Prostate cancer I

Prostate cancer epidemiology

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Because more and more men are being diagnosed with prostate cancer worldwide, knowledge about and prevention of this disease is important. Epidemiological studies have provided some insight about the cause of prostate cancer in terms of diet and genetic factors. However, compared with other common cancers such as breast and lung cancer, the causes remain poorly understood. Several important issues could help in our understanding of this disease—the variation in incidence of prostate cancer between ethnic populations and the factors leading to familial clustering of the diseases.

Prostate cancer is the sixth most common cancer in the world (in the number of new cases), the third most common cancer in men, and the most common cancer in men in Europe, North America, and some parts of Africa. In 2000, the number of new cases of prostate cancer was estimated at 513 000 worldwide,[1] and this disease accounts for 9·7% of all cancers in men (15·3% in developed countries and 4·3% in developing countries). Incidence of prostate cancer is increasing steadily in almost all countries, yet we know little about what causes this disease. However, in the past 10 years interest in and funding for prostate cancer research have increased and several promising risk modifiers have been identified—eg, genetic predisposition, insulin growth factor (IGF) concentrations, and lycopene consumption. Here, I review the epidemiology and possible preventive agents of prostate cancer.

Epidemiology

Prostate cancer is diagnosed in very few people aged younger than 50 years (<0·1% of all patients). The mean age of patients with this disorder is 72–74 years, and about 85% of patients are diagnosed after age 65 years (figure 1). At age 85 years the cumulative risk of prostate cancer ranges from 0·5% to 20% worldwide.[1,2] Results of autopsy studies,[3] however, suggest that most men aged older than 85 years have histological prostate cancer. In a study of 600 men in Detroit, MI, USA the rate of latent prostate cancer was high at all ages: 30% for men in their 30s, 50% for men in their 50s, and more than 75% for men older than 85 years.[3]

Incidence of prostate cancer varies widely between ethnic populations and countries (figure 2) and rates of this disease differ by as much as 90-fold between populations. The lowest rates are usually in Asia, especially Chinese people in Tianjin, China (1·9 per 100 000 per year),[1] and the highest are in North America and Scandinavia, especially in African-American people in the USA (137 per 100 000 per year). These differences are caused by a combination of underlying differences such as genetic susceptibility, exposure to unknown external risk factors, or artifactual reasons such as cancer registration and differences in health care. In 15 years time, prostate cancer is predicted to be the most common cancer in men.[4]

Many factors could account for these wide differences. The access to and quality of health care and the accuracy of cancer registers affect how rates of prostate cancer are reported. Before reliable data were available from African countries, rates of prostate cancer in Africa were thought to be much the same as those in Asia. However, in Uganda[5] and Nigeria,[6,7] prostate cancer is very common, and in Nigeria it is the most common cancer in men. Migration studies have shown that when Japanese people move from Japan (a country with low incidence) to the USA (high incidence), incidence of prostate cancer in these people increases; however, the increase is only to about 50% of the rate for white people and to 25% of that for African-American people in the USA.[8] These findings suggest that differences between ethnic populations are real and not explained only by differences in health care and cancer registration.

Incidence of prostate cancer is increasing in both high-risk and low-risk populations,[4] the reasons for which vary between countries. In the USA, the increases are mainly because of a growing awareness of prostate cancer and widespread screening with the prostate-specific antigen (PSA) in men who do not have any symptoms.[9] Although such screening is much less common in Sweden, incidence of prostate cancer has increased by almost 100% over the past 30 years—mostly because of more frequent use of transurethral resection of the prostate and more intense and refined diagnostic procedures such as random biopsies.[9] Another important factor is that the number of people dying from other causes, particularly cardiovascular diseases, has decreased.[10] The increase in rates of prostate cancer in developing countries is more difficult to explain. Osegbe[7] speculated that unidentified external risk factors for prostate cancer have increased in Nigeria.

Genetic factors

The clustering of prostate cancer in families can be because of genetic susceptibility, exposure to common environmental factors, or chance alone since prevalence of this cancer is so high. 10–15% of patients with prostate

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See Commentary page 798

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Search strategy and selection criteria

I searched PubMed from 1960 to 2002 for articles with the terms prostate cancer, epidemiology, risk factors, diet, genetic, and chemoprevention. The search was restricted to English-language papers.

