention trial in Qidong, People's Republic of China: Study design and clinical outcomes. Cancer Epidemiol Biomarkers Prev 6:257–265.
Jaffee EM, Hruban RH, Canto M, Kern SE. 2002. Focus on pancreas cancer. Cancer Cell 2:25–28.
Jemal A, Thomas A, Murray T, Thun M. 2002. Cancer statistics, 2002. CA Cancer J Clin 52:23–47.
Jiang Z, Woda BA, Rock KL, Xu Y, Savas L, Khan A, Pihan G, Cai F, Babcook JS, Rathanaswami P, Reed SG, Xu J, Fanger GR. 2001. P504S: A new molecular marker for the detection of prostate carcinoma. Am J Surg Pathol 25:1397–1404.
Jiang Z, Wu CL, Woda BA, Dresser K, Xu J, Fanger GR, Yang XJ. 2002. P504S/alpha-methylacyl-CoA racemase: A useful marker for diagnosis of small foci of prostatic carcinoma on needle biopsy. Am J Surg Pathol 26:1169–1174.
Kensler TW. 1997. Chemoprevention by inducers of carcinogen detoxication enzymes. Environ Health Perspect 4(105 Suppl):965–970.
Kensler TW, He X, Otieno M, Egner PA, Jacobson LP, Chen B, Wang JS, Zhu YR, Zhang BC, Wang JB, Wu Y, Zhang QN, Qian GS, Kuang SY, Fang X, Li YF, Yu LY, Prochaska HJ, Davidson NE, Gordon GB, Gorman MB, Zarba A, Enger C, Munoz A, Helzlsouer KJ, et al. 1998. Oltipraz chemoprevention trial in Qidong, People's Republic of China: Modulation of serum aflatoxin albumin adduct biomarkers. Cancer Epidemiol Biomarkers Prev 7:127–134.
Kibel AS, Faith DA, Bova GS, Isaacs WB. 2000. Loss of heterozygosity at 12P12-13 in primary and metastatic prostate adenocarcinoma. J Urol 164:192–196.
Kim MJ, Cardiff RD, Desai N, Banach-Petrosky WA, Parsons R, Shen MM, Abate-Shen C. 2002. Cooperativity of Nkx3.1 and Pten loss of function in a mouse model of prostate carcinogenesis. Proc Natl Acad Sci USA 99: 2884–2889.
Kinzler KW, Vogelstein B. 1997. Cancer-susceptibility genes. Gatekeepers and caretakers [news; comment] [see comments]. Nature 386:761, 763.
Knize MG, Salmon CP, Mehta SS, Felton JS. 1997. Analysis of cooked muscle meats for heterocyclic aromatic amine carcinogens. Mutat Res 376:129–134.
Koivisto P, Kononen J, Palmberg C, Tammela T, Hyytinen E, Isola J, Trapman J, Cleutjens K, Noordzij A, Visakorpi T, Kallioniemi OP. 1997. Androgen receptor gene amplification: A possible molecular mechanism for androgen deprivation therapy failure in prostate cancer. Cancer Res 57:314–319.
Kolonel LN. 2001. Fat, meat, and prostate cancer. Epidemiol Rev 23:72–81.
Krieger JN, Nyberg L, Jr., Nickel JC. 1999. NIH consensus definition and classification of prostatitis. JAMA 282: 236–237.
Leav I, McNeal JE, Ho SM, Jiang Z. 2003. Alpha-methylacyl-CoA racemase (P504S) expression in evolving carcinomas within benign prostatic hyperplasia and in cancers of the transition zone. Hum Pathol 34:228–233.
Lee WH, Morton RA, Epstein JI, Brooks JD, Campbell PA, Bova GS, Hsieh WS, Isaacs WB, Nelson WG. 1994. Cytidine methylation of regulatory sequences near the pi-class glutathione *S*-transferase gene accompanies human prostatic carcinogenesis. Proc Natl Acad Sci USA 91:11733–11737.
Leitzmann MF, Stampfer MJ, Ma J, Chan JM, Colditz GA, Willett WC, Giovannucci E. 2002. Aspirin use in relation to risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 11:1108–1111.
Levy MZ, Allsopp RC, Futcher AB, Greider CW, Harley CB. 1992. Telomere end-replication problem and cell aging. J Mol Biol 225:951–960.
Li DM, Sun H. 1998. PTEN/MMAC1/TEP1 suppresses the tumorigenicity and induces G1 cell cycle arrest in human glioblastoma cells. Proc Natl Acad Sci USA 95:15406–15411.
Li J, Yen C, Liaw D, Podsypanina K, Bose S, Wang SI, Puc J, Miliaresis C, Rodgers L, McCombie R, Bigner SH, Giovanella BC, Ittmann M, Tycko B, Hibshoosh H, Wigler MH, Parsons R. 1997. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 275:1943–1947.
Liavag I. 1968. Atrophy and regeneration in the pathogenesis of prostatic carcinoma. Acta Path Microbiol Scandinav 73:338–350.
Lijinsky W, Shubik P. 1964. Benzo(a)pyrene and other polynuclear hydrocarbons in charcoal-broiled meat. Science 145:53–55.
Lin X, Tascilar M, Lee WH, Vles WJ, Lee BH, Veeraswamy R, Asgari K, Freije D, van Rees B, Gage WR, Bova GS, Isaacs WB, Brooks JD, DeWeese TL, De Marzo AM, Nelson WG. 2001. GSTP1 CpG island hypermethylation is responsible for the absence of GSTP1 expression in human prostate cancer cells. Am J Pathol 159:1815–1826.
Luo J, Duggan DJ, Chen Y, Sauvageot J, Ewing CM, Bittner ML, Trent JM, Isaacs WB. 2001. Human prostate cancer and benign prostatic hyperplasia: Molecular dissection by gene expression profiling. Cancer Res 61: 4683–4688.

