

REVIEW ARTICLE

MECHANISMS OF DISEASE

Prostate Cancer

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PROSTATE CANCER IS A LEADING CAUSE OF ILLNESS AND DEATH AMONG men in the United States and Western Europe. Autopsy series have revealed small prostatic carcinomas in up to 29 percent of men 30 to 40 years of age and 64 percent of men 60 to 70 years of age.¹ Moreover, the risk of prostate cancer is 1 in 6 and the risk of death due to metastatic prostate cancer is 1 in 30.² (Fig. 1 shows multiple foci of prostate cancer.) With widespread screening for prostate-specific antigen (PSA) and digital rectal examination, as well as early treatment of localized prostate cancer, however, the age-adjusted rates of death due to prostate cancer have begun to decrease.^{3,4} In 2002, an estimated 189,000 men received a diagnosis of prostate cancer, and there were an estimated 30,200 deaths due to prostate cancer.²

Dietary factors, lifestyle-related factors, and androgens have long been recognized as contributors to the risk of prostate cancer. During the past decade, molecular studies have provided unexpected clues as to how prostate cancers arise and progress. The identification and characterization of genes associated with inherited susceptibility to prostate cancer and of genes in prostate-cancer cells that tend to have somatic alterations hint that infection or inflammation of the prostate contributes to the development of prostate cancer. Newly recognized mechanisms by which environmental carcinogens might promote the progression of prostate cancer and new insights into the way in which androgen receptors modulate the phenotype of prostate-cancer cells have emerged. In this article, we review recent discoveries in the genetics of prostate cancer and in the acquired molecular defects that accumulate in prostatic-carcinoma cells.

DIET, LIFESTYLE, AND PROSTATE CANCER

In a study of the risk of cancer among 44,788 pairs of twins in Sweden, Denmark, and Finland,⁵ 42 percent of cases of prostate cancer (95 percent confidence interval, 29 to 50 percent) were attributed to inheritance, with the remainder most likely attributable to environmental factors. Epidemiologic evidence also supports a major contribution of environmental factors to the development of prostate cancer. The incidence of prostate cancer and mortality due to prostate cancer are high in the United States and Western Europe, with the highest rates among black men in the United States, whereas lower rates are more characteristic of Asia.⁶ The risk of prostate cancer among Asians increases when they immigrate to North America — again implicating the environment and lifestyle-related factors in causing prostate cancer in the United States.⁷⁻⁹

CARCINOGENS IN THE DIET

The lifestyle-related factor that represents the most likely culprit in the promotion of prostate cancer in the United States is diet. The typical U.S. diet is rich in animal fats and meats and poor in fruits and vegetables. In the Health Professionals Follow-up Study, a

prospective cohort study involving 51,529 men, increased total fat intake, animal fat intake, and consumption of red meat were associated with an increased risk of prostate cancer.¹⁰ The level of consumption of red meat was also correlated with the risk of prostate cancer in the Physicians' Health Study¹¹ and in a large cohort study in Hawaii.¹² Although the components of red meats that promote prostate cancer have not been identified, when meats are cooked at high temperatures or broiled on charcoal grills, heterocyclic aromatic amine and polycyclic aromatic hydrocarbon carcinogens form.¹³⁻¹⁶ One such heterocyclic amine carcinogen, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), causes prostate cancer when fed to rats.^{17,18}

DIETARY COMPONENTS THAT PROTECT AGAINST PROSTATE CANCER

Vegetables may protect against prostate cancer.¹⁹ In the Physicians' Health Study, high plasma levels of the antioxidant carotenoid lycopene, resulting from a high intake of tomatoes, have been associated with a reduced risk of prostate cancer.²⁰ In a recent clinical trial, men given tomato sauce-based pasta dishes for three weeks before radical prostatectomy had increased lycopene levels in the blood and the prostate, decreased oxidative genomic damage in leukocytes and prostate cells, and a reduction in the serum PSA level.²¹ Other antioxidants, such as vitamin E and selenium, may also reduce the risk of prostate cancer.²²⁻²⁴ A large clinical trial of supplementation with vitamin E and selenium to prevent prostate cancer has just been initiated.²⁵ High intake of cruciferous vegetables containing the chemoprotective isothiocyanate sulforaphane was correlated with a diminished risk of prostate cancer in a case-control study.²⁶ Sulforaphane prevents cancers in animal models by inducing the expression of carcinogen-detoxification enzymes that limit the cell and genomic damage caused by carcinogens.^{27,28} By increasing the expression of carcinogen-detoxification enzymes, sulforaphane can also act indirectly as an antioxidant.^{29,30}

INHERITED PROSTATE-CANCER-SUSCEPTIBILITY GENES

Studies in twins that compare the concordant occurrence of prostate cancer in monozygotic twins with that in dizygotic twins have consistently revealed a stronger hereditary component in the risk

of prostate cancer than in any other type of cancer in humans.^{5,31-33} In 1990, Steinberg et al. reported that men with prostate cancer were more likely than their spouses to report having an affected brother or father and estimated that the presence of one, two, or three affected family members increased the risk of prostate cancer in first-degree relatives by a factor of 2, 5, and 11, respectively, whereas the risk in a more distant relative was only marginally increased.³⁴ These findings have been confirmed by other studies.³⁵⁻⁴¹

Complex segregation analyses have suggested that rare autosomal dominant alleles account for a substantial proportion of cases of inherited, early-onset prostate cancer (defined as cancer occurring before 55 years of age).⁴²⁻⁴⁵ In families with men in whom prostate cancer is diagnosed at an older age, an X-linked allele may be responsible.^{46,47} The first molecular genetic study of familial prostate cancer in which polymorphic markers were used identified several regions of linkage; the chromosomal region 1q24-25, designated the locus of the hereditary prostate cancer (*HPC1*) gene, has been the most thoroughly investigated.⁴⁸ Some analyses have confirmed a link between *HPC1* and prostate cancer, but others have failed to detect an association.⁴⁹ In addition to *HPC1*, six other loci have received attention.⁵⁰⁻⁵⁵

RNASEL

The *RNASEL* gene encodes a widely expressed latent endoribonuclease that participates in an interferon-inducible RNA-decay pathway that is thought to degrade viral and cellular RNA.⁵⁶⁻⁶⁰ *RNASEL* has been linked to *HPC1*.⁶¹ In one family, four brothers with prostate cancer carried a disabling mutation of *RNASEL*, and in another family, four of six brothers with prostate cancer carried a base substitution affecting the *RNASEL* initiator methionine codon.⁶¹ In preliminary population studies, the *RNASEL* allele with a termination codon at amino acid position 265 was found in 0.54 percent of unaffected white men, and the allele with the defective initiator methionine codon was not detected in any unaffected men.⁶¹ The *RNASEL* allele with a termination codon at amino acid position 265 was also detected in 4.3 percent of Finnish men with familial prostate cancer and only 1.8 percent of control men.⁶² Another study identified a mutant *RNASEL* allele, with a deletion at codon 157, in an Ashkenazi Jewish population; this allele was present in 6.9 percent of the men with

prostate cancer and 2.9 percent of the elderly men without prostate cancer.⁶³ An increased risk of prostate cancer was also associated with yet another mutant RNASEL allele that encodes a less active enzyme.⁶⁴ A single study failed to detect any association between RNASEL alleles with inactivating mutations and prostate cancer.⁶⁵

MSR1

The macrophage-scavenger receptor 1 (MSR1) gene, located at 8p22, has also emerged as a candidate prostate-cancer-susceptibility gene.⁶⁶ It encodes subunits of a macrophage-scavenger receptor that is capable of binding a variety of ligands, including bacterial lipopolysaccharide and lipoteichoic acid, and oxidized high-density lipoprotein and low-density lipoprotein in the serum.⁶⁷ Germ-line MSR1 mutations have been linked to prostate cancer in some families with hereditary prostate cancer, and one mutant MSR1 allele has been detected in approximately 3 percent of men with nonhereditary prostate cancer but only 0.4 percent of unaffected men ($P=0.05$).^{66,68} Expression of MSR1 appears to be restricted to macrophages in the prostate that are abundant at sites of inflammation.

AR, CYP17, AND SRD5A2

Polymorphic variants of three genes involved in androgen action, the androgen-receptor (AR) gene, the cytochrome P-450c17 (CYP17) gene, and the steroid-5- α -reductase type II (SRD5A2) gene, have been implicated in modifying the risk of prostate cancer in genetic epidemiologic studies. In the case of AR, which encodes the androgen receptor, polymorphic polyglutamine (CAG) repeats have been described.⁶⁹ Functional studies have suggested that shorter polyglutamine repeats may be associated with increased androgen-receptor transcriptional transactivation activity.⁷⁰⁻⁷³ Black Americans, who have a relatively high risk of prostate cancer, tend to have shorter androgen-receptor polyglutamine repeats, whereas Asians, who have a relatively low risk of prostate cancer, tend to have longer androgen-receptor polyglutamine repeats. Several genetic epidemiologic studies have shown a correlation between an increased risk of prostate cancer and the presence of short androgen-receptor polyglutamine repeats, but other studies have failed to detect such a correlation.⁷⁴⁻⁸⁰ Polymorphic polyglycine (GGC) repeats are also characteristic of AR and may also influence the risk of prostate cancer.^{76,79-81}

Figure 1 (facing page). Multiple Foci of Proliferative Inflammatory Atrophy, High-Grade Prostatic Intraepithelial Neoplasia, and Prostatic Carcinoma in the Peripheral Zone of the Human Prostate.

