

CHAPTER 1

Prostate Cancer Epidemiology

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United States—recent trends in incidence and mortality

Incidence

Prostate cancer is the most common non-skin cancer diagnosed among American males, affecting roughly one in six men (16.15%) over the course of their lifetime. Prostate cancer is also the second leading cause of cancer-related deaths in American men. According to the most recent data from the Surveillance Epidemiology and End Results (SEER) database, an estimated 241 740 men were diagnosed with prostate cancer and over 28 000 died of it in the United States in 2012 [1]. The incidence of prostate cancer spiked in the United States in the early 1990s because of the advent of more aggressive prostate-specific antigen (PSA) screening [2]. This was followed by a sharp decline from 1992 to 1995 during which incidence rates returned to a new baseline which remained approximately two and a half times the pre-PSA era rate, likely due to the fact that increased screening in prior years had successfully diagnosed much of the previously undetected prostate cancer patients in the population.

Mortality and survival

Most recent data show that mortality rates due to prostate cancer have been declining, with a 3.5% decrease between 2000 and 2009 [3]. In addition, 5-year survival rates have also been increasing, jumping from 76% between 1983 and 1985 to 98% between 1992 and 1998 [4]. While this staggering rise in survival and decline in mortality can in part be attributed

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to the recent trend in earlier detection and more aggressive treatment [5], screening overdiagnosis of preclinical prostate cancers which may never progress clinically is likely a major contributor as well. Overall, 5-year relative survival is nearly 100%, relative 10-year survival is 98%, and relative 15-year survival is 93%.

The stage of the prostate cancer is a major contributor to survival, as patients with local and regional disease had relative 5-year survival rates nearing 100%, while patients with distant metastasis had a relative 5-year survival of only 28% [6]. As screening is advancing, there has been an increase in incidence of organ-confined and regional diseases and a decrease in incidence of metastatic diseases [7].

International trends

Prostate cancer is the second most common cancer among men in the United States and fifth most common cancer worldwide [8]. However, incidence and mortality of this disease differ greatly depending on the geographical area. Incidence is highest in Scandinavia and North America (especially among African-Americans, with an annual rate of 236.0 per 100 000 men) and lowest in Asia (1.9 cases per 100 000 annually) [1, 8]. With respect to mortality rates, the highest rates are found in the Caribbean (at 26.3 deaths per 100 000 annually) and the lowest rates are found in Asia (<3 deaths per 100 000 annually). There are numerous explanations for these drastically different mortality rates among countries. Two major factors are differences in treatment and misattribution of cause of death. Environment is likely to play a role as well. One study comparing Japanese men living in the United States with Japanese men living abroad found that Japanese men living in the United States had more similar rates of prostate cancer to persons of similar ancestry living in the United States than to the Japanese men living in Japan [9].

Advancing age

Advancing age is the principal risk factor for acquiring prostate cancer. From 2005 to 2009, the median age of diagnosis was 67 years, with approximately 90% of diagnoses occurring at the age of 55 years and above. In addition, older men are more likely to be diagnosed with high-risk prostate cancer leading to lower overall and cancer-specific survival [1].

Race/ethnicity

Race is a major risk factor for prostate cancer, both with respect to incidence and mortality; however, the reasons as to why are less clear. African-Americans have the highest incidence of prostate cancer than any other race or ethnicity in the United States (between 2005 and 2009, 236.0 per 100 000 men annually). This is in contrast to other groups living in the United States, including white American males (146.9 per 100 000 men annually), Asian/Pacific Islanders (85.4 per 100 000 men annually), American Indian/Alaska Natives (78.4 per 100 000 men annually), and Hispanics (125.9 per 100 000 men annually). African-Americans also have the highest mortality rate (between 2005 and 2009, 53.1 per 100 000 men annually) once diagnosed with prostate cancer. Again, white American males (21.7 per 100 000 men annually), Asian/Pacific Islanders (10.0 per 100 000 men annually), American Indian/Alaska Natives (19.7 per 100 000 men annually), and Hispanics (17.8 per 100 000 men annually) all had significantly lower mortality rates in comparison [1].

There are numerous explanations for this disparity in outcomes among races. Higher mortality in African-Americans has been attributed to lower socioeconomic status [10–12], less frequent PSA screening [13], less aggressive treatment [14], and a lack of access to advanced treatment facilities [15]. However, even in studies which seemingly control for economic status, PSA screening, diagnostic approaches, and treatment barriers worse outcomes are still found in African-American males [16, 17]. Further research is warranted to elucidate both biologic and societal causes of such disparate outcomes among races.