Luo J, Zha S, Gage WR, Dunn TA, Hicks JL, Bennett CJ, Ewing CM, Platz EA, Ferdinandusse S, Wanders RJ, Trent JM, Isaacs WB, De Marzo AM. 2002. Alpha-methylacyl-CoA racemase: A new molecular marker for prostate cancer. Cancer Res 62:2220–2226.

Macoska JA, Trybus TM, Wojno KJ. 2000. 8p22 loss concurrent with 8c gain is associated with poor outcome in prostate cancer. Urology 55:776–782.

Magee JA, Araki T, Patil S, Ehrig T, True L, Humphrey PA, Catalona WJ, Watson MA, Milbrandt J. 2001. Expression profiling reveals hepsin overexpression in prostate cancer. Cancer Res 61:5692–5696.

Magi-Galluzzi C, Luo J, Isaacs WB, Hicks JL, De Marzo AM, Epstein JI. 2003. Alpha-methylacyl-CoA racemase: A variably sensitive immunohistochemical marker for the diagnosis of small prostate cancer foci on needle biopsy. Am J Surg Pathol 27:1128–1133.

Marcelli M, Ittmann M, Mariani S, Sutherland R, Nigam R, Murthy L, Zhao Y, DiConcini D, Puxeddu E, Esen A, Eastham J, Weigel NL, Lamb DJ. 2000. Androgen receptor mutations in prostate cancer. Cancer Res 60: 944–949.

McClintock B. 1941. The stability of broken ends of chromosomes in *Zea mays*. Genetics 26:234–282.

McMenamin ME, Soung P, Perera S, Kaplan I, Loda M, Sellers WR. 1999. Loss of PTEN expression in paraffin-embedded primary prostate cancer correlates with high Gleason score and advanced stage. Cancer Res 59:4291–4296.

McNeal JE. 1969. Origin and development of carcinoma in the prostate. Cancer 23:24–34.

McNeal JE. 1984. Ageing and the prostate. In: Brocklehurst JC, editor. Urology in the elderly. Edinburgh, UK: Churhill Livingstone. pp 193–202.

McNeal JE. 1988. Normal histology of the prostate. Am J Surg Pathol 12:619–633.

McNeal JE. 1997. Prostate. In: Sternberg SS, editor. Histology for pathologists. Philadelphia, PA: Lippincott-Raven. pp 997–1017.

McNeal JE, Bostwick DG. 1986. Intraductal dysplasia: A premalignant lesion of the prostate. Hum Pathol 17: 64–71.

Meeker AK, Hicks JL, Platz EA, March GE, Bennett CJ, De Marzo AM. 2002. Telomere shortening is an early somatic DNA alteration in human prostate tumorigenesis. Cancer Res 62:6405–6409.

Meng MV, Dahiya R. 2002. Molecular genetics of prostate cancer. In: Carroll PR, Grossfeld GD, editors. Prostate cancer. Hamilton, Ontario, BC: Decker, Inc.

Michaud DS, Augustsson K, Rimm EB, Stampfer MJ, Willet WC, Giovannucci E. 2001. A prospective study on intake of animal products and risk of prostate cancer. Cancer Causes Control 12:557–567.

Millar DS, Ow KK, Paul CL, Russell PJ, Molloy PL, Clark SJ. 1999. Detailed methylation analysis of the glutathione *S*-transferase pi (*GSTP1*) gene in prostate cancer [in process citation]. Oncogene 18:1313–1324.

Miller GJ. 1999. Prostate cancer among the Chinese: Pathological and epidemiological and nutritional considerations. In: Resnick MI, Thompson IM, editors. Advanced therapy of prostate disease. Hamilton, Ontario, BC: Decker, Inc. pp 18–27.

Mirchandani D, Zheng J, Miller GJ, Ghosh AK, Shibata DK, Cote RJ, Roy-Burman P. 1995. Heterogeneity in intratumor distribution of p53 mutations in human prostate cancer. Am J Pathol 147:92–101.

