The American Cancer Society originally predicted 334,500 new cases and 41,800 deaths from prostate cancer for 1997; the estimate of new cases was recently revised to 209,000 to reflect the 24% decline in incidence rate between 1992 and 1994. Prostate cancer is the most common malignancy other than superficial skin cancer and the second leading cause of cancer death in American men.

Between 1976 and 1994, prostate cancer rates doubled and mortality increased by 20% (Table 1). The reasons for the increase are not known, but increasing life expectancy, growing disease prevalence resulting from environmental carcinogens, and increasing use of novel diagnostic modalities have been suggested as causes. The most plausible explanation, however, is that concern over the disease among patients and in the medical community has led to increasing efforts to detect the disease. The most significant advance in this area has been the development of prostate-specific antigen (PSA) testing, but improvements in transrectal ultrasonography and even in biopsy technology also have contributed.

Although the overall number of cases diagnosed increased in all age groups, the increase is most evident in the younger age groups: The percentage of men younger than 70 years diagnosed with prostate cancer increased from 38% to 47% between 1986 and 1993. Another recent trend is that men diagnosed with prostate cancer are now more likely to present with clinically localized disease (53% in 1986 compared with 74% in 1996) and lower grade tumors. A similar trend is reflected in pathologically staged cases, in which an increase in organ-confined disease is seen in men whose diagnosis was based on detection by an elevation in PSA level.

These data suggest that it is not so much the prevalence of prostate cancer that is increasing but that we may be diagnosing more cases from a pool of men with latent, previously unsuspected disease and that these diagnoses occur at an earlier, more localized stage of the disease process. The number of newly diagnosed cases now may be leveling off because the intensity of screening with PSA is dimin-

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**Table 1**

| Year | Incidence | Mortality Rate |
|------|-----------|----------------|
| 1994 | 144.0     | 26.0           |
| 1992 | 190.1     | 26.7           |
| 1990 | 132.0     | 26.5           |
| 1985 | 88.0      | 23.4           |
| 1976 | 73.5      | 22.1           |

Adapted from Ries et al.
ishing or the currently detectable pool of cases is being exhausted.2,7
Prostate cancer is also increasing in significance worldwide (Table 2). Clinical incidence is low in Asian men and highest in African-Americans and Scandinavians.1 However, even in Japan, where the age-adjusted death rate per 100,000 population is 4.0 in comparison with 17.5 for men in the United States, the number of newly identified cases is expected to double by the year 2000 and to quadruple by 2010. When Japanese men move to the United States, their incidence and mortality rates increase and approximate those of American men.8 The reasons behind these marked differences must be illuminated so that we may learn what causes the disease process and, consequently, devise rational strategies for prevention, early diagnosis, and treatment.

Although the cause of the disease is not known, it is probably multifactorial. Epidemiologic studies of potential genetic, environmental, and social issues may provide important clues. Differences among various populations may yield information about cellular, genetic, and biochemical events responsible for prostate cancer carcinogenesis. Evaluating the histopathologic and molecular genetic characteristics of early malignant and possible premalignant changes in prostate tissues can provide further valuable information. This article reviews the rapidly accumulating, sometimes conflicting, and always controversial data about the epidemiology of prostate cancer.

**Worldwide Epidemiology**

Great geographic variations exist in the impact of prostate cancer, as mentioned earlier (Table 2).1,9,10 The significance of environmental factors is highlighted by data showing that when individuals from a low incidence/mortality region move to a high incidence/mortality region, within their own generation the disease becomes more common.8,10 For example, when Japanese men relocate to the United States or other countries, their prostate cancer statistics start to resemble those of the local population.8,10

| Country          | Mortality Rate |
|------------------|----------------|
| Trinidad, Tobago | 32.9           |
| Switzerland      | 22.5           |
| Norway           | 22.1           |
| Sweden           | 21.1           |
| Denmark          | 19.5           |
| New Zealand      | 19.0           |
| Cuba             | 19.0           |
| United States    | 17.5           |
| United Kingdom   | 17.1           |
| Canada           | 17.0           |
| France           | 16.8           |
| Hungary          | 15.8           |
| Portugal         | 15.3           |
| Costa Rica       | 15.0           |
| Argentina        | 13.6           |
| Spain            | 13.2           |
| Italy            | 11.6           |
| Mexico           | 10.6           |
| Israel           | 9.2            |
| Greece           | 8.7            |
| Russian Fed.     | 6.9            |
| Singapore        | 4.4            |
| Japan            | 4.0            |

