Risk factors for prostate cancer

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INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide, according to data from the World Health Organization (WHO) GLOBOCAN database. The current lifetime risk of prostate cancer for men living in the United States is estimated to be approximately one in eight [1], but incidence is highly dependent on screening with prostate-specific antigen (PSA), and the number of PSA-driven biopsies.

Rates of prostate cancer differ over 50-fold among various international populations (figure 1) [2]. However, interpretation of these data is complicated by dramatic changes in the incidence of prostate cancer in the United States and other Western countries that have taken place over the past several decades. These changes have been primarily driven by the increased frequency of prostate biopsies performed in asymptomatic men because of an elevated PSA level. In the United States, the incidence of prostate cancer dramatically rose in the early 1990s concomitant with the increasing utilization of PSA testing. After an initial peak, incidence rates fell, but they have persisted at a rate nearly twice that recorded in the pre-PSA era. A central argument against routine PSA screening is that many of these cancers, if left undetected, would never have become clinically meaningful during a man's lifetime. (See "Screening for prostate cancer".)

Ascertainment biases constitute an important, but incomplete, explanation for the observed international variations in prostate cancer incidence. Countries that do not utilize PSA testing typically have a much lower rate of prostate cancer compared with those that do. Unless studies

control for the number of prostate biopsies performed, it is difficult, if not impossible, to be definitive in the conclusions regarding epidemiologic studies.

Of the several known prostate cancer risk factors, the most important are age, ethnicity, genetic factors, and possibly dietary factors. The known risk factors for prostate cancer are reviewed here. Screening for prostate cancer and the clinical manifestations and diagnosis of this disorder are discussed separately. (See "Screening for prostate cancer" and "Clinical presentation and diagnosis of prostate cancer".)

This review will focus on the most common histologic type of prostate malignancy (adenocarcinoma) which comprises over 99 percent of the malignancies which affect this organ. Other histologies include small cell neuroendocrine tumors, sarcomas, and lymphomas, which are rarely encountered. (See "Interpretation of prostate biopsy".)

AGE

Prostate cancer has one of the strongest relationships between age and any human malignancy (figure 2).

Clinically diagnosed prostate cancer rarely occurs before the age of 40, but the incidence rises rapidly thereafter, peaking between the ages 65 and 74. In data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, the percentages of new cases of prostate cancer for men ages 35 to 44, 45 to 54, 55 to 64, 65 to 74, 75 to 84, and 85 between 2011 and 2015 were 0.5, 9.0, 32.7, 38.8, 15.1, and 3.9 percent, respectively.

The prevalence of malignancy based on histologic examination of the prostate from men without clinical evidence of prostate cancer is much higher than the rate of clinically diagnosed disease [3]. Although the reported prevalence rates for occult prostate cancer have varied substantially in different studies, the prevalence increased dramatically with age in all studies.

The widespread prevalence of occult prostate cancer in older men and the dramatic increase with age are illustrated by a review of autopsy studies conducted in multiple countries [3]:

- 20 to 30 years, 2 to 8 percent of men with occult cancer
- 31 to 40 years, 9 to 31 percent
- 41 to 50 years, 3 to 43 percent
- 51 to 60 years, 5 to 46 percent
- 61 to 70 years, 14 to 70 percent
- 71 to 80 years, 31 to 83 percent

- 81 to 90 years, 40 to 73 percent

The variability between reports may reflect differences in pathologic techniques, or geographic differences due to environmental or ethnic factors.

Although the overall incidence is very low, at least some data suggest that the incidence of prostate cancer in younger men may be increasing globally [4-6]. As an example, in a study derived from the SEER database of the United States National Cancer Institute and the Institute for Health Metrics and Evaluation's Global Burden of Disease database, the number of men diagnosed with prostate cancer at age <40 years has approximately doubled since 1995 (from approximately 0.1 per 100,000 to 0.2 per 100,000), with most of the increase in men aged 30 to 40 [4]. Notably, men under the age of 40 at diagnosis were at a high risk of metastatic disease, and they had a higher death rate compared with men in older age groups. One of the limitations of this study was the lack of information on how much of the increased incidence was because of prostate-specific antigen screening. The risks and benefits of screening men in this age group for prostate cancer are unknown. (See "Screening for prostate cancer".)

ETHNICITY

Prostate cancer is more common in Black compared with White or Hispanic men, perhaps related to a combination of dietary and/or genetic factors (figure 3) [7-10]. The annualized average incidence rates for men in their early 70s per 100,000 population is approximately 1600, 1000, and 700 for African Americans, White Americans, and Asian Americans, respectively. Although incidence rates in Native Americans are even lower than in Asian Americans, ascertainment biases prevent credible comparisons for this subpopulation. Data on African Americans being at higher risk precede the prostate-specific antigen (PSA) era, and PSA testing cannot explain the higher incidence of disease in this group of men.

In addition to higher incidence rates, the age of onset in African American men is earlier than for comparative groups. In a multi-institutional series of over 12,000 cases, 8.3 percent of Black men and 3.3 percent of White men were less than 50 years of age [11].

Many studies have found that African American men also have higher serum PSA levels, have worse Gleason scores, have a more advanced stage of disease at the time of diagnosis [12-14], and receive less guideline-concordant care [15,16]. In the population-based Prostate Cancer Outcomes Study, the increased risk of advanced-stage disease persisted in African American men, even after adjustment for socioeconomic, clinical, and pathologic variables [12]. One

report found that African American men diagnosed at an early stage still had a higher than expected rate of biochemical recurrence [17].

Poor health literacy has been implicated as a factor for advanced stage at presentation, irrespective of race [18]. Also of interest, African American men aged 60 and older (but not other age groups) with clinically localized prostate cancer received aggressive treatment significantly less often than either White American or Hispanic American men [19]. Similar results have been noted by others [20]. The reasons for the differences in care received are not completely known.

However, others have shown that an African American man with prostate cancer of any stage who receives appropriate treatment has the same risk of death as a White man with the disease [14,21-25]:

- An individual patient data meta-analysis of 8452 patients with metastatic castration-resistant prostate cancer treated in nine randomized phase III trials using docetaxel found no difference in median overall survival between African American and White American men (21.0 versus 21.2 months) [22]. On multivariable analysis adjusting for established risk factors, the pooled outcome showed better results in the African American population (hazard ratio [HR] for death 0.81, 95% CI 0.72-0.92).

- A separate analysis compared outcome data for Black and White men with localized prostate cancer who were reported to the population-based Surveillance, Epidemiology, and End Results (SEER) registry, enrolled in four randomized clinical trials conducted by the Radiation Therapy Oncology Group (RTOG), or treated at one of five equal-access regional medical centers within the Veterans Affairs (VA) health system [23]. Stage for stage, equal treatment (ie, in a clinical trial or within the VA system) gave essentially equal outcomes for African American men in terms of prostate cancer-specific mortality. However, mortality from non-prostate-cancer causes was much higher for African American men.

