

# EPIDEMIOLOGY OF PROSTATE CANCER

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## ABSTRACT

Prostate cancer incidence and mortality rates vary worldwide. In the United States, prostate cancer is the most common malignancy affecting men and is the second-leading cause of cancer death. Risk of developing prostate cancer is associated with advancing age, African American ethnicity, and a positive family history, and may be influenced by diet and other factors. The incidence of prostate cancer increased sharply after the introduction of widespread screening for prostate-specific antigen (PSA), although rates have now returned to levels seen before that time. PSA screening has been associated with a shift toward diagnosis of earlier-stage disease, but this has not been accompanied by a shift toward a lower histologic grade. Although overall prostate cancer mortality rates decreased during the 1990s, it was largely because of reductions in deaths among men diagnosed with distant disease. In contrast, mortality rates for men diagnosed with localized or regional disease increased gradually during most of the 1990s before decreasing slightly among white men and reaching plateaus among African Americans. *UROLOGY* 62 (Suppl 6A): 3–12, 2003. © 2003 Elsevier Inc.

Prostate cancer accounts for 33% of all newly diagnosed malignancies among men in the United States.<sup>1</sup> According to the American Cancer Society, an estimated 220,900 men will be diagnosed with prostate cancer in 2003, and 28,900 men will die of it, making it the second most common cause of cancer death in men. The incidence of prostate cancer varies worldwide, with the highest rates found in the United States, Canada, and Scandinavia, and the lowest rates found in China and other parts of Asia.<sup>2,3</sup> These differences are caused by genetic susceptibility, exposure to unknown external risk factor or differences in health care and cancer registration, or even a combination of these factors.<sup>3</sup> Similarly, prostate cancer mortality varies worldwide, with the highest rates reported in the Caribbean and Scandinavia and the lowest rates in China, Japan, and countries of the former Soviet Union (Figure 1).<sup>1</sup> The number of men  $\geq 65$  years is expected to increase 4-fold worldwide between the years 2000 and 2050, representing an increase from 12.4% of the population in 2000 to 19.6% in 2030.<sup>4,5</sup> These statistics portend a substantial increase in the number of men

who will be diagnosed with prostate cancer and who will require treatment for their malignancy.

## RISK FACTORS

### AGE AND ETHNICITY

Prostate cancer is a disease associated with aging. In the United States, >70% of all cases of prostate cancer are diagnosed in men >65 years of age.<sup>1</sup> It is relatively rare for prostate cancer to be diagnosed in men <50 years of age, but after this age, the incidence and mortality rates increase exponentially.<sup>6</sup> The probability of developing prostate cancer increases from 0.005% among individuals aged <39 years to 2.2% (1 in 45) for those aged 40 to 59 years and 13.7% (1 in 7) for those aged 60 to 79 years.<sup>1</sup> Overall, the lifetime risk of developing prostate cancer is 16.7% (1 in 6). The results of autopsy studies, however, suggest that the probability of developing histologic evidence of prostate cancer is even higher. Carter *et al.*<sup>7</sup> showed that 20% of men aged 50 to 60 years and 50% of those aged 70 to 80 years had histologic evidence of malignancy. It has been estimated that a 50-year-old man has a lifetime risk of 42% for developing histologic evidence of prostate cancer, a 9.5% risk of developing clinical disease, and a 2.9% risk of dying of prostate cancer.<sup>8</sup>

African Americans have among the highest rates of prostate cancer in the world (275.3 per 100,000 men).<sup>1</sup> The incidence among African Americans is

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nearly 60% higher than among whites (172.9 per 100,000), which, in turn, is higher than the rates for Hispanics (127.6 per 100,000) and Asians/Pacific Islanders (107.2 per 100,000). Moreover, for the period from 1992 to 1999, the mortality rate for African Americans was 2.3 times higher than for whites, 3.3 times higher than for Hispanics, and 5 times higher than for Asians/Pacific Islanders.<sup>1</sup> Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program indicate that a higher percentage of African Americans present with metastatic disease, but they are not more likely than whites to present with high-grade lesions.<sup>9,10</sup> For the last 3 decades, 5-year survival rates have improved significantly for African Americans, but they remain lower than for whites (93% vs 98% for cases diagnosed from 1992 to 1998), although the gap between the 2 races appears to have narrowed.<sup>1,11</sup>

#### FAMILY HISTORY AND GENETIC SUSCEPTIBILITY

The risk of developing prostate cancer doubles for men who have a father or brother affected by prostate cancer, and risk increases further when multiple first-degree relatives are affected.<sup>12,13</sup> Epidemiologic studies indicate that men with a positive family history are diagnosed at an earlier age—on average 6 to 7 years earlier—than those without affected first-degree relatives.<sup>14</sup> These studies estimate that 5% to 10% of all prostate cancer cases and up to 40% of those occurring at <55 years of age may have a hereditary basis.<sup>13,14</sup> Other than being diagnosed at an earlier age, hereditary prostate cancer does not differ clinically from disease that arises sporadically. The familial clustering of prostate cancer may be caused by inheritance of a susceptibility gene, but it may also be caused by exposure to common environmental factors or simply from chance alone because of the high incidence of this malignancy.<sup>3</sup>