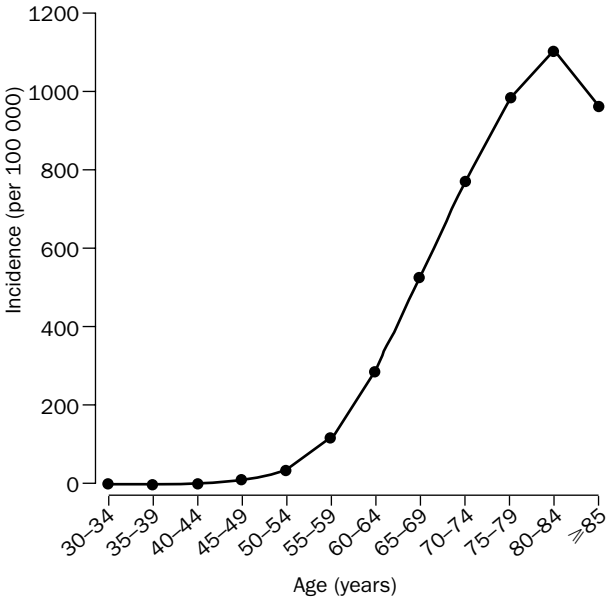

Figure 1: **Age-specific incidence of prostate cancer in Sweden 1995–99**

cancer (white, African, or Asian) have at least one relative who is also affected[11,12] and first-degree relatives of patients with prostate cancer have a two-fold to three-fold increased risk for developing this disease. Furthermore, the risk of developing prostate cancer in relatives increases with an increase in the number of affected individuals in the family and with a decrease in the age at diagnosis of the index prostate cancer case. Men who have a brother who has prostate cancer are more likely to develop this disease than are those who only have a father who is affected, suggesting that the disease is recessive or linked to the X chromosome.[13]

The concordance rate of prostate cancer has been compared between monozygotic and dizygotic twins, making it possible to assess genetic and environmental factors. Such studies from Nordic countries[14,15] and the USA[16] consistently show a high concordance rate in monozygotic twins. In a meta-analysis from three twin registries in Sweden, Denmark, and Finland,[15] the estimated heritability for prostate cancer was 42%, which was the highest of all studied cancers. Results of several segregation analyses[17–20] of white people living in Australia, Sweden, and the USA lend support to autosomal dominant inheritance of a high-risk gene. However, the estimated frequency of the gene was between 0·15% and 1·7% and penetrance was between 63% and 85% of a high-risk gene. In one study,[20] the evidence for a dominant inheritance came mostly from men diagnosed with prostate cancer who were younger than 60 years old, with little evidence of inherited factors in men diagnosed with this disease after age 70 years.

Linkage analysis[21–26] based on genome-wide scans has mapped susceptibility loci for prostate cancer to chromosomes 1, X, 20, 17, and 8. In 1996, the disease was first mapped to the *HPC1* locus on the long arm of chromosome 1 in 91 high-risk families from Sweden and the USA.[21] In families with linked prostate cancer, the main characteristics were that the disease developed at a young age (<65 years), affected five or more family members, and spanned two generations.[27] Linkage of prostate cancer to this gene has been confirmed by some,[28,29] but not all investigators.[30,31] Because these findings conflicted, the International Consortium for Prostate Cancer Genetics (ICPCG) did a pooled meta-analysis on 772 families with hereditary prostate cancer. Their results showed weak evidence of linkage in 6% of families,[32] but the subset of families who met the criteria of *HPC1* linkage had strong evidence of linkage. Germline mutations in the *RNASEL* gene in the *HPC1* region were reported to segregate with prostate cancer in two high-risk families.[33] The *RNASEL* gene regulates proliferation and apoptosis of cells through the interferon-regulated 2–5A pathway and has been suggested as a tumour suppressor gene. Thus, this gene is a strong candidate for the first prostate cancer susceptibility gene. However, mutations in this gene account for very few cases of prostate cancer segregation in families and this finding needs to be confirmed. Confirmation of other loci has also been troublesome and reflects the difficulty of identifying susceptibility genes in common complex diseases.[34]