Thus, it seems likely that causes other than prostate cancer might be implicated in the excess mortality rates reported for African American men with prostate cancer. For clinicians caring for African American men, managing comorbid conditions such as diabetes and hypertension may be just as important as managing prostate cancer. Optimal care should include comanagement with primary care clinicians.

FAMILY HISTORY AND GENETIC FACTORS

Prostate cancer has a strong inherited component. Men with a family history of prostate cancer on either side of the family, particularly those with a first-degree relative who was diagnosed at

age <65 years, are at increased risk for prostate cancer [26-30]. In addition, having a family history of other potentially heritable cancers (eg, breast cancer diagnosed at age <50 years, male breast cancer, colorectal cancer, ovarian cancer, pancreatic cancer, melanoma) may also increase the risk of prostate cancer. Men with a family history of breast cancer are also at a higher risk of prostate cancer [31].

Heritable (germline) factors contributing to genetic risk for prostate cancer can be divided into two main categories:

- Rare deleterious changes (often termed "pathogenic variants" or "mutations") disrupt the function of a known gene. In general, pathogenic variants, such as those in DNA repair pathways (eg, breast cancer susceptibility gene 2 [*BRCA2*], ataxia telangiectasia mutated [*ATM*]), are uncommon in the population but are associated with a high lifetime risk of cancer (high penetrance), including prostate cancer.

- More common variants, often single-nucleotide polymorphisms (SNPs), may be identified within the regulatory or protein-coding regions of a gene or in the intra- or intergenic regions of DNA. These SNPs may directly influence the regulation or function of the gene containing the variant, or the SNP may associate with or regulate a nearby or distant gene that has yet to be directly implicated in the disease. SNPs are relatively common, with allele frequencies of 1 to 5 percent in the population, but they individually confer very modest increases in risk.

The genetic factors associated with prostate cancer and the implications for referral for screening and genetic evaluation are discussed separately. (See "Genetic risk factors for prostate cancer".)

DIET

Comprehensive reviews of the association between intake of nutrients and the risk of prostate cancer are available [32,33]. The most important components of the diet and the intake of some vitamin and mineral supplements will be discussed here. The use of some of these compounds as chemopreventive agents is discussed in detail elsewhere. All studies that implicate diet in prostate cancer risk are observational and should not be considered definitive. (See "Chemoprevention strategies in prostate cancer".)

Animal fat — A diet high in animal fat may be an important factor in the development of prostate cancer [34-38]. In particular, intake of large amounts of alpha-linolenic acid and low

amounts of linoleic acid appear to be associated with increased risk; this combination is common in red meat and some dairy products [37-39].

Vegetables — A diet low in vegetables may be another risk factor for prostate cancer [35,40,41]. A case-control study found a higher prostate cancer risk in men who consume fewer than 14 servings of vegetables weekly, compared with 28 or more servings (adjusted odds ratio 1.54) [40].

On the other hand, there was no association between fruit and/or vegetable consumption and the risk of prostate cancer among 29,361 men in the screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, 1338 of whom developed prostate cancer [42]. High intake of cruciferous vegetables (particularly broccoli and cauliflower) was associated with a significantly lower risk of extra-prostatic tumors (stage III or IV (table 1 and table 2)) at presentation. Because the PLCO trial controls for prostate cancer screening, these data may be viewed as a particularly important study of dietary habits and prostate cancer risk.

Lycopene and tomato based products — Tomato-based products are rich in lycopene, which has potent anti-oxidant properties. These observations have led to analyses of the impact of lycopene and tomato-based products on the incidence and natural history of prostate cancer.

Initial studies of the impact of lycopene-containing foods on the risk of prostate cancer gave conflicting results [43-45]; a 2007 United States Food and Drug Administration evidence-based review concluded that there was no credible evidence to support an association between lycopene intake and a reduced risk of prostate cancer, and only limited evidence to support an association between tomato consumption and reduced prostate cancer risk [46].

More recently, an analysis of a prospective cohort of 51,529 men from the Health Professionals Follow-Up Study has suggested that dietary intake of lycopene is associated with a lower incidence of prostate cancer and a decreased risk of lethal prostate cancer [47]. Analysis of tumor biomarkers was consistent with a possible role of inhibition of tumor neoangiogenesis as the mechanism underlying these observations.

Potential explanations for the difference between these observations and the conflicting results seen earlier include more detailed assessment of dietary lycopene, a wider range of lycopene levels compared with earlier studies, and the focus on the more aggressive prostate cancers. However, these data are observational and the possible role of confounding factors cannot be excluded.

Soy intake — Phytoestrogens (flavones, isoflavones, lignans) are naturally occurring plant compounds that have estrogen-like activity. Genistein and daidzein, the predominant

isoflavones in human nutrition, are derived mainly from soybeans and other legumes.

It is postulated that phytoestrogens such as those found in soy foods may reduce prostate cancer risk either via their inherent estrogenic properties (which favorably alters the hormonal milieu), or by inhibition of the enzyme 5-AR, which decreases concentrations of the more prostate-active androgen dihydrotestosterone. The higher intake of soy products among Asian men has been hypothesized to be one reason for the lower incidence of prostate cancer among these men.

Although few human studies have been conducted, cohort studies have shown a modest protective benefit of soy intake on prostate cancer risk [48-50]. A meta-analysis of two cohort and six case-control studies addressing the protective benefit of soy food intake on the risk of prostate cancer yielded an overall risk estimate of 0.70 (95% CI 0.59-0.83) [51]. The utility of soy protein as a chemopreventive agent is discussed elsewhere. (See "Chemoprevention strategies in prostate cancer".)

Omega-3 fatty acids and fish oil — Case-control analyses of serum samples from two large trials (Prostate Cancer Prevention Trial [PCPT], Selenium and Vitamin E Cancer Prevention Trial [SELECT]) found that high levels of omega-3 fatty acids, such as those found in fish oil, were associated with an increased risk of clinically significant, high grade prostate cancer [52,53]. These studies cannot be considered definitive, but these data concerning the effect of omega-3 fatty acids on prostate cancer risk should be considered in balancing the potential risks and benefits of these agents. (See "Fish oil: Physiologic effects and administration".)

Alcohol — Studies examining the association between alcohol intake and prostate cancer risk have reported mixed results:

- A 2001 meta-analysis based on 235 studies that included over 117,000 cases failed to identify a consistent relationship between alcohol intake and prostate cancer [54].
- This issue was subsequently addressed in the prospective PCPT [55]. There was no association between alcohol consumption and prostate cancer risk in 10,660 men with no or moderate alcohol intake (0 to <50 g/day). However, among the 260 men consuming ≥50 g/day (2.4 percent of the entire population), the relative risk [RR] of high-grade prostate cancer was 2 (95% CI 1.3-3.1).
- On the other hand, a prospective cohort study using the Health Professionals Follow-Up Study suggested that alcohol consumption was associated with a lower risk of lethal prostate cancer (any versus none, hazard ratio [HR] 0.84, 95% CI 0.71-0.99) [56]. Among men with prostate cancer, total alcohol consumption was not associated with progression

to lethal prostate cancer, whereas moderate red wine intake was associated with a lower risk (any versus none, HR 0.50, 95% CI 0.29-0.86).