Family history

Family history is one of the strongest risk factors when considering who will develop prostate cancer. Having an affected relative, the number of affected relatives, and the age of onset of prostate cancer in the affected relative are all risk factors for developing prostate cancer. Risk of prostate cancer doubles for a male who has one affected first-degree relative [18–22]. For males with more than one affected relatives, the risk is further increased [20]. Age of onset in affected first-degree relatives is also important, as younger age of onset correlates with increased risk as well [20, 23]. Another study from Sweden found prognostic correlation in

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families where both the father and son had prostate cancer. When comparing fathers who survived for 5 or more years versus fathers who survived less than 2 years, sons of fathers who survived for 5 or more years had a hazard ratio of 0.62 (95% CI) [24].

These familial factors point to a possible hereditary component in the development of prostate cancer. This notion is corroborated by a study of 45 000 twin pairs from Sweden, Denmark, and Finland which found that there was a higher concordance for prostate cancer diagnosis in monozygotic twins (18%) versus dizygotic twins (3%). This study estimated that potentially 42% of the risk of developing prostate cancer could be due to heritable causes [25]. Inheritance patterns of prostate cancer are not yet well understood, although segregation analyses of prostate cancer families point to an autosomal dominant [26], X-linked, or recessive inheritance [27].

Hormonal factors

Androgens

Androgens are important for the normal development of the prostate gland and are likely important in the carcinogenesis of the prostate as well. The results of the Prostate Cancer Prevention Trial demonstrated that inhibition of the conversion of testosterone to dihydrotestosterone by finasteride, a 5 α -reductase inhibitor, significantly decreased incidence of prostate cancer, thus confirming the role of androgens in the development of prostate cancer [28]. However, a meta-analysis of 18 studies showed that normal variations in serum androgen levels were not correlated with an increased risk of developing prostate cancer [29].

Insulin-like growth factor-1

Higher concentrations of insulin-like growth factor-1 (IGF-1), which normally promotes proliferation and apoptotic inhibition of normal prostate cells [30], have been associated with an increased risk of prostate cancer [31]. A pooled analysis of 12 studies also found that IGF binding protein 3 was weakly associated with increased risk of prostate cancer as well [31]. IGF-1 levels are both genetically and nutritionally dependent, which may be a reason why certain countries and populations have higher or lower rates of prostate cancer.

Lifestyle decisions

Smoking cigarettes

A meta-analysis determined that smoking was not associated with increased risk of developing prostate cancer, but was associated with fatal prostate cancer [32]. Smokers had a 24–30% increased risk of death due to prostate cancer compared with nonsmokers. A large study also found that smokers actually had an 18% decreased risk of developing prostate cancer, but a 67% increased risk of mortality due to prostate cancer [33].

Alcohol

Most studies have shown that there is no effect of alcohol consumption on the incidence or mortality of prostate cancer [34–36]. Additionally, red wine has not been shown to have any protective effect on prostate cancer [35]. These studies suggest that alcohol consumption does not play a major role in the development of prostate cancer.

Diet

Obesity

The role of obesity, as defined by high body mass index (BMI), in the pathogenesis of prostate cancer is not well defined. Many studies show that excess body weight does not lead to increased cases of prostate cancer [37–39], although some have shown a positive association [40, 41]. What studies have shown more conclusively is that obesity is associated with cases of higher-grade and fatal prostate cancer [42, 43].

Fats

Early studies found a positive correlation between fat consumption and prostate cancer incidence and mortality [44]. Subsequent case-control studies, including one comparing various races [20], also found a positive association between increased fat consumption and risk of developing prostate cancer [45]. In addition to increased incidence, a handful of prospective studies have shown that fat intake correlated with the higher-stage disease [20, 46]. The causes of these findings are likely multifactorial, including increased oxidative stress due to increased adipose tissue, increased difficulty of prostate detection in obese men, and increased production of IGF-1. However, the European Prospective Investigation into

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Cancer and Nutrition (EPIC) study, a meta-analysis of seven prospective studies, failed to demonstrate any association between fat consumption and incidence of disease or stage of disease [47]. Currently, it is unclear if fat consumption does indeed raise the risk of developing prostate cancer.

Lycopene

Lycopene, a carotenoid with potent antioxidant properties found primarily in tomatoes, has been hypothesized to reduce the risk of prostate cancer, but the results have been inconclusive. A meta-analysis found that when comparing the group with the lowest consumption of raw tomato products with the highest-consumption group, there was an 11% reduction in the risk of prostate cancer. This reduction was increased to 19% when cooked tomato products were considered [48]. However, a recent nested case-control study examining the effect of lycopene on various cancers found no reduction in prostate cancer risk [49].