Even if several highly penetrant prostate cancer genes are identified, they will account for only a small proportion of the familial aggregation and genetic susceptibility of the disease. The large effect of genes on prostate cancer suggested by studies in twins[14–16] might also be accounted for by polymorphisms in important genes for prostate development and function,[35,36] which might result in quantitative and qualitative functional differences in protein expression in the physiology of healthy tissue. In prostate cancer, polymorphisms in genes regulating androgen metabolism, metabolites of oxidative stress of apoptosis are obvious candidates. Investigators of several studies[32,37,38] have reported significant associations between prostate cancer and polymorphisms, suggesting a modification of risk. The

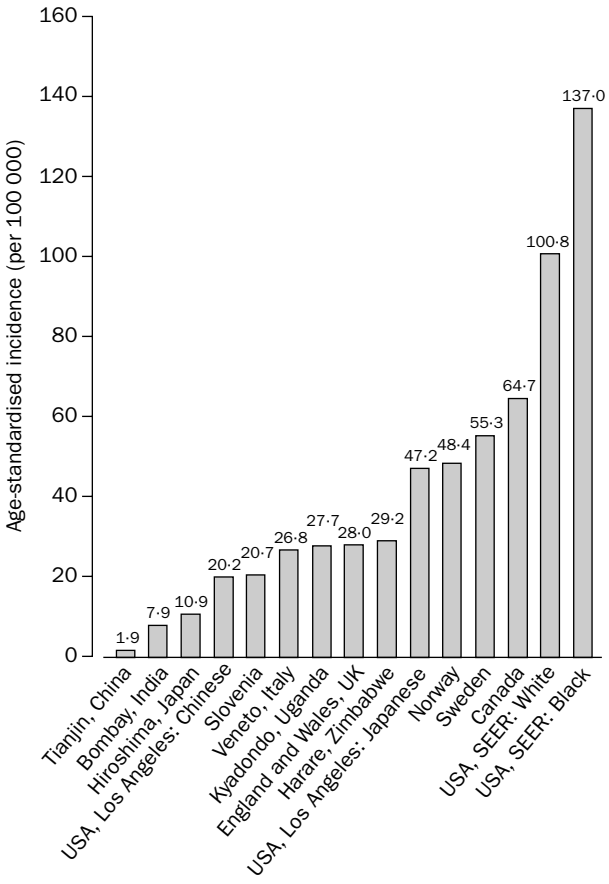

Figure 2: **Age-standardised incidence rates (per 100 000) for prostate cancer[1]**

most studied polymorphisms are in the androgen receptor,[32,37–39] vitamin D-receptor, CYP17 (17α-hydroxylase),[40,41] *SRD5A2* (5α-reductase),[42,43] and the *ELAC*/*HPC2*[44–46] in exon 1 of the androgen receptor gene, which has two three nucleotide repeats (CAG and GGC)—variants that affect transcription and activation of this gene.[47] In a study of 49 patients with prostate cancer,[48] patients with fewer than 22 CAG repeats had three-fold increased risk compared with those with more than 22 repeats. This report prompted almost 20 further published studies of CAG repeats associated with prostate cancer. Unfortunately, few studies have confirmed this finding and most were too small (100–300 patients) and did not have the statistical power to detect small to moderate (20–50%) modifications in risk. Of those that did confirm the association, most were confirmatory only in subgroup analyses. Investigations of association of genetic polymorphisms have not been able to account for the large genetic effect suggested by epidemiological studies. Larger studies (2000–10 000 patients) that use the increasing knowledge of the human genome and have the ability to genotype single nucleotide polymorphisms in high-throughput laboratories will probably identify several important genetic variants that affect risk of prostate cancer.

