

Epidemiology of prostate cancer: current status

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Abstract. – Prostate cancer is one of the most common cancers affecting men with > 1,100,000 new cases and 300,000 deaths worldwide each year. The disease is more common among older men, with a median age at diagnosis around age above 60 years. Prostate cancer is a major medical problem that needs immediate attention as the disease is indolent, shows prolonged latency in association with high morbidity and mortality. Administration of diagnostic tests including PSA test and biopsies and the advances in other diagnostic procedures have led to early detection of the disease with therapeutic steps being taken early on, there has been a steady decline in the disease-specific mortality. Global incidence and mortality rates show that the disease is more prevalent among black people, even though the differences cannot be attributed entirely to race, as the influence of socioeconomic situation and the resultant limited access to medical technologies and treatment could not be ruled out completely. Several genes have been identified that when mutated confer high risk for the disease. Besides the genetic factors, family history and nutritional factors such as lack of enough vitamin D, high intake of calcium, obesity and high fat diets have been implicated as risk factors for prostate cancer. Therapeutic measures for prostate cancer involve mostly radical prostatectomy followed by radiotherapy in combination with hormonal treatment as needed.

Key Words:

Prostate cancer, Epidemiology, Current Status.

prostate cancer varies greatly worldwide based on geographic region and this variation is partly due to the routinely used serum prostate specific antigen (PSA) measurement and digital rectal examination for prostate cancer and variability in the implementation of these techniques. Thus, countries such as the United States, Australia, and New Zealand and in Europe with the highest rates of prostate cancer testing have the highest reported rates of prostate cancer, whereas Asian and African countries with low rates of testing have the lowest incidence (Figure 1) rates³⁻⁵. Epidemiological studies in migrated populations between continents suggested that lifestyle and environmental risk factors determine prostate cancer risk⁶. In fact, much of the elevated prostate cancer incidence in Western countries, is attributed to the widespread practice of prostate-specific antigen (PSA) testing, that detects even the asymptomatic tumors, majority of which are not apparent clinically and are indolent⁶. On the other hand, in countries such as USA, with high prostate cancer incidence, there is discrepancy with the associated mortality rates (Figure 2). Thus, even though about 240,000 new prostate cancer cases are diagnosed annually in the USA, only > 15% of these men actually die of cancer^{7,8} and this low rate of mortality compared to the incidence of prostate cancer, is thought to be due to the widespread implementation of PSA testing and effective treatment at early-stage of prostate cancer disease⁹.

Introduction

Prostate cancer is the second most common malignancy in men with nearly 1 million new cases being diagnosed of which about one-third cases are fatal, every year and accounts for ~10% of all new cancer cases in men worldwide^{1, 2}. However, in Western countries including European countries and USA, approximately 25% of new cancer cases in males are due to prostate cancer. Incidence of

Age

Prostate cancer is predominant in men above 40 years of age. Histological examination of tissue samples from autopsy studies worldwide have indicated that prostate cancer incidence increases with age and nearly 75% of men above 80 years display some evidence of latent disease¹⁰. It is estimated that in while the incidence of prostate cancer is about 1 in 55 men in the age group 40-60 years, this increases by almost 8 times, to 1 in 7