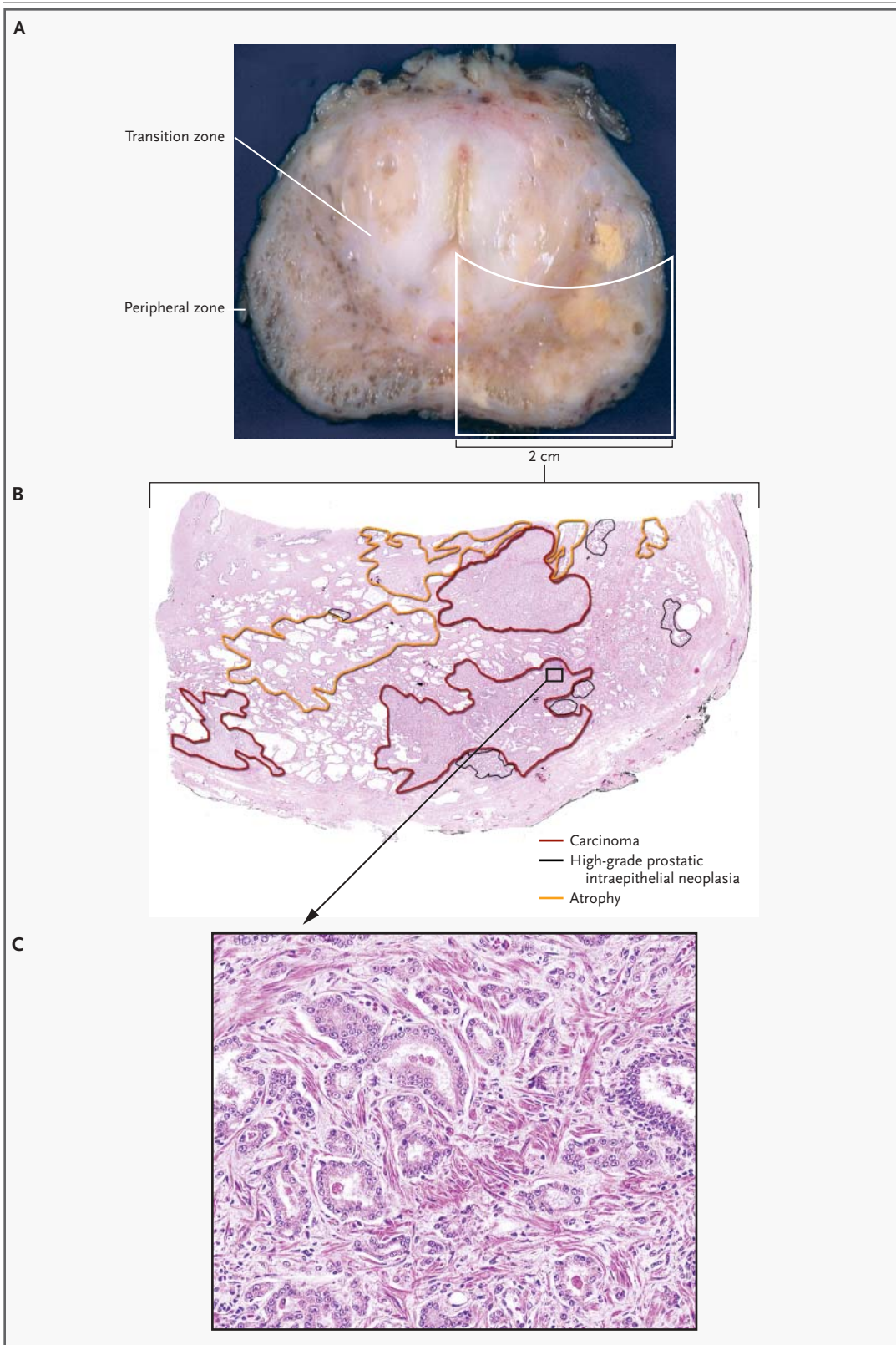
Panel A is a photograph of a single slice of a prostate from a radical prostatectomy. The transition zone, where most (>90 percent) benign prostatic hyperplasia develops, and the peripheral zone, where most (>70 percent) prostate cancer develops, are indicated. Areas with yellowish discoloration represent regions containing prostate cancer. Panel B is a low-magnification microscopical image of the region indicated in Panel A (hematoxylin and eosin). Panel C is a higher-magnification image of a prostate-cancer lesion (hematoxylin and eosin).

CYP17 encodes cytochrome P-450c17 α , an enzyme that catalyzes key reactions in sex-steroid biosynthesis. A variant CYP17 allele has been subjected to both population and genetic-linkage analyses to determine its association with prostate cancer, with inconsistent results.^{75,82-88} However, linkage data suggest that another variant CYP17 allele is associated with prostate cancer.⁸⁹

SRD5A2 encodes the predominant isozyme of 5- α -reductase in the prostate, an enzyme that converts testosterone to the more potent dihydrotestosterone. Two common polymorphic variant SRD5A2 alleles have been described.^{90,91} The alleles that encode enzymes with increased activity have been associated with an increased risk of prostate cancer and with a poor prognosis for men with prostate cancer.^{90,92} In addition to AR, CYP17, and SRD5A2, polymorphic variants of a number of other genes have been proposed as possible contributors to the risk of prostate cancer.⁹³

GENETIC SUSCEPTIBILITY TO PROSTATE CANCER

As we have seen, the genetics of the prostate have proved difficult to study. Prostate cancer, once generally diagnosed at an advanced stage in older men, is now more often detected at an early stage in younger men as a consequence of more widespread screening for the disease. This trend toward earlier diagnosis of prostate cancer has most likely changed the definition of a "case" of cancer, since many men who would have qualified as controls in previous genetic and epidemiologic studies are now known to have prostate cancer as a result of PSA screening. Despite these limitations, genetic studies have provided remarkable clues to the causes of prostate cancer. For example, in addition to the ex-



pected role of androgens in facilitating the development of prostate cancer, the possibility that viral or bacterial infections might lead to prostate cancer has been raised with the identification of RNASEL and MSR1 as familial prostate-cancer genes — an insight that will profoundly affect future studies of the etiology of prostate cancer and may ultimately lead to new approaches to the prevention of prostate cancer (Table 1).^{61,66,67,94}

abnormalities has been seen in different cases, in different lesions in the same case, and in different areas within the same lesion. Additional somatic genomic alterations appear to arise in association with the progression of prostate cancer.⁹⁶⁻¹⁰⁰ Mutations in the TP53 gene, which are present in a minority of primary prostate cancers, may undergo clonal selection in the process of progression to metastatic prostate cancer.^{101,102}

SOMATIC GENE DEFECTS
IN PROSTATE CANCER

At the time of diagnosis, prostate-cancer cells contain many somatic mutations, gene deletions, gene amplifications, chromosomal rearrangements, and changes in DNA methylation (Fig. 2 and Table 2). These alterations probably accumulate over a period of several decades.¹ The most commonly reported chromosomal abnormalities appear to be gains at 7p, 7q, 8q, and Xq, and losses at 8p, 10q, 13q, and 16q.⁹⁵ A striking heterogeneity in chromosomal

GSTP1

Hypermethylation of CpG island sequences encompassing the regulatory region of GSTP1, encoding the π -class glutathione S-transferase (GSTP), may link exposure to genome-damaging stress to increased genomic instability during prostatic carcinogenesis.¹⁰³⁻¹⁰⁶ In the normal prostate epithelium, GSTP1 is expressed in basal cells but not in columnar secretory cells, although the enzyme may be induced in columnar epithelial cells that are subjected to genome-damaging stresses. In contrast, the enzyme is rarely present in prostate-cancer cells.

Table 1. Prostate-Cancer–Susceptibility Genes.

Gene	Location	Alterations*	Phenotypic Consequences
RNASEL	1q24–25	Base substitutions leading to Met11le, Glu265X, and Arg462Gln alleles Four-base deletion at codon 157 leading to premature protein truncation at codon 164	Encodes endoribonuclease that participates in an interferon-inducible 2',5'-oligoadenylate-dependent RNA-decay pathway RNaseL ^{-/-} mice have diminished interferon- α antiviral activity
ELAC2	17p11	Base insertion leading to premature termination 67 amino acids after codon 157; base substitutions leading to Arg781His, Ser217Leu, and Ala541Thr alleles	Unknown
MSR1	8p22	Base substitutions leading to Arg293X, Pro36Ala, Ser41Tyr, Val113Ala, Asp174Tyr, Gly369Ser, and His441Arg alleles	Encodes subunits of class A macrophage-scavenger receptor Msr-A ^{-/-} mice have an increased sensitivity to serious infection with <i>Listeria monocytogenes</i> , <i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , and herpes simplex virus type 1
AR	Xq11–12	Polymorphic polyglutamine (CAG) and polyglycine (GGC) repeats	Encodes androgen receptor, an androgen-dependent transcription factor Different polymorphic alleles may be associated with different transcriptional transactivation activities
CYP17	10q24.3	Base substitution in transcriptional promoter (T→C transition leading to new Sp1 recognition site)	Encodes cytochrome P-450c17 α , an enzyme that catalyzes key reactions in sex-steroid biosynthesis
SRD5A2	2p23	Base substitutions leading to Val89Leu and Ala49Thr alleles	Encodes the predominant 5- α -reductase in the prostate, converts testosterone to dihydrotestosterone

* X denotes a nonsense mutation.

In more than 90 percent of cases of prostate cancer, the absence of GSTP1 in prostate-cancer cells can be attributed to hypermethylation of the CpG island sequences in GSTP1, a somatic change that prevents the transcription of GSTP1.¹⁰⁵ The absence of GSTP1 and hypermethylation of CpG island sequences of GSTP1 are also characteristic of cells in lesions of prostatic intraepithelial neoplasia, which are thought to be precursors of prostate cancer.¹⁰⁷

Although cells carrying inactivated GSTP1 alleles accumulate during the development of prostate cancer, GSTP1 does not appear to act as a tumor-suppressor gene.¹⁰⁵ Instead, GSTP1 probably serves as a “caretaker” gene,¹⁰⁸ defending prostate cells against genomic damage mediated by carcinogens, such as PhIP, found in well-done or charred meats, or various oxidants, found at sites of inflammation (Fig. 3).^{17,18,109} Cultured cells from a prostate-cancer line (LNCaP) that have been modified to express GSTP1 form substantially fewer promutagenic PhIP–DNA adducts on exposure to metabolically activated PhIP than do unmodified LNCaP cells.¹⁰⁹ GSTP1-expressing LNCaP prostate-cancer cells also form fewer oxidized DNA bases on exposure to oxidant stresses than do unmodified LNCaP cells; however, in response to oxidant stress, unmodified LNCaP prostate-cancer cells survive better than do LNCaP prostate-cancer cells that have been modified to express high levels of GSTP1 (unpublished data). This curious tolerance to oxidative genomic damage associated with the loss of the caretaker function of GSTP1 may underlie the apparent preferential growth of cells with inactivated GSTP1 alleles during carcinogenesis in the prostate.