Soy

Soy is high in phytoestrogens, compounds which may reduce 5 α -reductase activity, induce differentiation of prostate cells, and modulate estrogen receptors which inhibit androgen activity [50]. A meta-analysis of six case-control and two cohort studies [51], as well as the US Multiethnic Cohort Study [52], showed a reduction in the risk of prostate cancer in males with high soy consumption. The latter study also found a 30% reduction in the risk of being diagnosed with advanced disease. Thus, Asian soy-based diets may be contributing to lower rates of prostate cancer in this population. However, active surveillance studies have failed to produce the same results [53]. Although promising, the benefit of soy in reducing prostate cancer risk has not been substantiated.

Vitamins/minerals/trace elements

Vitamin D/calcium

No association between vitamin D intake and prostate cancer has been found in studies which have examined this relationship [54–56]. Conversely, numerous studies, including the Cancer Prevention Study II Nutrition Cohort, have reported positive associations between high calcium intake and increased incidence of as well as increased mortality from prostate cancer [55, 57, 58]. With the abundance of calcium

supplementation in the United States, more studies are needed to evaluate these potentially increased risks.

Vitamin E

Results of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) as well as the Physicians' Health Study II were equivocal when examining the effect of vitamin E on the risk of prostate cancer [59, 60]. However, α -tocopherol, the most potent form of naturally occurring vitamin E, has shown to decrease the risk of prostate cancer in smokers [61]. Interestingly though, subsequent follow-up of this same cohort showed no association of vitamin E with incidence of prostate cancer [62], blurring the validity of this association.

Selenium

The Nutritional Prevention of Cancer Study showed that selenium supplementation reduced the risk of prostate cancer by 65% compared with placebo [63]; these results have been corroborated by subsequent studies [64, 65]. However, these findings conflict with the results of the SELECT trial [59]. Further research is needed before any steadfast conclusions can be made regarding selenium's protective role in prostate cancer.

Genetics

Single-nucleotide polymorphisms (8q24 region)

Genome-wide association studies have demonstrated that certain genetic variations called single-nucleotide polymorphisms (SNPs) when found in aggregate in a male are associated with an increased risk of developing prostate cancer [66]. Allelic foci have been found in the 8q24 [67, 68] and 17q regions [66].

BRCA1/BRCA2 mutations

Risk of developing prostate cancer is increased if a BRCA1 (17q21) or BRCA2 (13q12) mutation is present. BRCA1 mutations roughly double the risk of prostate cancer [69, 70]. BRCA2 mutation carriers have a five- to sevenfold increase in risk [71], an early onset of disease [72], a worse prognosis [72, 73], and a higher Gleason score [74].

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Natural history of prostate cancer

The natural history of a disease is the course a disease takes if left untreated. In other words, it is the prognosis of the disease and the incidence of parameters of interest over time. It is of great interest that physicians are aware of the natural history of diseases, and particularly that of prostate cancer, as many prostate cancers grow slowly and the treatment is not without any side effects. A cost–benefit analysis must be done to determine whether treatment at all and what treatment is appropriate on an individual basis.

The incidence of prostate cancer is high. Autopsy studies have demonstrated that 60–70% of older men have some area showing cancer within the prostate [75, 76]. It is estimated that a 50-year-old man has a lifetime risk of 42% of developing prostate cancer, but only a 9.5% risk of developing the disease clinically and being diagnosed and a 2.9% risk of dying from prostate cancer [77]. This shows the highly protracted course and natural history of prostate cancer. However, our understanding of prostate cancer's natural history is incomplete and an individual's prognosis proves difficult to predict. With the advent of PSA screening, prostate cancer is being detected at earlier stages. The clinical behavior can vastly differ in different men with prostate cancer of similar staging, PSA levels, and histological appearance. Of the 234 460 men diagnosed with prostate cancer yearly, 91% present with localized disease [78]. Clinicians are faced with the challenge of predicting more aggressive forms of localized disease and “clinically insignificant” forms of disease (organ-confined cancer <0.5 mL, no Gleason grade 4 or 5).

A majority of prostate cancers turn out to be small, low grade, and non-invasive with doubling times of 2–4 years. It has been shown that up to 20% of cancers found on pathology after prostatectomy fit in this category and pose no immediate risk to the patient's health [79], suggesting possible overtreatment of prostate cancer. Making the diagnosis of prostate cancer more complicated is the fact that it can be a multifocal disease. Studies have shown the presence of multiple carcinomas in at least 50% of radical prostatectomy specimens, typically having different grades [80]. This can lead to sampling errors and difficulty predicting the true grade of a patient's prostate from a standard biopsy. Standard TRUS biopsy may underestimate the grade and extent of disease, thus many physicians recommend curative treatment for even low-risk cancers found on biopsy.

