

Trends and Patterns of Prostate Cancer: What Do They Suggest?

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INTRODUCTION

Prostate cancer is the most commonly diagnosed non-skin cancer in most western countries (1). In the United States, it is the second leading cause of cancer death following only lung cancer (2, 3). During the year 2001, an estimated 31,500 US men will die of prostate cancer and 198,100 men will be newly diagnosed (2). Despite the substantial morbidity and mortality, the etiology of prostate cancer is unknown. The only established risk factors are age, race, and a family history of prostate cancer. Descriptive studies examining incidence and mortality trends and patterns may yield unique clues to etiology. In this review, we present patterns and trends of prostate cancer in various countries to provide further insights for future epidemiologic studies.

INCIDENCE TRENDS AND PATTERNS

International comparisons

It has been well documented that the most striking epidemiologic observation about prostate cancer is the very large differences in incidence rates among racial/ethnic groups despite the current belief that the prevalence of microscopic (latent) prostate tumors in most populations is similar (1). Figure 1 shows the age-adjusted incidence of prostate cancer in selected countries on several continents (1, 4–7). As shown, there is a 40-fold difference in the reported incidence of prostate cancer between the populations with the highest and lowest risk. During 1988–1992, the highest reported rates (age-adjusted world standard), exceeding 130 per 100,000 man-years, were observed among US blacks, in contrast to the very lowest rates, less than 3 per 100,000 man-years, observed among men in China. Rates were also relatively high among US whites and in Canada. Rates were somewhat lower in Scandinavia, Europe, and Oceania, and lower still in Asia. Within Scandinavia, rates in Sweden and Norway were almost double those in Denmark. In Europe, rates were higher in France and notably lower in the United Kingdom, Italy, and Spain. Rates in Oceania were similar to those in

Europe. Within Asia, the rates in Israel were more like those in Europe and more than twice those in Singapore, Japan, Hong Kong, and Bombay, each of which was at least three times the rate in Shanghai, China.

Despite the very large population variation in incidence, rates of prostate cancer have risen during recent decades in virtually every population-based registry around the world (figure 1) (4–8). Both high- and low-risk countries generally have larger relative increases (percent increases) than medium-risk countries in Europe. From 1973–1977 to 1988–1992, rates more than doubled among US whites, Canadians in British Columbia, French men in Bas-Rhin, and Chinese in Singapore.

Factors affecting reported incidence

Reasons for the large racial/ethnic differences are unclear. However, it should be mentioned that the reported incidence includes both clinically significant prostate cancer and tumors identified through screening, in particular screening with the prostate-specific antigen test. Several other factors, such as changes over time in diagnosis and population differences in access to medical care, quality of cancer diagnosis, and completeness and accuracy of cancer reporting may also have affected the reported incidence in various countries. Thus, comparison of rates between high- and low-risk populations needs to take these factors into consideration. For example, it has been suggested that under-reporting may, in part, contribute to the much lower reported incidence, relative to that of African-Americans, of prostate cancer in most African countries. Several recent reports have suggested that in spite of under-ascertainment in Africa, prostate cancer has become the most common cancer in Nigeria, accounting for 11–15 percent of the male cancers (9, 10).

Screening

Screening is the single most important factor that affects the reported incidence of prostate cancer. The impact of screening on prostate cancer incidence is reviewed in more detail in two other presentations in this special issue of *Epidemiologic Reviews*. Briefly, since prostate cancer generally is a slow-growing tumor with a long latency, and since the prevalence of microscopic (latent) prostate tumors has been shown to be quite high in the elderly in most populations (at least 50 percent in men over the age of 70 years) (11), screening may identify many of the silent tumors