Montironi R, Mazzucchelli R, Scarpelli M. 2002. Precancerous lesions and conditions of the prostate: From morphological and biological characterization to chemoprevention. Ann NY Acad Sci 963:169–184.

Moore RA. 1936. The evolution and involution of the prostate gland. Am J Pathol 12:599–624.

Morgenthaler PM, Holzhauser D. 1995. Analysis of mutations induced by 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in human lymphoblastoid cells. Carcinogenesis 16:713–718.

Mousses S, Wagner U, Chen Y, Kim JW, Bubendorf L, Bittner M, Pretlow T, Elkahloun AG, Trepel JB, Kallioniemi OP. 2001. Failure of hormone therapy in prostate cancer involves systematic restoration of androgen responsive genes and activation of rapamycin sensitive signaling. Oncogene 20:6718–6723.

Myers MP, Stolarov JP, Eng C, Li J, Wang SI, Wigler MH, Parsons R, Tonks NK. 1997. P-TEN, the tumor suppressor from human chromosome 10q23, is a dual-specificity phosphatase. Proc Natl Acad Sci USA 94:9052–9057.

Myers MP, Pass I, Batty IH, Van der Kaay J, Stolarov JP, Hemmings BA, Wigler MH, Downes CP, Tonks NK. 1998. The lipid phosphatase activity of PTEN is critical for its tumor supressor function. Proc Natl Acad Sci USA 95: 13513–13518.

Nakamura N, Ramaswamy S, Vazquez F, Signoretti S, Loda M, Sellers WR. 2000. Forkhead transcription factors are critical effectors of cell death and cell cycle arrest downstream of PTEN. Mol Cell Biol 20:8969–8982.

Nakayama M, Bennett CJ, Hicks JL, Epstein JI, Platz EA, Nelson WG, De Marzo AM. 2003a. Hypermethylation of the human GSTP1 CpG island is present in a subset of proliferative inflammatory atrophy lesions but not in normal or hyperplastic epithelium of the prostate: A detailed study using laser-capture microdissection. Am J Pathol 163:923–933.

Nakayama M, Gonzalgo ML, Yegnasubramanian S, Lin X, Demarzo AM, Nelson WG. 2003b. GSTP1 CpG island hypermethylation as a molecular biomarker for prostate cancer. J Cell Biochem (in press).

Nazareth LV, Weigel NL. 1996. Activation of the human androgen receptor through a protein kinase A signaling pathway. J Biol Chem 271:19900–19907.

Nelson JE, Harris RE. 2000. Inverse association of prostate cancer and non-steroidal anti-inflammatory drugs (NSAIDs): Results of a case–control study. Oncol Rep 7:169–170.

Nelson PS, Han D, Rochon Y, Corthals GL, Lin B, Monson A, Nguyen V, Franza BR, Plymate SR, Aebersold R, Hood L. 2000. Comprehensive analyses of prostate gene expression: Convergence of expressed sequence tag databases, transcript profiling and proteomics. Electrophoresis 21:1823–1831 [pii].

Nelson CP, Kidd LC, Sauvageot J, Isaacs WB, De Marzo AM, Groopman JD, Nelson WG, Kensler TW. 2001a. Protection against 2-hydroxyamino-1-methyl-6-phenylimidazo[4,5-b]pyridine cytotoxicity and DNA adduct formation in human prostate by glutathione *S*-transferase P1. Cancer Res 61:103–109.

Nelson WG, De Marzo AM, DeWeese TL. 2001b. The molecular pathogenesis of prostate cancer: Implications for prostate cancer prevention. Urology 57:39–45.

Nelson WG, De Marzo AM, Isaacs WB. 2003. Prostate cancer. N Engl J Med 349:366–381.

Neshat MS, Mellinghoff IK, Tran C, Stiles B, Thomas G, Petersen R, Frost P, Gibbons JJ, Wu H, Sawyers CL. 2001. Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR. Proc Natl Acad Sci USA 98:10314–10319.

Newmark JR, Hardy DO, Tonb DC, Carter BS, Epstein JI, Isaacs WB, Brown TR, Barrack ER. 1992. Androgen receptor gene mutations in human prostate cancer. Proc Natl Acad Sci USA 89:6319–6323.

Nickel JC. 1994. Prostatic inflammation in benign prostatic hyperplasia—The third component? Can J Urol 1: 1–4.

Nickel JC, Downey J, Young I, Boag S. 1999. Asymptomatic inflammation and/or infection in benign prostatic hyperplasia. BJU Int 84:976–981.

Norrish AE, Jackson RT, McRae CU. 1998. Non-steroidal anti-inflammatory drugs and prostate cancer progression. Int J Cancer 77:511–515.

Norrish AE, Ferguson LR, Knize MG, Felton JS, Sharpe SJ, Jackson RT. 1999. Heterocyclic amine content of cooked meat and risk of prostate cancer. J Natl Cancer Inst 91: 2038–2044.