It is unknown whether low-risk tumors over time acquire the necessary mutations to progress or if they undergo a dedifferentiation process. In one

study of patients undergoing active surveillance for the prostate cancer, 17% were found to have higher-grade cancers (poorer differentiation) on repeat biopsies within 6 years [81]. However, it is difficult to conclude whether this is due to dedifferentiation of the initial cancer biopsied or reflect prostate heterogeneity and a sampling error in the initial diagnosis.

Watchful waiting

Watchful waiting is an approach to conservative management of prostate cancer where treatment is not begun until the man develops clinical signs of progression, at which time androgen-deprivation therapy is started. This modality of treatment is sometimes used for older men with shorter life expectancies or with comorbidities. In these cases, curative treatment may not prolong the man's life and may instead pose a risk to his health. Clinical studies following men designated to a watchful waiting protocol allows us to look at the natural history of prostate cancer.

Outcomes of 828 men with prostate cancer who were conservatively managed with watchful waiting were assessed in a pooled analysis. In this study, they measured disease-specific survival 10 years after the diagnosis, which was found to be 87% for low-grade cancers, and 34% for those with high-grade cancers. About 81% of those with low-grade cancers at diagnosis remained metastasis-free, whereas only 26% of those with high-grade cancers were metastasis-free [82].

In a prospective cohort study done in Sweden [83–85], 223 men were followed for over three decades. A total of 223 subjects were diagnosed with localized prostate cancer and initial treatment was deferred. It was initially found that these men had good disease-specific survival after 15 years [83], demonstrating an indolent course at first; however, mortality rates increased with further follow-up between 15 and 20 years after diagnosis. Survival without metastases decreased from 76.9% at 15 years to 51.2% at 20 years, and disease-specific survival decreased from 78.7% to 54.4%. At 15 years, the prostate cancer mortality rate was 15 per 1000 person-years and increased to 44 per 1000 person-years at 20 years post-diagnosis. The authors concluded from this prospective study that watchful waiting may be appropriate for men who have less than 15 years of life expectancy, as prostate cancer seemed to rapidly progress after 15 years. As of June 2011, this cohort had been followed for 32 years at which point only 3 of the 223 original patients were alive. As per the initial protocol of the study, men who developed symptomatic progression or

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metastasis of prostate cancer were treated with hormone therapy. About 142 of the 223 men (64%) remained untreated over the course of the trial. They remained metastasis-free and did not die of prostate cancer, indicating that a majority of the men had a cancer that never became clinically significant. In contrast to this good prognosis, 38 of the 79 men (almost 50%) who were hormonally treated died of prostate cancer [85]. In contrast to their prior study, no increase in the rate of progression and mortality was found when follow-up was extended beyond 20 years. It is likely that the increase in progression after 15 years was likely due to the small size of the surviving subjects. Supporting this is another watchful waiting study, a retrospective cohort review of 767 men diagnosed with localized prostate cancer followed up with a mean observation of 24 years. No significant difference in the rate of progression or mortality after 15 years was found [86]. In this cohort, men with high-grade cancer (Gleason score 8–10) at the time of diagnosis had a much higher probability of dying from prostate cancer (121 deaths per 1000 person-years) compared with those with low-grade cancer (Gleason score 2–4, 6 deaths per 1000 person-years) [86].

The diagnoses of the subjects in these studies were made prior to the use of PSA screening, which makes it difficult to correlate it to today's patients. Tumors detected by PSA screening have a lead time between 5 and 7 years [87] and may progress differently than those found clinically as in the studies above. The first watchful waiting study done in the PSA era found the highest predictive parameters for progression of localized disease were PSA level at time of diagnosis and Gleason score of the initial biopsy [88]. In a prospective cohort study done during the contemporary PSA era, disease-specific survival rates were found to be more favorable, reflecting the lead time discussed above and the indolent course of prostate cancer. The 10-year prostate-cancer-specific mortality was 8.3% for men with well-differentiated tumors, 9.1% for those with moderately differentiated tumors, and 25.6% for those with poorly differentiated tumors [89].

The natural history of prostate cancer still leaves much to the unknown. Although localized cancer often remains clinically insignificant, progression and metastasis may still develop after several years. Factors including PSA level, Gleason score, patient's age, and overall health should be assessed when determining appropriate treatment. However, it is important to consider that these are not concrete risk factors, as some men who possess the high-risk factors do not progress to a clinically significant cancer and, similarly, the low-risk men do not always maintain an indolent course.

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