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Incidence

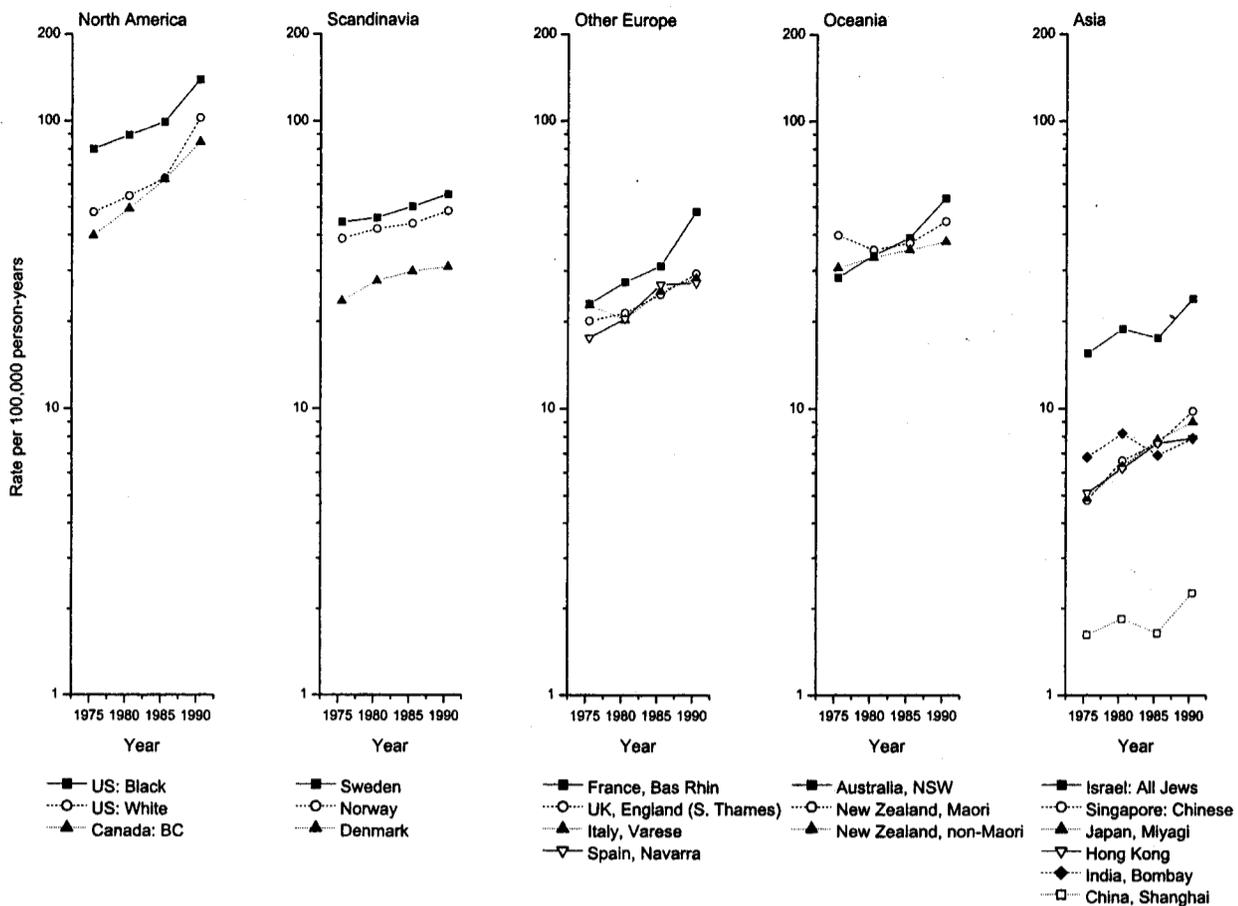


FIGURE 1. Age-adjusted prostate cancer incidence trends by geographic region, 1973–1977 to 1988–1992 (world standard).

(stage A1, usually asymptomatic) in the population, thereby elevating the reported incidence. Western countries, such as the United States, where there has been aggressive screening and widespread use of transurethral resection of the prostate and prostate-specific antigen testing, experienced rapid rises in reported incidence between 1986 and 1992 (12, 13).

Changes in prevalence of risk factors

Changes in prevalence of risk factors in the population will also impact the reported, and the real, incidence. Depending on the exposure and its effect on a particular stage of the prostate cancer natural history, some changes in exposures in the population may result in a rapid change in incidence, while the effects of other exposures may take a long time to become evident. In figure 1, in countries such as China, Japan, the United Kingdom, and Denmark where prostate cancer screening is not as aggressive or not recommended, the rise in incidence may represent changes in prevalence of risk factors in the population.

Age-adjusted incidence and mortality in the United States

Age-adjusted (1970 US standard) incidence trends in US men between 1973 and 1993 are shown in figure 2. From 1973, the first year of the Surveillance, Epidemiology, and End Results (SEER) program, incidence rose at fairly constant rates through the mid-1980s among both whites and blacks, but the increases accelerated rapidly until peaking at 190 among whites in 1992 and at 277 among blacks in 1993 (3). Subsequently, rates declined to 132 and 214 among whites and blacks, respectively, during 1997, the most recent data available. At least part of the rising rates during the 1980s was related to the increasing use of transurethral resection of the prostate (12), and the rapid increases during the late 1980s and early 1990s were related to spread of prostate-specific antigen testing (12, 13). The more recent decline in rates may be related, in part, to decreasing use of prostate-specific antigen screening (14, 15) and exhaustion of latent tumors in the population due to earlier screening. The most recent rates appear in line with continuations of

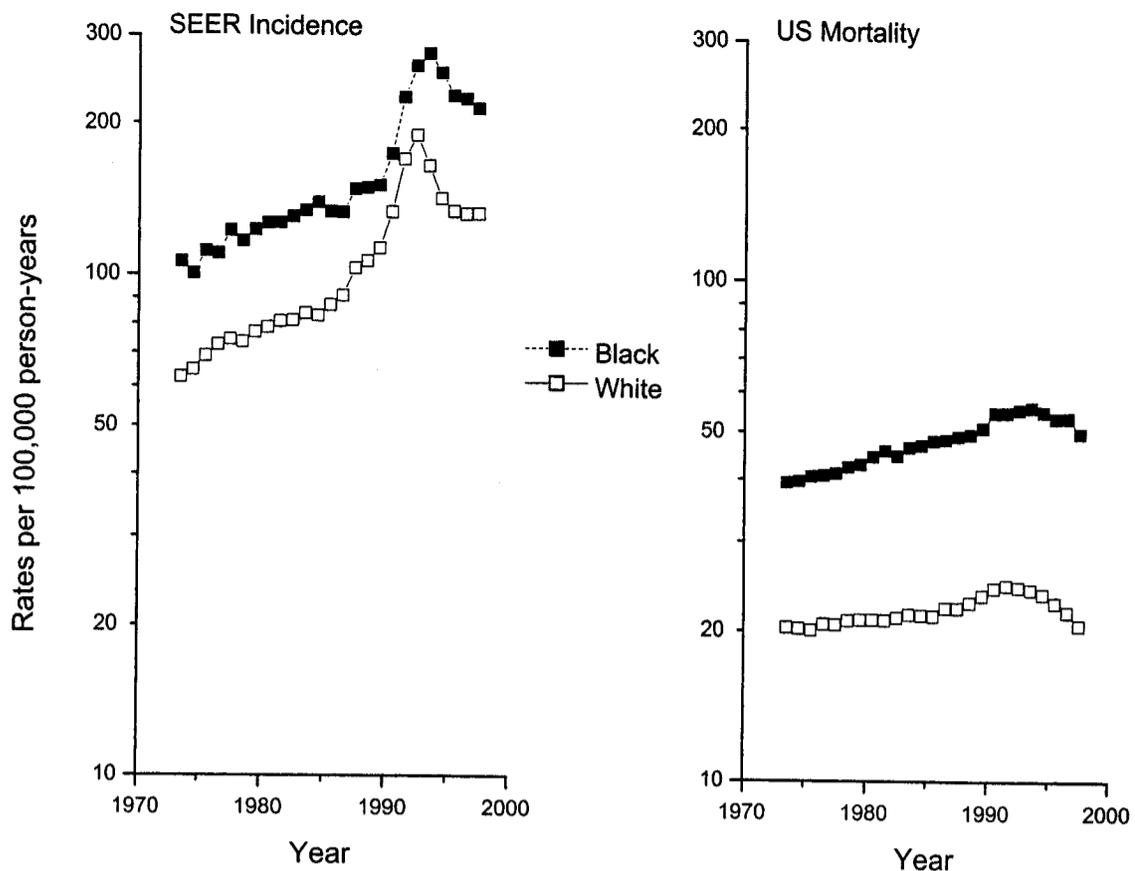


FIGURE 2. Age-adjusted prostate cancer Surveillance, Epidemiology, and End Results (SEER) incidence and US mortality trends by race, 1973-1997 (1970 US standard).

the long-term increases in prostate cancer incidence rates. Despite the increase over time in both races, blacks consistently have higher incidence than whites.