There have been 7 susceptibility loci for prostate cancer identified, but demonstrating linkage of currently known candidate genes has proved to be problematic.<sup>15</sup> Using linkage analysis based on a genome-wide search, Smith *et al.*<sup>16</sup> first mapped prostate cancer susceptibility to the hereditary prostate cancer *HPC1* locus on the long arm of chromosome 1 in high-risk families from Sweden and the United States. In these families, prostate cancer developed at an early age, affected  $\geq 5$  family members, and spanned 2 generations.<sup>17</sup> A subsequent pooled meta-analysis of 772 families with hereditary prostate cancer showed weak evidence of a genetic linkage to *HPC1* in only 6% of the families.<sup>18</sup> However, strong evidence of linkage was found in a subset of 8 families; in 2 of these families, a gene within the *HPC1* locus—the 2',5'-oligoadenylate synthetase-dependent ribonu-

lease L (*RNASEL*) gene—showed deleterious germline mutations.<sup>19</sup> The *RNASEL* gene is believed to be a tumor suppressor gene that regulates cellular proliferation and apoptosis. Although *RNASEL* may represent a prostate cancer susceptibility gene, mutations of this gene will likely account for only a limited number of hereditary prostate cancer cases.

The familial clustering may also occur because of polymorphisms in genes that are important for prostate development and function. Among candidate genes, there is the transactivation domain encoded by exon 1 of the androgen receptor gene, which has 2 different nucleotide repeat variants (CAG and GGC) that affect gene transcription and activation.<sup>15</sup> The CAG sequence varies in length from 11 to 31 repeats in healthy men, and the number of repeats is inversely related to the transcriptional activity of the androgen receptor. Some studies have suggested that a shorter CAG repeat length is associated with increased prostate cancer risk, whereas other studies have failed to confirm this relation. Another candidate gene is *SRD5A2*, which encodes the 5 $\alpha$ -reductase type 2 that catalyzes the conversion of testosterone to the more active dihydrotestosterone. The Ala49Thr variant increases the catalytic activity of the enzyme and increases prostate cancer risk, particularly in African Americans and Hispanics.<sup>20</sup>

#### DIET

An influence of diet and environment on prostate cancer risk is suggested by studies of Japanese men who relocated to the United States.<sup>21–23</sup> Instead of maintaining the low prostate cancer incidence and mortality rates of their native land, their risk started to reflect the prevailing local rates. Notably, higher risk correlated with a younger age at the time of immigration and a longer time living in the new environment. The Western lifestyle, particularly the higher intake of fat, meat, and dairy products, may be responsible for conveying the higher prostate cancer risk. In a multicenter study of dietary factors, prostate cancer risk was associated with total fat intake in whites, African Americans, and Asian Americans.<sup>22</sup> About 10% to 15% of the difference in prostate cancer incidence among these ethnicities was attributed to differences in saturated fat intake. Other studies have linked consumption of diets rich in red meat with prostate cancer risk.<sup>24,25</sup> Beef and dairy products are major sources of dietary branched fatty acids. An enzyme that plays a key role in the peroxisomal oxidation of these fatty acids ( $\alpha$ -methyl-coenzyme-M-reductase) is upregulated in prostate cancer but not in the healthy prostate.<sup>3</sup> The oxidation process generates hydrogen peroxide, which may be a source of carcinogenic oxidative damage to the prostate