O'Shaughnessy JA, Kelloff GJ, Gordon GB, Dannenberg AJ, Hong WK, Fabian CJ, Sigman CC, Bertagnolli MM, Stratton SP, Lam S, Nelson WG, Meyskens FL, Alberts DS, Follen M, Rustgi AK, Papadimitrakopoulou V, Scardino PT, Gazdar AF, Wattenberg LW, Sporn MB, Sakr WA, Lippman SM, Von Hoff DD. 2002. Treatment and prevention of intraepithelial neoplasia: An important target for accelerated new agent development. Clin Cancer Res 8:314–346.

Ornstein DK, Cinquanta M, Weiler S, Duray PH, Emmert-Buck MR, Vocke CD, Linehan WM, Ferretti JA. 2001. Expression studies and mutational analysis of the androgen regulated homeobox gene *NKX3.1* in benign and malignant prostate epithelium. J Urol 165:1329–1334.

Parsons JK, Gage WR, Nelson WG, De Marzo AM. 2001a. P63 protein expression is rare in prostate adenocarcinoma: Implications for cancer diagnosis and carcinogenesis. Urology 58:619–624.

Parsons JK, Nelson CP, Gage WR, Nelson WG, Kensler TW, De Marzo AM. 2001b. GSTA1 expression in normal, preneoplastic, and neoplastic human prostate tissue. Prostate 49:30–37.

Platt N, Gordon S. 2001. Is the class A macrophage scavenger receptor (SR-A) multifunctional?—The mouse's tale. J Clin Invest 108:649–654.

Platz EA. 1998. Prostatitis and prostate cancer. New Developments in Prostate Cancer Treatment 3:71–73.

Podsypanina K, Ellenson LH, Nemes A, Gu J, Tamura M, Yamada KM, Cordon-Cardo C, Catoretti G, Fisher PE, Parsons R. 1999. Mutation of Pten/Mmac1 in mice causes neoplasia in multiple organ systems. Proc Natl Acad Sci USA 96:1563–1568.

Podsypanina K, Lee RT, Politis C, Hennessy I, Crane A, Puc J, Neshat M, Wang H, Yang L, Gibbons J, Frost P, Dreisbach V, Blenis J, Gaciong Z, Fisher P, Sawyers C, Hedrick-Ellenson L, Parsons R. 2001. An inhibitor of mTOR reduces neoplasia and normalizes p70/S6 kinase activity in Pten± mice. Proc Natl Acad Sci USA 98: 10320–10325.

Prescott JL, Blok L, Tindall DJ. 1998. Isolation and androgen regulation of the human homeobox cDNA, NKX3.1. Prostate 35:71–80.

Putzi MJ, De Marzo AM. 2000. Morphologic transitions between proliferative inflammatory atrophy and high-grade prostatic intraepithelial neoplasia. Urology 56: 828–832.

Qian J, Bostwick DG, Takahashi S, Borell TJ, Herath JF, Lieber MM, Jenkins RB. 1995. Chromosomal anomalies in prostatic intraepithelial neoplasia and carcinoma detected by fluorescence in situ hybridization. Cancer Res 55:5408–5414.

Ramaswamy S, Nakamura N, Vazquez F, Batt DB, Perera S, Roberts TM, Sellers WR. 1999. Regulation of G1 progression by the PTEN tumor suppressor protein is linked to inhibition of the phosphatidylinositol 3-kinase/Akt pathway. Proc Natl Acad Sci USA 96:2110–2115.

Ramos-Gomez M, Kwak MK, Dolan PM, Itoh K, Yamamoto M, Talalay P, Kensler TW. 2001. From the cover: Sensitivity to carcinogenesis is increased and chemoprotective efficacy of enzyme inducers is lost in nrf2 transcription factor-deficient mice. Proc Natl Acad Sci USA 98:3410–3415.

Reznik G, Hamlin MH II, Ward JM, Stinson SF. 1981. Prostatic hyperplasia and neoplasia in aging F344 rats. Prostate 2:261–268.

Rich AR. 1934. On the frequency of occurrenec of occult carcinoma of the prostate. J Urol 33:215–223.

Roberts RO, Lieber MM, Rhodes T, Girman CJ, Bostwick DG, Jacobsen SJ. 1998. Prevalence of a physician-assigned diagnosis of prostatitis: The Olmsted county study of urinary symptoms and health status among men. Urology 51:578–584.

Roberts RO, Jacobson DJ, Girman CJ, Rhodes T, Lieber MM, Jacobsen SJ. 2002. A population-based study of daily nonsteroidal anti-inflammatory drug use and prostate cancer. Mayo Clin Proc 77:219–225.

Rubin MA, Zhou M, Dhanasekaran SM, Varambally S, Barrette TR, Sanda MG, Pienta KJ, Ghosh D, Chinnaiyan AM. 2002. Alpha-methylacyl coenzyme A racemase as a tissue biomarker for prostate cancer. JAMA 287: 1662–1670.