The trends in age-adjusted rates by clinical stage and tumor grade support the critical role of screening in reported incidence rates (figures 3 and 4). Since prostate cancer is rarely diagnosed at the preinvasive or in situ stage, they are not shown in figure 3. The distinction between localized and regional stage was made until 1994; since then, the two stages have been grouped together. By far the most common stage at diagnosis among both whites and blacks has been localized, and it is clear that the diagnosis of these tumors has driven the overall prostate cancer incidence trends. Cases with regional spread of disease at diagnosis occurred much less frequently, but the trends are quite similar to those for localized disease, as are the patterns for the group of combined localized and regional disease. The rates for localized disease both alone and in combination with regional disease rose over time, with steep increases during the early 1990s. In contrast, rates for distant stage disease rose less rapidly during the 1970s and 1980s than for the other stages and have plummeted by 60 percent during the 1990s among both blacks and whites. These patterns strongly suggest rising detection of early-stage disease, including cases that in the past would not have been

detected until distant spread had occurred. The trends in rates of unstaged disease have been erratic, declining through the early 1980s, rising rapidly through the early 1990s, and plummeting during the mid-1990s. Thus, part of the early increases in localized and regional disease may have been related to improved ascertainment of stage, but since then the patterns have followed those for total prostate cancer. Of special interest is the fact that African-Americans have much higher rates for tumors of distant stage compared with US whites, which cannot be entirely explained by screening, access to medical care, or quality of care.

Age-adjusted incidence trends according to tumor grade are presented in figure 4. Among both whites and blacks, the most rapid increases occurred for moderately differentiated tumors, rising 10-fold from 1974-1975 to 1996-1997. The diagnosis of well and poorly differentiated tumors also rose rapidly before peaking during the early 1990s; there has been a shift from well to poorly differentiated tumors being the more common grade diagnosed. The diagnosis of undifferentiated tumors has been the least frequent of all, and rates have drifted downward among both whites and blacks. It should be mentioned that for tumors of each grade, African-Americans have higher rates than US whites and the disparity is most pronounced for undifferentiated tumors.

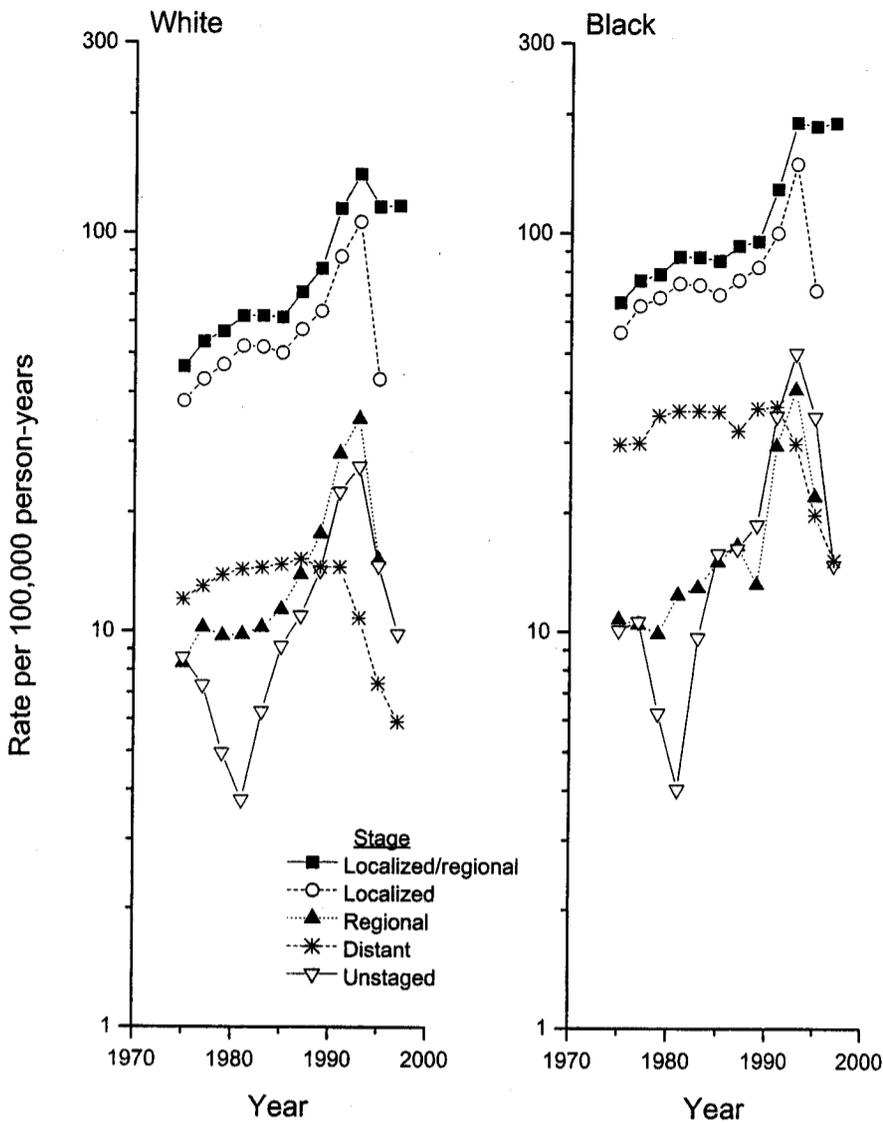


FIGURE 3. Age-adjusted prostate cancer Surveillance, Epidemiology, and End Results (SEER) incidence trends by race and stage, 1974–1975 to 1996–1997 (1970 US standard).