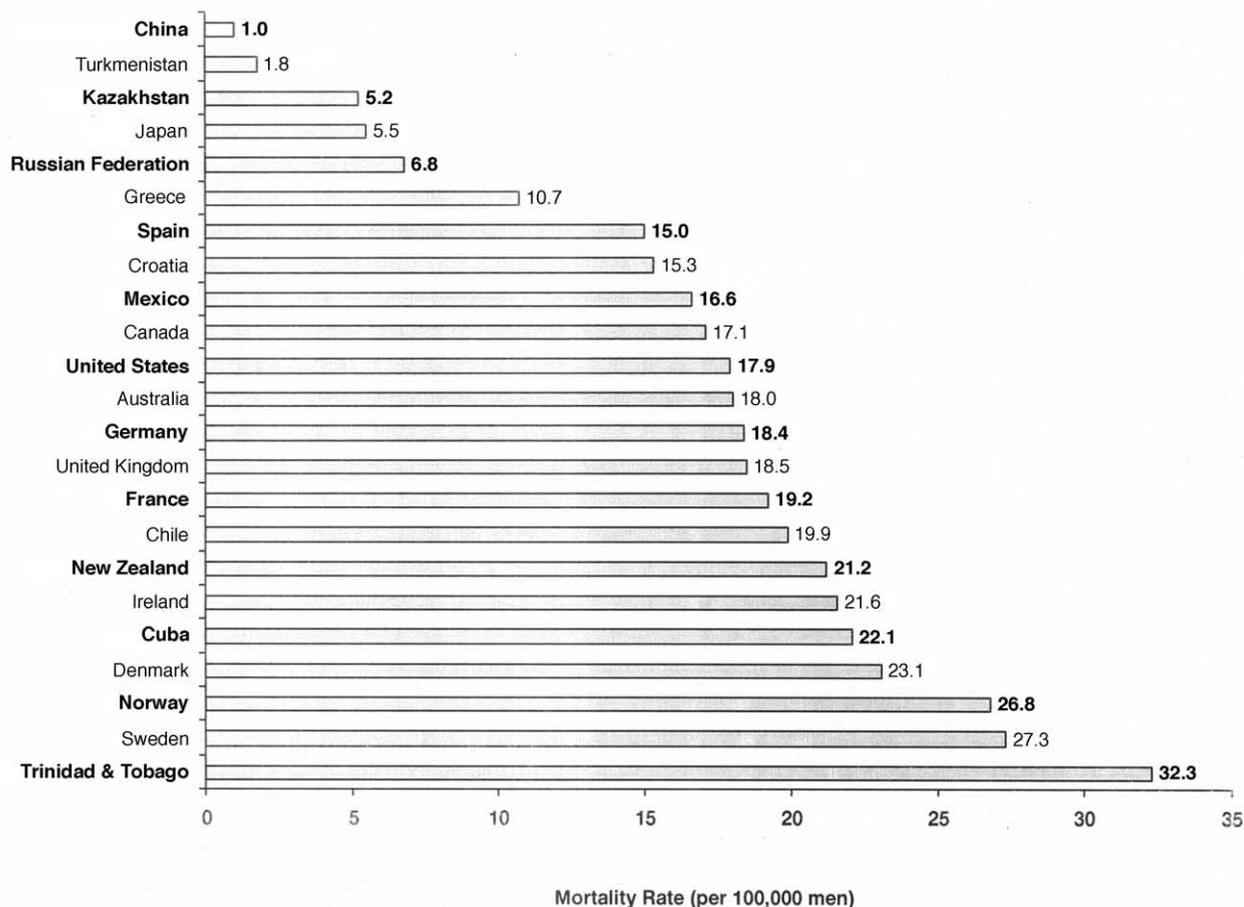


FIGURE 1. Age-adjusted prostate cancer mortality rates per 100,000 men in various countries for the year 2000. (Adapted with permission from the American Cancer Society, Cancer Facts & Figures 2003.<sup>1</sup>)

genome. Similarly, grilling or frying meats at high temperatures produces heterocyclic amines and other potent carcinogens that increase risk of certain malignancies, although a link with prostate cancer has not yet been established.<sup>26</sup>

The lower incidence of prostate cancer in Japan than in the United States may be related to the difference in intake of soybean products that are rich in isoflavones, such as genistin and daidzin. Experimental studies suggest that these isoflavones can inhibit protein tyrosine kinases that are important in cell proliferation and transformation, as well as in angiogenesis, and thereby limit the development and metastasis of prostate tumors.<sup>26</sup> Alternatively, these isoflavones may reduce circulating androgen concentrations and increase the concentration of sex hormone-binding globulin.<sup>3</sup>

Differences in diet may also help to explain the relation observed between plasma levels of insulin-like growth factor-1 (IGF-1) and prostate cancer risk. IGF-1 is primarily secreted by the liver; high fat and caloric diets stimulate growth hormone and insulin production and in turn IGF-1 production. This factor is known to regulate the proliferation and differentiation of cancer cells and to prevent them from undergoing apoptosis. In 3 prospective

cohort studies, men in the highest quartile of IGF-1 concentrations had a 1.7- to 4.3-fold higher risk of prostate cancer than those in the lowest quartile.<sup>27-29</sup>

#### HORMONAL AND OTHER FACTORS

The growth and differentiation of the prostate is under androgen control. Men who underwent castration before puberty and those with congenital abnormalities in androgen metabolism do not develop prostate cancer.<sup>6</sup> Moreover, androgen blockade with 5 $\alpha$ -reductase inhibitors is effective in causing involution of benign prostatic hyperplasia (BPH), whereas androgen ablation either surgically or with luteinizing hormone-releasing hormone agonists is an effective strategy in the treatment of advanced prostate cancer. Nevertheless, plasma testosterone or dihydrotestosterone concentrations determined either prospectively or at the time of cancer diagnosis have not been convincingly associated with increased risk of prostate cancer.<sup>30</sup> However, if androgens are indeed important in prostate cancer development, then measurement may need to be done in early adulthood, years before prostate cancer is actually detected.