Adapted from Parker et al.111
Younger age at the time of relocation and the length of time living in the new environment appear to correlate with the increase. In contrast, African-American men have a 47% higher incidence and a 128% higher mortality rate than white men living in the same geographic location. Thus, although black men have more advanced disease upon diagnosis (they are 40% more likely to present with metastases), they have a higher mortality rate even when compared with white men presenting with identical disease stages.

Obviously, to understand the genetic, environmental, or social basis of the epidemiologic differences noted between black and white Americans, it is important to understand the biology of prostate cancer in Africa. These data are sparse and have started to accumulate only recently. Because of political instability, economic difficulties, shorter life expectancy, and competing morbidities, comprehensive clinical and histopathologic data are yet to be produced. Nevertheless, new evidence exists that prostate cancer is a surprisingly common disease in black Africans. In South African whites, the rates are more similar to those of men living in Britain (32.6 per 100,000) than to those of black Africans. Some of these variations can almost certainly be correlated with socioeconomic status and life expectancy. Compared with black South Africans, white South Africans are wealthier and have a longer life expectancy (73 years versus 63 years). Prostate cancer in Zimbabwe is the fifth most frequently diagnosed malignancy, representing 8.2% of all cancers in males. The peak age for prostate cancer development in Africa is 55 to 64 years, and disease is advanced in 90% of cases at presentation.

**Risk Factors**

**AGE**

Prostate cancer has been known as a disease of elderly men. Diagnosis is rare before the age of 50 years, but after this age incidence and mortality rates both increase almost exponentially. The Surveillance, Epidemiology, and End Results (SEER) age-adjusted incidence rates in 1990 were 45.2 per 100,000 men age 50 to 55 years, 337.5 per 100,000 for those age 60 to 64 years, and more than 1,000 per 100,000 for men older than 65 years. The lifetime probability at birth of being diagnosed with prostate cancer in the United States has been estimated to be 8%. Prostate cancer increases faster with age than does any other malignancy, and with an increase in the elderly population because of longer life expectancy, prostate cancer will continue to be a major health concern. The age-related increases in latent prostate cancer parallel
the rising incidence of clinically detected cancer.21,22

FAMILY HISTORY
Prostate cancer has a hereditary component. Male relatives of prostate cancer patients have an increased risk of developing the disease.23-27 A higher incidence of prostate cancer also has been reported among male relatives of breast cancer patients.23

Cannon and colleagues24 showed familial clustering of prostate cancer among Mormons living in Utah. Prostate cancer showed a stronger familial aggregation than did colon and breast carcinoma, two solid tumors that are well recognized as having a familial component. Spitz and colleagues25 showed a 2.41-fold increased risk for men with first-degree relatives who had prostate cancer. In Iceland, the relative risk was increased by 1.5-fold.23 In a study of Scandinavian twins, Gronberg and coworkers26 found prostate cancer concordance rates of 0.192 and 0.043 for monozygotic versus dizygotic twins, which suggests a pronounced genetic influence on prostate cancer development. Carter and colleagues27 showed that prostate cancer was diagnosed in 15% of men who had a father or brother affected by prostate cancer compared with 8% of a control population with no affected relatives. In their study, the risk of carcinoma increased proportionately to the number of affected relatives. Segregation and linkage analyses showed that some early-onset prostate cancers may be inherited in an autosomal dominant fashion.27

Compared with sporadic prostate cancer, however, hereditary factors are responsible for a low percentage of cases (approximately 9% of all cases) and most commonly affect men with early onset of disease.27 It has become prudent to inform men diagnosed with prostate cancer that their male relatives may have an increased risk of disease.