Coffee — Increasing consumption of coffee appears to be associated with a decreased risk of lethal prostate cancer (defined as fatal or metastatic). A prospective analysis of almost 48,000 men from the Health Professionals Follow-Up Study identified 5035 men with confirmed prostate cancer, including 642 who died or had metastatic disease, identified over a 20 year period [57]. The decrease in risk of lethal prostate cancer was inversely proportional to increases in coffee consumption (RR 0.44, 95% CI 0.22-0.75, for those drinking six or more cups of coffee per day), and the decreased risk was present after controlling for other known prostate cancer risk factors. The inverse relationship appeared to be related to coffee components other than caffeine; a similar level of protection was seen for those drinking regular and decaffeinated coffee.

Vitamin and mineral supplements

Multivitamins — The regular use of multivitamins does not appear to affect the risk of early or localized prostate cancer [58]. However, two reports have observed an increased risk of advanced or fatal prostate cancer in men using relatively large amounts of multivitamins [58,59].

The potential relationship between the self-reported frequency of multivitamin use and prostate cancer was illustrated by a prospective study of 295,000 men [58]. Multivariate analyses showed no significant increase in the overall incidence of prostate cancer, regardless of the frequency of multivitamin use. However, there was an increase in both advanced and fatal cases of prostate cancer among men using multivitamins more than seven times per week compared with those using such vitamins less frequently or not at all (RR 1.32, 95% CI 1.04-1.67 and RR 1.98, 95% CI 1.07-3.66, respectively).

This increased risk of advanced or fatal prostate cancer may have been due to the increased use of multivitamins in men with symptoms of undiagnosed disease. Additional study of a possible relationship is needed.

Folic acid and B12 — High serum folic acid and B12 levels may be associated with a small increase in the risk of prostate cancer. Data supporting a possible causal relationship come from cohort studies and from a secondary analysis of a randomized trial.

- A nested case-control analysis using individual participant data from six cohort studies compared 6875 men with prostate cancer with 8104 controls [60]. Higher folate levels were associated with an increased risk of prostate cancer (odds ratio for top one-fifth

versus bottom one-fifth 1.13, 95% CI 1.02-1.26), but the increased risk was limited to high-grade disease (odds ratio 2.30, 95% CI 1.28-4.12). Higher B12 levels also were associated with an increased risk (odds ratio 1.12, 95% CI 1.01-1.25), but the risk did not differ by disease grade.

- In a trial to assess the chemoprevention of colorectal polyps, 34 histologically confirmed cases of prostate cancer were diagnosed among 643 evaluable men who had been randomly assigned to either folic acid (1 mg/day) or placebo [61]. At a median follow-up of seven years, the 10-year incidence of prostate cancer was significantly increased in those given folic acid (9.7 versus 3.3 percent with placebo, HR 2.63, 95% CI 1.23-5.65). However, there was no increase in the risk of prostate cancer among those with higher baseline dietary folate intake.

Additional studies are required to understand the relationship between folic acid and the development of prostate cancer.

Selenium and vitamin E — The relationship between prostate cancer, and selenium intake and level is complex.

Results from large randomized trials specifically assessing these compounds as chemopreventive agents have provided no evidence of any decrease in prostate cancer risk, and in fact, there may be a higher risk of prostate cancer with vitamin E, as shown in large prospective trials. (See "Chemoprevention strategies in prostate cancer", section on 'Selenium' and "Chemoprevention strategies in prostate cancer", section on 'Vitamin E'.)

Some of the most comprehensive data evaluating selenium levels and prostate cancer risk come from an individual patient data meta-analysis conducted by the Endogenous Hormones, Nutritional Biomarkers, and Prostate Cancer Collaborative Group [62]. This analysis included data from 15 studies including 6947 men with prostate cancer and 8170 controls.

- In the subset of cases where selenium levels were measured in the blood, the selenium level was not associated with a difference in the risk of prostate cancer (odds ratio 1.01, 95% CI 0.83-1.23). However, high blood levels were associated with lower risk of aggressive disease (advanced-stage disease and/or prostate cancer death).

- In those cases where selenium was measured in nails rather than blood, higher levels of nail selenium were associated with a decreased incidence of prostate cancer (odds ratio 0.29, 95% CI 0.22-0.40), both nonaggressive and aggressive disease.

On the other hand, this association could not be confirmed in a subsequent nested case-control study that examined toenail selenium and plasma selenoprotein P in a cohort of 27,178 men (including 1160 men who were diagnosed with advanced prostate cancer who were risk set-matched to one control) in a Danish "Diet, Cancer and Health" cohort; there were no associations between levels of toenail or plasma selenium and prostate cancer risk, including the risk of advanced, high-grade, or advanced-stage prostate cancer [63].

Zinc — At least two studies have suggested an association between zinc supplement use and an increased risk of prostate cancer [64,65]. In the Health Professionals Follow-Up Study, which included 46,974 American men, 2901 cases of prostate cancer were diagnosed over a 14 year period [64]. Compared with nonusers, men who consumed over 100 mg of supplemental zinc daily had a 2.29-fold increased risk of prostate cancer; the RR was 2.37 in those who took zinc for 10 or more years.

Calcium and vitamin D — A link between intake of dairy products and calcium and a higher risk of prostate cancer risk has been suggested in many [66-70] but not all studies [71,72]. In a meta-analysis examining the association of dairy product and calcium intake and prostate cancer risk, men with the highest intake of dairy products (RR 1.11, 95% CI 1.0-1.22) and calcium (RR 1.39, 95% CI 1.09-1.77) were more likely to develop prostate cancer than those with the lowest intake [69].

Epidemiologic studies suggest that the relationship between vitamin D levels and the incidence of prostate cancer is complex. Vitamin D deficiency has been suggested as a "common pathway" underlying the association of prostate cancer risk with other epidemiologic risk factors (eg, age, African American race, and geographic area of residence) [73]. Others have shown a link between certain haplotypes of the vitamin D receptor, vitamin D levels, and the risk of prostate cancer [9,68].

However, studies directly analyzing vitamin D levels and the risk of prostate cancer have been conflicting:

- Studies from Scandinavia, where there is a relatively high incidence of vitamin D deficiency, have suggested that there is an increased risk of prostate cancer in men with both the lowest and highest vitamin levels [74,75].

- In the United States, where vitamin D deficiency is less common, studies have not clarified the relationship between vitamin D levels and the risk of prostate cancer [76]. In a nested, case-control study derived from the PLCO Cancer Screening Trial, which examined the correlation between baseline levels of serum vitamin D and subsequent development of prostate cancer, there was no statistically significant trend in overall prostate cancer risk

associated with the serum vitamin D levels, although higher levels of vitamin D were associated with increased aggressiveness in those men diagnosed with prostate cancer (ie, Gleason score ≥7 or stage III or IV disease at diagnosis) [77]. This finding was not replicated in other United States cohorts, however [78-81]. Furthermore, an analysis of individual patient data from 19 prospective case-control studies derived from a variety of populations found that higher levels of circulating 25-hydroxyvitamin D were associated with a higher risk of nonaggressive prostate cancer but not prostate cancer with aggressive features [82].

