REVIEW ARTICLE

MECHANISMS OF DISEASE

Prostate Cancer

William G. Nelson, M.D., Ph.D., Angelo M. De Marzo, M.D., Ph.D., and William B. Isaacs, Ph.D.

From the Departments of Oncology (W.G.N., A.M.D., W.B.I.), Pathology (W.G.N., A.M.D.), and Urology (W.G.N., A.M.D., W.B.I.), Johns Hopkins University School of Medicine, Baltimore. Address reprint requests to Dr. Nelson at Rm. 151, Bunting-Blaustein Cancer Research Bldg., Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1650 Orleans St., Baltimore, MD 21231-1000, or at bnelson@jhmi.edu.

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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 Study[11] 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.

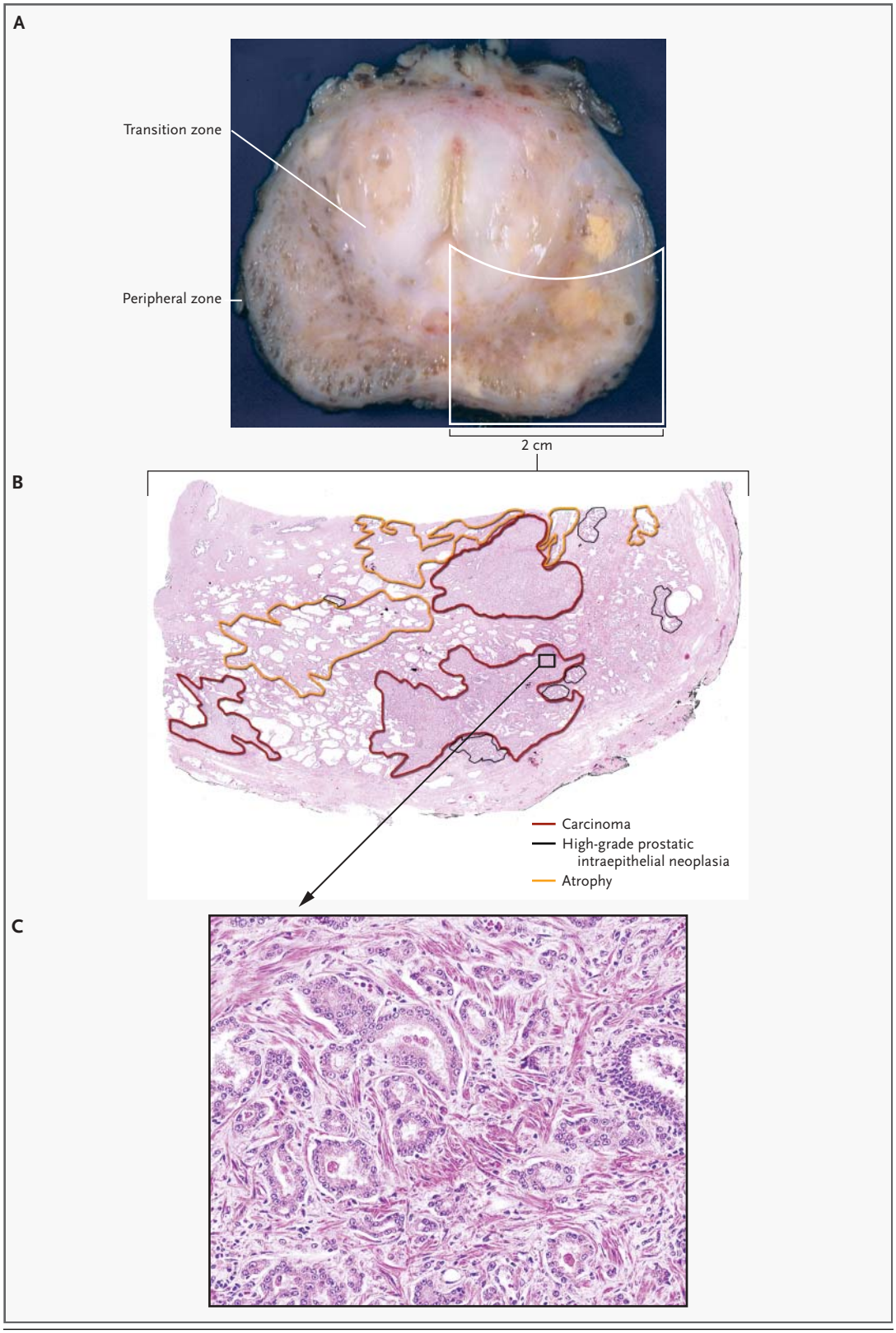
Panel A is a photograph of a single slice of a prostate from a radical prostatectomy. The transition zone, where most (>90 percent) benign prostatic hyperplasia develops, and the peripheral zone, where most (>70 percent) prostate cancer develops, are indicated. Areas with yellowish discoloration represent 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-450c17α, 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]

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 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]

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 Met1Ile, 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 *Listeria monocytogenes, Staphylococcus aureus, Escherichia coli,* 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-450c17α, 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.