RACE
In his recent review of racial differences in prostate cancer in North American men, Morton28 noted that African-Americans still develop the disease more frequently and have a worse prognosis than their white counterparts.

Black men have a probability of being diagnosed with prostate cancer of 18.8% compared with 18.5% in whites.2 Risk of mortality from prostate cancer is 4.5% for black men versus 3.6% for white men. The 5-year survival was 75% for black men and 90% for white men diagnosed from 1986 to 1993.2 Black men are more likely to present with more advanced stage disease. Stage for stage, their prognosis is worse, particularly for younger men.29,30 Recently, a crossover was noted after age 70 years, when black men have better disease-specific survival.29,30 Stratification for socioeconomic and educational level does not negate differences in incidence and mortality.13,26,31

Moul and colleagues32 showed that even in what is believed to be an equal-access health care setting, local failure after the treatment of similar stage, grade, and other clinical variables was still greater in black patients. However, a Veterans Administration study by Fowler and Terrell33 found that race did not affect the stage-specific survival of men who had localized prostate cancer treated with surgery or radiation therapy. Among men with similar clinical stage who were treated with surgery, the final pathologic stage and grade were similar in both groups.

In the large-scale screening study of Smith and colleagues,34 black men had a higher prevalence of detectable cancer and more were found with advanced cancer. However, those with clinically localized cancers who elected to undergo radical surgery had pathologic stages identical to those of white men. Although this study should be informative when long-term follow-up of recurrence
rates and survival data become available, even these results may be confounded by a potential selection bias: African-American men had a lower compliance rate for proceeding with a recommended biopsy than did white men, and fewer black men were willing to undergo radical surgery.34

Similar conclusions were reached by Schapira and colleagues35 based on an analysis of SEER data, suggesting that African-American men and white men receive different proportions and types of aggressive therapy for localized disease. This study and similar ones probing the impact of access to health care on prostate cancer outcomes suggest, however, that even if presumably equal access is available to various populations of patients, they may not take advantage of these opportunities equally. Thus, the decision-making process to respond to symptoms, to seek medical attention, to follow-up treatment recommendations, and to select therapy may be a complex multifactorial process that could ultimately explain some of the racial differences seen in outcome.

SOCIOECONOMIC STATUS

Differences in socioeconomic status have been suggested as a reason for the differences in incidence and mortality rates observed among various racial groups. Existing data suggest that the incidence of different types of cancer, including that of the prostate, increases with decreasing socioeconomic status.36 Several other studies failed to show an association between socioeconomic class and prostate cancer epidemiology or between educational level and cancer incidence.13,37

Although socioeconomic factors cannot explain the major differences observed among various racial groups, economic factors may influence access to health care, the type of care available, and even the attitudes and concern over health matters exhibited by the various populations. Powell and colleagues30 suggested in a large-scale Veterans Administration study that even when access and economic status are controlled for, significantly more black men present with advanced cancer. Interestingly, American Indians, who generally have a lower standard of living, have significantly lower rates of prostate cancer compared with other ethnic groups living in the same areas with a shared economic base.38 Hispanic men have lower prostate cancer rates than do white Americans.39

OCCUPATION

Men who live in rural areas present with higher stage prostate cancer than do men who reside in urban settings.40 Occupation is directly related to socioeconomic status and thus is difficult to study as an independent variable. Most studies focus on exposure to occupational hazards that may affect the biology of the disease. Farmers and city dwellers have similar incidences of disease. Those engaged in heavy physical labor may be at an increased risk.41 Workers in heavy industry, rubber manufacturing, and newspaper printing may have a slightly higher incidence.42 Critical evaluation of these data suggests that the proposed association is weak.

CIGARETTE SMOKING

The effects of cigarette smoking on the epidemiology of prostate cancer are inconclusive and difficult to interpret. Cigarette smoking has been well established as a cause of human malignancies such as lung cancer and has been associated with the development of many others, such as kidney and bladder cancer. Matzkin and Soloway43 reviewed the literature regarding the effects of cigarette smoking on prostate cancer and found conflicting reports. Some of the studies link prostate cancer to known carcinogens in tobacco smoke; others consider the effect of tobacco on serum hormone fluctuations. The data are not convincing
that cigarette consumption results in an increased risk of prostate cancer.