The role of vitamin D in chemoprevention of prostate cancer is discussed elsewhere. (See "Chemoprevention strategies in prostate cancer", section on 'Vitamin D analogs'.)

CIGARETTE SMOKING

Cigarette smoking may have an effect on both the risk of developing prostate cancer and its prognosis once a diagnosis is established.

There are conflicting data on whether tobacco use is an independent risk factor for prostate cancer [83]; cohort studies have largely failed to document a significant impact of smoking status on elevated risk [84-91], while most case-control studies have found either an increased risk for prostate cancer or more frequent high-grade prostate cancer and advanced stages in smokers [92-97]. These disparate results can be at least partially explained by selection bias (eg, men free of cancer at inclusion in cohorts versus prostate cancer patients in case-control studies), various smoking habits, and different smoking prevalence rates (eg, based on geographic region) [83].

Another potential confounder is race. Most studies examining smoking as a risk factor for prostate cancer have focused on White populations. However, smoking appears to have a much larger impact in African Americans. As an example, in a study that analyzed 1085 men with prostate cancer, African American heavy smokers had a statistically significant increased risk of prostate cancer diagnosis (odds ratio 2.6) and high-grade prostate cancer (odds ratio 1.9) compared with never smokers and light smokers [92]. By contrast, among White American men, a positive history of heavy cigarette use (ie, 20 or more cigarettes smoked per day) did not confer increased odds of being diagnosed with prostate cancer.

There are more consistent data on the association of smoking at the time of diagnosis with risk of a cancer recurrence and cancer-related mortality [98-105]:

- The largest published systematic review and meta-analysis of the impact of smoking included data from over 50,000 men with prostate cancer and over 11,000 deaths [105]. In an analysis of the primary endpoint there was a significantly increased risk of death from prostate cancer (relative risk 1.24, 95% CI 1.18-1.31), and the increased risk was correlated with increasing number of cigarettes smoked. The relationship between incidence of prostate cancer and smoking was unclear with different trends in the pre- and post-prostate-specific antigen era.

- In a second meta-analysis of 16 observational studies totaling 22,549 men treated for localized prostate cancer, compared with never smokers, current smokers had a significantly higher risk of biochemical recurrence (hazard ratio [HR] 1.59, 95% CI 1.40-1.80), as did former smokers (HR 1.19, 95% CI 1.09-1.30) [102]. Current smokers were also at a higher risk for metastasis (HR 2.51, 95% CI 1.80-3.51) and prostate cancer-specific mortality (HR 1.89, 95% CI 1.37-2.60), while former smokers were not (HR for metastasis 1.61, 95% CI 0.65-3.97; HR for prostate cancer-specific mortality 1.05, 95% CI 0.81-1.37). Results were similar in men treated with radical prostatectomy or radiation therapy.

Men with prostate cancer should be strongly encouraged to stop smoking. (See "Overview of smoking cessation management in adults".)

HORMONE LEVELS AND OBESITY

Serum concentrations of androgens and insulin-like growth factor 1 (IGF-1) have been studied as possible risk factors for prostate cancer.

Sex hormones — Multiple studies have looked at the relationship between serum levels of various sex hormones and the risk of developing prostate cancer. The most definitive data regarding the relationship between serum sex hormone levels and prostate cancer come from a pooled analysis of 18 prospective trials, which included 3886 men with prostate cancer and 6438 controls [106]. Serum concentrations of testosterone, dihydrotestosterone (DHT), and other active androgen derivatives obtained prior to diagnosis were NOT associated with an increased risk of subsequent prostate cancer. In addition, no association was seen with prediagnosis serum levels of estrogens (estradiol, free estradiol).

In addition, testosterone supplementation as a treatment for hypogonadism does not appear to be associated with an increased risk of prostate cancer, although monitoring for prostate abnormalities is recommended. (See "Approach to older men with low testosterone", section on

'Prostate cancer' and "Testosterone treatment of male hypogonadism", section on 'Prostate cancer'.)

A possible link between androgenic stimulation and prostate cancer provided the rationale for the Prostate Cancer Prevention Trial (PCPT) and the REDUCE Trial, which used finasteride and dutasteride, respectively, to block the conversion of testosterone to its more active derivative DHT. The results and interpretation of this trial are discussed separately. 5-alpha reductase inhibitors have been associated with a higher risk of high-grade disease, and the US Food and Drug Administration (FDA) has attached warnings regarding this association to the labels of both finasteride and dutasteride. (See "Chemoprevention strategies in prostate cancer", section on '5-Alpha reductase inhibitors'.)

Insulin and insulin-like growth factor — Multiple studies have analyzed the relationship between insulin and insulin-like growth factor (IGF) and the subsequent development of prostate cancer.

A meta-analysis based on individual patient data from 3700 men with prostate cancer and 5200 controls found a modest increased risk of prostate cancer in those men with the highest circulating levels of IGF-1 (odds ratio 1.38, 95% CI 1.19-1.60, for the highest versus lowest quintile) [107]. The association appeared strongest for low-grade, rather than high-grade, prostate cancers.

Similarly, most [108-111] but not all [112] series support a relationship between higher serum insulin levels, waist-hip ratio (WHR; a marker of body fat distribution) and prostate cancer risk. In a representative case-control study of Chinese men, those in the highest tertiles of WHR and serum insulin levels had an 8.55-fold higher risk of prostate cancer than men in the lowest tertiles of both factors [109].

Obesity — Multiple studies analyzing the relationship between the incidence of prostate cancer and weight have varied substantially in their results; however, meta-analyses have consistently demonstrated a small but statistically significant association between obesity and prostate cancer incidence [113-116].

Interpretation of the effect of weight on prostate cancer incidence may be made more difficult by the observation that increasing body mass index is associated with a decrease in serum prostate-specific antigen (PSA), which may minimize the diagnosis of prostate cancer based on PSA screening [117].

Among men with prostate cancer, there is a clear relationship between obesity and disease aggressiveness, with an increase in both biochemical recurrence rate following treatment and

prostate cancer-specific mortality [118-120]. The increases in recurrence rate and mortality are proportional to the degree of obesity. The pathogenesis is debatable, and explanations are unclear for this relationship.