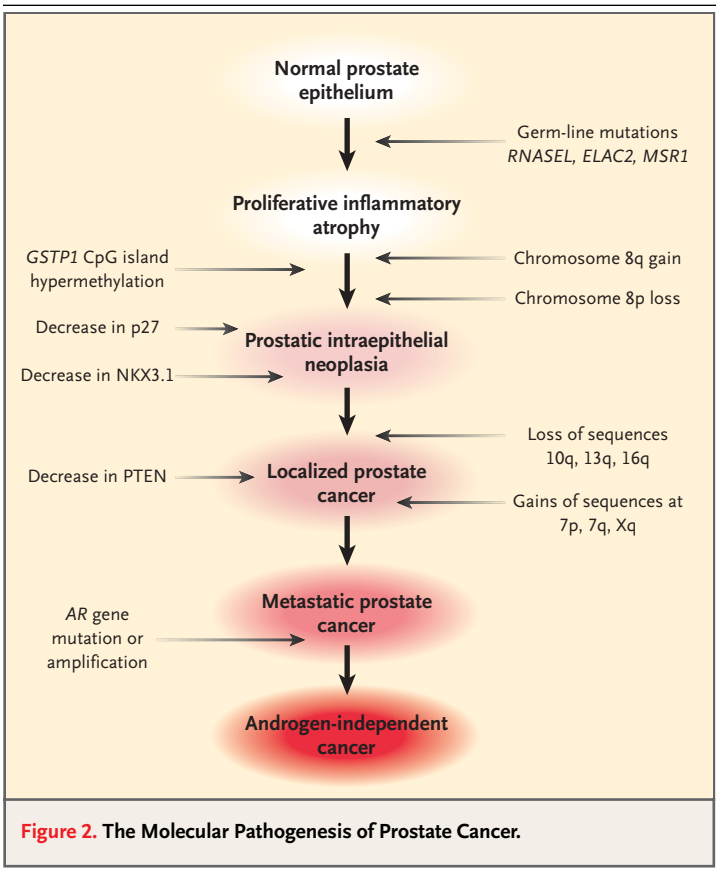


Figure 2. The Molecular Pathogenesis of Prostate Cancer.

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

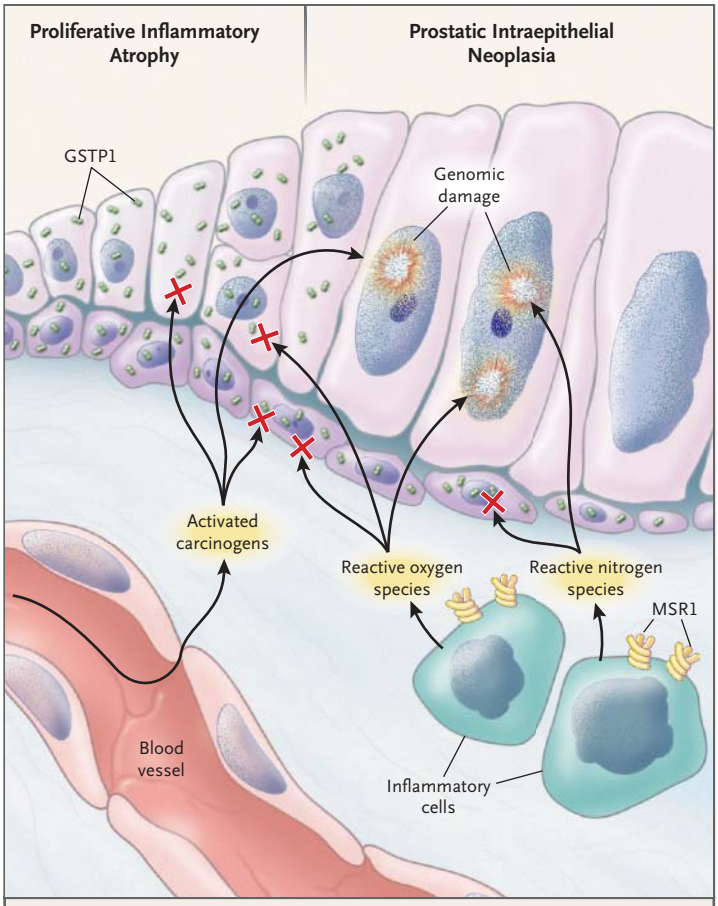


Figure 3. Loss of *GSTP1* Caretaker Activity in Prostate Cells and Increased Vulnerability to Genomic Damage Mediated by Carcinogens.