HEAVY METAL EXPOSURE

The prostate gland contains the highest level of zinc of all the organs in the body. Zinc is an essential ingredient of proper enzyme function and is required for DNA and RNA replication and repair. Cancerous prostate glands contain less zinc than do normal glands.44 No correlation has been found between serum levels of zinc and prostate cancer, but at least one study suggests that increased zinc intake may be a risk factor for prostate cancer.45 It has been postulated that zinc is somehow involved with retinoic acid metabolism and that diminished intraprostatic zinc levels may decrease the availability of retinol-binding protein. The cause and effect relationship of zinc levels and prostate cancer is yet to be confirmed.

Another trace element, cadmium, is an inhibitor of zinc metabolism. Overexposure to this agent also has been implicated in prostate cancer pathogenesis. High levels of cadmium may result from industrial exposure in those who work with batteries, paint, and cigarette manufacturing, and in other occupations. Prostate cancer mortality in workers with long-term exposure to high levels of cadmium has been disproportionately high, and cadmium workers often have clinically more aggressive tumors.46 Cadmium exposure may contribute to prostate cancer risk directly, or the risk may result from the effect of cadmium on zinc availability.

SEXUAL ACTIVITY AND SEXUALLY TRANSMITTED INFECTIONS

Considerable attention has been paid to patterns of sexual behavior and the development of prostate cancer. In different studies, the frequency of sexual activity has been found to have both a direct and an inverse relationship to the consequent development of the disease. Interpretation of these studies is hindered by the accuracy of data collection, assumptions made regarding marital status and degree of sexual activity, and associations with other variables, such as sexually transmitted diseases or vasectomy.

Some studies suggest that prostate cancer is related to early intercourse or sexual precocity, number of sexual partners, venereal disease, fertility as established by the number of children reported, and married versus unmarried life.24,47 By contrast, several studies found no change in the incidence of prostate cancer among Catholic priests48 and no association with the frequency of sexual activity, venereal disease, marital status, or number of children; some even found a decreased incidence of venereal disease among prostate cancer patients.49

Bacterial prostatitis, particularly a history of gonorrhea, has been suggested as an increased risk factor for prostate cancer. Several types of viruses have been isolated from cancer cells, such as human papillomavirus, cytomegalovirus, and herpesvirus, but so far only association, rather than causation, has been shown. This area is currently under intense investigation because many of these viruses are prevalent in the general population, and geographic, or possibly racial, variables may exist among the various subtypes, with different potential for carcinogenesis.

VASECTOMY

Recently, a history of vasectomy has been associated with an increased risk for prostate cancer.50-52 Although an equal number of studies provide evidence to the contrary.53 Studies that showed a positive relationship suggested that the relative risk of vasectomized men was 1.6-fold greater than that of controls; the risk correlated with the length of time elapsed since vasectomy.50,51 Many ongoing studies are addressing this issue, but deficiency of experimental design and methodologic
discrepancies limit their utility.\textsuperscript{54}

Why vasectomy should increase the risk of prostate cancer is currently unclear. Some studies suggest that vasectomy may increase serum androgen levels,\textsuperscript{55,56} although other studies failed to detect elevations in androgens.\textsuperscript{57} Vasectomy may induce antisperm antibodies, and an immunologic reaction may be responsible for elevation of prostate cancer rates.\textsuperscript{58,59} Vasectomy may cause an imbalance in the growth hormones or their inhibitors reaching the prostate. In addition, patterns of sexual activity, frequency of sexually transmitted diseases, or infections also may be altered.