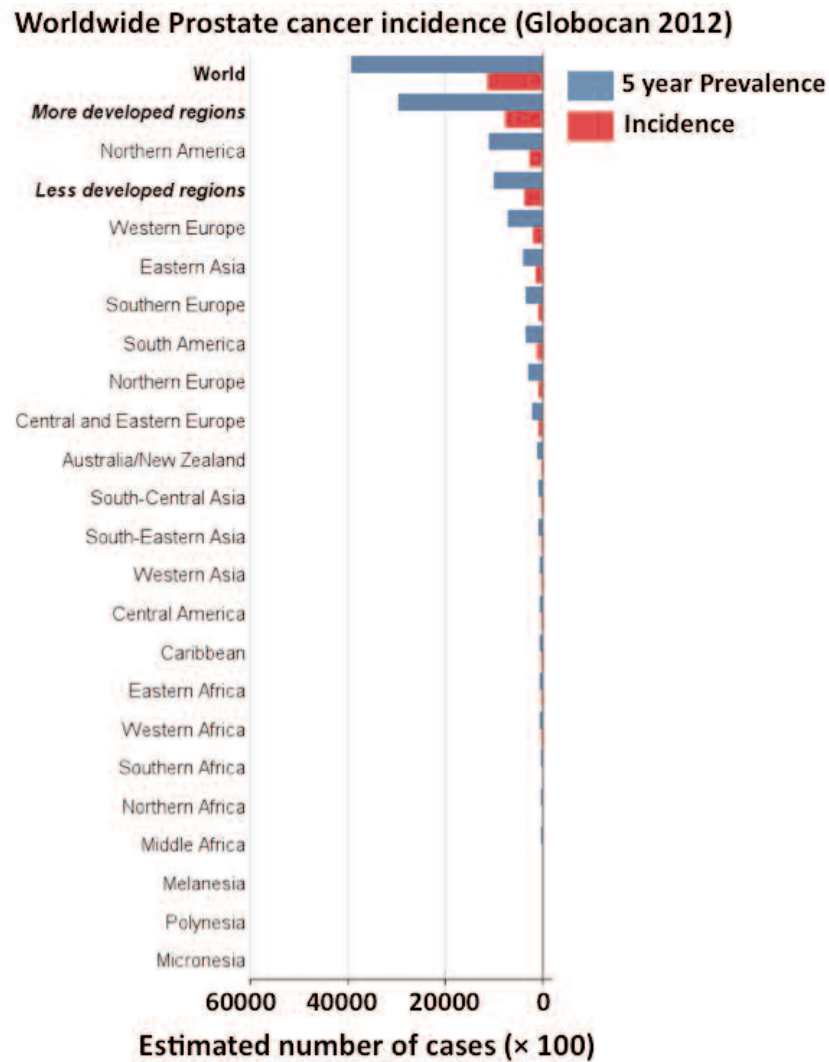


Figure 1. Worldwide prostate cancer 5-year prevalence and incidence. Data available from Globocan 2012 database was analyzed to generate this graph. Overall, more developed countries have much greater 5-year prevalence and incidence whereas these rates are much lower in underdeveloped countries.

men, in the age group of 60-80 years and also clinically presentation with the disease is often in men from this later age group¹¹. It has been suggested that the higher risk of prostate cancer among older men is likely because these men were not screened intensely at their younger age¹². A study on the information available in SEER database (Surveillance, Epidemiology, and End Results) on prostate cancer patients in the US during the period 1999 to 2006 suggested that over this 7-year period the incidence of high-risk featured prostate cancer decreased in the USA^{13,14}.

Family History

Besides age and racial background, family history of the disease is another major risk factor for

prostate cancer, which has high probability of heritability Alberti et al¹⁵⁻¹⁷. This is also supported by epidemiological studies in a Swedish cohort, which indicated about 11.6% of prostate cancer cases could be accounted by familial factors¹⁸ and that the risk is much greater for men with brothers suffering from prostate cancers¹⁹. Thus, it has been observed that first degree relatives of prostate cancer patients suffer almost double the risk as normal population for developing prostate cancer. This familial risk in first-degree relatives is more than 4-fold for early-onset cases occurring under 60 years of age^{20,21}. Also studies on Nordic twin registries showed monozygotic twins suffer ~50% higher risk in than the dizygotic twins, which strongly indi-

cates that genetic factors play a more important role in determining the risk rather than the lifestyle factors¹⁷.

Race

Several studies have shown the preponderance of prostate cancer is much higher among black men who also have a higher stage of disease at presentation. Significant epidemiological evidence for an increased prostate cancer incidence in African Americans in comparison to Asian Americans has been presented, which is suggestive of both genetic as well as racial differences²². Besides, mortality was also found to be higher among black men with

prostate cancer as compared to white men with the disease²³. The possibility of shared genetics was indicated in a recent study²⁴ that demonstrated high-grade prostate cancer at similar rates among black men from different countries including the USA, Jamaica, West Africa, and other sub-Saharan African countries (Figures 1 and 2), even though the role of sociodemographic disadvantage could not be ruled out. The exact significance of genetic versus socioeconomic factors including access to and utilization of early detection and treatment, or differences in diet and other environmental exposures in the observed differences in prostate cancer incidence is not clear²⁵.

Worldwide prostate cancer incidence and mortality (Globocan 2012)

