Ministry of Defence

Synopsis of Causation

Cancer of the Prostate

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1. Prostate cancer is the most common cancer of men in the United Kingdom, with a lifetime risk of having the disease of 1 in 12. It is the second most common cause of cancer deaths. A number of different histological types occur, but the great majority (95%) are adenocarcinomas.[1]

1.2. The incidence of the disease in the UK is around 7.5 per 100,000 men, and nearly 70% of prostate cancer cases occur in men age 65 and older. It accounts for some 6% of all male cancer deaths in the UK.

2. Clinical features

2.1. The clinical course is usually predictable and based upon tumour grade and stage. For example, just 15% of patients with poorly differentiated localised prostate cancer survive 10 years..

2.2. With advancing age, most men develop microscopic foci of prostate cancer, and autopsy studies have shown that approximately 30% of men over the age of 50 have histological evidence of the disease. However only a small percentage of these slow-growing tumours will develop into invasive prostate cancer and an even smaller proportion will cause premature death.[2]

2.3. Although prostate cancer may present with local symptoms, such as urinary frequency, decreased urine stream, urinary urgency or urinary retention, none of these symptoms is unique to prostate cancer and each could arise from a variety of other conditions. Occasionally the patient may present with signs and symptoms of distant spread.

2.4. Like all malignant conditions the ability to diagnose prostate cancer early in the course of its development is important, as prompt treatment offers the chance of eliminating the disease or controlling it for long periods. The physician is alerted to the possible presence of the condition by abnormalities in the size and consistency of the prostate on digital rectal examination (DRE), and a raised prostate-specific antigen (PSA) level.

2.5. **PSA testing**

2.5.1. In 1986 the PSA level was introduced as a method of detecting prostate cancer. PSA is a large protein secreted exclusively by the prostate gland. It is excreted in small quantities into the bloodstream, and is used as a marker of prostatic activity. The PSA level is elevated in prostatic infection, benign prostatic hyperplasia (BPH), prostate cancer and (very rarely), prostatic infarction. With age, the prostate enlarges and PSA levels increase. However, prostatic size is very variable and the concept of a "normal" PSA is misleading. In addition the quantity of PSA excreted by a gland of a given size varies significantly.

2.5.2. The normal range for PSA levels is a matter of controversy. Typically, the reference range has been considered to be 0-4 µg/l, but most clinicians employ an age-related reference range. If the normal value is set lower; say, 0-3 µg/l, more biopsies are performed and more prostate cancer is detected but whether this is clinically significant disease is unknown. Certainly, rapidly rising PSA levels should be investigated thoroughly.

2.5.3. In prostate cancer the PSA does rise, but by a variable amount. In early cancers localised to the prostate gland the increase may be small, and some individuals with confirmed prostate cancer may have a PSA level of less than 4 µg/l. It is rare to find a case of metastatic prostate cancer where the PSA is under 20 µg/l. If the PSA is greater than 60 nmol/l, it is probable that the patient has metastases, and in advanced disseminated cancer the PSA may exceed 1000 µg/l.

2.5.4. In the range to 40 µg/l up to 60% of patients may have BPH. In prostatic infection the PSA may be significantly raised - occasionally as high as 100 µg/l.[3]

2.5.5. Advocates of screening contend that it leads to earlier detection and greater numbers of patients whose tumours can be cured with local therapy. However opponents of screening take the view that there is no proof that earlier detection leads to improvement in prostate cancer mortality and that increased treatment may do more harm than good. Screening large populations of men for prostate cancer therefore remains controversial and most clinicians in the UK perform the test selectively, based on age, symptoms, family history, physical examination findings, and, often, the patient's request for the test. In the UK, the overall annual rate of testing in men with no prior diagnosis of prostate cancer has been estimated to be 6.0 per 100 men.[4]

2.5.6. Various methods for increasing the usefulness and accuracy of serum PSA estimation (e.g. PSA velocity, PSA density, age-specific PSA reference ranges, and measurement of the molecular forms of PSA) have been developed to improve the specificity of the PSA test. At present, these methods are employed for more detailed investigations and require further evaluation before widespread deployment.