Ruijter ET, Miller GJ, van de Kaa CA, van Bokhoven A, Bussemakers MJ, Debruyne FM, Ruiter DJ, Schalken JA. 1999. Molecular analysis of multifocal prostate cancer lesions. J Pathol 188:271–277.

Ruska KM, Sauvageot J, Epstein JI. 1998. Histology and cellular kinetics of prostatic atrophy. Am J Surg Pathol 22:1073–1077.

Sadar MD, Gleave ME. 2000. Ligand-independent activation of the androgen receptor by the differentiation agent butyrate in human prostate cancer cells. Cancer Res 60:5825–5831.

Sakr WA, Haas GP, Cassin BF, Pontes JE, Crissman JD. 1993. The frequency of carcinoma and intraepithelial neoplasia of the prostate in young male patients [see comments]. J Urol 150:379–385.

Sakr WA, Grignon DJ, Crissman JD, Heilbrun LK, Cassin BJ, Pontes JJ, Haas GP. 1994. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20–69: An autopsy study of 249 cases. In Vivo 8:439–443.

Schatteman PH, Hoekx L, Wyndaele JJ, Jeuris W, Van Marck E. 2000. Inflammation in prostate biopsies of men

without prostatic malignancy or clinical prostatitis: Correlation with total serum PSA and PSA density. Eur Urol 37:404–412.

Schmitz W, Albers C, Fingerhut R, Conzelmann E. 1995. Purification and characterization of an alpha-methylacyl-CoA racemase from human liver. Eur J Biochem 231:815–822.

Schoenberg MP, Hakimi JM, Wang S, Bova GS, Epstein JI, Fischbeck KH, Isaacs WB, Walsh PC, Barrack ER. 1994. Microsatellite mutation (CAG24 → 18) in the androgen receptor gene in human prostate cancer. Biochem Biophys Res Commun 198:74–80.

Sciavolino PJ, Abrams EW, Yang L, Austenberg LP, Shen MM, Abate-Shen C. 1997. Tissue-specific expression of murine Nkx3.1 in the male urogenital system. Dev Dyn 209:127–138.

Shah R, Mucci NR, Amin A, Macoska JA, Rubin MA. 2001. Postatrophic hyperplasia of the prostate gland: Neoplastic precursor or innocent bystander? Am J Pathol 158: 1767–1773.

Shah RB, Zhou M, LeBlanc M, Snyder M, Rubin MA. 2002. Comparison of the basal cell-specific markers, 34betaE12 and p63, in the diagnosis of prostate cancer. Am J Surg Pathol 26:1161–1168.

Shih IM, Zhou W, Goodman SN, Lengauer C, Kinzler KW, Vogelstein B. 2001. Evidence that genetic instability occurs at an early stage of colorectal tumorigenesis. Cancer Res 61:818–822.

Shimizu H, Ross RK, Bernstein L, Yatani R, Henderson BE, Mack TM. 1991. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles county. Br J Cancer 63:963–966.

Shirai T, Sano M, Tamano S, Takahashi S, Hirose M, Futakuchi M, Hasegawa R, Imaida K, Matsumoto K, Wakabayashi K, Sugimura T, Ito N. 1997. The prostate: A target for carcinogenicity of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) derived from cooked foods. Cancer Res 57:195–198.

Signoretti S, Waltregny D, Dilks J, Isaac B, Lin D, Garraway L, Yang A, Montironi R, McKeon F, Loda M. 2000. P63 is a prostate basal cell marker and is required for prostate development [in process citation]. Am J Pathol 157:1769–1775.

Solit DB, Zheng FF, Drobnjak M, Munster PN, Higgins B, Verbel D, Heller G, Tong W, Cordon-Cardo C, Agus DB, Scher HI, Rosen N. 2002. 17-Allylamino-17-demethoxygeldanamycin induces the degradation of androgen receptor and HER-2/neu and inhibits the growth of prostate cancer xenografts. Clin Cancer Res 8:986–993.

Sommerfeld HJ, Meeker AK, Piatyszek MA, Bova GS, Shay JW, Coffey DS. 1996. Telomerase activity: A prevalent marker of malignant human prostate tissue. Cancer Res 56:218–222.

Stamey TA, Warrington JA, Caldwell MC, Chen Z, Fan Z, Mahadevappa M, McNeal JE, Nolley R, Zhang Z. 2001. Molecular genetic profiling of Gleason grade 4/5 prostate cancers compared to benign prostatic hyperplasia. J Urol 166:2171–2177.

Stanbrough M, Leav I, Kwan PW, Bubley GJ, Balk SP. 2001. Prostatic intraepithelial neoplasia in mice expressing an androgen receptor transgene in prostate epithelium. Proc Natl Acad Sci USA 98:10823–10828.