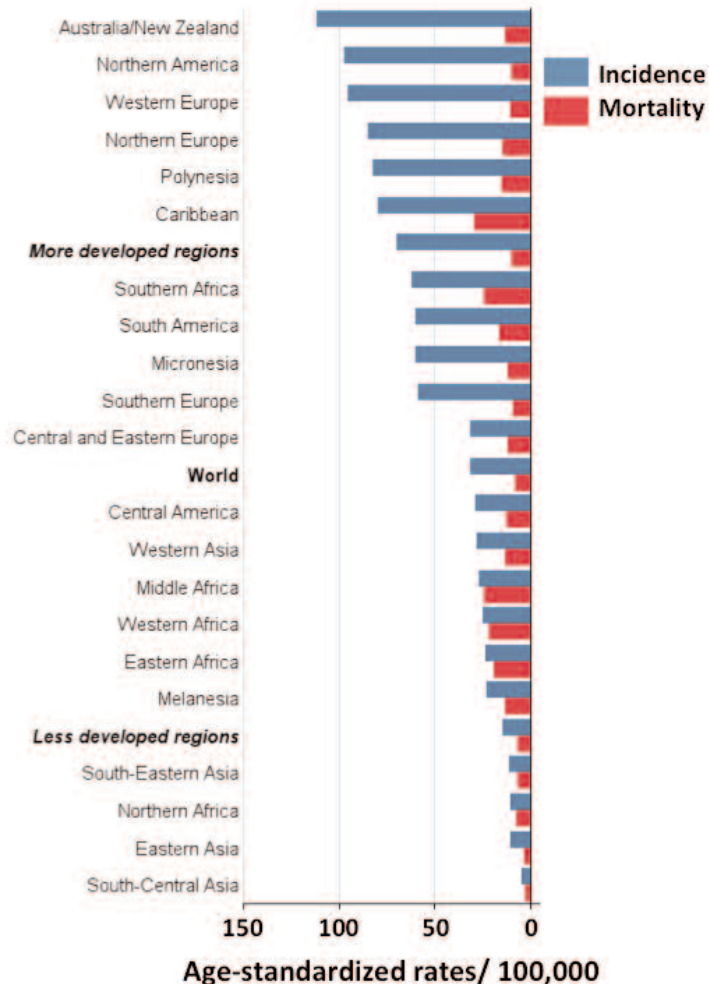


Figure 2. Worldwide prostate cancer incidence and mortality. Data available from Globocan2012 database was analyzed to generate this graph. While the incidence rates are much higher in developed countries the associated mortality rates are quite low. However, in less developed countries, even though the incidence rates appear to be low, the associated mortality rates are almost similar to the incidence rates indicating very fatality due to prostate cancer in these countries.

Effect of Diet on Prostate Cancer Incidence

Consumption of diets low in fat and high in vegetables and plant-based foods have a negative impact on the incidence of prostate cancer according to few epidemiological studies^{26,27}. Thus, a reduced intake of high caloric foods, in particular fatty foods such as red meat and dairy products, and lowered calcium intake along with adequate intake of vitamin D or exposure to sunlight and lycopene have been suggested to lower the risk of prostate cancer^{28,29}. However, there is no general agreement for the view that there is inverse relation between prostate cancer risk and the consumption of lycopene and selenium and similarly a positive relation between the risk and calcium intake². Also there is no clear consensus about the risk conferred by smoking³⁰ and alcohol³¹. Similarly, no consensus has been reached on the role of exercise, adiposity and energy balance, and the associated regulatory factors including insulin and insulin-like growth factor levels, in the development of prostate cancer³². Obesity was found to be associated with increased incidence of aggressive prostate cancer as well as prostate cancer recurrence. Prostate cancer-specific mortality is also likely to be elevated significantly by obesity³³. The overall evidence for a protective role of vitamin D against prostate cancer is weak, when only the circulating levels of 25-hydroxy vitamin D are considered without the inclusion of genetic factors³⁴. However, in areas where there is higher probability of vitamin D deficiency, such as high latitude regions, there appears to be stronger link between vitamin D status and prostate cancer incidence³⁵. Considering the relatively shorter (3 weeks) half life of 25-hydroxy vitamin D in blood, the studies on the association of serum vitamin D and prostate cancer need to be examined cautiously, as the levels of vitamin D measured may not reflect either the risk or the onset of prostate cancer.

Genetic Factors

Among the several prostate cancer risk loci identified by linkage studies, with the strongest linkage was noted on chromosome 1, with candidate genes including HPC1 on chromosome 1q23-35, PCAP on chromosome 1q42-43, and CAPB on chromosome 1p36³⁶. Besides, results from the International Consortium for Prostate Cancer Genetics (ICPCG) led to the discovery of 12 additional prostate cancer risk regions on dif-

ferent chromosomes, including 1q23, 5q11, 5q35, 6p21, 8q12, 11q13, and 20p11-q11³⁷. Even though BRCA gene mutations are relatively rare in prostate cancer with < 0.3% cases, there is elevated risk of prostate cancer in men above 65 years of age, with germline mutations in the BRCA1 (risk increased by 3.5 fold) and BRCA2 (8.6 fold increase in risk) genes³⁸. In fact, there is an association between carriers of mutations in BRCA2 and more poorly differentiated and larger prostate tumors³⁹. In spite of the observations that BRCA mutations can be highly penetrant and likely contribute to the aggressive prostate cancer, their use in clinical screening is limited because of their low incidence⁴⁰. Other mutations in DNA repair related genes including PALB2, BRIP1, CHEK2, NBS1 genes and also mutations in DNA mismatch repair genes MLH1, MSH2, MSH6, and PMS2, have been found to be associated with elevated risk of prostate cancer^{41,42}, even though the extent of the risk was later found to be much lower than that estimated earlier.