Age-specific incidence in the United States

The age-specific incidence trends are shown in figure 5. As shown, increases through the early 1990s were apparent across all age groups among both whites and blacks, even in the youngest group (35–44 years of age), with acceleration in the rises during the late 1980s and early 1990s being particularly pronounced among men aged 45–74 years. Rates peaked and were followed by declining rates among men aged 65 years and older, with recent rates among men aged 85 years and older considerably lower than during the early 1970s. Rates continued to increase over the entire study period among men aged 45–54 years, rising from less than 20 to more than 70 among whites and from about 30 to 150 among blacks. These patterns suggest that increases in rates related to improved diagnosis and screening were particularly pronounced among younger compared with older men

and that the recent declines in diagnosis were most evident among older men. Whether the latter is due to less screening or to real declines in the diagnosis of malignant disease, perhaps as a result of early identification of premalignant disease, is unclear.

MORTALITY TRENDS AND PATTERNS

International comparisons

Because screening detects tumors that are not clinically significant, and because there exist large differences in screening practices among populations, mortality is a useful endpoint to evaluate the risk and burden of prostate cancer. Internationally, mortality trends and patterns of prostate cancer mirror those for incidence, although the differences are less substantial and the rises less rapid than for incidence

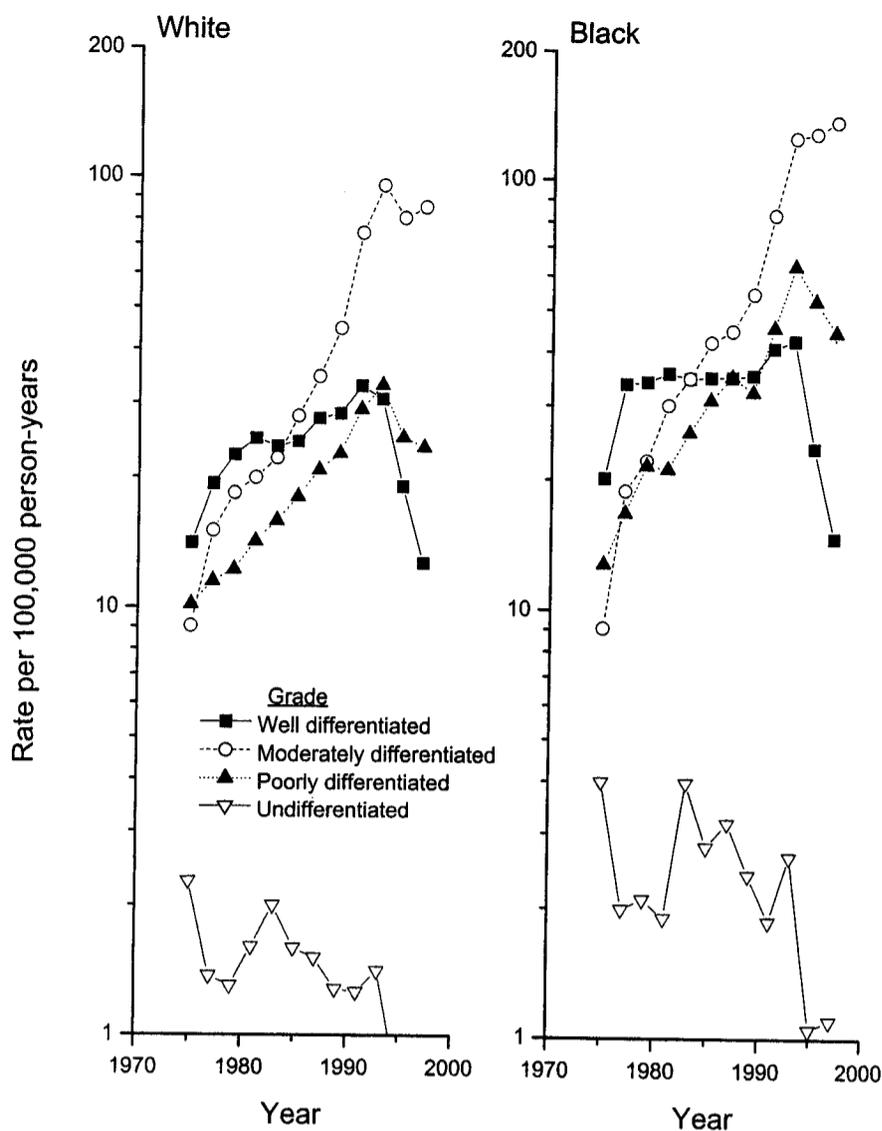


FIGURE 4. Age-adjusted prostate cancer Surveillance, Epidemiology, and End Results (SEER) incidence trends by race and grade, 1974–1975 to 1996–1997 (1970 US standard).

(figure 6)(8). The most rapid increases, more than 50 percent from 1973–1977 to 1988–1992, occurred in Japan and Singapore, exceeding 30 percent increase in Hong Kong, Denmark, and England and Wales. Prostate cancer mortality rates consistently have been highest among US blacks. In contrast to incidence being second-highest among US whites, their mortality rates were exceeded by those in Canada, Sweden, Denmark, France, and Australia. International variation has been smaller for mortality than for incidence, ranging from 34.3 among US blacks to 2.8 in Hong Kong, a 12-fold difference. As for annual mortality trends in the United States (figure 2), rates changed little among whites and rose relatively slowly among blacks during the 1970s, then increased during the late 1980s among both groups, peaking during 1991 among whites and 1993 among blacks. This is thought to be partially related to “attribution bias” on death certificates (16), but the 1997

rates were lower than those in 1989 among blacks and in 1978 among whites, suggesting that earlier diagnosis and improved survival may be influencing the mortality rates, especially among whites.