Recent results from epidemiologic studies suggest that a high body mass index (BMI) and bone mass may be associated with prostate cancer. In the Cancer Prevention Study II, >400,000 men who were free of cancer were observed prospectively for 16 years.<sup>31</sup> Risk of prostate cancer mortality increased significantly in association with higher baseline BMI ( $P < 0.001$ ). Men with a BMI of 35.0 to 39.9 had a 34% greater risk of dying of prostate cancer than those with a normal BMI. However, this relation was less pronounced than for other malignancies. In contrast, BMI and other measures of body size at age 21 were unrelated to prostate cancer risk in an Australian case-control study.<sup>32</sup> Data from the Framingham Study suggest that high bone mass may increase risk of prostate cancer by 60% to 90%.<sup>33</sup> A total of 1012 white men who had hand radiographs between 1967 and 1970 were observed until 1999. The prostate cancer incidence rate for patients with the lowest quartile of bone mass was 3.8 per 1000 person-years, whereas it was 7.4 and 6.5 per 1000 person-years in the third and highest quartiles, respectively. The biologic mechanism underlying this relation is unclear, but cumulative exposure to higher levels of androgen, IGF-1, and calcium was suggested. High calcium intake was also related to an increased prostate cancer risk in the Physicians' Health Study.<sup>34</sup>

Other factors including vasectomy, sexual activity, smoking, alcohol consumption, physical activity, and social class have not been shown to affect prostate cancer risk.<sup>3,6,35,36</sup>

#### PROTECTIVE FACTORS

Epidemiologic and case-control studies suggest that intake of tomatoes and tomato products is associated with a lower risk of prostate cancer.<sup>37</sup> It has been suggested that lycopene, a compound in raw and processed tomato products, may be responsible for the lower risk, although other carotenoids and phytochemicals in these products may also contribute to the benefit. In a study of 2481 men, high levels of lycopene consumption were associated with a 16% lower risk of prostate cancer as compared with consumption of small amounts of lycopene.<sup>38</sup> A controlled dietary intervention study is needed to confirm the benefit of lycopene and tomato products. In addition, the mechanism by which lycopene may reduce risk remains to be established.

Several studies suggest that selenium, an essential trace element found largely in grains, fish, and meat, may also protect against prostate cancer.<sup>39,40</sup> In a population-based, case-controlled study of white and African American men, serum selenium was inversely associated with prostate cancer risk.<sup>40</sup> Men with the highest quartile of serum selenium had 29% lower risk than those in the lowest

quartile. This pattern was similar for both whites and African Americans. The reduction in risk was found at selenium levels  $> 0.135 \mu\text{g/mL}$ . Notably, the strongest relation was found for men with low serum  $\alpha$ -tocopherol concentrations, suggesting that the benefit may relate to an antioxidant mechanism.

Finally, men with diabetes mellitus appear to have a lower risk of developing prostate cancer. In a population-based cohort study conducted in Sweden, men hospitalized for diabetes had a 9% lower risk of prostate cancer, and those hospitalized for a diabetic complication had an 18% lower risk than men in other population-based registers.<sup>41</sup> In a hospital-based, case-control study, diabetes was associated with a 40% lower risk of prostate cancer overall and a 53% lower risk of regional or advanced prostate cancer.<sup>42</sup> This effect was found mainly in whites and Hispanics, but not in African Americans. Obesity and hyperinsulinemia are associated with diabetes, and both may reduce IGF-1 levels and alter endogenous steroid metabolism. It remains to be determined, however, whether these effects contribute to the observed inverse relation between diabetes and prostate cancer risk.

#### SCREENING AND DIAGNOSIS

The American Cancer Society recommends annual prostate-specific antigen (PSA) and digital rectal examination (DRE) screening starting at the age of 50 years for all men with a life expectancy of  $\geq 10$  years.<sup>43</sup> Men at high risk, including African Americans and those with a first-degree relative affected by prostate cancer, should be screened starting at age 45, and those with multiple first-degree relatives should be tested starting at age 40. A similar screening algorithm is recommended by the American Urological Association.<sup>44</sup> Although PSA is prostate specific, it is not specific for prostate cancer. Abnormal findings may be caused by BPH or prostatitis, and therefore a definitive diagnosis of prostate cancer is made by transrectal ultrasound (TRUS)-guided needle biopsy.

The rationale for screening high-risk patients at earlier ages is illustrated by a longitudinal screening study.<sup>45</sup> In a large sample of men aged  $\geq 50$  years, abnormal PSA or DRE findings were obtained in 36%, and prostate cancer was diagnosed subsequently in 6.4%. For African Americans and men with a positive family history, abnormal screening results were found at similar rates (34% and 42%, respectively), but prostate cancer was diagnosed in 10.3% and 10.5%, respectively. Notably, prostate cancer was diagnosed in 17.5% of African American men with a positive family history. The positive predictive value of screening, taking

into account only those who actually underwent biopsy, was somewhat higher for high-risk patients (48% for African Americans and 38% for men with a positive family history) than for men without these risk factors (30%). When men in these high-risk groups were screened while in their 40s, abnormal screening results were found in 8%, and about half who underwent subsequent biopsy had cancer detected, which in most cases was confined to the prostate.