Physical activity — Although the data linking body mass index and prostate cancer aggressiveness would suggest that regular physical activity may be beneficial, whether exercise protects against the development or progression of prostate cancer is uncertain. This issue was addressed in a study using data from the Health Professionals Follow-Up Study, a cohort of 47,620 United States health professionals followed from 1986 to 2000 [121]. There was no association overall between prostate cancer incidence and total, vigorous or non-vigorous physical activity in the entire population. However, men over the age of 65 who were in the highest category of vigorous activity (more than three hours per week of vigorous activity) had a significantly lower risk of advanced (relative risk [RR] 0.33, 95% CI 0.17-0.62) or fatal (RR 0.26, 95% CI 0.11-0.66) prostate cancer. Younger men derived no benefit. However, in all age groups, men with high levels of physical activity (more than 29 metabolic equivalent hours versus none) were less likely to be diagnosed with high-grade (Gleason score ≥7) prostate cancers.

Some (but not all) of the beneficial effects of exercise in older men may be related to sun exposure while exercising outdoors. In a sample of men in this cohort, men who reported higher levels of physical activity had higher circulating levels of 25-hydroxyvitamin D [122]. However, while both vigorous and non-vigorous activity were associated with higher vitamin D concentrations, only vigorous activity was associated with a lower risk of advanced prostate cancer.

In contrast to these data, another report from the same investigators suggests that young lean men who are more physically active have an increased risk of developing metastatic disease and fatal prostate cancer if they had a high energy intake [123].

Thus, although there are many benefits from regular physical exercise, it is not clear that a reduced incidence of prostate cancer is among them.

OTHER FACTORS

5-alpha reductase inhibitors — The US Food and Drug Administration (FDA) has concluded that although 5-alpha reductase inhibitors lower the prostate-specific antigen (PSA), they potentially increase the risk of high-grade prostate cancer. The role of these agents for prostate cancer chemoprevention is discussed separately. (See "Chemoprevention strategies in prostate cancer", section on '5-Alpha reductase inhibitors'.)

Infection and chronic inflammation — Several different infectious etiologies have been postulated as contributory factors in the development of prostate cancer.

Prostatitis — The available data from case-control studies, cohort studies, and meta-analyses suggest a significant but modest increase (approximately 1.5- to 2-fold) in the risk of prostate cancer in men with prostatitis, but the data are generally of low quality and the relationship between prostatitis and prostate cancer remains unclear in African Americans [124-128]. Despite a significant body of work relating inflammation to cancer, a cause and effect relationship has not been established between prostate cancer and prostatitis. Furthermore, PSA values can be elevated with prostatitis, leading to more prostate biopsies and a greater likelihood of making the diagnosis of cancer.

As discussed in the introduction, ascertainment biases are significant in prostate cancer. Any factor associated with an elevation in the serum PSA would be expected to lead to more biopsies being performed, and consequently, more cancers being detected. (See 'Introduction' above.)

Trichomonas vaginalis infection — Case-control series from the Health Professionals Follow-Up Study and the Physician's Health Study both have shown an increased incidence of seropositivity for antibodies against trichomonas vaginalis in men who subsequently are diagnosed with prostate cancer [129,130]. This association was more pronounced in those with more advanced or higher Gleason grade tumors.

Environmental carcinogens

Agent Orange — Exposure to Agent Orange, an herbicide defoliant sprayed extensively in Vietnam between 1965 and 1971 that contained dioxins, appears to be associated with an increased incidence of prostate cancer. The cases of prostate cancer arising in those exposed to Agent Orange appear to be more aggressive [131-133].

The initial studies that analyzed a possible relationship between exposure to Agent Orange and the subsequent development of prostate cancer yielded conflicting results [131,134-136]. These studies were limited by relatively limited numbers of patients, the young age of the cohorts involved, and potential biases of recall about Agent Orange exposure.

The most extensive study analyzed the history of Agent Orange exposure in a cohort of 13,124 Vietnam veterans from the Veterans Administration electronic medical record database [137]. Prostate cancer developed significantly more frequently in those exposed to Agent Orange (239 of 6214 men exposed [3.8 percent] versus 124 of 6930 unexposed [2 percent]). Among those with prostate cancer, a Gleason score of 8 to 10 was significantly more frequent in those

exposed to Agent Orange, as was the likelihood of having metastatic disease at presentation (21.8 versus 10.5 and 13.4 versus 4 percent, respectively). There was no difference in the history of PSA screening in those with and without Agent Orange exposure, and a history of Agent Orange exposure was established prior to the diagnosis of prostate cancer in all cases. Implications for Agent Orange exposure for United States veterans can be significant with regards to designation of service-connected illnesses.

Chlordecone — Chlordecone is an organochlorine insecticide with estrogenic properties, which was widely used in the West Indies from 1973 to 1993. Chlordecone has been shown to be carcinogenic in laboratory animal models. A case-control series compared plasma levels of chlordecone and exposure history in 623 men with prostate cancer with 671 controls [138]. There was a statistically significant increase in the incidence of prostate cancer, which was related to the measured level of this agent as well as exposure history. The mechanisms underlying these observations require further study.

Bisphenol A — Exposure to abnormal concentrations of estrogen early in life may initiate changes in prostate stem cells. These changes have been postulated to persist into later life and potentially contribute to the development of prostate cancer [139].

Bisphenol A is widely used in the manufacture of a variety of products such as plastics and resins that are widely present in the environment. In vitro studies and animal models have demonstrated that bisphenol A has significant estrogenic effects on human prostate stem cells, at concentrations consistent with its presence in the environment [140]. The potential contribution of exposure to bisphenol early in life to the subsequent development of prostate cancer remains uncertain.

Use of NSAIDs — Intake of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with a decreased risk of some cancers, particularly colorectal cancer. (See "NSAIDs (including aspirin): Role in prevention of colorectal cancer".)

An inverse association between long-term NSAID use and prostate cancer risk has also been suggested, although the magnitude of the risk reduction is unclear [141-144].

- The largest cohort study examined the association between NSAID use and prostate cancer incidence among 70,144 men in the American Cancer Society Cancer Prevention Study II Nutrition Cohort [141]. Information on use of NSAID was obtained from questionnaires completed at study entry and five to six years later. Over a nine-year follow-up period, 4853 cases of incident prostate cancer were diagnosed. Long duration regular use (30 or more pills per month for five or more years) of either NSAIDs (relative risk [RR]

0.82, 95% CI 0.71-0.94) or adult-strength aspirin (RR 0.85, 95% CI 0.73-0.99) was associated with a significantly reduced incidence of prostate cancer.

- A meta-analysis that looked specifically at the potential effects of aspirin analyzed data from 24 observational studies [145]. There was a decreased risk for the overall incidence of prostate cancer and for advanced prostate cancer (RRs 0.86, 95% CI 0.81-0.92, and 0.83, 95% CI 0.75-0.91, respectively).

- Additional data on the effects of aspirin come from the Physician's Health Study, in which 22,071 men were randomly assigned to aspirin, carotene, both, or placebo in 1981 to 1982 [146]. The aspirin component of the trial was terminated in 1988, but most men continued to take aspirin in an open-label fashion because of its cardiovascular benefits. By 2009, 509 men had died of lethal prostate cancer, and there was a decreased risk of lethal prostate cancer among regular aspirin users (≥3 tablets per week, hazard ratio [HR] 0.68, 95% CI 0.52-0.89).