Mortality maps

Geographic variation within the same population may also provide clues into the potential role of socioeconomic status, urbanization, and other factors. For example, there was a distinct geographic pattern among white males for prostate cancer mortality within the United States, with a concentration of elevated rates in the northwest, Rocky Mountain, and north-central areas, and with low mortality in the south-central areas (17) (figure 7). An inverse urban-rural gradient was also suggested, with high rates in less populated areas of New England, the midwestern, northern

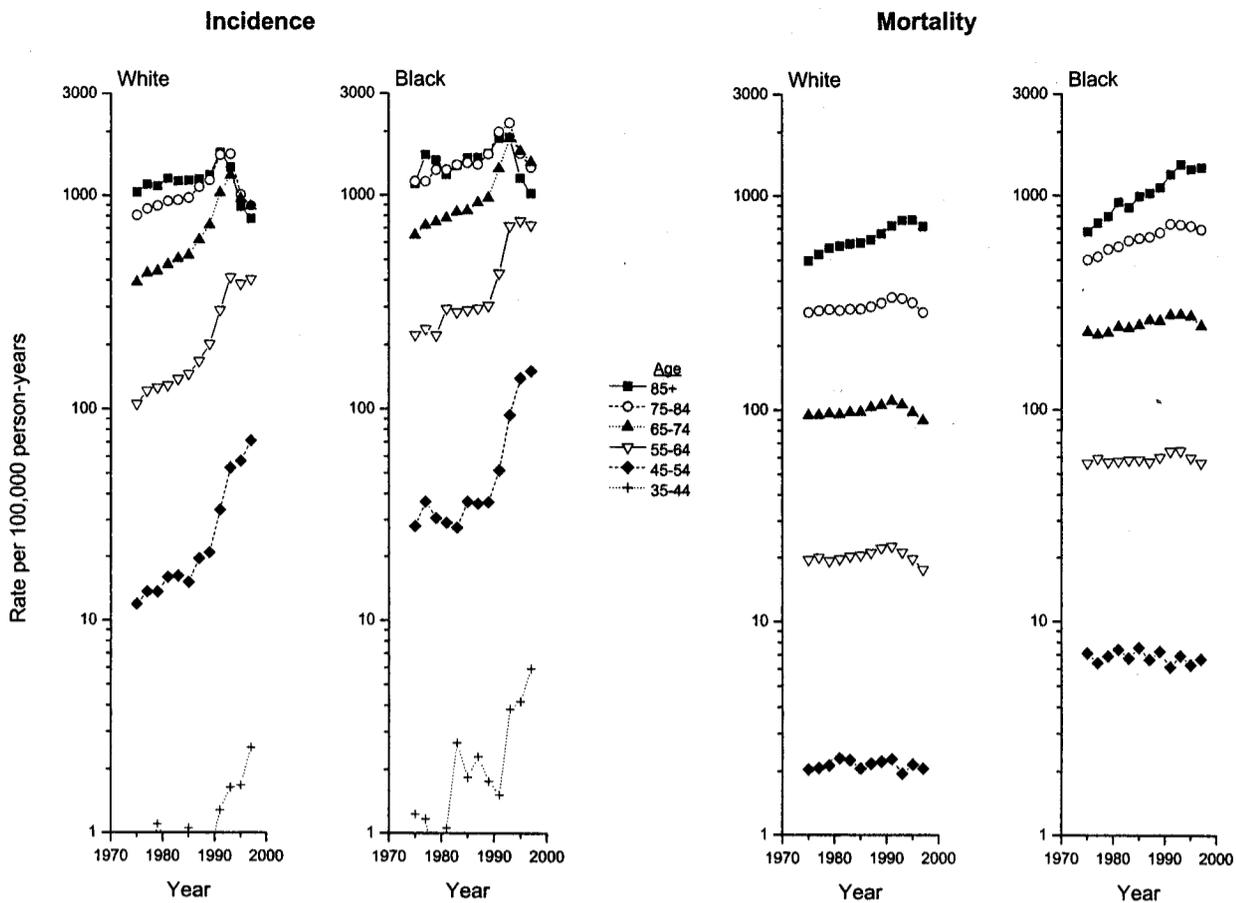


FIGURE 5. Age-specific prostate cancer Surveillance, Epidemiology, and End Results (SEER) incidence and US mortality trends by race, 1974–1975 to 1996–1997 (age-adjusted within age groups, 1970 US standard).

plains, and Rocky Mountain states and of the west. The recent patterns for white males have revealed more pronounced clustering in the northwest sector of the country than in earlier years. Black males have especially high mortality from prostate cancer, with pockets of elevated rates in the southeastern part of the country (figure 7).

It is unclear whether the patterns are partly related to screening and treatment practices, but there is some evidence that agricultural exposures may contribute to the geographic variation, including the high rates among whites in farming communities in the north-central and western states (18) and among blacks in the southeastern states (19, 20).

RACIAL/ETHNIC DIFFERENCES IN RISK

Between African-Americans and US Caucasians

The large US black-white disparities in risk have been widely recognized, although the reasons are unclear. In addition to the consistent black-white difference in incidence and mortality over time, it is of special interest that in every age group, every clinical stage, and every histologic grade, African-Americans have much higher rates

than US whites (as shown in figures 2–5), despite the generally lower socioeconomic status and the slightly lower prevalence of screening in African-Americans (21). It has been suggested that prostate tumors in African-Americans may exhibit different biologic behavior, since for African-Americans within the same stage and grade the survival is worse than that of US whites (22), although some studies have shown that the racial difference in survival disappeared after taking into account socioeconomic status, stage, and grade (23). Data from molecular studies suggest that tumor biology in blacks may differ from that of whites (24, 25).