Dietary factors

Results of ecological studies[49,50] suggest that prostate cancer is associated with a western lifestyle and in particular, diet that includes a high intake of fat, meat, and dairy products. The association between dietary factors and prostate cancer has now been investigated in epidemiological studies of 30–40 populations. The results of these studies are mostly conflicting or negative[51–53] but some dietary components are consistently associated with prostate cancer—eg, high intakes of α-linolenic acid (a polyunsaturated fatty acid in vegetables and dairy products)[54–58] and calcium.[59] In the Physicians' Health Study,[59] 1012 patients with prostate cancer had been prospectively assessed for dietary calcium intake before they were diagnosed with prostate cancer. Men who had more than 600 mg Ca per day from dairy products were 1·32 (95% CI 1·08–1·63) times more likely to develop prostate cancer than were those who consumed 150 mg Ca per day or less, and the risk was highest in patients with advanced and metastatic disease.[59] This finding was confirmed in a large Swedish case-control study.[60] In several studies in animals, high concentrations of fatty acids and their metabolites were associated with prostate cancer. Results of one study[61] showed that the *AMACR* (α-methyl-CoA remarcase) gene is up-regulated and over-expressed in prostate cancer tumours but not in the healthy prostate. AMACR plays a key part in peroxisomal oxidation of dietary branched fatty acids, and peroxisomal β oxidation generates hydrogen peroxide—a potential source of carcinogenic oxidative damage. Because beef and dairy products are major sources of dietary branched-fatty acids, up-regulation of *AMACR* might explain some of the association between dairy products and prostate cancer.

Large consumption of red meat has also been linked to prostate cancer,[53,55,62] and in particular it might not be the intake of meat but the cooking and preparation that is important for this disease.[63] One hypothesis is that cooking at high temperatures (eg, charcoal grilling or frying) results in formation of very potent carcinogens such as heterocyclic amines, which have been correlated with colorectal, bladder, and kidney cancer.[63] For prostate cancer, this hypothesis needs more study.

One explanation for the low incidence of prostate cancer in Asia might be high consumption of dietary phyto-oestrogens. Soybeans (generally processed into soymilk or tofu) have one of the highest contents of phyto-oestrogens, especially flavonoids, which have a prophylactic effect on prostate cancer.[64–67] In a study in mice with human androgen sensitive prostate cancer cells, a diet based on rye bread and soy protein reduced the tumour size, increased apoptosis, and decreased secreted PSA.[68,69] Thus, several mechanisms might explain how these natural oestrogens affect prostate cancer cells: an antioestrogenic effect via the oestrogen receptor; reduction of circulating concentrations of androgens by increasing the concentration of the sex hormone binding globulin; increase of apoptosis; or regulation of angiogenesis.

Frequent intake of tomato-based products, particularly tomato sauce, is associated with a reduced risk of prostate cancer. Tomatoes contain lycopene, a carotenoid and potent antioxidant. In a study of 2481 men with prostate cancer, those who consumed large amounts of lycopene had a 16% lower risk than people who consumed small amounts of lycopene.[70] In men with localised prostate cancer, a high intake of tomato sauce 3 weeks before radical prostatectomy resulted in a decrease of PSA, an increase of the concentration of lycopene in serum and in the prostate, and a decrease of the oxidative damage in the prostate.[71] Thus, lycopene is a promising compound for chemoprevention.

Of the micronutrients that have been investigated in prostate cancer, selenium and vitamin E are the most promising. Selenium is a non-metallic trace element and is essential to human development. Furthermore, it inhibits tumorigenesis, including prostate cancer tumours.[72] Several potential mechanisms might explain the antitumorigenic effect of selenium, including antioxidant effects, enhancement of the immune system, induction of apoptosis, and an effect on production of testosterone.[73] After 4·5 years of follow-up of 1312 patients with a history of skin cancer, incidence of this disease did not differ between those given selenium and those given placebo; however, prostate cancer was 66% lower in the selenium group than in the placebo group.[74,75] Vitamin E (α-tocopherol) is a fat-soluble vitamin that has antioxidant effects with particular activity in oxidative induced DNA damage. Results from the Finnish randomised prevention trial, the Alpha Tocopherol-Beta Carotene cancer trial,[76] showed a 40% decrease in incidence and mortality in prostate cancer in men taking α-tocopherol compared with those taking placebo.