NKX3.1

No “gatekeeper” genes for the development of prostate cancer, analogous to the adenomatous polyposis coli (APC) gene in colorectal cancer, have been confidently identified.¹⁰⁸ NKX3.1, located at 8p21, encodes a prostate-specific homeobox gene that is likely to be essential for normal prostate development and is therefore a candidate gatekeeper gene.^{110,111} NKX3.1 binds DNA and represses expression of the PSA gene.^{112,113} Mice carrying one or two disrupted *Nkx3.1* alleles manifest prostatic epithelial hyperplasia and dysplasia.^{114,115} In men, the loss of 8p21 DNA sequences occurs early during prostatic carcinogenesis, with 63 percent of lesions of prostatic intraepithelial neoplasia, and more than 90 percent of prostate cancers, showing a loss of heterozygosity at polymorphic 8p21 marker se-

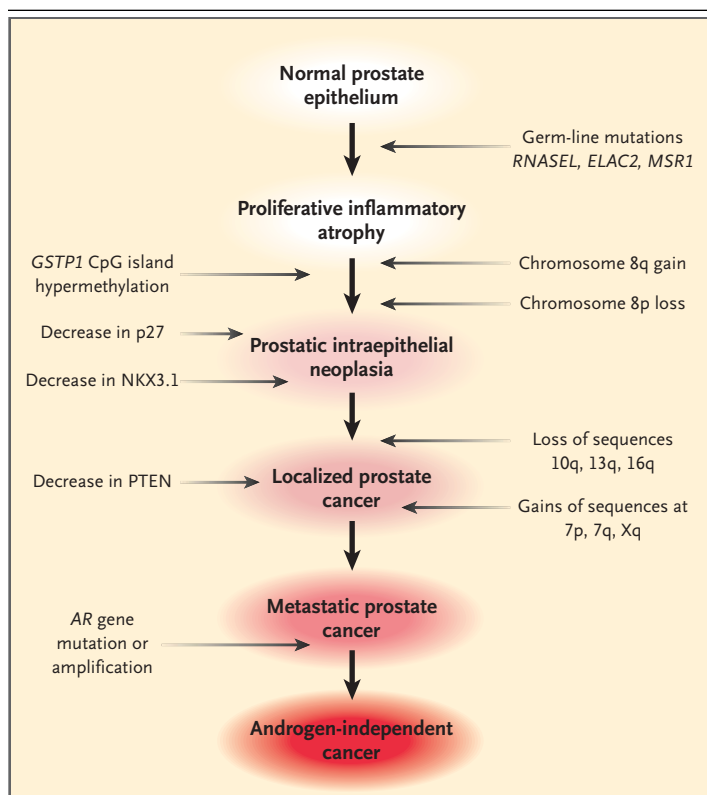


Figure 2. The Molecular Pathogenesis of Prostate Cancer.

quences.¹¹⁶ Although mapping studies have indicated that NKX3.1 lies within a common region of deletion at 8p21 in prostate cancer, molecular analyses have not yet established NKX3.1 as a somatic target for inactivation during prostatic carcinogenesis—principally because, although one of two NKX3.1 alleles is frequently deleted in prostate-cancer DNA, somatic mutations have not been detected at the remaining allele.^{117–119} Nonetheless, the loss of NKX3.1 expression does appear to be related to the progression of prostate cancer. One study found that NKX3.1 was absent in 20 percent of lesions of prostatic intraepithelial neoplasia, 6 percent of low-stage prostate cancers, 22 percent of high-stage prostate cancers, 34 percent of androgen-independent prostate cancers, and 78 percent of prostate-cancer metastases.¹²⁰

PTEN

The gene for phosphatase and tensin homologue (PTEN), a tumor-suppressor gene encoding a phosphatase active against both proteins and lipid substrates, is a common target for somatic alteration

Table 2. Somatic Gene Alterations in Prostate Cancers.*

Gene	Location	Alterations	Phenotypic Consequences
<i>GSTP1</i>	11q13	CpG island hypermethylation (decreased expression)	Encodes carcinogen-detoxification enzyme <i>Gstp1/2^{-/-}</i> mice show increased skin tumorigenesis when exposed to topical carcinogen
<i>NKX3.1</i>	8p21	Allelic losses (decreased expression)	Encodes a prostate-specific homeobox gene essential for normal prostate development <i>Nkx3.1^{+/-}</i> and <i>Nkx3.1^{-/-}</i> mice manifest prostatic hyperplasia and dysplasia
<i>PTEN</i>	10q23.31	Allelic losses, mutations, probable CpG island hypermethylation (decreased expression, function, or both)	Encodes a phosphatase active against protein and lipid substrates <i>Pten^{+/-}</i> mice have prostatic hyperplasia and dysplasia Prostatic intraepithelial neoplasia develops in <i>Pten^{+/-}Nkx3.1^{+/-}</i> and <i>Pten^{+/-}Nkx3.1^{-/-}</i> mice Prostate cancer with a poor prognosis develops in <i>Pten^{+/-}-TRAMP</i> mice
<i>CDKN1B</i>	12p12–13	Allelic losses (decreased expression)	Encodes p27, a cyclin-dependent kinase inhibitor <i>Cdkn1b^{-/-}</i> mice have prostatic hyperplasia Prostate cancer develops in <i>Pten^{+/-}-Cdkn1b^{-/-}</i> mice
<i>AR</i>	Xq11–12	Amplification, mutations (increased expression, altered function)	Encodes androgen receptor <i>Pb-mAR</i> transgenic mice have prostatic hyperplasia, and prostatic intraepithelial neoplasia develops in them

* TRAMP denotes transgenic mice with prostate cancer.

during the progression of prostate cancer (Fig. 4).^{121–130} PTEN is present in normal epithelial cells and in cells in prostatic intraepithelial neoplasia.¹³¹ In prostate cancers, the level of PTEN is frequently reduced, particularly in cancers of a high grade or stage.¹³¹ Furthermore, in prostate cancers that do contain PTEN, a considerable heterogeneity in levels, with regions that are devoid of PTEN, has been described.¹³¹ In a study of prostate-cancer metastases recovered at autopsy, somatic *PTEN* alterations were more common than they are in primary prostate cancers, and heterogeneity in the *PTEN* defects in different metastatic deposits in the same patient was also evident.¹²⁹

Somatic allelic losses in both *PTEN* and *NKX3.1* appear to be common in prostate cancers, but somatic alterations affecting the remaining alleles are not frequent. Nonetheless, haploinsufficiency for *PTEN* and *NKX3.1* may promote abnormal proliferation of prostate cells. Although mice that are heterozygous for *Nkx3.1* and mice that are heterozygous for *Pten* display prostatic hyperplasia and dysplasia, crossbreeding of these mice yields offspring that are heterozygous for *Pten* with zero or one *Nkx3.1* allele; in all these offspring, prostatic

intraepithelial neoplasia develops.^{114,132–134} The mechanism by which PTEN might act as a tumor suppressor in the prostate and elsewhere may involve the inhibition of the phosphatidylinositol 3'-kinase–protein kinase B (PI3K–Akt) signaling pathway that is essential for cell-cycle progression and cell survival.^{135–138}

CDKN1B

Reduced levels of p27, a cyclin-dependent kinase inhibitor encoded by the *CDKN1B* gene, also are common in prostate cancers, particularly in prostate cancers with a poor prognosis.^{139–144} The basis for the low p27 levels is unknown, although the somatic loss of DNA sequences at 12p12–13, encompassing *CDKN1B*, has been described in 23 percent of localized prostate cancers, 30 percent of metastases of prostate cancer in regional lymph nodes, and 47 percent of distant metastases of prostate cancer.¹⁴⁵ Levels of p27 are suppressed by the PI3K–Akt signaling pathway.^{136,138,146,147} By inhibiting PI3K–Akt, PTEN can increase the levels of *CDKN1B* messenger RNA and p27 protein.¹⁴⁸ For this reason, low p27 levels may be as much a result of the loss of PTEN function as of *CDKN1B* alterations.

These interactions have been recapitulated in a mouse model: although the targeted disruption of *Cdkn1b* leads only to prostatic hyperplasia, prostate cancer develops by three months of age in mice that are heterozygous for *Pten* and have no *Cdkn1b* alleles.^{142,149}

AR

Metastatic prostate cancer is usually treated with androgen suppression, antiandrogens, or a combination of the two.¹⁵⁰⁻¹⁵² Despite an initial response, progression is inevitable, because of the emergence of androgen-independent prostate-cancer cells. In most androgen-independent prostate cancers, expression of the receptor and many aspects of its function are maintained (Fig. 5).¹⁵⁴⁻¹⁵⁷ There is evidence that receptors drive the proliferation of androgen-independent prostate-cancer cells even in the absence of androgens.¹⁵⁸ Many somatic alterations of AR have been detected in prostate cancers, especially in those that progress despite hormonal treatment.¹⁵⁹⁻¹⁷² AR amplification, accompanied by overexpression of androgen receptors, may promote the growth of androgen-independent prostate-cancer cells by increasing the sensitivity of prostate-cancer cells to low levels of circulating androgens.¹⁶⁰ In many AR mutations, the ligand-specificity of the receptor can be altered, permitting activation by nonandrogens or even by antiandrogens.¹⁷³⁻¹⁷⁵ In a recent analysis of 44 mutant androgen receptors from prostate cancers, 16 percent had a loss of function, 7 percent maintained wild-type function, 32 percent demonstrated partial function, and 45 percent displayed a gain of function.¹⁷⁶ In the absence of AR mutations, androgen-independent prostate cancer may progress through the activation of ligand-independent androgen-receptor signaling pathways.¹⁷⁷⁻¹⁸⁰

A MOLECULAR DESCRIPTION OF THE PROSTATE-CANCER CELL

The identification of key molecular alterations in prostate-cancer cells implicates carcinogen defenses (GSTP1), growth-factor–signaling pathways (NKX3.1, PTEN, and p27), and androgens (AR) as critical determinants of the phenotype of prostate-cancer cells and defines specific targets for the detection, diagnosis, and treatment of prostate cancer. Although the drugs that are currently in use for the treatment of prostate cancer disrupt androgen action, in the future, new drugs that interfere with other growth-signaling pathways will be pursued.¹³⁰

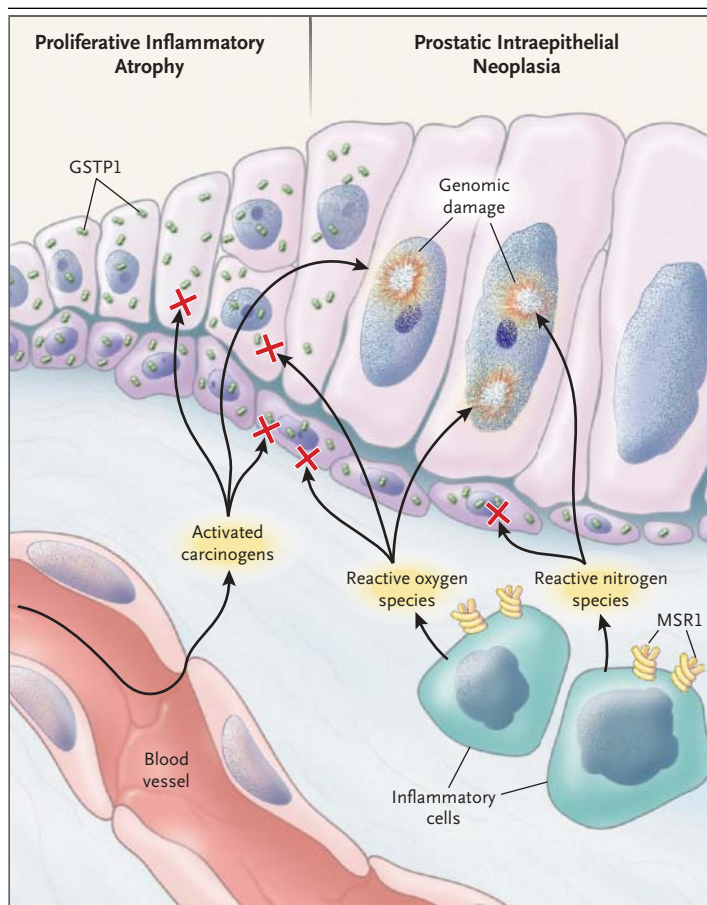


Figure 3. Loss of GSTP1 Caretaker Activity in Prostate Cells and Increased Vulnerability to Genomic Damage Mediated by Carcinogens.