Between African-Americans, African-Jamaicans, and Africans

The reported incidence of prostate cancer in African-Americans is about four times that among native Africans (1, 7). The much lower reported rates in Africa—possibly due to under-diagnosis, under-reporting, lack of screening, a relatively shorter life span, a greater presence of competing morbidity, or a lower prevalence of risk factors—are of special interest, since Africans share ancestry and inherited fac-

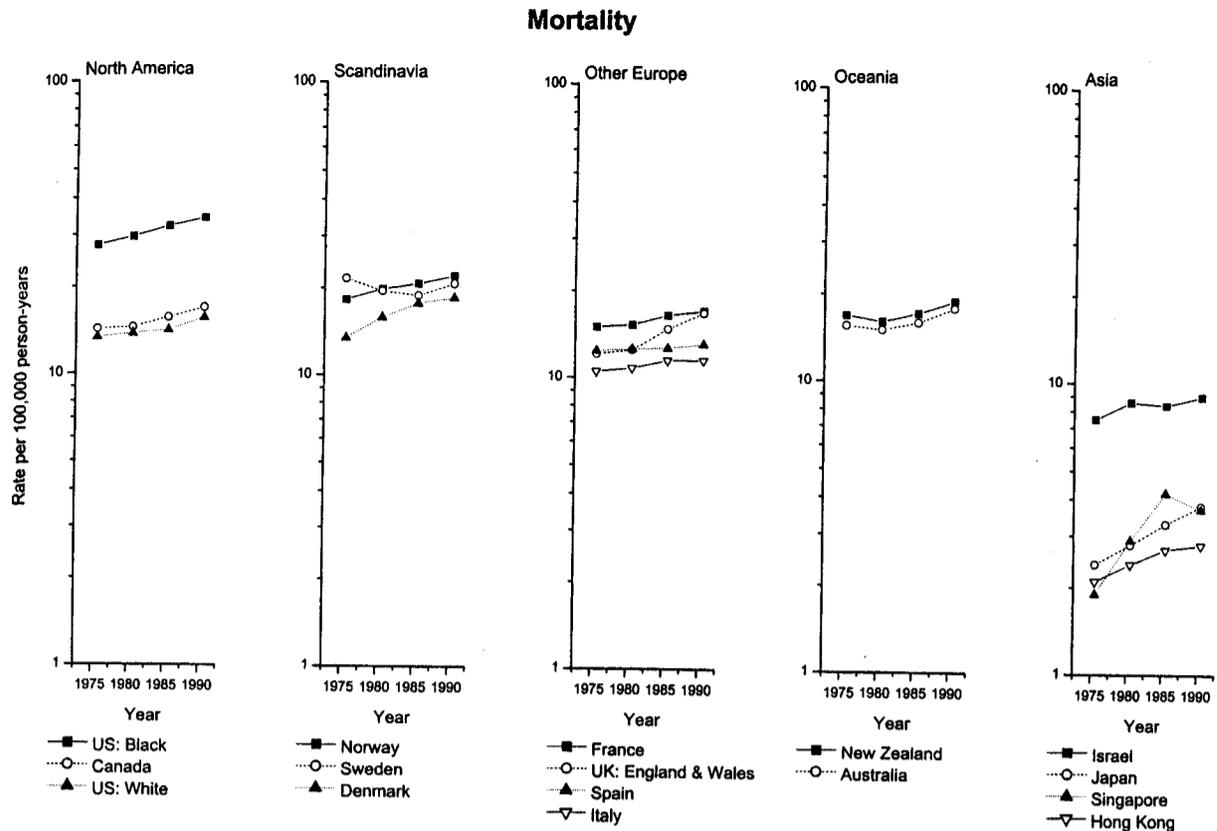


FIGURE 6. Age-adjusted prostate cancer mortality trends by geographic region, 1973–1977 to 1988–1992 (world standard).

tors with African-Americans. However, the real magnitude of the difference in incidence rates between these two populations is unclear, since the quality of cancer registration and medical care differs greatly, and since long-term population-based incidence data from Africa are scarce. For many years, it has been accepted that the rates in Africa are low, although more recent data suggest that the incidence of prostate cancer in Africa is rising and that prostate cancer has become the most common cancer in Nigerian men, accounting for 11 percent of male cancers (9, 10). One recent paper further suggests that “westernization” in Africa may be associated with rising rates of prostate cancer in Africans (26).

Similarly, although the consensus has long been that African-Americans have the highest reported incidence in the world, more recent data indicate that, despite the possibility of under-reporting and less screening, blacks in Jamaica may have much higher rates than African-Americans (304 per 100,000 men) (27, 28). The validity of the very high reported rates in Jamaica is unclear and needs further confirmation. If confirmed, the high rates in Jamaica and other Caribbean populations are of great interest, since African-Americans and African-Caribbeans share similar ancestors, suggesting that certain genetic predispositions in men of African ancestry play an important role in the development of prostate cancer.

Between US Caucasians and Europeans

Incidence rates for US Caucasians are twice those for their counterparts living in Europe. Although European countries, especially in Scandinavia, are less aggressive in the use of prostate-specific antigen screening (29), the differences in rates between US whites and Europeans are unlikely to be explained entirely by more aggressive screening in the United States, since higher rates in US whites were found long before prostate-specific antigen testing was available. Differences in the quality of cancer registration and medical care also cannot explain the excess risk in US Caucasians, since the quality of medical care and cancer registration in these European countries is quite high. Thus, the excess risk in US white men suggests that factors associated with American life styles, such as fat intake, obesity, and sedentary habits, may play a role in the etiology of prostate cancer.

Between Western and Asian men

The large disparity in incidence between Western and Asian men is striking (about 40-fold). This observation remains one of the most intriguing etiologic clues for prostate cancer. Although the lack of prostate-specific antigen screening and some degree of under-reporting may contribute to part of the very low reported rates in Asian

Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)
Prostate Gland: 1970-94

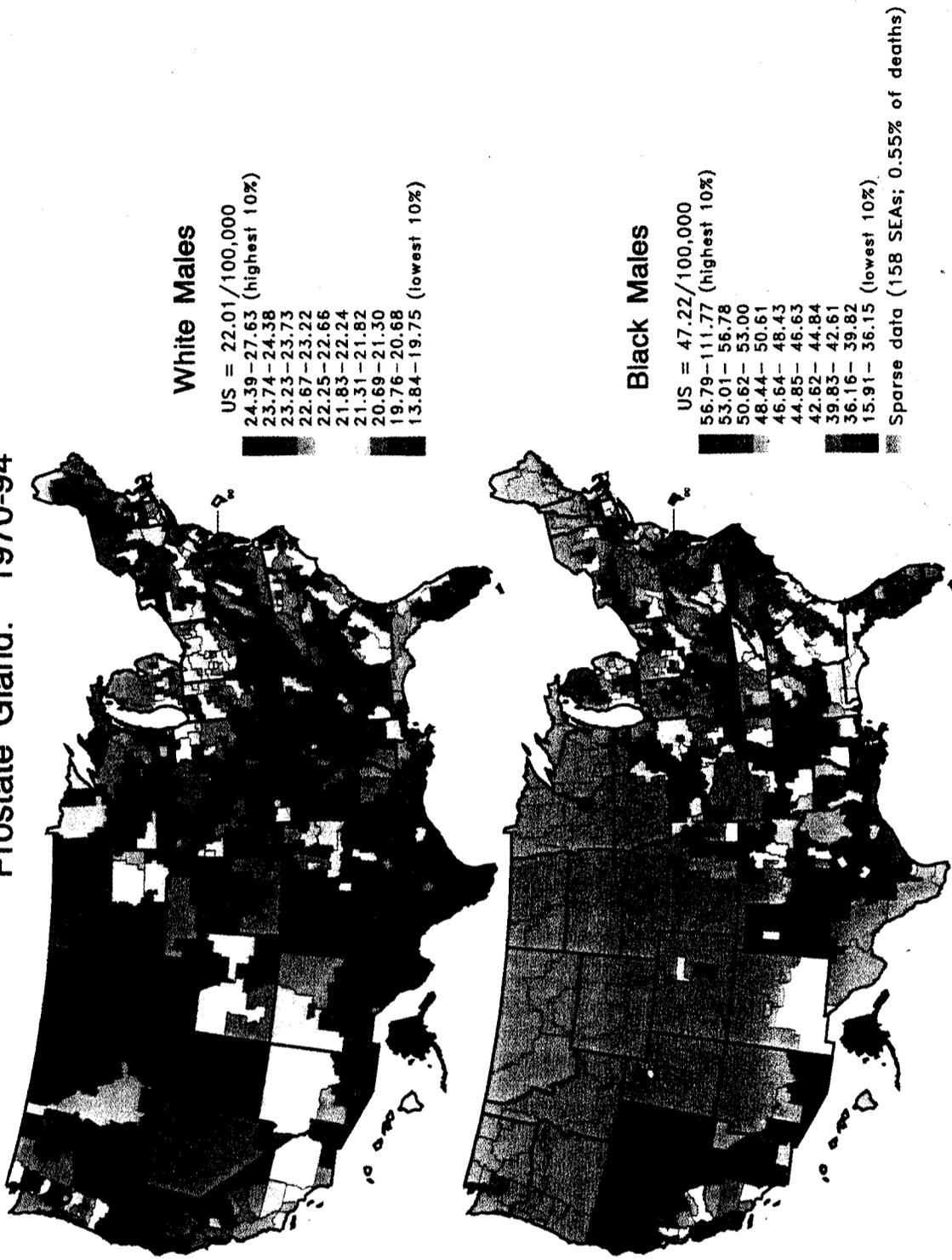


FIGURE 7. Geographic variation in US prostate cancer mortality rates by state economic area, 1970-1994: top, white males; bottom, black males.

countries, it is likely that the real racial/ethnic difference in risk remains relatively large (more than several-fold) for several reasons: 1) the quality of data, including percent of cases histologically confirmed, has been quite high in some of the Asian countries, including China, Japan, and Singapore; 2) the reported patterns in Asian countries have been consistent over the last 15 years, suggesting a certain degree of stability and consistency of cancer reporting in these countries; 3) only some, but not all, cancers, including cancer of the prostate, have such large racial differences (the international differences in rates for cancers of the colon and breast only range from three- to fivefold); and 4) within Asia, the degree of country-specific westernization parallels the magnitude of incidence rates, with Japan having the highest rates, followed by Singapore and Hong Kong. An earlier report showed that after adjustment for the differences in detection and screening practices between populations, prostate cancer rates in Japan would be approximately three times the rates reported to the International Agency for Research on Cancer, which would still be less than half those reported for African-Americans and US Caucasians (30, 31). Based on these observations, it is apparent that some of the differences in incidence between high- and low-risk populations must be due to differences in the prevalence of risk factors.

From descriptive data to epidemiologic studies

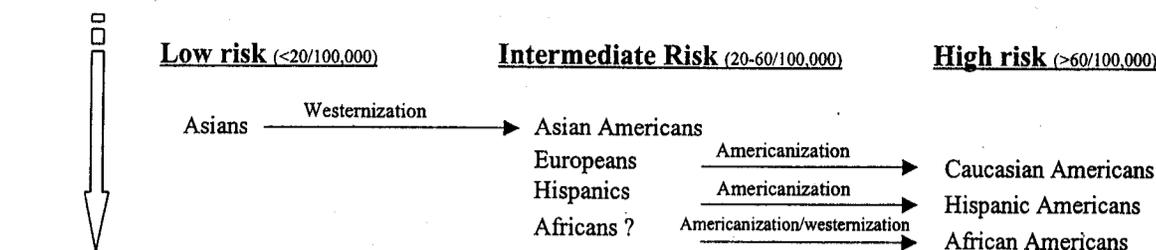
It is obvious that there are relatively large racial/ethnic differences in prostate cancer risk and that careful examination of the incidence and mortality trends and patterns is useful in providing insights into the etiology of prostate cancer. On these bases, several key hypotheses have been developed. These hypotheses include: 1) soy and green tea may account for the very low risk in Asians by inhibiting prostate cancer progression (32, 33); 2) westernization, including increased intake of animal fat, obesity, insulin resistance, and reduced physical activity, may explain part of the rising trends in Asia and the much higher risk of prostate cancer among Asian-Americans (34-37); 3) population differences in serum androgen and androgen metabolism may account for part of the large racial/ethnic differences in risk (38-40); 4) certain genetic factors, in particular those involved in androgen biosynthesis, metabolism, and transport, may help explain part of the racial/ethnic differences in prostate cancer risk (41-47); and 5) there are differences in aggressiveness and biologic behavior of tumors between populations. These hypotheses are promising, but they have not been fully tested or confirmed in population-based epidemiologic studies. Some of the leads have been pursued in previous studies, including a large population-based case-control study conducted in Asian-Americans, US Caucasians, and African-Americans (48), a population-based case-control study in US black and white men (49, 50), and studies in low-risk populations, such as China and Japan (34-36, 51, 52). Results from these studies suggest that dietary fat, obesity, and sexual factors may be associated with increased prostate cancer risk in certain populations, but they explain only a small part of the racial/ethnic differences in risk.