The positive predictive value of PSA screening depends on the cutoff level. When a PSA >4 ng/mL is used, the positive predictive value averaged 37% across 11 screening studies, and the negative predictive value was 91%.<sup>46</sup> At the higher cutoff point of 10 ng/mL, the positive predictive value improved to 47%, but this came at the expense of a reduction in the sensitivity of screening. An abnormal DRE finding increases the likelihood that prostate cancer will be found on biopsy at both PSA cutoff points. But perhaps more importantly, prostate cancer is detected based only on DRE in 10% to 20% of men with PSA levels <4  $\mu$ g/dL.

Several methods have been evaluated in an effort to improve the predictive value of PSA screening.<sup>8,46</sup> The use of age-related reference ranges for PSA increases the sensitivity of screening in younger men but reduces it in older men. Nevertheless, the positive predictive value of PSA screening does not change with age because of the counteracting effects of increasing tumor size and increasing prevalence of BPH that occur with aging. The use of prostatic volume or density corrects the measured value of PSA according to the volume or weight of the prostate determined by TRUS. These measures are influenced by the variable ratio of epithelial to stromal tissue in the prostate, as well as by methodologic variability. PSA velocity is based on the rate of change in PSA over time, with values >0.75 ng/mL per year being more likely in men with prostate cancer than those with BPH or a healthy prostate. However, the predictive value of PSA velocity may be limited by significant intra-subject variability in PSA measurements. Finally, measurement of the different forms of PSA—total, free, and complex—although more costly, may improve the discrimination between prostate cancer and BPH. These methods improve the specificity of the PSA measurement, and therefore may reduce the number of unnecessary biopsies for men with borderline PSA values.<sup>46</sup>

## TRENDS IN INCIDENCE AND MORTALITY

The impact of widespread PSA screening is evident in trends of prostate cancer incidence. Data from the SEER program show that the incidence of prostate cancer in the United States increased

steadily in the 1980s. With the advent of widespread PSA screening, the incidence increased by 85% between 1987 and 1992 to reach an age-adjusted rate of 190.1 per 100,000 men.<sup>47,48</sup> The incidence then decreased by 29% between 1992 and 1996, likely reflecting the earlier diagnosis of patients through PSA screening. However, thereafter, the incidence again increased to approximately the rates seen before widespread PSA screening. For the period between 1995 and 1999, the prostate cancer incidence rate in the United States was 168.9 per 100,000 men.<sup>1</sup>

Mortality data from the SEER program show that rates increased gradually from 1976 (22.1 per 100,000 men) to 1992 (26.7 per 100,000 men) but then decreased steadily through 1997 (15.9 per 100,000 men).<sup>1,6,47,48</sup> For white men aged 50 to 84 years, age-adjusted mortality rates peaked in 1991 and then decreased by 27% between 1991 and 1999.<sup>49</sup> For white men in each of the age groups 50 to 59 years, 60 to 69 years, and 70 to 79 years, mortality rates in 1998 and 1999 were at their lowest level since 1950. For African American men, age-adjusted mortality rates began to plateau around 1990 and then decreased by 17% between 1994 and 1999. Nevertheless, mortality rates remained on average 2-fold higher than for white men.<sup>47-49</sup> The decrease in mortality rates observed during the 1990s was largely because of a reduction in death of men diagnosed with distant disease.<sup>49</sup> Mortality rates for men diagnosed with localized or regional disease actually increased gradually during most of the 1990s, decreasing slightly after 1997 among white men but not among African Americans (Figure 2).<sup>49</sup>

The relation between PSA screening and prostate cancer incidence and mortality was evaluated, using the British Columbia Cancer Registry from 1985 to 1999.<sup>50</sup> In all, 88 health areas were classified as low, medium, or high according to their intensity of PSA screening. Overall, the incidence of prostate cancer among men aged 50 to 74 years increased by 53% from 1985 to 1989 and 1990 to 1994, consistent with the increases in incidence seen in the United States. Notably, the increase in incidence was seen in health areas with medium- or high-intensity PSA screening, but little change was observed in the low-intensity screening areas (Figure 3). Although mortality rates were stable over this period, they decreased by 18% in 1995 to 1999 relative to 1985 to 1989. However, the reduction in mortality was related inversely to the intensity of PSA screening. It is likely that a longer time lag will be necessary before the benefit of PSA screening on mortality rates will be apparent.