Dietary carcinogens, activated by liver cytochrome P-450 enzymes, and oxidant carcinogens, elaborated by inflammatory cells (shown expressing the trimeric macrophage-scavenger receptor MSR1), can be detoxified in basal epithelial cells and in cells of proliferative inflammatory atrophy by the π -class glutathione S-transferase (GSTP1, shown as a dimer). Cells of prostatic intraepithelial neoplasia, devoid of GSTP1, undergo genomic damage mediated by such carcinogens. A red X indicates interception and detoxification of carcinogens.

PROSTATIC INFLAMMATION AND PROSTATIC CARCINOGENESIS

Chronic or recurrent inflammation probably has a role in the development of many types of cancer in humans, including prostate cancer.¹⁸¹ Symptomatic prostatitis occurs in 9 percent or more of men between 40 and 79 years of age; about half of these men have more than one episode of prostatitis by 80 years of age.¹⁸² The prevalence of asymptomatic prostatitis is not known.^{183,184} In most cases, no causal infectious agent can be identified, which

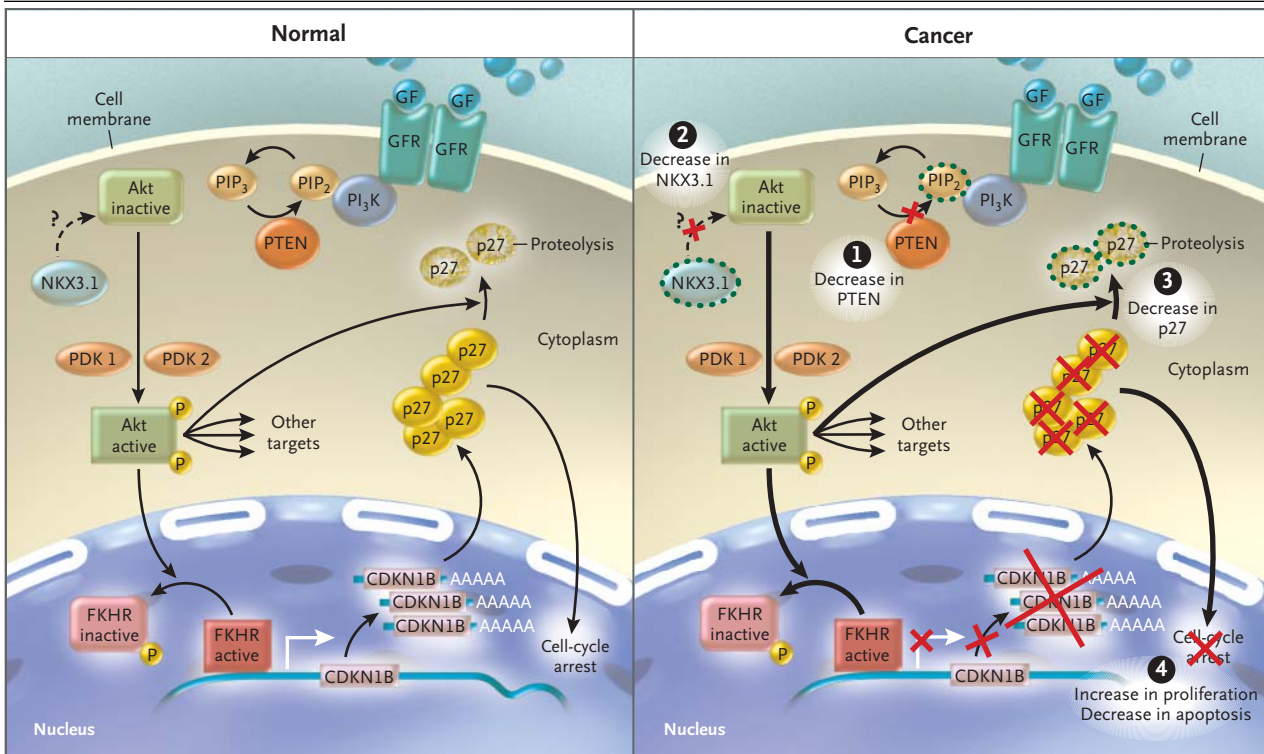


Figure 4. Molecular Events in the Pathogenesis of Prostate Cancer.

In the normal prostate, NKX3.1, PTEN, and p27 regulate the growth and survival of prostate cells. Inadequate levels of PTEN (1) and NKX3.1 (2) lead to a reduction in p27 levels (3) by a variety of mechanisms and to increased proliferation and decreased apoptosis (4). GF denotes growth factor, GFR growth-factor receptor, PIP₃ phosphatidylinositol 3,4,5-triphosphate, PIP₂ phosphatidylinositol 4,5-diphosphate, PI₃K phosphatidylinositide 3-OH kinase, PTEN phosphatase and tensin homologue, Akt protein kinase B, PDK1 3-phosphoinositide-dependent protein kinase-1, PDK2 3-phosphoinositide-dependent protein kinase-2, and FKHR forkhead transcription factor. A red X indicates blocked processes and molecules that have not been produced, a dotted outline reduced levels of molecules, and an A the poly-A tail of messenger RNA. The question mark and dotted arrow in the left-hand panel represent the suspicion, not yet proven, that NKX3.1 interacts directly with Akt.

makes it difficult to link symptomatic or asymptomatic prostatitis with prostate cancer in epidemiologic studies. However, an increased risk of prostate cancer has been associated with sexually transmitted infections, regardless of the pathogen, suggesting that inflammation, rather than infection, initiates prostatic carcinogenesis.^{185,186}

Inflammatory cells elaborate numerous microbicidal oxidants that might cause cellular or genomic damage in the prostate.^{187,188} The decreased risk of prostate cancer associated with the intake of antioxidants or nonsteroidal antiinflammatory drugs is consistent with this possibility.^{20,22-24,189-191} Two of the candidate prostate-cancer-susceptibility genes identified thus far, RNASEL and MSR1, encode proteins with critical functions in host responses to infections.^{61,66,67,94}

PROLIFERATIVE INFLAMMATORY ATROPHY

In 1999, De Marzo et al. proposed that a prostatic lesion called proliferative inflammatory atrophy is a precursor to prostatic intraepithelial neoplasia and prostate cancer (Fig. 6).¹⁹² Focal areas of epithelial atrophy have long been noticed in the prostate and have been thought to be important in prostatic carcinogenesis.^{181,193} Such atrophic areas, containing proliferative epithelial cells that fail to differentiate into columnar secretory cells, tend to occur in the periphery of the prostate, where prostate cancers most commonly arise.^{153,192,194} The term “proliferative inflammatory atrophy” applies to focal atrophic lesions that are associated with chronic inflammation and are often directly adjacent to lesions of prostatic intraepithelial neoplasia, prostate cancers, or both.^{153,192,195,196} Somatic genomic abnor-

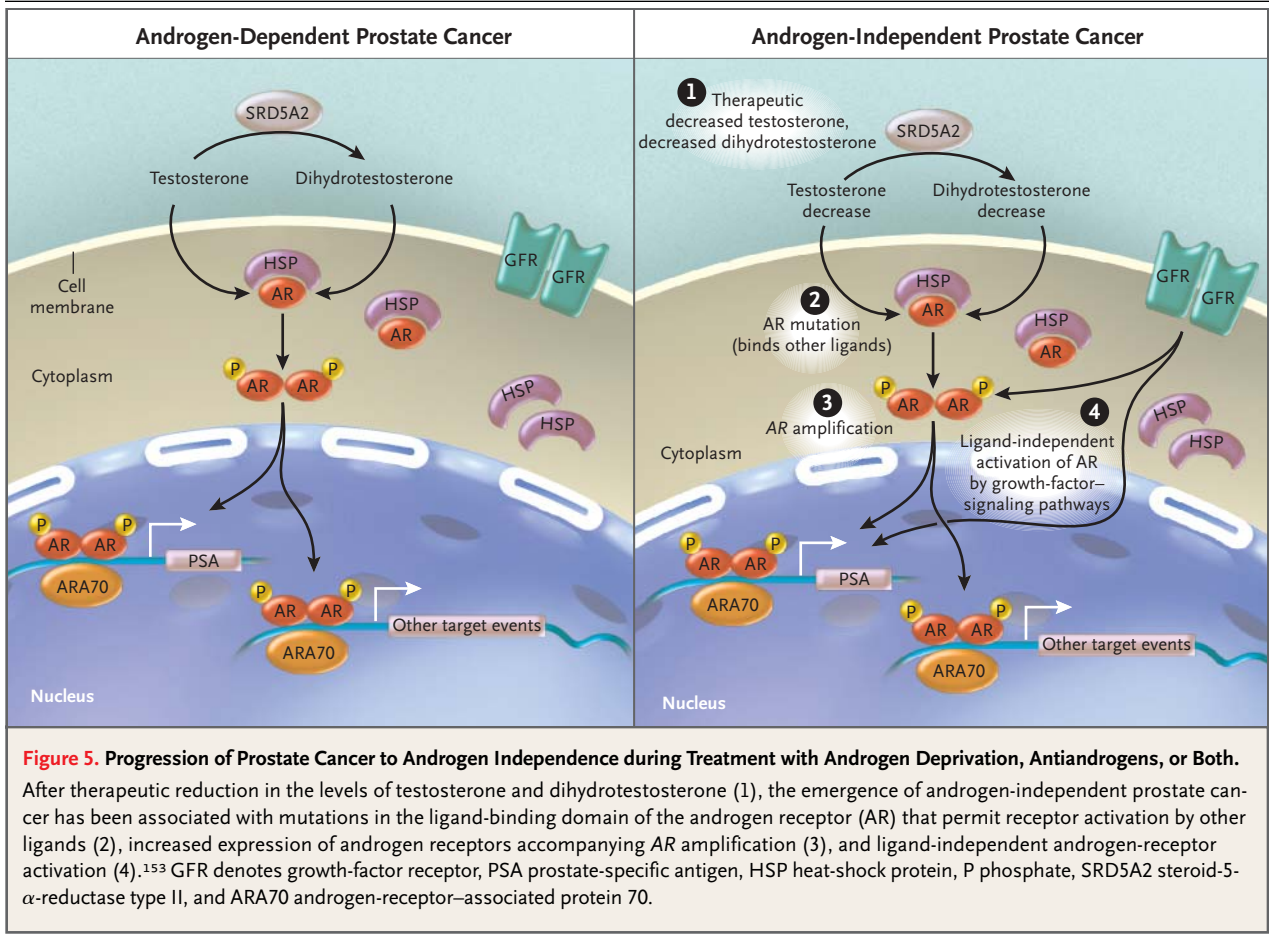


Figure 5. Progression of Prostate Cancer to Androgen Independence during Treatment with Androgen Deprivation, Antiandrogens, or Both. After therapeutic reduction in the levels of testosterone and dihydrotestosterone (1), the emergence of androgen-independent prostate cancer has been associated with mutations in the ligand-binding domain of the androgen receptor (AR) that permit receptor activation by other ligands (2), increased expression of androgen receptors accompanying AR amplification (3), and ligand-independent androgen-receptor activation (4).¹⁵³ GFR denotes growth-factor receptor, PSA prostate-specific antigen, HSP heat-shock protein, P phosphate, SRD5A2 steroid-5- α -reductase type II, and ARA70 androgen-receptor-associated protein 70.