Statins — Although multiple epidemiologic studies have yielded equivocal results regarding the impact of statins on the incidence of prostate cancer, the epidemiologic evidence suggests that statin use may have a beneficial impact on prostate cancer progression and mortality.

Vasectomy — Whether a prior vasectomy increases a man's risk of getting prostate cancer is controversial, but the preponderance of the evidence suggests that, if there is a risk, it is very low [147-158]. The following reflects the range of findings:

- In the Cancer Prevention Study II, 7451 of 363,726 men died from prostate cancer between 1982 and 2012 [147]. There was no association between vasectomy and prostate cancer mortality (HR 1.01, 95% CI 0.93-1.10). In a subset of 66,542 men, there was no association of vasectomy with the incidence of either overall (HR 1.02, 95% CI 0.96-1.08) or high-grade prostate cancer (HR 0.91, 95% CI 0.78-1.07).

- Similarly, in a European Prospective Investigation into Cancer and Nutrition (EPIC) study, 84,753 men were followed for an average of 15 years [148]. Overall, 4377 men were diagnosed with prostate cancer, including 641 who had a prior vasectomy, and there was no statistically significant association between prior vasectomy and prostate cancer incidence or death.

- On the other hand, in a multivariate analysis of a cohort study of almost 50,000 men in the Health Professionals Follow-Up Study, in which 6023 developed prostate cancer, vasectomy was associated with a significant increase in the risk of high-grade (Gleason 8 to 10), lethal

(death or the development of metastatic disease), or advanced (T3b or higher, or lethal) prostate cancer (RRs 1.22, 1.19, and 1.20, respectively) [149].

- An increased risk was also noted in a large population-based study of Danish men born between 1937 and 1966; overall, 26,238 cases of prostate cancer occurred among 2,150,162 men, and vasectomized men had a small but significantly higher risk (RR 1.15, 95% CI 1.10-1.20) [150]. The increased risk persisted for at least 30 years after the procedure and was observed regardless of age at vasectomy and cancer stage at diagnosis.

- A year 2017 meta-analysis that incorporated data from 16 cohort studies, 33 case-control series, and four cross-sectional studies concluded that there was at most a weak association between vasectomy and prostate cancer, and that there was no association with high-grade, advanced, or fatal disease [151].

Although observational studies such as these may show an association, they do not prove a causal relationship between vasectomy and prostate cancer and cannot exclude bias. Although some clinicians performing vasectomy choose to discuss the small potential risk in the interest of full disclosure, we continue to follow the 2015 guidelines of the American Urological Association (AUA), which state that clinicians do not need to routinely discuss prostate cancer in pre-vasectomy counseling. (See "Vasectomy", section on 'Prostate cancer'.)

Ejaculatory frequency — An association between ejaculatory frequency and a lower risk of prostate cancer has been suggested in two case-control studies:

- In a study which compared men under the age of 70 who had prostate cancer with age-matched controls, men who had five or more ejaculations per week while in their 20s (but not their 30s or 40s) had a significantly lower risk of prostate cancer (odds ratio 0.66) than those who had fewer ejaculations [159].

- A report from the Health Professionals Follow-Up Study compared men who developed prostate cancer (n = 3839) with controls of a similar age group who had similar ejaculatory frequency but no prostate cancer [160]. On multivariable analysis, the incidence of prostate cancer was significantly reduced for men having more than 21 ejaculations per month compared with those with 4 to 7 ejaculations per month between ages 20 and 29 years (HR 0.81, 95% CI 0.72-0.92). The HR for those reporting more than 21 versus 4 to 7 ejaculations per month between ages 40 and 49 years was 0.78 (95% CI 0.69-0.89).

The validity of this relationship has been called into question because of the lack of association of prostate cancer with ejaculation frequency in older men and the fact that other studies have

failed to show a protective effect from being married or having more sexual partners [161]. Moreover, the problem of recall bias also casts doubt on the interpretation of studies that use this methodology.

Infertility — Given that prostate cancer and many forms of infertility are androgen related, a possible link between these disorders has been explored, with variable findings:

- Three American studies reported an increased risk of prostate cancer in men with impaired semen quality [162-164].
- On the other hand, three Scandinavian studies, an American study, and a meta-analysis indicated a lower risk of prostate cancer in childless men [165-169].

One reason for these conflicting findings is that neither fatherhood nor sperm parameters represent ideal markers for male infertility. Furthermore, the reports generally included men with an average age of ≥60 years, and it is possible that those with earlier onset or more aggressive disease may already have died from their disease.

The most recent study, which used data collected from multiple Swedish registers, compared prostate cancer diagnoses among men who fathered children via in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), or natural conception [170]. The average age at follow-up was 45 years. Men who became fathers through assisted reproduction had a significantly higher risk of prostate cancer compared with those who conceived naturally (HR 1.64 [95% CI 1.25-2.15] for ICSI; HR 1.33 [95% CI 1.06-1.66] for IVF), and they also had a higher incidence of early onset disease before age 55 years (HR 1.86 [95% CI 1.25-2.77] for ICSI; HR 1.51 [95% CI 1.09-2.08] for IVF). Excluding men receiving testosterone replacement therapy had a negligible effect on this elevated risk.

Causality is not established by these data, and additional studies in this population are warranted.

Ultraviolet light exposure — In one case-control study exposure to ultraviolet (UV) light had a protective effect on the development of prostate cancer [171]. Furthermore, cases with low UV exposure developed at a younger median age (68 versus 72 years old). A similar associated has been reported by others [172-174]. It is not clear that any exposure pattern can successfully reduce the risk of prostate cancer without increasing the risk for basal cell skin cancer [174]. (See "Epidemiology, pathogenesis, clinical features, and diagnosis of basal cell carcinoma", section on 'Ultraviolet radiation'.)

Although the mechanism underlying this association is unclear, involvement of vitamin D and/or its receptor has been hypothesized [174]. (See 'Calcium and vitamin D' above.)

Diagnostic radiologic procedures — A possible increase in risk of prostate cancer due to diagnostic radiologic procedures was suggested in a case-control series of 431 men diagnosed at age 60 years or less and 409 matched controls [175]. Procedures associated with an increased risk included barium enema and hip or pelvis radiographs at least five years prior to the diagnosis of prostate cancer.

EBRT for rectal cancer — Although external beam radiation therapy (EBRT) for prostate cancer is associated with an increased risk of rectal cancer, RT for rectal cancer has not been associated with an increased risk of subsequent prostate cancer. (See "Colorectal cancer: Epidemiology, risk factors, and protective factors", section on 'Other risk factors'.)

In a study based on the Surveillance, Epidemiology, and End Results (SEER) database, the risk of prostate cancer was decreased by 72 percent in 1572 men who had previously received EBRT as a component of their treatment for rectal cancer [176]. By contrast, the incidence or prostate cancer among 3114 men with rectal cancer and 24,578 with colon cancer who were treated without RT was similar to that expected in the general population.