**BENIGN PROSTATIC HYPERPLASIA**

Because of numerous similarities in pathophysiology, benign prostatic hyperplasia (BPH) has been investigated as a possible premalignant condition or precursor for prostate cancer. It has been suggested that BPH may predispose to cancer or that a common factor influences the development of both diseases. Studies to date, however, have been inconclusive.\textsuperscript{60}

BPH is a common condition in men that increases steadily with age, as prostate cancer does. By ages 70 and 90 years, 70\% and 90\% of men, respectively, are affected.\textsuperscript{61} BPH and prostate cancer are often found concurrently, and the diagnosis of prostate cancer is frequently made during the evaluation of obstructive symptoms associated with BPH. Both lesions are considered to be under similar androgenic hormone regulation. Although BPH arises from the transition zone of the prostate and most prostate cancers originate in the peripheral zone, approximately 20\% of cancers do develop from the transitional area. The frequency of incidental prostate cancer (stage A or TI) found at transurethral prostatectomy for BPH was as high as 20\% to 25\% in the pre-PSA era but has been declining as patients are evaluated for possible cancer before surgery.\textsuperscript{1}

These findings led investigators to search for a link between BPH and prostate cancer. Men diagnosed with BPH have been reported to be more likely (by as much as fivefold) to develop prostate cancer than are age-matched controls.\textsuperscript{62} In contrast, Greenwald and colleagues\textsuperscript{63} followed 838 cases of BPH and 802 age-matched controls for more than 10 years but failed to identify any difference in prostate cancer incidence between the two groups. Current efforts are directed toward establishing morphologic linkages between early lesions and clinical cancer and searching for common molecular markers of neoplastic transformation.\textsuperscript{60,64}

Because both conditions are generally found in the same age groups, any increase of cancer detected in men who are symptomatic from BPH may be simply a reflection of the increased intensity of the evaluation.

**HORMONES**

The prostate gland consists of stromal and epithelial elements under androgenic influence. The hypothalamus produces luteinizing hormone–releasing hormone, which stimulates the anterior pituitary to produce luteinizing hormone and follicle-stimulating hormone. Luteinizing hormone stimulates the Leydig cells of the testicles to produce testosterone. Testosterone enters androgen-sensitive cells of organs such as the prostate and is converted by the enzyme 5-alpha-reductase into dihydrotestosterone (DHT), the active metabolite influencing prostatic development. Other hormones, such as estrogen and prolactin, also may influence the growth of the prostate gland, either directly or indirectly by negative feedback inhibition.

Eunuchs, prepubertal castrates, and men with congenital abnormalities of androgen metabolism do not develop either BPH or prostate malignancy. Surgical or chemical androgen blockade can cause involution of benign prostatic hy-
perplasia and carcinoma; such blockade has been a successful treatment modality for metastatic disease. All of this is compelling evidence for the role of hormones in the pathogenesis of prostate cancer. Yet no consistent linkage has been established between steroid metabolism and development of prostate cancer, and inconclusive or conflicting reports abound in the literature.

Several studies have measured plasma androgen levels among men with prostate cancer and age-matched controls. Some studies found elevated testosterone and DHT levels among those with cancer, whereas others either did not detect any differences or actually found lower testosterone levels. The incidence of prostate cancer is lower in men with cirrhosis of the liver, a condition associated with elevated levels of circulating estrogens and decreased testosterone.

In contrast, a few studies found lower levels of circulating estrogens in men diagnosed with prostate cancer. Habib measured higher levels of tissue testosterone but lower levels of DHT in the prostates of men with prostate cancer compared with men who had benign prostatic hyperplasia, but the two groups had identical plasma levels. Geller and colleagues similarly noted lower DHT levels in patients with prostate cancer versus those with benign prostatic hyperplasia, but Drafta et al found the opposite.

Ross and colleagues showed that serum testosterone levels were approximately 15% higher in young African-American men than in white men; they suggested that this difference may explain the increased risk of prostate cancer in blacks. Japanese men, in contrast, were found to have lower levels of 5-alpha-reductase activity and consequently lower DHT levels than American men. Interestingly, DHT levels were similar among African-American men with or without prostate cancer, although cancer patients had elevated plasma testosterone levels. Lower levels of urinary aldosterone and testosterone were found in normal African black men compared with black men living in the United States, whereas black and white American men had similar levels.