malities, similar to those in cells of prostatic intraepithelial neoplasia and prostate-cancer cells, have been found in cells in proliferative inflammatory atrophy.¹⁹⁶

The frequent association of lesions of proliferative inflammatory atrophy with chronic inflammation suggests that these lesions arise as a consequence of the regenerative proliferation of prostate epithelial cells in response to injury caused by inflammatory oxidants.¹⁹² Epithelial cells in lesions of proliferative inflammatory atrophy show many molecular signs of stress, such as high levels of GSTP1, glutathione S-transferase A1 (GSTA1), and cyclooxygenase-2 (COX-2).^{192,197,198} Loss of GSTP1, probably as a result of hypermethylation of the CpG island sequences of GSTP1, may define the transition between proliferative inflammatory atrophy and prostatic intraepithelial neoplasia or prostate cancer.^{105,107,195} Prostatic inflammation,

accompanied by focal epithelial atrophy, may also contribute to the development of prostate cancer in rats.^{199,200}

SUMMARY

Genes, dietary factors, and lifestyle-related factors contribute to the development of prostate cancer. Two inherited susceptibility genes, RNASEL and MSR1, may have roles in responses to infections, raising the possibility that prostate infection or inflammation initiates prostatic carcinogenesis. A new prostate-cancer-precursor lesion, proliferative inflammatory atrophy, may be another link between prostatic inflammation and prostate cancer. Loss of the GSTP1 caretaker function, as cells of proliferative inflammatory atrophy give rise to cells of prostatic intraepithelial neoplasia and to prostate-cancer cells, increases the prostate's vulnera-

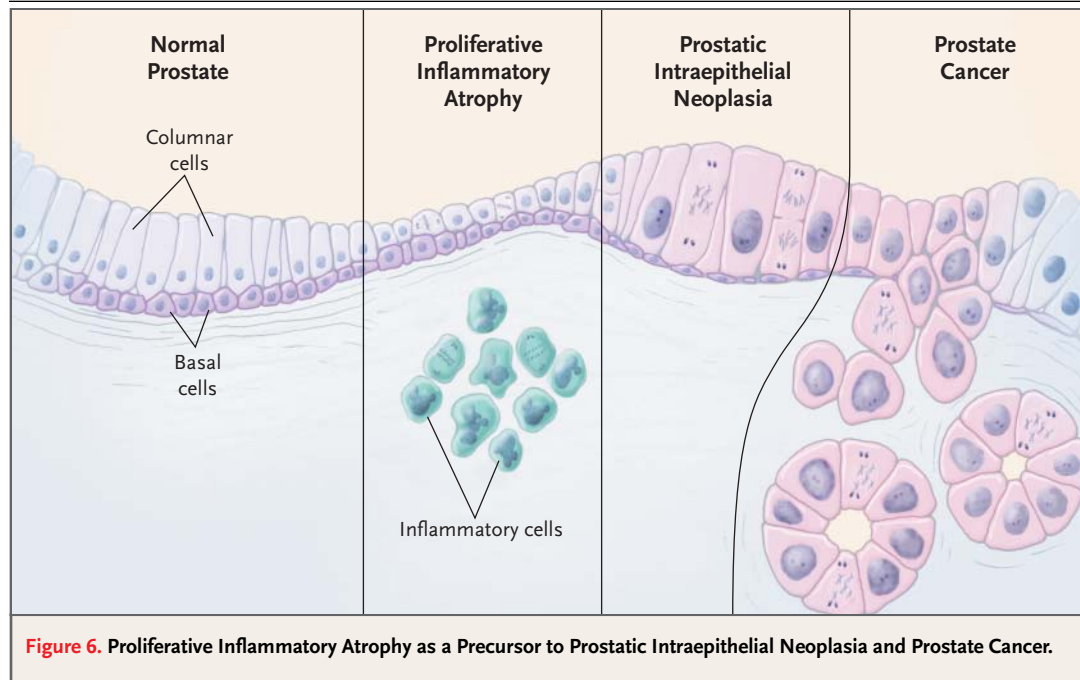


Figure 6. Proliferative Inflammatory Atrophy as a Precursor to Prostatic Intraepithelial Neoplasia and Prostate Cancer.

bility to genomic damage caused by inflammatory oxidants and dietary carcinogens. Somatic targets of genomic damage include *NKX3.1*, a candidate gatekeeper gene, as well as *PTEN* and *AR*, genes that may modulate the progression of prostate cancer. Inherited polymorphic variants of genes mediating androgen action, *AR*, *CYP17*, and *SRD5A2*, also influ-

ence the development and progression of prostate cancer.

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REFERENCES

1. Sakr WA, Grignon DJ, Crissman JD, et al. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20-69: an autopsy study of 249 cases. *In Vivo* 1994;8:439-43.
2. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. *CA Cancer J Clin* 2002;52:23-47. [Errata, *CA Cancer J Clin* 2002;52:119, 181-2.]
3. Hankey BF, Feuer EJ, Clegg LX, et al. Cancer surveillance series: interpreting trends in prostate cancer. I. Evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. *J Natl Cancer Inst* 1999;91:1017-24.
4. Bartsch G, Horninger W, Klocker H, et al. Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria. *Urology* 2001;58:417-24.
5. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer — analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000;343:78-85.
6. Hsing AW, Tsao L, Devesa SS. International trends and patterns of prostate cancer incidence and mortality. *Int J Cancer* 2000;85:60-7.
7. Whittemore AS, Kolonel LN, Wu AH, et al. 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* 1995;87:652-61.
8. Haenszel W, Kurihara M. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *J Natl Cancer Inst* 1968;40:43-68.
9. Shimizu H, Ross RK, Bernstein L, Yatsuni R, Henderson BE, Mack TM. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. *Br J Cancer* 1991;63:963-6.
10. Giovannucci E, Rimm EB, Colditz GA, et al. A prospective study of dietary fat and risk of prostate cancer. *J Natl Cancer Inst* 1993;85:1571-9.
11. Gann PH, Hennekens CH, Sacks FM, Grodstein F, Giovannucci EL, Stampfer MJ. Prospective study of plasma fatty acids and risk of prostate cancer. *J Natl Cancer Inst* 1994;86:281-6. [Erratum, *J Natl Cancer Inst* 1994;86:728.]
12. Le Marchand L, Kolonel LN, Wilkens LR, Myers BC, Hirohata T. Animal fat consumption and prostate cancer: a prospective study in Hawaii. *Epidemiology* 1994;5:276-82.
13. Gross GA, Turesky RJ, Fay LB, Stillwell WG, Skipper PL, Tannenbaum SR. Heterocyclic aromatic amine formation in grilled bacon, beef and fish and in grill scrapings. *Carcinogenesis* 1993;14:2313-8.
14. Morgenthaler PM, Holzhauser D. Analysis of mutations induced by 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in human lymphoblastoid cells. *Carcinogenesis* 1995;16:713-8.
15. Knize MG, Salmon CP, Mehta SS, Felton JS. Analysis of cooked muscle meats for heterocyclic aromatic amine carcinogens. *Mutat Res* 1997;376:129-34.
16. Lijinsky W, Shubik P. Benzo(a)pyrene and other polynuclear hydrocarbons in charcoal-broiled meat. *Science* 1964;145:53-5.