In contrast to the findings from the SEER study, a decrease in the incidence of prostate cancer was not observed in two Swedish studies of men receiving EBRT for rectal cancer [177]. A possible explanation for the discrepant findings is that substantially lower doses of EBRT were used in the Swedish studies (25 Gy in five fractions versus typical regimens of 45 to 54 Gy in 1.8 to 2 Gy fractions in the United States).

At least two mechanisms could contribute to a reduction in the apparent risk of prostate cancer following EBRT for pelvic cancer. Incidental RT to the prostate may have a biologic effect, reducing or sterilizing subclinical areas of disease. Alternatively inadvertent irradiation of the prostate can decrease the serum PSA, which would diminish the diagnosis of prostate cancer without affecting its incidence [178,179].

Depression — The antecedent diagnosis of a depressive disorder adversely affects the choice of therapy. In a cohort study of 41,275 men with clinically localized prostate cancer from the SEER-Medicare database, 1894 (4.6 percent) had been diagnosed with a depression in the two years prior to diagnosis of prostate cancer [180]. These men were significantly less likely to receive definitive treatment (radical prostatectomy or RT) and more likely to be managed with androgen deprivation therapy alone, active surveillance, or watchful waiting compared with those without such a history.

Marijuana use — Marijuana use may increase risk for prostate cancer, although the data are somewhat conflicting, and some studies report an antineoplastic effect of cannabinoids [181-185]. (See "Cannabis use: Epidemiology, pharmacology, comorbidities, and adverse effects".)

Marijuana use has also been associated with infertility, and this may indirectly increase risk for prostate cancer [184,186]. (See 'Infertility' above and "Causes of male infertility", section on 'Drugs and radiation' and "Cannabis use: Epidemiology, pharmacology, comorbidities, and adverse effects".)

USING RISK FACTORS TO ESTIMATE PROSTATE CANCER RISK

An online prostate cancer risk calculator has been developed based on data from the Prostate Cancer Prevention Trial (PCPT; and independently validated [187]) in an attempt to permit men being screened for prostate cancer to estimate their risk of being diagnosed with the disease on prostate biopsy based on certain risk factors, such as age, serum prostate-specific antigen (PSA) level, the results of digital rectal examination (DRE), family history, race, and a prior history of negative biopsy [188]. The risk estimates are based on data from over 5000 men who were enrolled in the control group of the finasteride PCPT, and they apply only to men age 50 and older, without a prior diagnosis of prostate cancer, who have undergone screening with serum PSA and DRE within the last year.

A potentially more useful risk calculator has been developed based on data from the European Randomized Study of Screening for Prostate Cancer (ERSPC) [189]. This calculator has been implemented in clinical practice in a variety of settings [190,191], and it has been validated by other groups, at least for non-Asian men [192-194].

The utility of risk calculators such as these is limited as they do not provide guidance as to what level of risk should prompt prostate biopsy. Regardless, they are useful in terms of communicating risk to patients and helping to understand that risk is a continuum of PSA level.

Prostate cancer screening and prostate cancer chemoprevention are discussed elsewhere. (See "Chemoprevention strategies in prostate cancer" and "Screening for prostate cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given

condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topic (see "Patient education: Prostate cancer screening (Beyond the Basics)")

SUMMARY

- The most important risk factor for the development of prostate cancer is increasing age. Although prostate cancer is rare in men less than 40 years, its incidence increases progressively thereafter. (See 'Age' above.)
- Epidemiologic studies have shown that the risk of prostate cancer is higher in African Americans compared with other ethnic groups, and that it occurs at an earlier age. Although some data suggest that prostate cancer is associated with a more aggressive clinical course in African Americans than in other ethnic groups, others have shown that African American men with prostate cancer of any stage who receive appropriate treatment have the same (or perhaps even better) risk of death as White men with the disease. (See 'Ethnicity' above.)
- Genetic factors, especially germline mutations in DNA repair genes (such as breast cancer susceptibility gene 2 [*BRCA2*], ataxia telangiectasia mutated [*ATM*], etc), appear to play an important role in the development of certain prostate cancers and may be associated with more aggressive disease. (See "Genetic risk factors for prostate cancer".)
- Other factors, such as diet, hormone levels, and obesity, have been studied with the goal of developing strategies to reduce the risk of prostate cancer. Although such factors may have some effect on incidence, their role appears limited. (See 'Diet' above and 'Hormone levels and obesity' above and "Chemoprevention strategies in prostate cancer".)

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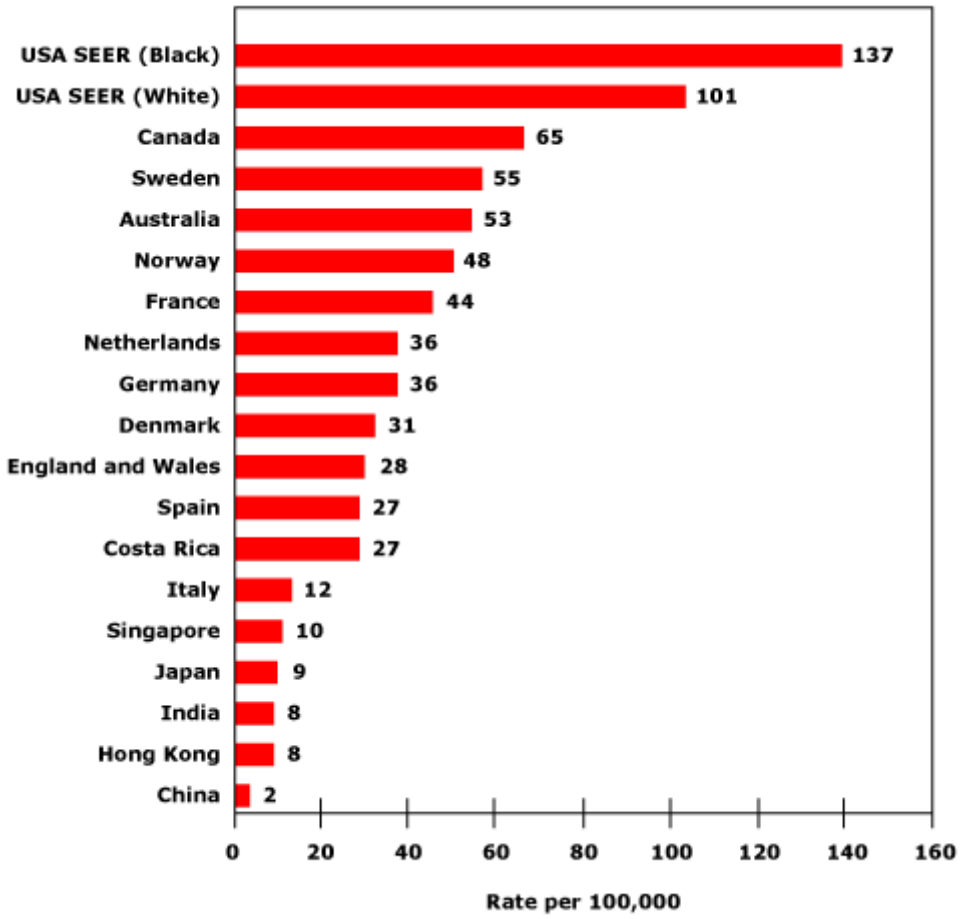
Topic 6938 Version 71.0