Diet
Dietary patterns have been long implicated in the development of different types of malignancies. Consumed food components may be metabolized to carcinogens, may alter hormonal balance, or may contain vitamins, minerals, and nutrients that could protect against the development of certain cancers. The role of diet in the pathogenesis of prostate cancer is under intense scrutiny. Dietary differences among racial groups, socioeconomic classes, and geographic sites may explain some of the differences noted in prostate cancer epidemiology and biologic behavior.

Circulating androgen levels are altered by dietary patterns. Men on vegetarian or high-fiber diets have lower testosterone and plasma estradiol levels. Fibers excreted in feces may bind sex steroids, thereby lowering plasma levels by increased excretion. Black South African men on a Western diet had increased urinary excretion of androgens and estrogens compared with those eating traditional food, whereas the opposite was true for black American men fed a vegetarian diet. The rising rate of

A positive association of prostate cancer risk and total fat intake was found in all ethnic groups.
prostate cancer in Japan has been attributed to “Westernization” of the diet.

An association appears to exist between high dietary intake of animal fat and increased risk for the development of prostate cancer. Dietary fat intake is diametrically opposite in areas with a high risk for cancer development and areas with a low risk for cancer development. A multinational survey highly correlated prostate cancer deaths with total fat consumption. Whittemore et al in a large, multicenter study of dietary factors in black, white, and Asian-Americans with prostate cancer found a positive association of prostate cancer risk and total fat intake in all ethnic groups. They estimated that saturated fat intake accounts for 10% of the differences in the incidence of prostate cancer between black and white men and about 15% of the differences between white and Asian-American men.

For Asian-Americans, the length of time elapsed since immigration to North America was also correlated with cancer incidence. Similar relationships exist for breast and colon cancer incidence. Mortality from prostate cancer is lower in men who consume yellow and green vegetables daily. Some studies propose that obese men have a 2.5-fold increased risk of prostate cancer mortality. Diets rich in cereals also have a protective effect, as do those rich in fruits, tomatoes, beans, peas, and lentils.

Some studies have shown that beta-carotene has a protective effect, but the results have to be interpreted with caution. Many of the data in these studies come from retrospective analysis, in which other significant factors are difficult to control. Ligans and isoflavonoids, phytoestrogens found in soybean products, whole-grain cereals, seeds, nuts, and berries have been studied recently for their protective effects. It is hypothesized that intestinal bacteria convert these substances into hormone-like compounds with antioxidative and many other activities with a profound inhibitory influence on malignant transformation, cell proliferation, and angiogenesis.

Vitamin D deficiency has been implicated in the development of prostate cancer. Support for this hypothesis stems from the observation that men living in southern climates have a lower incidence of and mortality from prostate cancer than do their northern counterparts. It is theorized that ultraviolet light exposure in southern climates activates vitamin D, which, if present in sufficient amounts, has a protective effect.

Vitamin A, or retinoic acid, is another vitamin that is essential for normal differentiation of epithelial cells. Vitamin A deficiency has been linked to a variety of malignancies. It has been shown to have a chemopreventive role in head and neck malignancies and in experimentally induced prostate cancer in animal models. Retinoic acid is fat soluble, and intake of retinoic acid derived from vegetable sources is inversely proportional to prostate cancer incidence. Clinical trials are ongoing to study the role of retinoic acid derivatives in the prevention of human prostate cancer in high-risk patients.

**Latent Prostate Cancer**

The term *latent cancer* is used in the pathology literature to characterize malignancies that are discovered only on postmortem examination. Although the term may imply low virulence, the malignant potential for individual cancers discovered after death cannot be ascertained. Most prostate cancers are slowly progressive malignancies, and many are present for years before clinical diagnosis as latent neoplasms that are evident only histologically.

The length of time from the first histologically recognizable form of prostate cancer to clinically evident cancer is not known, but it probably varies widely. For the small subset of all histologic...
cancers that come to clinical discovery during the lifetime of the individual, studies of tumor doubling time indicate that this process may take more than 10 to 15 years.