Other than genetic predisposition, most hypotheses are related to westernization, including changes in body size and in androgen biosynthesis and metabolism. The United States-Asia and United States-Africa disparities suggest that westernization is related to an increased prostate cancer risk, while the United States-Europe differences suggest that Americanization (or acculturation) may be linked to prostate cancer. Westernization/acculturation is a complex process that may involve the loss of protective factors and/or adoption of lifestyle factors that might increase prostate cancer risk. Figure 8 summarizes some of the possible factors related to this complex process. It seems unlikely that differences in risk of such large magnitude can be explained solely by one or two single risk factors (if this were true, we probably would have discovered them by now). The more likely explanation for the substantial racial/ethnic variation in prostate cancer is the complex interplay of genetic and lifestyle factors. Most of the putative risk factors, such as diet, obesity, and physical inactivity, may be related to westernization and work through the hormonal or insulin-like growth factor pathways to influence the risk of prostate cancer (figure 8). In addition to westernization, differences in genetic susceptibility related to hormone biosynthesis and metabolism between populations have been hypothesized to contribute to the large west-east differences in risk (34, 38, 40, 41). Although genetic makeup does not change over time, it is possible that as people in low-risk populations adopt a more western lifestyle, those with certain genetic predispositions are more likely to develop prostate cancer. Epidemiologic evidence for these putative risk factors is reviewed in detail in several presentations included in this special issue of *Epidemiologic Reviews*. Many of these potential etiologic leads have not been exploited fully and should be pursued further. Whether population differences in the prevalence of these risk factors corresponds to the large disparity in prostate cancer risk needs to be clarified in future epidemiologic studies.

FUTURE RESEARCH

Clearly, data from descriptive studies are useful in providing etiologic leads for epidemiologic studies. For prostate cancer, a better understanding of the true incidence in Africa and the Caribbean will help shed new light on the role of both genetics and "westernization" in prostate cancer etiology. A better definition and more precise classification of race/ethnicity are critical to clarify racial and ethnic cancer trends and patterns, since there are now more than 100 ethnic groups in the United States census. Although African-Americans are commonly treated as one group, within this group there is substantial genetic heterogeneity due to genetic admixture. Cancer trends in migrants, in particular studies with information on birth-place and time since migration, are useful in providing unique insights into the role of westernization and acculturation in prostate cancer progression. With the availability of newly developed molecular tools, the time may be ripe to conduct another population-based pathologic sur-

Racial/Ethnic Differences in Prostate Cancer Risk



Possible Reasons

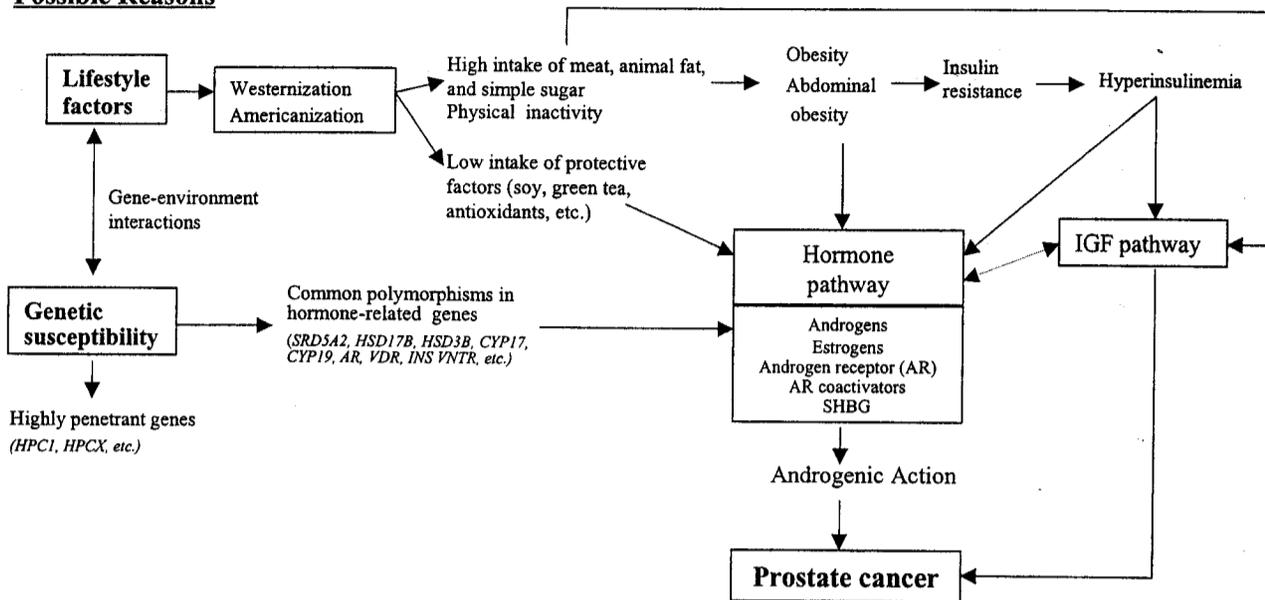


FIGURE 8. Putative relations: westernization and racial/ethnic differences in prostate cancer risk.

vey in high- and low-risk populations to confirm whether the prevalence of latent tumors remains similar in most populations. The last survey was conducted more than 20 years ago. The new study should use an interdisciplinary approach with a common protocol to examine the prevalence of both latent foci and prostatic intraepithelial neoplasia, a putative precursor lesion of prostate cancer, in populations with varying risk. Continual monitoring of incidence and mortality trends and patterns in both high- and low-risk populations remains an important element in etiologic research on prostate cancer as well as in cancer control and prevention.

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