17. Stuart GR, Holcroft J, de Boer JG, Glickman BW. Prostate mutations in rats induced by the suspected human carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine. *Cancer Res* 2000;60:266-8.
18. Shirai T, Sano M, Tamano S, et al. The prostate: a target for carcinogenicity of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) derived from cooked foods. *Cancer Res* 1997;57:195-8.
19. Chan JM, Giovannucci EL. Vegetables, fruits, associated micronutrients, and risk of prostate cancer. *Epidemiol Rev* 2001;23:82-6.
20. Gann PH, Ma J, Giovannucci E, et al. Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. *Cancer Res* 1999;59:1225-30.
21. Chen L, Stacewicz-Sapuntzakis M, Duncan C, et al. Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. *J Natl Cancer Inst* 2001;93:1872-9.
22. Clark LC, Dalkin B, Krongrad A, et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol* 1998;81:730-4.
23. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. *JAMA* 1996;276:1957-63. [Erratum, *JAMA* 1997;277:1520.]
24. Heinonen OP, Albanes D, Virtamo J, et al. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *J Natl Cancer Inst* 1998;90:440-6.
25. Hoque A, Albanes D, Lippman SM, et al. Molecular epidemiologic studies within the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *Cancer Causes Control* 2001;12:627-33.
26. Cohen JH, Kristal AR, Stanford JL. Fruit and vegetable intakes and prostate cancer risk. *J Natl Cancer Inst* 2000;92:61-8.
27. Zhang Y, Kensler TW, Cho CG, Posner GH, Talalay P. Anticarcinogenic activities of sulforaphane and structurally related synthetic norbornyl isothiocyanates. *Proc Natl Acad Sci U S A* 1994;91:3147-50.
28. Zhang Y, Talalay P, Cho CG, Posner GH. A major inducer of anticarcinogenic protective enzymes from broccoli: isolation and elucidation of structure. *Proc Natl Acad Sci U S A* 1992;89:2399-403.
29. Dinkova-Kostova AT, Talalay P. Persuasive evidence that quinone reductase type 1 (DT diaphorase) protects cells against the toxicity of electrophiles and reactive forms of oxygen. *Free Radic Biol Med* 2000;29:231-40.
30. Gao X, Dinkova-Kostova AT, Talalay P. Powerful and prolonged protection of human retinal pigment epithelial cells, keratinocytes, and mouse leukemia cells against oxidative damage: the indirect antioxidant effects of sulforaphane. *Proc Natl Acad Sci U S A* 2001;98:15221-6.
31. Page WF, Braun MM, Partin AW, Caporaso N, Walsh P. Heredity and prostate cancer: a study of World War II veteran twins. *Prostate* 1997;33:240-5.
32. Ahlbom A, Lichtenstein P, Malmstrom H, Feychting M, Hemminki K, Pedersen NL. Cancer in twins: genetic and nongenetic familial risk factors. *J Natl Cancer Inst* 1997;89:287-93.
33. Gronberg H, Damber L, Damber JE. Studies of genetic factors in prostate cancer in a twin population. *J Urol* 1994;152:1484-9.
34. Steinberg GD, Carter BS, Beaty TH, Childs B, Walsh PC. Family history and the risk of prostate cancer. *Prostate* 1990;17:337-47.
35. Morganti G, Gianferrari L, Cresseri A, Arrigoni G, Lovati G. Recherches clinico-statistiques et génétiques sur les néoplasies de la prostate. *Acta Genet Stat Med* 1956;6:304-5.
36. Lesko SM, Rosenberg L, Shapiro S. Family history and prostate cancer risk. *Am J Epidemiol* 1996;144:1041-7.
37. Ghadirian P, Howe GR, Hislop TG, Maisonneuve P. Family history of prostate cancer: a multi-center case-control study in Canada. *Int J Cancer* 1997;70:679-81.
38. Glover FE Jr, Coffey DS, Douglas LL, et al. Familial study of prostate cancer in Jamaica. *Urology* 1998;52:441-3.
39. Rodriguez C, Calle EE, Miracle-McMahill HL, et al. Family history and risk of fatal prostate cancer. *Epidemiology* 1997;8:653-7.
40. Whittemore AS, Wu AH, Kolonel LN, et al. Family history and prostate cancer risk in black, white, and Asian men in the United States and Canada. *Am J Epidemiol* 1995;141:732-40.
41. Spitz MR, Currier RD, Fueger JJ, Babian RJ, Newell GR. Familial patterns of prostate cancer: a case-control analysis. *J Urol* 1991;146:1305-7.
42. Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC. Mendelian inheritance of familial prostate cancer. *Proc Natl Acad Sci U S A* 1992;89:3367-71.
43. Gronberg H, Damber L, Damber JE, Iseilius L. Segregation analysis of prostate cancer in Sweden: support for dominant inheritance. *Am J Epidemiol* 1997;146:552-7.
44. Schaid DJ, McDonnell SK, Blute ML, Thibodeau SN. Evidence for autosomal dominant inheritance of prostate cancer. *Am J Hum Genet* 1998;62:1425-38.
45. Verhage BA, Baffoe-Bonnie AB, Baglietto L, et al. Autosomal dominant inheritance of prostate cancer: a confirmatory study. *Urology* 2001;57:97-101.
46. Cui J, Staples MP, Hopper JL, English DR, McCredie MR, Giles GG. Segregation analyses of 1,476 population-based Australian families affected by prostate cancer. *Am J Hum Genet* 2001;68:1207-18.
47. Monroe KR, Yu MC, Kolonel LN, et al. Evidence of an X-linked or recessive genetic component to prostate cancer risk. *Nat Med* 1995;1:827-9.
48. Smith JR, Freije D, Carpten JD, et al. Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. *Science* 1996;274:1371-4.
49. Ostrander EA, Stanford JL. Genetics of prostate cancer: too many loci, too few genes. *Am J Hum Genet* 2000;67:1367-75.
50. Berthon P, Valeri A, Cohen-Akenine A, et al. Predisposing gene for early-onset prostate cancer, localized on chromosome 1q42.2-43. *Am J Hum Genet* 1998;62:1416-24.
51. Gibbs M, Stanford JL, McIndoe RA, et al. Evidence for a rare prostate cancer-susceptibility locus at chromosome 1p36. *Am J Hum Genet* 1999;64:776-87.
52. Xu J, Meyers D, Freije D, et al. Evidence for a prostate cancer susceptibility locus on the X chromosome. *Nat Genet* 1998;20:175-9.
53. Berry R, Schroeder JJ, French AJ, et al. Evidence for a prostate cancer-susceptibility locus on chromosome 20. *Am J Hum Genet* 2000;67:82-91.
54. Tavtigian SV, Simard J, Teng DH, et al. A candidate prostate cancer susceptibility gene at chromosome 17p. *Nat Genet* 2001;27:172-80.
55. Xu J, Zheng SL, Hawkins GA, et al. Linkage and association studies of prostate cancer susceptibility: evidence for linkage at 8p22-23. *Am J Hum Genet* 2001;69:341-50.
56. Silverman RH, Jung DD, Nolan-Sorden NL, Dieffenbach CW, Kedar VP, SenGupta DN. Purification and analysis of murine 2-5A-dependent RNase. *J Biol Chem* 1988;263:7336-41.
57. Jacobsen H, Czarniecki CW, Krause D, Friedman RM, Silverman RH. Interferon-induced synthesis of 2-5A-dependent RNase in mouse JLS-V9R cells. *Virology* 1983;125:496-501.
58. Floyd-Smith G, Slattery E, Lengyel P. Interferon action: RNA cleavage pattern of a (2'-5')oligoadenylate-dependent endonuclease. *Science* 1981;212:1030-2.
59. Clemens MJ, Williams BR. Inhibition of cell-free protein synthesis by pppA2'p5'A2'p5'A: a novel oligonucleotide synthesized by interferon-treated L cell extracts. *Cell* 1978;13:565-72.
60. Zhou A, Hassel BA, Silverman RH. Expression cloning of 2-5A-dependent RNAase: a uniquely regulated mediator of interferon action. *Cell* 1993;72:753-65.
61. Carpten J, Nupponen N, Isaacs S, et al. Germline mutations in the ribonuclease L gene in families showing linkage with HPC1. *Nat Genet* 2002;30:181-4.
62. Rokman A, Ikonen T, Seppala EH, et al. Germline alterations of the RNASEL gene, a candidate HPC1 gene at 1q25, in patients and families with prostate cancer. *Am J Hum Genet* 2002;70:1299-304.
63. Rennert H, Bercovich D, Hubert A, et al. A novel founder mutation in the RNASEL

- gene, 471delAAAG, is associated with prostate cancer in Ashkenazi Jews. *Am J Hum Genet* 2002;71:981-4.
64. Casey G, Neville PJ, Plummer SJ, et al. RNASEL Arg462Gln variant is implicated in up to 13% of prostate cancer cases. *Nat Genet* 2002;32:581-3.
65. Wang L, McDonnell SK, Elkins DA, et al. Analysis of the RNASEL gene in familial and sporadic prostate cancer. *Am J Hum Genet* 2002;71:116-23.
66. Xu J, Zheng SL, Komiya A, et al. Germline mutations and sequence variants of the macrophage scavenger receptor 1 gene are associated with prostate cancer risk. *Nat Genet* 2002;32:321-5.
67. Platt N, Gordon S. Is the class A macrophage scavenger receptor (SR-A) multifunctional? The mouse's tale. *J Clin Invest* 2001;108:649-54.
68. Dejager S, Mietus-Snyder M, Frieri A, Pitas RE. Dominant negative mutations of the scavenger receptor: native receptor inactivation by expression of truncated variants. *J Clin Invest* 1993;92:894-902.
69. Edwards A, Hammond HA, Jin L, Caskey CT, Chakraborty R. Genetic variation at five trimeric and tetrameric tandem repeat loci in four human population groups. *Genomics* 1992;12:241-53.
70. Chamberlain NL, Driver ED, Miesfeld RL. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. *Nucleic Acids Res* 1994;22:3181-6.
71. Kazemi-Esfarjani P, Trifiro MA, Pinsky L. Evidence for a repressive function of the long polyglutamine tract in the human androgen receptor: possible pathogenetic relevance for the (CAG)_n-expanded neuropathies. *Hum Mol Genet* 1995;4:523-7.
72. Irvine RA, Ma H, Yu MC, Ross RK, Stallcup MR, Coetzee GA. Inhibition of p160-mediated coactivation with increasing androgen receptor polyglutamine length. *Hum Mol Genet* 2000;9:267-74.
73. Beilin J, Ball EM, Favalaro JM, Zajac JD. Effect of the androgen receptor CAG repeat polymorphism on transcriptional activity: specificity in prostate and non-prostate cell lines. *J Mol Endocrinol* 2000;25:85-96.
74. Bennett CL, Price DK, Kim S, et al. Racial variation in CAG repeat lengths within the androgen receptor gene among prostate cancer patients of lower socioeconomic status. *J Clin Oncol* 2002;20:3599-604.
75. Latil AG, Azzouzi R, Cancel GS, et al. Prostate carcinoma risk and allelic variants of genes involved in androgen biosynthesis and metabolism pathways. *Cancer* 2001;92:1130-7.
76. Hsing AW, Gao YT, Wu G, et al. Polymorphic CAG and GGN repeat lengths in the androgen receptor gene and prostate cancer risk: a population-based case-control study in China. *Cancer Res* 2000;60:5111-6.
77. Hakimi JM, Schoenberg MP, Rondinelli RH, Piantadosi S, Barrack ER. Androgen receptor variants with short glutamine or glycine repeats may identify unique subpopulations of men with prostate cancer. *Clin Cancer Res* 1997;3:1599-608.
78. Giovannucci E, Stampfer MJ, Krithivas K, et al. The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. *Proc Natl Acad Sci U S A* 1997;94:3320-3.
79. Stanford JL, Just JJ, Gibbs M, et al. Polymorphic repeats in the androgen receptor gene: molecular markers of prostate cancer risk. *Cancer Res* 1997;57:1194-8.
80. Irvine RA, Yu MC, Ross RK, Coetzee GA. The CAG and AGC microsatellites of the androgen receptor gene are in linkage disequilibrium in men with prostate cancer. *Cancer Res* 1995;55:1937-40.
81. Platz EA, Giovannucci E, Dahl DM, et al. The androgen receptor gene GGN microsatellite and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev* 1998;7:379-84.
82. Stanford JL, Noonan E, Iwasaki L, et al. A polymorphism in the CYP17 gene and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2002;11:243-7.
83. Kittles RA, Panguluri RK, Chen W, et al. Cyp17 promoter variant associated with prostate cancer aggressiveness in African Americans. *Cancer Epidemiol Biomarkers Prev* 2001;10:943-7.
84. Haiman CA, Stampfer MJ, Giovannucci E, et al. The relationship between a polymorphism in CYP17 with plasma hormone levels and prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2001;10:743-8.
85. Habuchi T, Liqing Z, Suzuki T, et al. Increased risk of prostate cancer and benign prostatic hyperplasia associated with a CYP17 gene polymorphism with a gene dosage effect. *Cancer Res* 2000;60:5710-3.
86. Gsur A, Bernhofer G, Hinteregger S, et al. A polymorphism in the CYP17 gene is associated with prostate cancer risk. *Int J Cancer* 2000;87:434-7.
87. Wadelius M, Andersson AO, Johansson JE, Wadelius C, Rane E. Prostate cancer associated with CYP17 genotype. *Pharmacogenetics* 1999;9:635-9.
88. Lunn RM, Bell DA, Mohler JL, Taylor JA. Prostate cancer risk and polymorphism in 17 hydroxylase (CYP17) and steroid reductase (SRD5A2). *Carcinogenesis* 1999;20:1727-31.
89. Chang B, Zheng SL, Isaacs SD, et al. Linkage and association of CYP17 gene in hereditary and sporadic prostate cancer. *Int J Cancer* 2001;95:354-9.
90. Makridakis NM, Ross RK, Pike MC, et al. Association of mis-sense substitution in SRD5A2 gene with prostate cancer in African-American and Hispanic men in Los Angeles, USA. *Lancet* 1999;354:975-8.
91. Makridakis N, Ross RK, Pike MC, et al. A prevalent missense substitution that modulates activity of prostatic steroid 5 α -reductase. *Cancer Res* 1997;57:1020-2.
92. Nam RK, Toi A, Vesprini D, et al. V89L polymorphism of type-2, 5- α reductase enzyme gene predicts prostate cancer presence and progression. *Urology* 2001;57:199-204.
93. Chen C. Risk of prostate cancer in relation to polymorphisms of metabolic genes. *Epidemiol Rev* 2001;23:30-5.
94. Zhou A, Paranjape J, Brown TL, et al. Interferon action and apoptosis are defective in mice devoid of 2',5'-oligoadenylate-dependent RNase L. *Embo J* 1997;16:6355-63.
95. Elo JP, Visakorpi T. Molecular genetics of prostate cancer. *Ann Med* 2001;33:130-41.
96. Dong JT, Chen C, Stultz BG, Isaacs JT, Frierson HF Jr. Deletion at 13q21 is associated with aggressive prostate cancers. *Cancer Res* 2000;60:3880-3.
97. Elo JP, Harkonen P, Kyllonen AP, Lukkarinen O, Vihko P. Three independently deleted regions at chromosome arm 16q in human prostate cancer: allelic loss at 16q24.1-q24.2 is associated with aggressive behaviour of the disease, recurrent growth, poor differentiation of the tumour and poor prognosis for the patient. *Br J Cancer* 1996;79:156-60.
98. Takahashi S, Shan AL, Ritland SR, et al. Frequent loss of heterozygosity at 7q31.1 in primary prostate cancer is associated with tumor aggressiveness and progression. *Cancer Res* 1995;55:4114-9.
99. Nupponen NN, Kakkola L, Koivisto P, Visakorpi T. Genetic alterations in hormone-refractory recurrent prostate carcinomas. *Am J Pathol* 1998;153:141-8.
100. Takahashi S, Qian J, Brown JA, et al. Potential markers of prostate cancer aggressiveness detected by fluorescence in situ hybridization in needle biopsies. *Cancer Res* 1994;54:3574-9.
101. Brooks JD, Bova GS, Ewing CM, et al. An uncertain role for p53 gene alterations in human prostate cancers. *Cancer Res* 1996;56:3814-22.
102. Stapleton AM, Timme TL, Gousse AE, et al. Primary human prostate cancer cells harboring p53 mutations are clonally expanded in metastases. *Clin Cancer Res* 1997;3:1389-97.
103. Millar DS, Ow KK, Paul CL, Russell PJ, Molloy PL, Clark SJ. Detailed methylation analysis of the glutathione S-transferase pi (GSTP1) gene in prostate cancer. *Oncogene* 1999;18:1313-24.
104. Lee WH, Morton RA, Epstein JI, et al. Cytidine methylation of regulatory sequences near the pi-class glutathione S-transferase gene accompanies human prostatic carcinogenesis. *Proc Natl Acad Sci U S A* 1994;91:11733-7.
105. Lin X, Tascilar M, Lee WH, et al. GSTP1 CpG island hypermethylation is responsible for the absence of GSTP1 expression in human prostate cancer cells. *Am J Pathol* 2001;159:1815-26.
106. Nelson WG, De Marzo AM, DeWeese TL. The molecular pathogenesis of prostate cancer: implications for prostate cancer prevention. *Urology* 2001;57:39-45.
107. Brooks JD, Weinstein M, Lin X, et al. CG island methylation changes near the