Hormones and other risk factors

Androgens play an important part in development of the healthy prostate and in treatment of prostate cancer. In 1941, C Huggins received the Nobel Prize for his study of the role of androgen in this disease.[77] The prostate converts testosterone to dihydrotestosterone, a key substrate for downstream hormone metabolism. Withdrawal of testosterone by surgical or medical castration is a well known treatment for prostate cancer and is effective in 75–80% of patients with metastatic prostate cancer. In animals, testosterone and dihydrotestosterone have induced prostate cancer tumours. However, epidemiological data showing that differences in androgen concentrations in patients with prostate cancer are important are few.[78] Samples taken at diagnosis or prospectively (up to 15 years before diagnosis) are mainly negative.[78] However, these studies had several limitations in their methods that need to be taken into account when interpreting the results—most

Some risk factors for prostate cancer

Established
Ethnic origin
Age
Family history
IGF
Possible
Lycopene
Zinc
Selenium
Uncertain
AR polymorphisms
Vitamin D polymorpisms
Dietary fat
Excluded
Smoking
Alcohol
Vasectomy
Physical activity

used only a few patients and assessed only one or two of all possible hormones. In addition, the timing at which the samples were taken might affect the results. If testosterone is essential for the onset of prostate cancer, then the appropriate time to sample might be between ages 15 and 30 years. Other hormones such as oestrogen, insulin, and leptin[79,80] have also been investigated, but these hormones have not been consistently associated with prostate cancer.

Insulin growth factor (IGF)-I, a peptide growth factor that is easily measured in the circulation, regulates proliferation, differentiation, and apoptosis of cancer cells. Substantial variation has been identified between human beings. Recently, three well-designed independent prospective cohort studies showed people in the highest quartile of IGF-I concentrations had a 1·7–4·3 increased risk of prostate cancer compared with those in the lowest quartile.[81–83] The IGF system might be the link between the sedentary western lifestyle and prostate cancer: consumption of large amounts of fat result in raised production of insulin that in turn increases production of IGF, thus explaining how IGF could be a risk factor for prostate cancer.

Other factors such as smoking,[84] alcohol consumption,[85] vasectomy,[86] and physical activity[87] have been investigated in several studies, but the overall conclusion is that they do not affect risk of prostate cancer. The risk factors are summarised in the panel.

Chemoprevention

Primary prevention such as chemoprevention has potential to control the increasing number of prostate cancer cases worldwide. If chemoprevention delays the clinical course of prostate cancer by 2–5 years, incidence of and deaths from this disease would substantially decrease.[88,89] In earlier chemoprevention trials in which prostate cancer incidence or mortality were not the primary endpoints, selenium and vitamin E were reported to lower the risk of disease.[74–76] At present, at least two large controlled, randomised trials are assessing prevention of prostate cancer as a primary endpoint.

The Prostate Cancer Prevention Trial[90] is a randomised, double-blind, placebo-controlled trial in which the effect of finasteride is being investigated.[90] Finasteride is an effective 5α-reductase inhibitor that reduces concentrations of dihydrotestosterone in the prostate. From 1993 to 1996, the Prostate Cancer Prevention Trial recruited 18 882 men. After 7 years of treatment, all survivors will undergo a sextant biopsy to ascertain the prevalence of prostate cancer. The primary endpoint of this trial is prostate cancer proved by biopsy, and the trial is not designed to find differences in deaths from prostate cancer. Although death from prostate cancer is probably the best endpoint for this trial, the trial would have had to include at least 51 000 patients and persist for such a long time (15 years), that such an endpoint was deemed unrealistic. The preliminary results of this study will be published in 2003 or 2004.

On the basis of earlier chemoprevention trials of selenium and vitamin E in which prostate cancer decreased,[74–76] the Selenium and Vitamin E Cancer and Prevention Trial (SELECT)[91] was initiated in 2001. This study is a double blind, placebo controlled, two-by-two factorial study will include 32 400 men who have a normal digital rectal exam for prostate cancer and a normal serum PSA concentration. The men will be randomised to receive selenium alone, vitamin E alone, selenium and vitamin E, or placebo. The primary endpoint is clinical incidence of prostate cancer and the secondary endpoints are prostate cancer-free survival and all-cancer death and incidence. The final results will not be available until 2013.

Conflict of interest statement
None declared.

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