During this time many men die of unrelated causes and their disease never comes to attention. Others whose diagnosis is made by various methods of early detection may not have significant disease. Some clinically diagnosed tumors, however, may have an aggressive course over time. Men who are diagnosed in their 50s and 60s probably started to develop their disease in their 30s and 40s. Unfortunately, although excellent statistics are available for clinically diagnosed cases, the true prevalence of prostate cancer in men who are not yet diagnosed is not well known.

Several indirect means have been used to estimate prostate cancer prevalence in a given population. In the past, unsuspected carcinoma was found in approximately 20% to 25% of specimens after transurethral surgery for what was thought to be benign prostatic hyperplasia. The number of unsuspected carcinomas discovered in surgical specimens has diminished greatly because of two factors: the development of nonsurgical management of many patients with symptoms of obstruction and increased emphasis on early detection with widespread use of PSA testing.

The prevalence of prostate cancer also has been estimated by the frequency of prostate cancer in cystoprostatectomy specimens removed for indications other than prostate cancer. Three major studies of operative specimens in which bladder cancer was the most common indication for surgery found unsuspected prostate cancer in 25% to 40% of cases. However, evidence exists that the two malignancies may share a common pathway of carcinogenesis and may occur together at a frequency nearly 20 times more than that expected in the general population.

Several autopsy studies have assessed the prostates of representative populations of men deceased from unrelated causes. Autopsy data from around the world show that carcinoma of the prostate first becomes histologically detectable at about age 30 years in a few rare instances, and then becomes increasingly more common with advancing age. By age 80 to 90 years, 70% to 90% of men have evidence of histologic tumors on autopsy, regardless of national origin. Most of the early tumors are microscopic in size; they may be multifocal and are generally well to moderately differentiated. The prevalence of the lesions is similar among African-American, white, and Japanese subjects. The similarities persist among Japanese men whether they live in Japan or the United States. In another comparative study, the prostates of Japanese men were smaller and had smaller tumors than those of American men. More significantly, the frequency of latent prostate carcinoma in Japan nearly doubled for each age group when the two time periods 1965 to 1979 and 1982 to 1986 were compared.

These results suggest that although major differences exist in the clinical incidence and overall disease outcome of prostate cancer among various geographic and racial groups, the prevalence of histologically detectable disease is similar. This may mean that only a small subpopulation of all histologically detectable tumors would ever become clinically detectable disease. We cannot pre-

**Autopsy studies show a prevalence of histologically detectable prostate cancer beginning at an early age and increasing proportionately with age.**

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dict the biologic potential of these lesions at present, but that is clearly the goal of future research efforts.

A second possible explanation is that although early prostate cancer prevalence is identical among the various groups, differences in the biology of the disease are manifested only later in the progression of the disease. A final possibility is that the major differences observed among various racial groups result from social issues, such as access to care, willingness to seek treatment, and so forth, not from biologic, genetic, or even environmental differences.

**Precursors of Prostate Cancer**

Many studies have investigated the prevalence and relationship of latent and clinically detected prostate cancer, but little is known about the prevalence of the precursors of prostate cancer. This is partly because of the controversy regarding the definition of what constitutes a premalignant lesion of prostate cancer.

The diverse atypical epithelial lesions of the prostate have acquired a variety of diagnostic terms that are often confusing and poorly reproducible and frequently represent overlapping morphologic entities. Recently, most pathologists have gradually come to an agreement that classifies atypical proliferative lesions of prostatic epithelium into two categories. Lesions in which the lining epithelium of preexisting ducts and acini undergoes architectural and cytologic atypia acquired the term *prostatic intraepithelial neoplasia* (PIN).94-96 Lesions characterized by the formation of new ductal and acinar units with minimal cytologic atypia of the lining cells of the newly formed structures are referred to by most authors as *atypical adenomatous hyperplasia* (AAH) or *adenosis*.97

Bostwick was instrumental in defining the diagnostic criteria for and the morphologic variants and grades of PIN.94,96,98 He and others reported numerous associations between PIN and prostate cancer on epidemiologic, clinical, genetic, and molecular levels.98-101 The frequency of PIN in prostates with cancer was shown to be significantly increased compared with that in prostates not harboring carcinoma (82% versus 43%).94,95

Several authors have subsequently reported similar findings with regard to the increasing frequency of PIN with advancing age and its association with carcinoma. Qian et al93 found that 86% of 195 whole-mount radical prostatectomies with cancer contained high-grade PIN, usually within 2 mm of the area of the cancer.