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

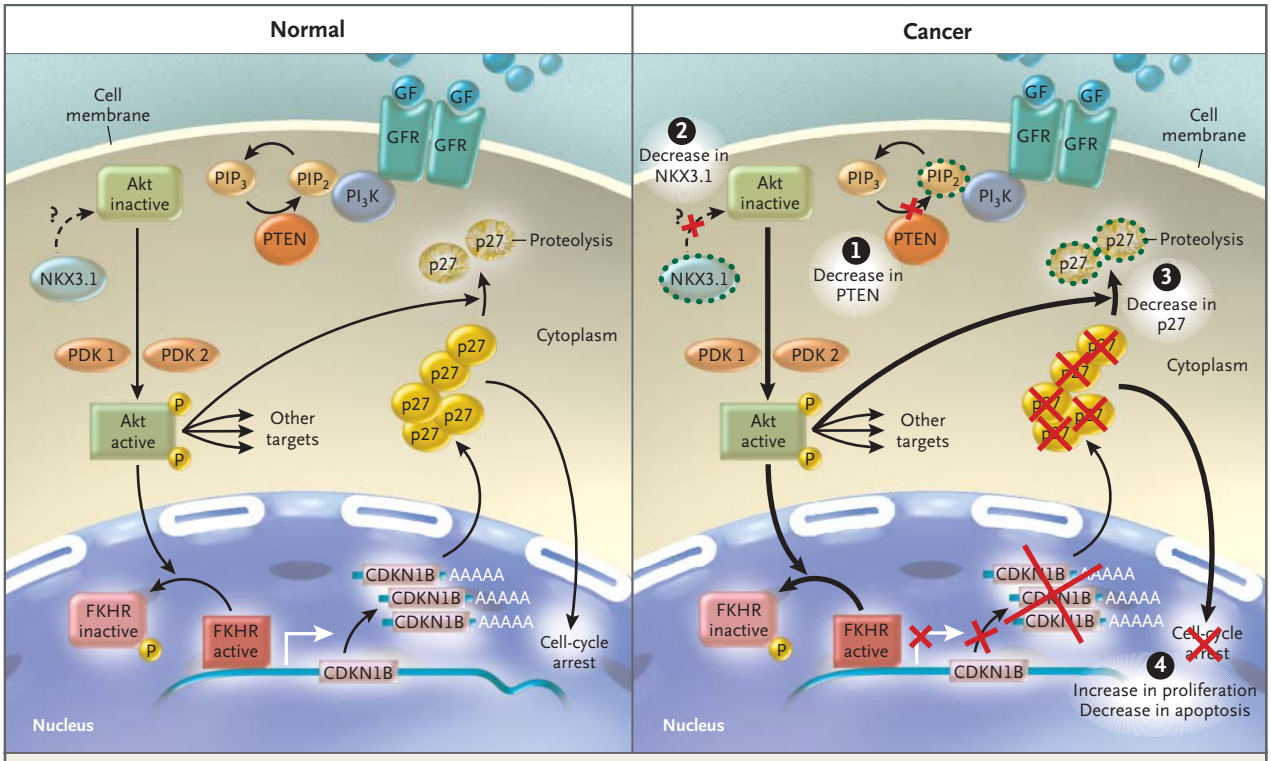


Figure 4. Molecular Events in the Pathogenesis of Prostate Cancer.

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, PIP_3 phosphatidylinositol 3,4,5-triphosphate, PIP_2 phosphatidylinositol 4,5-diphosphate, PI_3K 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-