- GSTP1 gene in prostatic intraepithelial neoplasia. *Cancer Epidemiol Biomarkers Prev* 1998;7:531-6.
108. Kinzler KW, Vogelstein B. Cancer-susceptibility genes: gatekeepers and caretakers. *Nature* 1997;386:761, 763.
109. Nelson CP, Kidd LC, Sauvageot J, et al. 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* 2001;61:103-9.
110. Bieberich CJ, Fujita K, He WW, Jay G. Prostate-specific and androgen-dependent expression of a novel homeobox gene. *J Biol Chem* 1996;271:31779-82.
111. Scivolino PJ, Abrams EW, Yang L, Austenberg LP, Shen MM, Abate-Shen C. Tissue-specific expression of murine Nkx3.1 in the male urogenital system. *Dev Dyn* 1997;209:127-38.
112. Steadman DJ, Giuffrida D, Gelmann EP. DNA-binding sequence of the human prostate-specific homeodomain protein NKX3.1. *Nucleic Acids Res* 2000;28:2389-95.
113. Chen H, Nandi AK, Li X, Bieberich CJ. NKX-3.1 interacts with prostate-derived Ets factor and regulates the activity of the PSA promoter. *Cancer Res* 2002;62:338-40.
114. Bhatia-Gaur R, Donjacour AA, Scivolino PJ, et al. Roles for Nkx3.1 in prostate development and cancer. *Genes Dev* 1999;13:966-77.
115. Abdulkadir SA, Magee JA, Peters TJ, et al. Conditional loss of Nkx3.1 in adult mice induces prostatic intraepithelial neoplasia. *Mol Cell Biol* 2002;22:1495-503.
116. Emmert-Buck MR, Vocke CD, Pozzatti RO, et al. Allelic loss on chromosome 8p12-21 in microdissected prostatic intraepithelial neoplasia. *Cancer Res* 1995;55:2959-62.
117. He WW, Scivolino PJ, Wing J, et al. A novel human prostate-specific, androgen-regulated homeobox gene (NKX3.1) that maps to 8p21, a region frequently deleted in prostate cancer. *Genomics* 1997;43:69-77.
118. Ornstein DK, Cinquanta M, Weiler S, et al. Expression studies and mutational analysis of the androgen regulated homeobox gene NKX3.1 in benign and malignant prostate epithelium. *J Urol* 2001;165:1329-34.
119. Voeller HJ, Augustus M, Madike V, Bova GS, Carter KC, Gelmann EP. Coding region of NKX3.1, a prostate-specific homeobox gene on 8p21, is not mutated in human prostate cancers. *Cancer Res* 1997;57:4455-9.
120. Bowen C, Bubendorf L, Voeller HJ, et al. Loss of NKX3.1 expression in human prostate cancers correlates with tumor progression. *Cancer Res* 2000;60:6111-5.
121. Wu X, Senechal K, Neshat MS, Whang YE, Sawyers CL. The PTEN/MMAC1 tumor suppressor phosphatase functions as a negative regulator of the phosphoinositide 3-kinase/Akt pathway. *Proc Natl Acad Sci U S A* 1998;95:15587-91.
122. Li J, Yen C, Liaw D, et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. *Science* 1997;275:1943-7.
123. Steck PA, Pershouse MA, Jasser SA, et al. Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. *Nat Genet* 1997;15:356-62.
124. Teng DH, Hu R, Lin H, et al. MMAC1/PTEN mutations in primary tumor specimens and tumor cell lines. *Cancer Res* 1997;57:5221-5.
125. Myers MP, Pass I, Batty IH, et al. The lipid phosphatase activity of PTEN is critical for its tumor suppressor function. *Proc Natl Acad Sci U S A* 1998;95:13513-8.
126. Myers MP, Stolarov JP, Eng C, et al. P-TEN, the tumor suppressor from human chromosome 10q23, is a dual-specificity phosphatase. *Proc Natl Acad Sci U S A* 1997;94:9052-7.
127. Maehama T, Dixon JE. The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. *J Biol Chem* 1998;273:13375-8.
128. Cairns P, Okami K, Halachmi S, et al. Frequent inactivation of PTEN/MMAC1 in primary prostate cancer. *Cancer Res* 1997;57:4997-5000.
129. Suzuki H, Freije D, Nusskern DR, et al. Interfocal heterogeneity of PTEN/MMAC1 gene alterations in multiple metastatic prostate cancer tissues. *Cancer Res* 1998;58:204-9.
130. Vivanco I, Sawyers CL. The phosphatidylinositol 3-Kinase AKT pathway in human cancer. *Nat Rev Cancer* 2002;2:489-501.
131. McMenamin ME, Soung P, Perera S, Kaplan I, Loda M, Sellers WR. Loss of PTEN expression in paraffin-embedded primary prostate cancer correlates with high Gleason score and advanced stage. *Cancer Res* 1999;59:4291-6.
132. Podsypanina K, Ellenson LH, Nemes A, et al. Mutation of Pten/Mmac1 in mice causes neoplasia in multiple organ systems. *Proc Natl Acad Sci U S A* 1999;96:1563-8.
133. Di Cristofano A, Pesce B, Cordon-Cardo C, Pandolfi PP. Pten is essential for embryonic development and tumour suppression. *Nat Genet* 1998;19:348-55.
134. Kim MJ, Cardiff RD, Desai N, et al. Cooperativity of Nkx3.1 and Pten loss of function in a mouse model of prostate carcinogenesis. *Proc Natl Acad Sci U S A* 2002;99:2884-9.
135. Furnari FB, Huang HJ, Cavenee WK. The phosphoinositide phosphatase activity of PTEN mediates a serum-sensitive G1 growth arrest in glioma cells. *Cancer Res* 1998;58:5002-8.
136. Li DM, Sun H. PTEN/MMAC1/TEP1 suppresses the tumorigenicity and induces G1 cell cycle arrest in human glioblastoma cells. *Proc Natl Acad Sci U S A* 1998;95:15406-11.
137. Ramaswamy S, Nakamura N, Vazquez F, et al. 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 U S A* 1999;96:2110-5.
138. Sun H, Lesche R, Li DM, et al. 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 U S A* 1999;96:6199-204.
139. Yang RM, Naitoh J, Murphy M, et al. Low p27 expression predicts poor disease-free survival in patients with prostate cancer. *J Urol* 1998;159:941-5.
140. Chevillet JC, Lloyd RV, Sebo TJ, et al. Expression of p27kip1 in prostatic adenocarcinoma. *Mod Pathol* 1998;11:324-8.
141. Cote RJ, Shi Y, Groshen S, et al. Association of p27Kip1 levels with recurrence and survival in patients with stage C prostate carcinoma. *J Natl Cancer Inst* 1998;90:916-20.
142. Cordon-Cardo C, Koff A, Drobnjak M, et al. Distinct altered patterns of p27KIP1 gene expression in benign prostatic hyperplasia and prostatic carcinoma. *J Natl Cancer Inst* 1998;90:1284-91.
143. Guo Y, Sklar GN, Borkowski A, Kyprianou N. Loss of the cyclin-dependent kinase inhibitor p27(Kip1) protein in human prostate cancer correlates with tumor grade. *Clin Cancer Res* 1997;3:2269-74.
144. De Marzo AM, Meeker AK, Epstein JI, Coffey DS. Prostate stem cell compartments: expression of the cell cycle inhibitor p27Kip1 in normal, hyperplastic, and neoplastic cells. *Am J Pathol* 1998;153:911-9.
145. Kibel AS, Faith DA, Bova GS, Isaacs WB. Loss of heterozygosity at 12p12-13 in primary and metastatic prostate adenocarcinoma. *J Urol* 2000;164:192-6.
146. Graff JR, Konicek BW, McNulty AM, et al. Increased AKT activity contributes to prostate cancer progression by dramatically accelerating prostate tumor growth and diminishing p27Kip1 expression. *J Biol Chem* 2000;275:24500-5.
147. Gottschalk AR, Basila D, Wong M, et al. p27Kip1 is required for PTEN-induced G1 growth arrest. *Cancer Res* 2001;61:2105-11.
148. Nakamura N, Ramaswamy S, Vazquez F, Signoretti S, Loda M, Sellers WR. Forkhead transcription factors are critical effectors of cell death and cell cycle arrest downstream of PTEN. *Mol Cell Biol* 2000;20:8969-82.
149. Di Cristofano A, De Acetis M, Koff A, Cordon-Cardo C, Pandolfi PP. Pten and p27KIP1 cooperate in prostate cancer tumor suppression in the mouse. *Nat Genet* 2001;27:222-4.
150. Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. *N Engl J Med* 1998;339:1036-42.
151. Crawford ED, Eisenberger MA, Mc-