It is important to recognize that the mortality rate only reflects cases where prostate cancer is listed as the underlying cause on the death certifi-

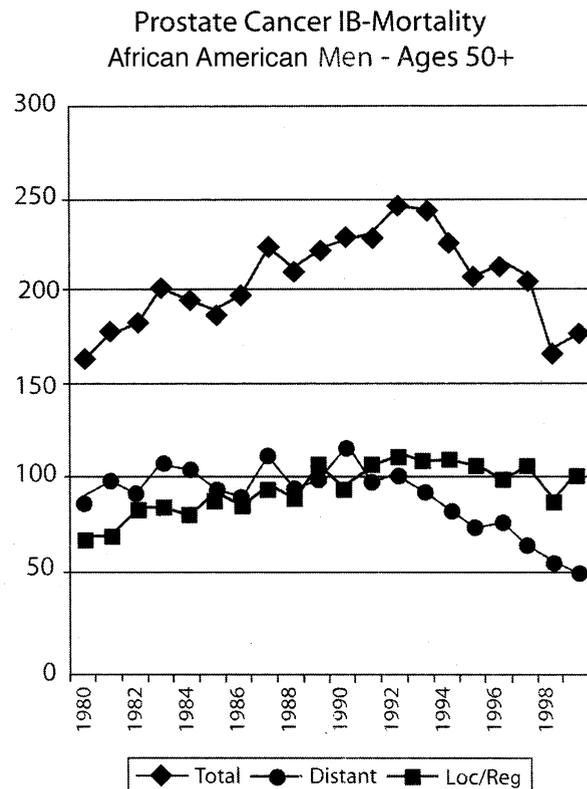
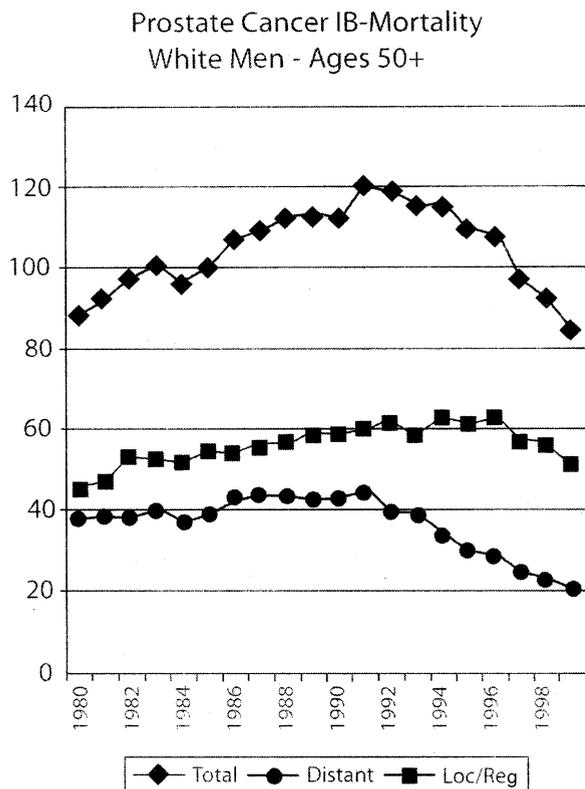


FIGURE 2. Prostate cancer incidence-based mortality rates for white men and African American men based on the disease stage at diagnosis. Loc = localized disease; Reg = regional disease. (Adapted with permission from Cancer.<sup>49</sup>)

cate. In a cohort of patients diagnosed with prostate cancer between 1980 and 1984, approximately 50% died of their malignancy, but the others died of comorbid conditions, most commonly of cardiovascular disease, other neoplasms, or respiratory conditions.<sup>51</sup> The risk of dying of prostate cancer was independently associated with younger age at diagnosis, African American race, and more advanced disease stage at diagnosis. The presence of comorbid cardiovascular disease at diagnosis was associated with a greater likelihood of dying of a cause other than prostate cancer.

### TRENDS IN DISEASE STAGE

PSA screening detects more tumors than DRE, and it detects them at an earlier stage.<sup>44</sup> In the current era of widespread PSA testing, approximately 75% of all prostate cancer cases are detected as a result of abnormal PSA findings. Importantly, the proportion of cases presenting with lymph node involvement or advanced disease has decreased considerably because of PSA screening. Marked stage migration was observed in a series of 2042 patients presenting with prostate cancer at the Walter Reed Army Medical Center between 1988 and 1998.<sup>52</sup> The proportion presenting with metastatic disease decreased from 17% from 1988

to 9% to 4% from 1996 to 1998, the proportion presenting with disease extending through the prostate capsule or into adjacent structures decreased from 15% to 6% over this period, while the proportion presenting with stage T1 tumors increased from 14% to 51% (Figure 4). Similarly, the Department of Defense Center for Prostate Disease Research database shows that the age of patients undergoing radical prostatectomy decreased during the 1990s.<sup>53</sup> The percentage of men <60 years of age increased from 24.3% in 1991 to 41.5% by 2000, whereas the proportion of men with stage T1 disease increased from 16.5% to 56.5% and the proportion with palpable stage T2 disease decreased from 81.7% to 41.9%. Importantly, younger patients who undergo radical prostatectomy have a more favorable disease-free outcome as compared with older men.<sup>54</sup>