Steck PA, Pershouse MA, Jasser SA, Yung WK, Lin H, Ligon AH, Langford LA, Baumgard ML, Hattier T, Davis T, Frye C, Hu R, Swedlund B, Teng DH, Tavtigian SV. 1997. Identification of a candidate tumour suppressor gene, *MMAC1*, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet 15:356–362.

Strickler HD, Goedert JJ. 2001. Sexual behavior and evidence for an infectious cause of prostate cancer. Epidemiol Rev 23:144–151.

Stuart GR, Holcroft J, de Boer JG, Glickman BW. 2000. Prostate mutations in rats induced by the suspected human carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine. Cancer Res 60:266–268.

Sun H, Lesche R, Li DM, Liliental J, Zhang H, Gao J, Gavrilova N, Mueller B, Liu X, Wu H. 1999. PTEN modulates cell cycle progression and cell survival by regulating phosphatidylinositol 3,4,5,-trisphosphate and Akt/protein kinase B signaling pathway. Proc Natl Acad Sci USA 96:6199–6204.

Suzuki H, Sato N, Watabe Y, Masai M, Seino S, Shimazaki J. 1993. Androgen receptor gene mutations in human prostate cancer. J Steroid Biochem Mol Biol 46:759–765.

Suzuki H, Akakura K, Komiya A, Aida S, Akimoto S, Shimazaki J. 1996. Codon 877 mutation in the androgen receptor gene in advanced prostate cancer: Relation to antiandrogen withdrawal syndrome. Prostate 29:153–158.

Suzuki H, Freije D, Nusskern DR, Okami K, Cairns P, Sidransky D, Isaacs WB, Bova GS. 1998. Interfocal heterogeneity of *PTEN*/*MMAC1* gene alterations in multiple metastatic prostate cancer tissues. Cancer Res 58:204–209.

Tan J, Sharief Y, Hamil KG, Gregory CW, Zang DY, Sar M, Gumerlock PH, deVere White RW, Pretlow TG, Harris SE, Wilson EM, Mohler JL, French FS. 1997. Dehydroepiandrosterone activates mutant androgen receptors expressed in the androgen-dependent human prostate cancer xenograft CWR22 and LNCaP cells. Mol Endocrinol 11:450–459.

Taplin ME, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata GK, Keer HN, Balk SP. 1995. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. N Engl J Med 332:1393–1398.

Taplin ME, Bubley GJ, Ko YJ, Small EJ, Upton M, Rajeshkumar B, Balk SP. 1999. Selection for androgen receptor mutations in prostate cancers treated with androgen antagonist. Cancer Res 59:2511–2515.

Tchou JC, Lin X, Freije D, Isaacs WB, Brooks JD, Rashid A, De Marzo AM, Kanai Y, Hirohashi S, Nelson WG. 2000. GSTP1 CpG island DNA hypermethylation in hepatocellular carcinomas. Int J Oncol 16:663–676.

Teng DH, Hu R, Lin H, Davis T, Iliev D, Frye C, Swedlund B, Hansen KL, Vinson VL, Gumpper KL, Ellis L, El-Naggar A, Frazier M, Jasser S, Langford LA, Lee J, Mills GB, Pershouse MA, Pollack RE, Tornos C, Troncoso P, Yung WK, Fujii G, Berson A, Steck PA, et al. 1997. MMAC1/PTEN mutations in primary tumor specimens and tumor cell lines. Cancer Res 57:5221–5225.

Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA, Jr. 2003. The influence of Finasteride on the development of prostate cancer. N Engl J Med 349:215–224.

Tilley WD, Buchanan G, Hickey TE, Bentel JM. 1996. Mutations in the androgen receptor gene are associated with progression of human prostate cancer to androgen independence. Clin Cancer Res 2:277–285.

Torres-Rosado A, O'Shea KS, Tsuji A, Chou SH, Kurachi K. 1993. Hepsin, a putative cell-surface serine protease, is required for mammalian cell growth. Proc Natl Acad Sci USA 90:7181–7185.

True LD, Berger RE, Rothman I, Ross SO, Krieger JN. 1999. Prostate histopathology and the chronic prostatitis/chronic pelvic pain syndrome: A prospective biopsy study. J Urol 162:2014–2018.

Tsuji A, Torres-Rosado A, Arai T, Le Beau MM, Lemons RS, Chou SH, Kurachi K. 1991. Hepsin, a cell membrane-associated protease. Characterization, tissue distribution, and gene localization. J Biol Chem 266:16948–16953.

Tsujimoto Y, Takayama H, Nonomura N, Okuyama A, Aozasa K. 2002. Postatrophic hyperplasia of the prostate in Japan: Histologic and immunohistochemical features and *p53* gene mutation analysis. Prostate 52:279–287.

van der Kwast TH, Schalken J, Ruizeveld de Winter JA, van Vroonhoven CC, Mulder E, Boersma W, Trapman J. 1991. Androgen receptors in endocrine-therapy-resistant human prostate cancer. Int J Cancer 48:189–193.

van Leenders G, Dijkman H, Hulsbergen-van de Kaa C, Ruiter D, Schalken J. 2000. Demonstration of intermediate cells during human prostate epithelial differentiation in situ and in vitro using triple-staining confocal scanning microscopy. Lab Invest 80:1251–1258.