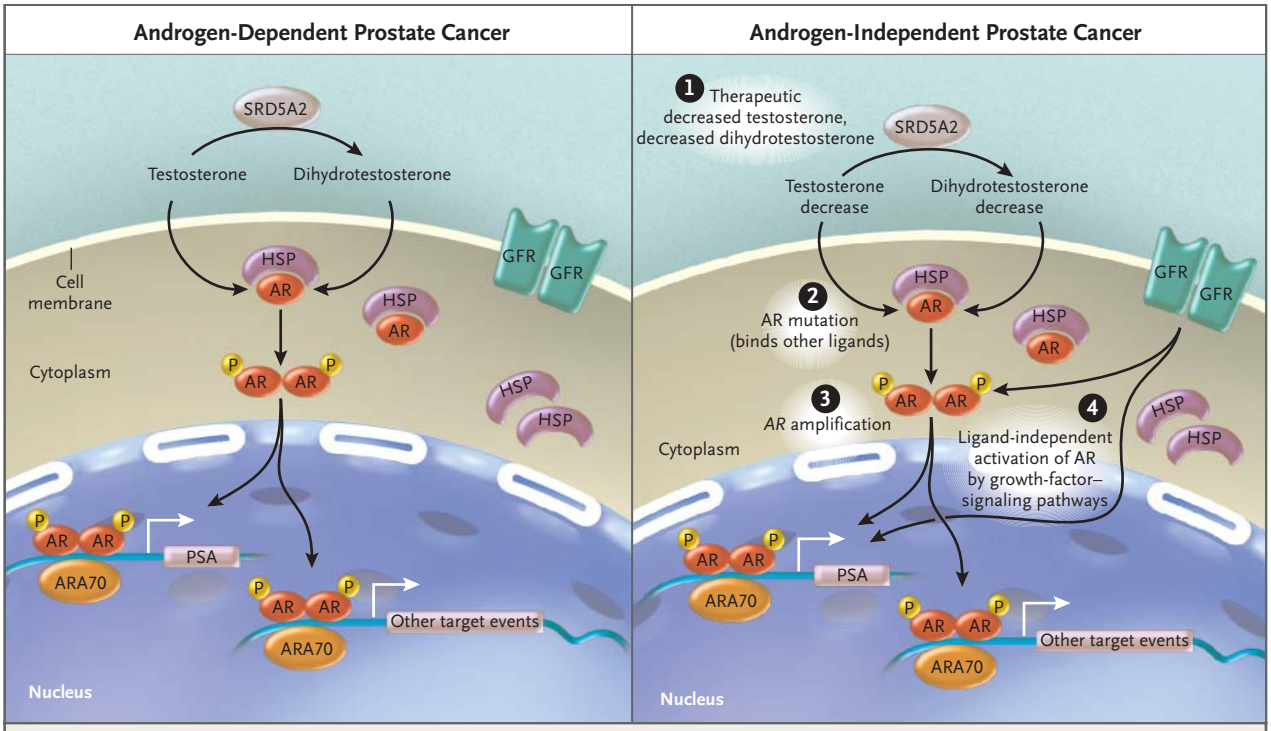


Figure 5. Progression of Prostate Cancer to Androgen Independence during Treatment with Androgen Deprivation, Antiandrogens, or Both.
After therapeutic reduction in the levels of testosterone and dihydrotestosterone (1), the emergence of androgen-independent prostate cancer has been associated with mutations 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-

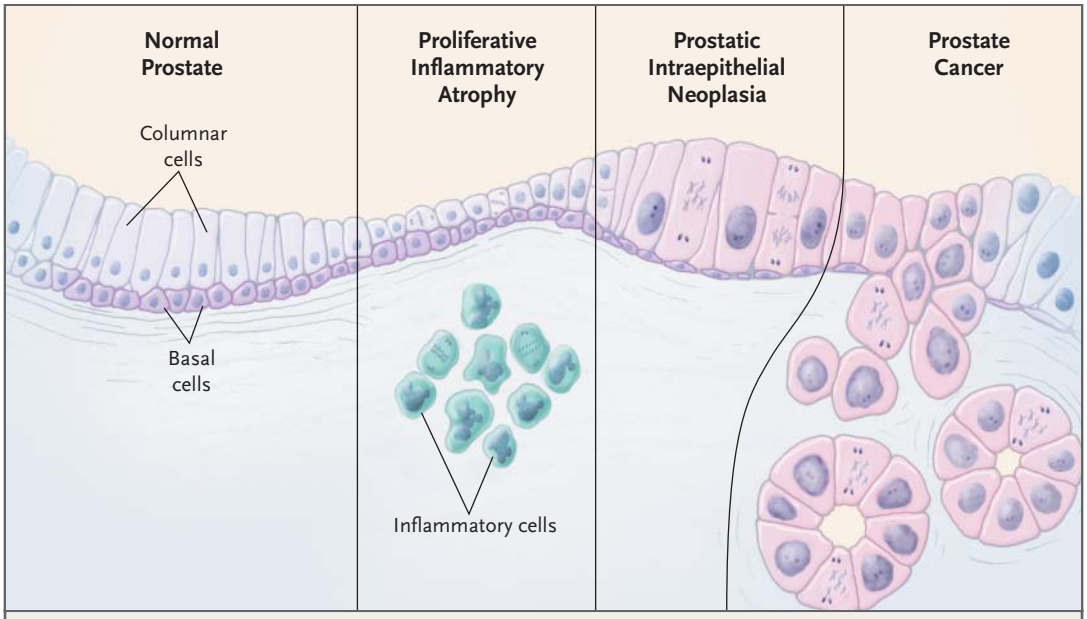


Figure 6. Proliferative Inflammatory Atrophy as a Precursor to Prostatic Intraepithelial Neoplasia and Prostate Cancer.

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 influence the development and progression of prostate cancer.

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