The shift in disease stage at diagnosis has been seen across all ethnicities in the United States.<sup>9</sup> According to data from the SEER program, the percentage of patients presenting with distant disease decreased substantially between 1975 to 1987 and 1988 to 1997: 18.1% to 7.5% for white men, 27.2% to 12.4% for African American men, and 17.8% to 9.7% for Hispanic men, respectively. Over the same periods, 5-year survival rates increased sig-

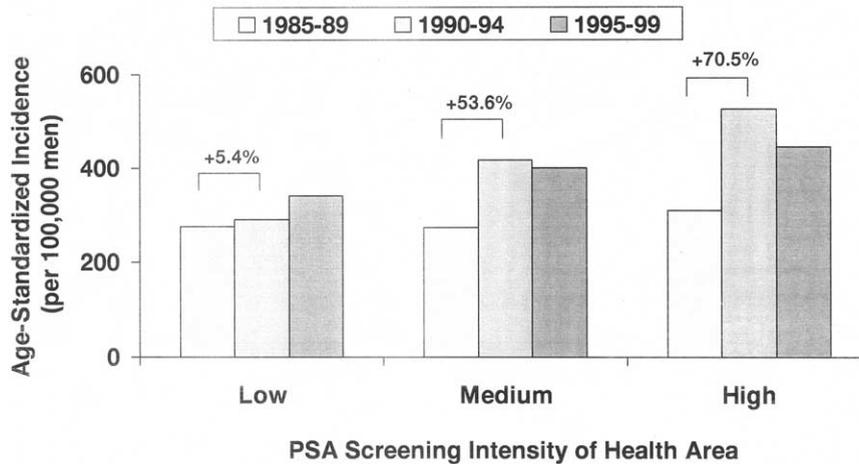


FIGURE 3. Age-standardized incidence of prostate cancer incidence rates for men aged 50 to 74 years by the intensity of prostate-specific antigen (PSA) screening of small health areas in British Columbia. In all, 30 areas had low-intensity screening, 29 had moderate-intensity screening, and 29 had high-intensity screening. (Adapted from CMAJ.<sup>50</sup>)

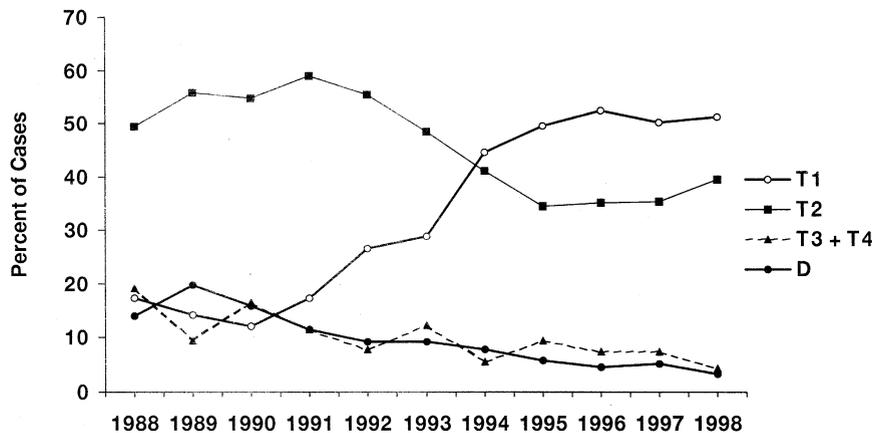


FIGURE 4. Trends in clinical stage at diagnosis of prostate cancer for 2042 men registered at Walter Reed Army Medical Center, Washington, DC. (Adapted with permission from Urology.<sup>52</sup>)

nificantly for men of each ethnicity/racial group ( $P < 0.01$ ).

Despite the shift toward earlier-stage disease, widespread PSA screening did not cause a shift toward low-grade disease. The increase in prostate cancer incidence, after introduction of widespread PSA testing, consisted primarily of an increase in the rate of moderately differentiated tumors (Gleason grade 5 to 7), whereas the rates of well-differentiated (grade 2 to 4) and poorly differentiated (grade 8 to 10) tumors increased to a lesser extent.<sup>55</sup> This pattern was seen consistent for both whites and African Americans, as well as for men aged  $<65$  or  $>65$  years (Figure 5). In 1995, approximately 60% of all diagnosed cases were moderately differentiated, 20% were poorly differentiated, and the remaining cases were either well differentiated or of unknown grade. The histologic grade is an important prognostic factor for sur-

vival. With conservative management, the 15-year mortality rate increases from 4% to 7% for men with well-differentiated tumors to 60% to 87% for those with poorly differentiated tumors.<sup>56</sup> Patients with several comorbidities were nearly twice as likely to die as those with few or no comorbidities; however, the probability of dying of prostate cancer tended to be only slightly higher.