Van Leenders GJ, Gage WR, Hicks JL, Van Balken B, Aalders TW, Schalken JA, De Marzo AM. 2003. Intermediate cells in human prostate epithelium are enriched in proliferative inflammatory atrophy. Am J Pathol 162:1529–1537.

Varambally S, Dhanasekaran SM, Zhou M, Barrette TR, Kumar-Sinha C, Sanda MG, Ghosh D, Pienta KJ, Sewalt RG, Otte AP, Rubin MA, Chinnaiyan AM. 2002. The polycomb group protein EZH2 is involved in progression of prostate cancer. Nature 419:624–629.

Veldscholte J, Voorhorst-Ogink MM, Bolt-de Vries J, van Rooij HC, Trapman J, Mulder E. 1990. Unusual specificity of the androgen receptor in the human prostate tumor cell line LNCaP: High affinity for progestagenic and estrogenic steroids. Biochim Biophys Acta 1052:187–194.

Verhagen AP, Ramaekers FC, Aalders TW, Schaafsma HE, Debruyne FM, Schalken JA. 1992. Colocalization of basal and luminal cell-type cytokeratins in human prostate cancer. Cancer Res 52:6182–6187.

Visakorpi T, Hyytinen E, Koivisto P, Tanner M, Keinanen R, Palmberg C, Palotie A, Tammela T, Isola J, Kallioniemi OP. 1995. In vivo amplification of the androgen receptor gene and progression of human prostate cancer. Nat Genet 9:401–406.

Vivanco I, Sawyers CL. 2002. The phosphatidylinositol 3-kinase AKT pathway in human cancer. Nat Rev Cancer 2:489–501.

Voeller HJ, Augustus M, Madike V, Bova GS, Carter KC, Gelmann EP. 1997. Coding region of *NKX3.1*, a prostate-specific homeobox gene on 8p21, is not mutated in human prostate cancers. Cancer Res 57:4455–4459.

von Zglinicki T, Pilger R, Sitte N. 2000. Accumulation of single-strand breaks is the major cause of telomere shortening in human fibroblasts. Free Radic Biol Med 28:64–74.

Vukovic B, Park PC, Al-Maghrabi J, Beheshti B, Sweet J, Evans A, Trachtenberg J, Squire J. 2003. Evidence of multifocality of telomere erosion in high-grade prostatic intraepithelial neoplasia (HPIN) and concurrent carcinoma. Oncogene 22:1978–1987.

Waghray A, Schober M, Feroze F, Yao F, Virgin J, Chen YQ. 2001. Identification of differentially expressed genes by serial analysis of gene expression in human prostate cancer. Cancer Res 61:4283–4286.

Walker MG, Volkmuth W, Sprinzak E, Hodgson D, Klingler T. 1999. Prediction of gene function by genome-scale expression analysis: Prostate cancer-associated genes. Genome Res 9:1198–1203.

Wang SI, Parsons R, Ittmann M. 1998. Homozygous deletion of the PTEN tumor suppressor gene in a subset of prostate adenocarcinomas. Clin Cancer Res 4:811–815.

Wang JS, Shen X, He X, Zhu YR, Zhang BC, Wang JB, Qian GS, Kuang SY, Zarba A, Egner PA, Jacobson LP, Munoz A, Helzlsouer KJ, Groopman JD, Kensler TW. 1999. Protective alterations in phase 1 and 2 metabolism of aflatoxin B1 by oltipraz in residents of Qidong, People's Republic of China. J Natl Cancer Inst 91:347–354.

Wechter WJ, Leipold DD, Murray ED, Jr., Quiggle D, McCracken JD, Barrios RS, Greenberg NM. 2000. E-7869 (R-flurbiprofen) inhibits progression of prostate cancer in the TRAMP mouse. Cancer Res 60:2203–2208.

Weinstein MH, Signoretti S, Loda M. 2002. Diagnostic utility of immunohistochemical staining for p63, a sensitive marker of prostatic basal cells. Mod Pathol 15:1302–1308.

Welsh JB, Sapinoso LM, Su AI, Kern SG, Wang-Rodriguez J, Moskaluk CA, Frierson HF, Jr., Hampton GM. 2001. Analysis of gene expression identifies candidate markers and pharmacological targets in prostate cancer. Cancer Res 61:5974–5978.

Whittemore AS, Kolonel LN, Wu AH, John EM, Gallagher RP, Howe GR, Burch JD, Hankin J, Dreon DM, West DW, et al. 1995. Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the United States and Canada. J Natl Cancer Inst 87:652–661.

Wilson MJ, Ditmanson JV, Sinha AA, Estensen RD. 1990. Plasminogen activator activities in the ventral and dorsolateral prostatic lobes of aging Fischer 344 rats. Prostate 16:147–161.