Association between prostate cancer and the chromosomal region 8q24, which was suggested earlier in linkage studies⁴³, was confirmed in more recent genome-wide association study (GWAS)⁴⁴. Further studies on the fine mapping of 8q24 have led to the identification of more than 8 variants located within 5 separate prostate cancer susceptibility regions⁴⁵. Among these risk attributing single nucleotide polymorphisms (SNPs), MYC is the closest annotated gene and this is an important oncogene in prostate cancer, as it is often amplified in tumors, and its association also confirmed in animal experiments⁴⁰. Further GWAS studies identified nearly 80 different genetic variants on 20 different chromosomes, that are associated with increased prostate cancer risk and the chances of prostate cancer appear to increase if an individual carries more risk alleles⁴⁶. It has been estimated that these SNPs can explain nearly 30% of the familial risk of prostate cancer in Europe⁴⁷. A panel of 23 prostate cancer risk SNPs was found to significantly improve the prediction of disease outcome in combination with PSA and family history⁴⁸. Prostate cancer has also been found to be associated with SNPs on chromosome 19, which contains the kallikreins genes, including KLK2 and KLK3, a subgroup of serine proteases, of which, the KLK3/PSA is well-known⁴⁹. Despite the significant advances in the identification of genes associated prostate cancer risk, the risk-associated SNPs explain only about 30% of the observed familial risk^{17,47}.

Other Risk factors

Besides the above-mentioned risk factors, occupation associated risk factor for prostate cancer includes the use of and/or exposure to herbicides and pesticides even though no specific agent has been identified^{50,51}. Similarly exposure to Agent Orange or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was proposed to be causative factor for prostate cancer⁵², even though this was not proven in further studies². The underlying causes for the association between high levels of circulating androgens with increased prostate cancer risk are not yet well understood, as the serum levels of measured testosterone do not necessarily reflect locally bioavailable levels⁵³. There also appears to be an association between chronic intraprostatic inflammation and prostate cancer⁵⁴.

Treatment Options

Considering that the disease progression of prostate cancer varies among individuals and as the disease is slow and unpainful, approaches towards definitive treatment may also defer. It has been suggested from the experience of randomized clinical trials that even though radical prostatectomy followed by radiation treatment without or with hormonal therapy for younger patients with high and intermediate risk prostate cancer can prolong survival⁵⁵, it can negatively affect the quality of life⁵⁶. In high-risk prostate cancer cases it is rather common to note the infiltration of surgical margins and/or the involvement of seminal vesicles and pelvic nodes and because of this it becomes necessary to administer postoperative radiotherapy without or with hormone therapy. Even though the surgical approach removes the prostate, seminal vesicles, and pelvic lymph nodes, eradication of the whole disease is not always possible, particularly in the cases of high-risk prostate cancer. Three-dimensional conformal or intensity modulated radiotherapy approaches introduced recently, facilitate the delivery of higher and more focused radiation doses to the target tumor tissue, thereby, controlling and lowering the urinary and rectal toxicity⁵⁷. Erectile dysfunction due to radiation therapy may develop progressively in the elderly population, particularly in combination with hormonal therapy⁵⁸. Chemotherapy options include the use of inhibitors of 5 α -reductase, which catalyzes the conversion of testosterone into dihydrotestosterone, which is the most powerful androgen promoter of prostate cancer growth. A reduction in circulating dihydrotestosterone levels

can significantly lower the risk of prostate cancer progression. Among the two drugs tested, finasteride and dutasteride, the later was found to be more effective in reducing blood levels of dihydrotestosterone⁵⁹. Clinical trials also indicated that dutasteride significantly reduced the incidence of prostate cancer detected on biopsy among high-risk patients.

Conclusions

Prostate cancer is a serious medical problem afflicting predominantly the elderly men. The prolonged latency, high prevalence, and morbidity, associated with significant mortality make prostate cancer an immediate medical problem to resolve. Diagnostic tests including PSA for early detection, and the advances in other diagnostic and therapeutic procedures have led to a steady decline in the disease-specific mortality with the reduction in high-risk prostate cancers. The disease appears to be more prevalent among black people, even though the differences cannot be attributed entirely to race, as the influence of socioeconomic situation could not be ruled out completely. Several genes and SNPs have been identified that impose high risk on the incidence of prostate cancer, particularly when present collectively in a single individual. Role of nutritional state, and vitamin D and calcium status are yet to be addressed systematically. Current treatment options include surgery in combination with hormonal and radiation therapies.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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