- Leod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 1989;321:419-24.
152. Laufer M, Denmeade SR, Sinibaldi VJ, Carducci MA, Eisenberger MA. Complete androgen blockade for prostate cancer: what went wrong? *J Urol* 2000;164:3-9.
153. Ruska KM, Sauvageot J, Epstein JI. Histology and cellular kinetics of prostatic atrophy. *Am J Surg Pathol* 1998;22:1073-7.
154. Amler LC, Agus DB, LeDuc C, et al. Dysregulated expression of androgen-responsive and nonresponsive genes in the androgen-independent prostate cancer xenograft model CWR22-R1. *Cancer Res* 2000;60:6134-41.
155. Mousset S, Wagner U, Chen Y, et al. Failure of hormone therapy in prostate cancer involves systematic restoration of androgen responsive genes and activation of rapamycin sensitive signaling. *Oncogene* 2001;20:6718-23.
156. van der Kwast TH, Schalken J, Ruizeveld de Winter JA, et al. Androgen receptors in endocrine-therapy-resistant human prostate cancer. *Int J Cancer* 1991;48:189-93.
157. Feldman BJ, Feldman D. The development of androgen-independent prostate cancer. *Nat Rev Cancer* 2001;1:34-45.
158. Zegarra-Moro OL, Schmidt LJ, Huang H, Tindall DJ. Disruption of androgen receptor function inhibits proliferation of androgen-refractory prostate cancer cells. *Cancer Res* 2002;62:1008-13.
159. Visakorpi T, Hyytinen E, Koivisto P, et al. In vivo amplification of the androgen receptor gene and progression of human prostate cancer. *Nat Genet* 1995;9:401-6.
160. Koivisto P, Kononen J, Palmberg C, et al. Androgen receptor gene amplification: a possible molecular mechanism for androgen deprivation therapy failure in prostate cancer. *Cancer Res* 1997;57:314-9.
161. Haapala K, Hyytinen ER, Roiha M, et al. Androgen receptor alterations in prostate cancer relapsed during a combined androgen blockade by orchiectomy and bicalutamide. *Lab Invest* 2001;81:1647-51.
162. Marcelli M, Ittmann M, Mariani S, et al. Androgen receptor mutations in prostate cancer. *Cancer Res* 2000;60:944-9.
163. Taplin ME, Bubley GJ, Shuster TD, et al. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. *N Engl J Med* 1995;332:1393-8.
164. Taplin ME, Bubley GJ, Ko YJ, et al. Selection for androgen receptor mutations in prostate cancers treated with androgen antagonist. *Cancer Res* 1999;59:2511-5.
165. Tilley WD, Buchanan G, Hickey TE, Bentel JM. Mutations in the androgen receptor gene are associated with progression of human prostate cancer to androgen independence. *Clin Cancer Res* 1996;2:277-85.
166. Veldscholte J, Ris-Stalpers C, Kuiper GG, et al. A mutation in the ligand binding domain of the androgen receptor of human LNCaP cells affects steroid binding characteristics and response to anti-androgens. *Biochem Biophys Res Commun* 1990;173:534-40.
167. Schoenberg MP, Hakimi JM, Wang S, et al. Microsatellite mutation (CAG24→18) in the androgen receptor gene in human prostate cancer. *Biochem Biophys Res Commun* 1994;198:74-80.
168. Suzuki H, Akakura K, Komiya A, Aida S, Akimoto S, Shimazaki J. Codon 877 mutation in the androgen receptor gene in advanced prostate cancer: relation to antiandrogen withdrawal syndrome. *Prostate* 1996;29:153-8.
169. Suzuki H, Sato N, Watabe Y, Masai M, Seino S, Shimazaki J. Androgen receptor gene mutations in human prostate cancer. *J Steroid Biochem Mol Biol* 1993;46:759-65.
170. Newmark JR, Hardy DO, Tonb DC, et al. Androgen receptor gene mutations in human prostate cancer. *Proc Natl Acad Sci U S A* 1992;89:6319-23.
171. Gaddipati JB, McLeod DG, Heidenberg HB, et al. Frequent detection of codon 877 mutation in the androgen receptor gene in advanced prostate cancers. *Cancer Res* 1994;54:2861-4.
172. Evans BA, Harper ME, Daniells CE, et al. Low incidence of androgen receptor gene mutations in human prostatic tumors using single strand conformation polymorphism analysis. *Prostate* 1996;28:162-71.
173. Tan J, Sharief Y, Hamil KG, et al. Dehydroepiandrosterone activates mutant androgen receptors expressed in the androgen-dependent human prostate cancer xenograft CWR22 and LNCaP cells. *Mol Endocrinol* 1997;11:450-9.
174. Veldscholte J, Voorhorst-Ogink MM, Bolt-de Vries J, van Rooij HC, Trapman J, Mulder E. Unusual specificity of the androgen receptor in the human prostate tumor cell line LNCaP: high affinity for progestagenic and estrogenic steroids. *Biochim Biophys Acta* 1990;1052:187-94.
175. Culig Z, Hobisch A, Cronauer MV, et al. Mutant androgen receptor detected in an advanced-stage prostatic carcinoma is activated by adrenal androgens and progesterone. *Mol Endocrinol* 1993;7:1541-50.
176. Shi XB, Ma AH, Xia L, Kung HJ, de Vere White RW. Functional analysis of 44 mutant androgen receptors from human prostate cancer. *Cancer Res* 2002;62:1496-502.
177. Sadar MD, Gleave ME. Ligand-independent activation of the androgen receptor by the differentiation agent butyrate in human prostate cancer cells. *Cancer Res* 2000;60:5825-31.
178. Craft N, Shostak Y, Carey M, Sawyers CL. A mechanism for hormone-independent prostate cancer through modulation of androgen receptor signaling by the HER-2/neu tyrosine kinase. *Nat Med* 1999;5:280-5.
179. Hobisch A, Eder IE, Putz T, et al. Interleukin-6 regulates prostate-specific protein expression in prostate carcinoma cells by activation of the androgen receptor. *Cancer Res* 1998;58:4640-5.
180. Nazareth LV, Weigel NL. Activation of the human androgen receptor through a protein kinase A signaling pathway. *J Biol Chem* 1996;271:19900-7.
181. Gardner WA Jr, Bennett BD. The prostate — overview: recent insights and speculations. In: Weinstein RS, Gardner WA Jr, eds. Pathology and pathobiology of the urinary bladder and prostate. Baltimore: Williams & Wilkins, 1992:129-48.
182. Roberts RO, Lieber MM, Rhodes T, Girman CJ, Bostwick DG, Jacobsen SJ. Prevalence of a physician-assigned diagnosis of prostatitis: the Olmsted County Study of Urinary Symptoms and Health Status Among Men. *Urology* 1998;51:578-84.
183. Giovannucci E. Medical history and etiology of prostate cancer. *Epidemiol Rev* 2001;23:159-62.
184. Hoekx L, Jeuris W, Van Marck E, Wyndaele JJ. Elevated serum prostate specific antigen (PSA) related to asymptomatic prostatic inflammation. *Acta Urol Belg* 1998;66:1-2.
185. Hayes RB, Potters LM, Strickler H, et al. Sexual behaviour, STDs and risks for prostate cancer. *Br J Cancer* 2000;82:718-25.
186. Dennis LK, Dawson DV. Meta-analysis of measures of sexual activity and prostate cancer. *Epidemiology* 2002;13:72-9.
187. Xia Y, Zweier JL. Superoxide and peroxynitrite generation from inducible nitric oxide synthase in macrophages. *Proc Natl Acad Sci U S A* 1997;94:6954-8.
188. Eiserich JP, Hristova M, Cross CE, et al. Formation of nitric oxide-derived inflammatory oxidants by myeloperoxidase in neutrophils. *Nature* 1998;391:393-7.
189. Roberts RO, Jacobson DJ, Girman CJ, Rhodes T, Lieber MM, Jacobsen SJ. A population-based study of daily nonsteroidal anti-inflammatory drug use and prostate cancer. *Mayo Clin Proc* 2002;77:219-25.
190. Nelson JE, Harris RE. Inverse association of prostate cancer and non-steroidal anti-inflammatory drugs (NSAIDs): results of a case-control study. *Oncol Rep* 2000;7:169-70.
191. Norrish AE, Jackson RT, McRae CU. Non-steroidal anti-inflammatory drugs and prostate cancer progression. *Int J Cancer* 1998;77:511-5.
192. De Marzo AM, Marchi VL, Epstein JI, Nelson WG. Proliferative inflammatory atrophy of the prostate: implications for prostatic carcinogenesis. *Am J Pathol* 1999;155:1985-92.
193. Franks LM. Atrophy and hyperplasia in the prostate proper. *J Pathol Bacteriol* 1954;68:617-21.
194. Feneley MR, Young MP, Chinyama C, Kirby RS, Parkinson MC. Ki-67 expression in early prostate cancer and associated pathological lesions. *J Clin Pathol* 1996;49:741-8.
195. Putzi MJ, De Marzo AM. Morphologic transitions between proliferative inflammatory atrophy and high-grade prostatic intraepithelial neoplasia. *Urology* 2000;56:828-32.

- 196.** Shah R, Mucci NR, Amin A, Macoska JA, Rubin MA. Postatrophic hyperplasia of the prostate gland: neoplastic precursor or innocent bystander? *Am J Pathol* 2001;158:1767-73.
- 197.** Zha S, Gage WR, Sauvageot J, et al. Cyclooxygenase-2 is up-regulated in proliferative inflammatory atrophy of the prostate, but not in prostate carcinoma. *Cancer Res* 2001;61:8617-23.
- 198.** Parsons JK, Nelson CP, Gage WR, Nelson WG, Kensler TW, De Marzo AM. GSTA1 expression in normal, preneoplastic, and neoplastic human prostate tissue. *Prostate* 2001;49:30-7.
- 199.** Wilson MJ, Ditmanson JV, Sinha AA, Estensen RD. Plasminogen activator activities in the ventral and dorsolateral prostatic lobes of aging Fischer 344 rats. *Prostate* 1990;16:147-61.
- 200.** Reznik G, Hamlin MH II, Ward JM, Stinson SE. Prostatic hyperplasia and neoplasia in aging F344 rats. *Prostate* 1981;2:261-8.

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