## CONCLUSION

The advent of widespread PSA testing has led to the diagnosis of earlier-stage disease as well as the diagnosis of younger men. Nevertheless, the histologic grade has not shifted, with most patients still being diagnosed with moderately or poorly differentiated tumors. The impact of widespread PSA testing on mortality rates remains unclear. Although overall mortality rates in the United States

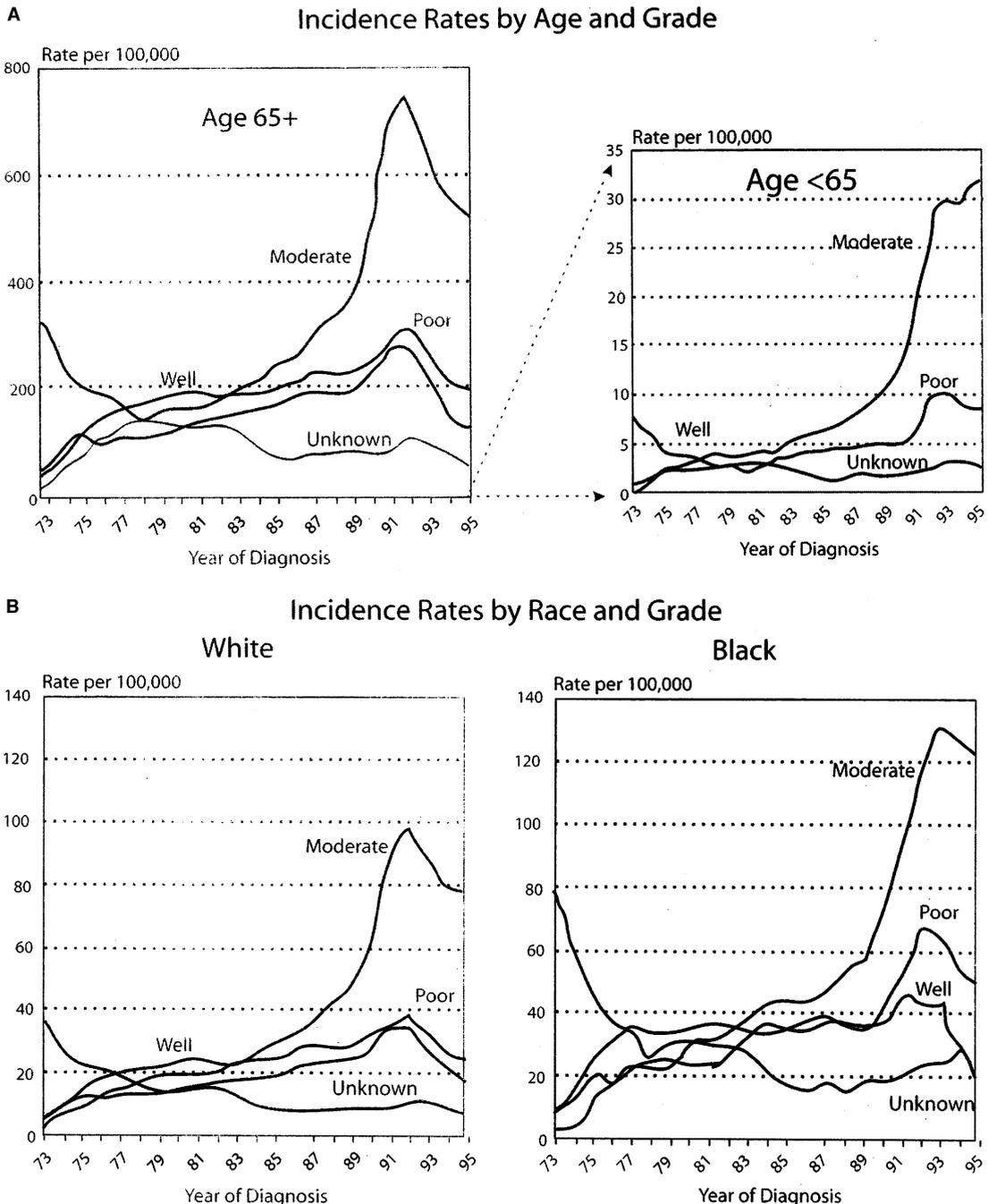


FIGURE 5. Trends in histologic grade of prostate cancer in the United States by age (A), race (B), and year of diagnosis. (Reprinted from National Cancer Institute, SEER Program.<sup>55</sup>)

decreased from peak levels in the early 1990s, this effect was largely because of reductions in deaths among men with distant disease. In contrast, mortality rates for men with localized or regional disease increased gradually during most of the 1990s before decreasing slightly among white men and reaching plateaus among African American men. These statistics underscore the need for chemopreventative strategies, as well as improvements in prostate cancer treatment.

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