Wu Q, Yu D, Post J, Halks-Miller M, Sadler JE, Morser J. 1998. Generation and characterization of mice deficient in hepsin, a hepatic transmembrane serine protease. J Clin Invest 101:321–326.

Xia Y, Zweier JL. 1997. Superoxide and peroxynitrite generation from inducible nitric oxide synthase in macrophages. Proc Natl Acad Sci USA 94:6954–6958.

Xu J, Stolk JA, Zhang X, Silva SJ, Houghton RL, Matsumura M, Vedvick TS, Leslie KB, Badaro R, Reed SG. 2000. Identification of differentially expressed genes in human prostate cancer using subtraction and microarray. Cancer Res 60:1677–1682.

Xu J, Zheng SL, Komiya A, Mychaleckyj JC, Isaacs SD, Hu JJ, Sterling D, Lange EM, Hawkins GA, Turner A, Ewing CM, Faith DA, Johnson JR, Suzuki H, Bujnovszky P,

Wiley KE, DeMarzo AM, Bova GS, Chang B, Hall MC, McCullough DL, Partin AW, Kassabian VS, Carpten JD, Bailey-Wilson JE, Trent JM, Ohar J, Bleecker ER, Walsh PC, Isaacs WB, Meyers DA. 2002a. Germline mutations and sequence variants of the macrophage scavenger receptor 1 gene are associated with prostate cancer risk. Nat Genet 32:321–325.

Xu J, Zheng SL, Turner A, Isaacs SD, Wiley KE, Hawkins GA, Chang BL, Bleecker ER, Walsh PC, Meyers DA, Isaacs WB. 2002b. Associations between hOGG1 sequence variants and prostate cancer susceptibility. Cancer Res 62:2253–2257.

Yaman O, Gogus C, Tulunay O, Tokatli Z, Ozden E. 2003. Increased prostate-specific antigen in subclinical prostatitis: The role of aggressiveness and extension of inflammation. Urol Int 71:160–164.

Yang RM, Naitoh J, Murphy M, Wang HJ, Phillipson J, deKernion JB, Loda M, Reiter RE. 1998. Low p27 expression predicts poor disease-free survival in patients with prostate cancer. J Urol 159:941–945.

Yang XJ, Wu CL, Woda BA, Dresser K, Tretiakova M, Fanger GR, Jiang Z. 2002. Expression of alpha-methylacyl-CoA racemase (P504S) in atypical adenomatous hyperplasia of the prostate. Am J Surg Pathol 26:921–925.

Yatani R, Chigusa I, Akazaki K, Stemmermann GN, Welsh RA, Correa P. 1982. Geographic pathology of latent prostatic carcinoma. Int J Cancer 29:611–616.

Yu IS, Chen HJ, Lee YS, Huang PH, Lin SR, Tsai TW, Lin SW. 2000. Mice deficient in hepsin, a serine protease, exhibit normal embryogenesis and unchanged hepatocyte regeneration ability. Thromb Haemost 84: 865–870.

Zegarra-Moro OL, Schmidt LJ, Huang H, Tindall DJ. 2002. Disruption of androgen receptor function inhibits proliferation of androgen-refractory prostate cancer cells. Cancer Res 62:1008–1013.

Zha S, Gage WR, Sauvageot J, Saria EA, Putzi MJ, Ewing CM, Faith DA, Nelson WG, De Marzo AM, Isaacs WB. 2001. Cyclooxygenase-2 is up-regulated in proliferative inflammatory atrophy of the prostate, but not in prostate carcinoma. Cancer Res 61:8617–8623.

Zhang Y, Talalay P, Cho CG, Posner GH. 1992. A major inducer of anticarcinogenic protective enzymes from broccoli: Isolation and elucidation of structure. Proc Natl Acad Sci USA 89:2399–2403.

Zhang Y, Kensler TW, Cho CG, Posner GH, Talalay P. 1994. Anticarcinogenic activities of sulforaphane and structurally related synthetic norbornyl isothiocyanates. Proc Natl Acad Sci USA 91:3147–3150.

Zhou A, Paranjape J, Brown TL, Nie H, Naik S, Dong B, Chang A, Trapp B, Fairchild R, Colmenares C, Silverman RH. 1997. Interferon action and apoptosis are defective in mice devoid of 2′,5′-oligoadenylate-dependent RNase L. EMBO J 16:6355–6363.

Zhou M, Jiang Z, Epstein JI. 2003a. Expression and diagnostic utility of alpha-methylacyl-CoA-racemase (P504S) in foamy gland and pseudohyperplastic prostate cancer. Am J Surg Pathol 27:772–778.

Zhou M, Shah R, Shen R, Rubin MA. 2003b. Basal cell cocktail (34betaE12 + p63) improves the detection of prostate basal cells. Am J Surg Pathol 27:365–371.