In a recent study from Brazil, Billis102 reported an 84.4% frequency of PIN in an autopsy series of 180 African-Brazilian and white Brazilian men 40 years of age or older. He indicated that PIN was more extensive and diffuse in African-Brazilians and appeared at a younger age compared with that found in whites. Isolated PIN (occurring without carcinoma) was found in approximately one-third of the individuals examined in this study. Extensive PIN was significantly higher in individuals older than 55 years.

This study supports previous reports indicating that PIN tends to occur predominantly in the peripheral zone of the prostate, where most cancers arise.103,104 Most foci of PIN are exclusively in the peripheral zone (63% of cases in one study) or simultaneously in the transition and peripheral zones (36%); only rarely (1%) are foci exclusively in the transition zone.

Kovi and colleagues105,106 reported that the highest frequency of PIN in the transition zone (37%) occurred in radical prostatectomy specimens with cancer; the frequency was significantly lower in transurethral resections. PIN was reported to be multifocal in 72% of radical prostatectomies with cancer, including 63% of those involving the nontransition zone and 7% of those involving the transition zone; 2% of cases had con-
comitant single foci in all zones.\textsuperscript{96,105-107} Most of these epidemiologic data are in accordance with the preliminary findings of a large, contemporary autopsy study conducted at Wayne State University in Detroit and the Wayne County Medical Examiners Office. The purpose of the study is to determine the prevalence of latent cancer and premalignant lesions of the prostate in African-American and white men.

We have documented a high prevalence of both latent cancer and PIN in a large cohort of men of the two races, with these neoplastic changes appearing as early as the third decade and increasing steadily with advancing age. Although we have reported a similar prevalence of latent cancer in the two races, preliminary findings indicate a higher prevalence of PIN in African-Americans, who also may have a more diffuse involvement of the gland by this lesion at a younger age compared with the age-matched white cohort of the study.\textsuperscript{22,88,108}

The epidemiologic data on AAH are not as well documented as are those concerning PIN. The reported prevalence of this lesion depends largely on the type of specimen evaluated. Unlike PIN, which is found predominately in the peripheral zone of the prostate, AAH occurs most frequently in the transition zone.\textsuperscript{90-93} Qian and Bostwick\textsuperscript{93} identified foci of AAH in 50 of 217 (23\%) totally embedded radical prostatectomy specimens. In 74\% of cases AAH was limited to the transition zone; in 12\% the foci were in other regions in addition to the transition zone, and in 14\% AAH was exclusively outside the transition zone. This localization is reflected in the much greater frequency of AAH in transurethral resection specimens than in needle biopsy specimens.\textsuperscript{109} With the increasing tendency to target the transition zone in needle biopsy, however, the frequency of AAH in needle biopsy specimens is increasing.\textsuperscript{110}

In conclusion, although both PIN and AAH have been discussed as potential precursors of prostate cancer, the evidence linking a premalignant entity to clinically detectable and potentially significant prostate cancer is much better established for PIN than for AAH.

**Summary**

Malignant transformation of the prostate and progression of carcinoma appear to be the consequence of a complex series of initiation and promotional events under genetic and environmental influences. Increased incidence of the condition may be the result of improved detection, greater awareness of the condition, and possibly an increased life expectancy accompanied by a decrease in competing causes of death rather than a true increase in the prevalence of the disease. The marked racial and geographic differences are probably multifactorial, with genetic, environmental, and possibly social influences affecting progression of the disease.

Among several risk factors, evidence for the familial inheritance of some prostate cancers is compelling. Dietary influences, hormonal milieu, and the role of environmental carcinogens are currently under intense investigation. As further risk factors are identified, it will become increasingly important to identify individuals at increased risk for the disease. These men should undergo regular evaluation with state-of-the-art methods.
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