GRAPHICS

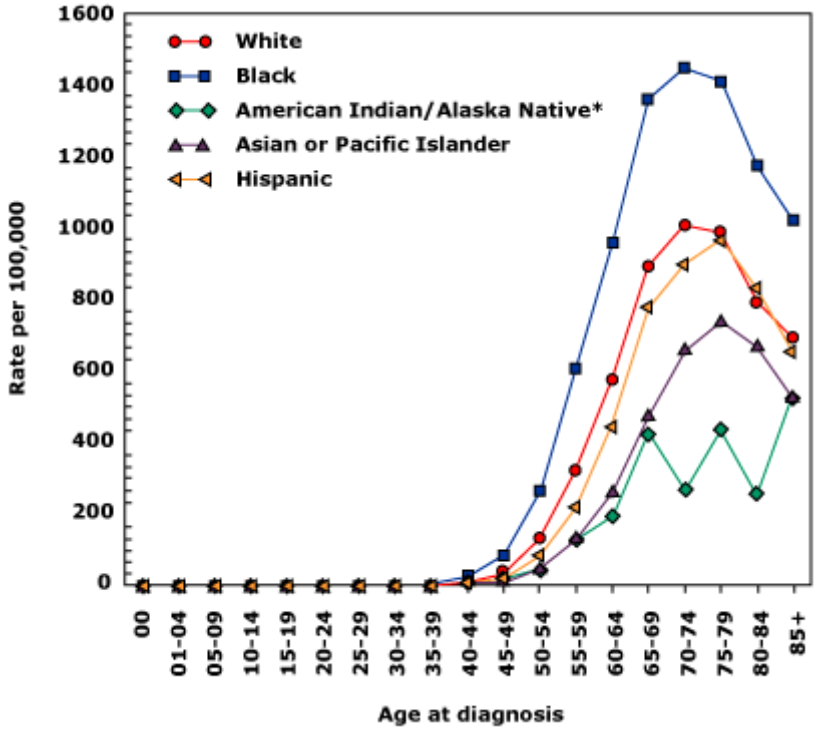
Incidence of prostate cancer: International comparisons



Data from: Netherlands Cancer Registry. Available online at www.ikcnet.nl/index.php (Accessed on March 6, 2007).

Graphic 50243 Version 1.0

Age-specific (crude) SEER incidence rates by 'expanded' race for prostate cancer, males SEER 17 registries for 2000-2003



* Statistics for American Indians/Alaska Natives do not include cases for the 2003 diagnosis year.

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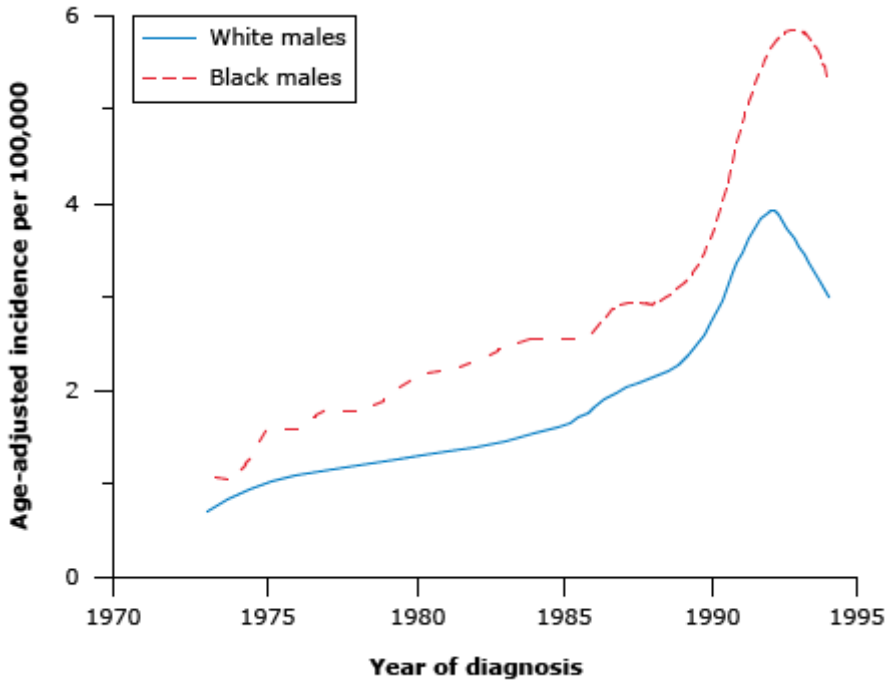
*Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 17 Regs Public-Use, Nov 2005 Sub (2000-2003), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2006, based on the November 2005 submission.*

Graphic 55572 Version 1.0

Prostate cancer is more common in Black males



Age-adjusted incidence rates for prostate cancer by race from 1973 to 1994 in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data base. Screening in the 1980s led to a progressive risk in the incidence of disease, with the rate being higher in Black people. The removal of these incident cases led to a decline in new cases of prostate cancer after 1992.

Data from Farkas A, Schneider D, Perrotti M, et al. National trends in the epidemiology of prostate cancer, 1973 to 1994: evidence for the effectiveness of prostate-specific antigen screening. Urology 1998; 52:444.

Graphic 62493 Version 4.0

Prostate cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
Clinical T (cT)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Pathological T (pT)	
T category	**T criteria**
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

NOTE: There is no pathological T1 classification.
NOTE: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.

Regional lymph nodes (N)

N category	N criteria
NX	Regional nodes were not assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)

Distant metastasis (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

NOTE: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.

Prostate-specific antigen (PSA)

PSA values are used to assign this category.

PSA values
<10
≥10 <20
<20
≥20
Any value

Histologic grade group (G)

Recently, the Gleason system has been compressed into so-called Grade Groups.

Grade Group	Gleason score	Gleason pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, or 5+3

5	9 or 10	4+5, 5+4, or 5+5

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110728 Version 10.0

Prostate cancer TNM prognostic stage groups AJCC UICC 8th edition

When T is…	And N is…	And M is…	And PSA is…	And Grade Group is…	Then the stage group is…
cT1a-c, cT2a	N0	M0	<10	1	I
pT2	N0	M0	<10	1	I
cT1a-c, cT2a, pT2	N0	M0	≥10 <20	1	IIA
cT2b-c	N0	M0	<20	1	IIA
T1-2	N0	M0	<20	2	IIB
T1-2	N0	M0	<20	3	IIC
T1-2	N0	M0	<20	4	IIC
T1-2	N0	M0	≥20	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

NOTE: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; PSA: prostate-specific antigen.

Graphic 110729 Version 10.0

Contributor Disclosures

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