2.6. **Investigation** of prostate disease, as indicated by abnormalities on DRE and/or elevation of PSA, is usually carried out by means of trans-rectal ultrasonography and biopsy. These procedures are generally safe and serious complications are rare, although complications of biopsy do occur in 1-5% of patients, and include haematuria and infection. Evaluation of disease is most accurately assessed by a combination of clinical (T) staging, imaging studies, such as CT, MR and bone scans and Gleason grade from histological examination of biopsy specimens. Probability nomograms based on these parameters greatly assist therapeutic decision-making.

2.7. **Progression** The majority of men present with local symptoms, such as urinary retention, urinary frequency, decreased urine stream or urinary urgency . Prostate cancer has a marked propensity to form distant metastases in bone.

2.8. **Treatment** There is considerable debate regarding the best mode of therapy for each stage of carcinoma of the prostate. The selection of treatment options often requires a compromise between maintaining quality of life and increasing the duration of survival. For example the older patient with carcinoma of the prostate will often have other co-morbid illnesses that may pose a greater threat to their overall survival and in low-grade, low volume disease a policy of “watchful waiting” may be the preferred option. Many prostate cancers are – at least initially – sensitive to androgen deprivation and he majority of patients are treated with anti-androgens and luteinising hormone-releasing hormone (LHRH) analogues. Surgical treatment, cryosurgery, radiotherapy and brachytherapy (temporary or permanent local application of radioactive material) are the main therapeutic alternatives but all carry the risk of undesirable side-effects, such as loss of potency, poor urinary control, urinary retention and proctitis.

3. Aetiology

3.1. Although the aetiology of prostate cancer has been widely investigated, the cause of the disease remains unknown. There is considerable evidence to suggest that both genetic and environmental factors play a role in the evolution of the disease, but although studies have identified a number of putative risk factors associated with its development, only those of **age,** and in 5-10% of patients a **family history of prostate cancer,** are well established.

3.2. Potential and putative risk factors include:

- Age
- Hereditary factors
- Androgen
- Vasectomy
- Race
- Diet
- Infection
- Miscellaneous factors, including height and weight, sexual activity, smoking, and alcohol consumption

3.3. **Age** Prostate cancer is predominantly a disease of elderly men, and age is the most important risk factor for the disease; more than 75% of new prostate cancers are diagnosed in men older than 65 years. The incidence of prostate cancer in men in their sixth decade of life, however, has increased significantly since the 1970s, and the reasons for this are not as yet understood.

3.4. **Hereditary factors** Hereditary susceptibility is now considered to be a significant risk factor for prostate cancer,[5] and although no specific gene has yet been identified with certainty, it is probable that a genetic cause exists in 5-10% of cases. The genetic mechanism involved is extremely complex and as yet imperfectly understood.

3.5. Familial clustering has been demonstrated in a number of case-control studies, and the generally accepted definition of familial prostate cancer is a nuclear family with two cases, or two first degree relatives who had a diagnosis before the age of 55 years, or prostate cancer in three successive generations. In one study the authors found that first-degree relatives of men with prostate cancer had a significantly higher risk of developing the disease than did controls. Men with one first-degree relative with prostate cancer had a twofold risk of developing prostate cancer, while men with two or three affected first-degree relatives had a 5- to 11-fold risk, respectively.[6] In a later population-based case-control study, the authors reported similar findings. The risk of developing prostate cancer was related both to the number of affected relatives and their age at diagnosis; a younger age being associated with a higher risk of the disease.[7] However, a family history of prostate cancer is only significant in 5-10% of patients.

3.6. **Androgens** appear to influence the progression of prostate cancer, The evidence from randomised controlled trials suggests that early androgen suppression for treatment of advanced prostate cancer reduces disease progression[8] and complications due to progression of these tumours temporarily regress after surgical or medical castration. The extent to which androgens contribute to prostate cancer risk is uncertain, but it is unlikely that they play a significant part. Investigations are complicated by normal diurnal variation in testosterone levels, uncertainties surrounding the importance of early or late exposure to androgens in a man's life, or the possibility that a change over time is the important factor. Other workers have postulated that the balance of androgens and oestrogens may be critical for prostate carcinogenesis.

3.7. **Vasectomy** There is as yet no established relationship between vasectomy and prostate cancer risk. Two large cohort studies (one retrospective and another prospective) reported an increased risk of prostate cancer in men who had undergone vasectomy.[9,10] The risk increased with time, so that men who underwent vasectomy at a younger age had a higher risk. A number of hypotheses have been proposed to identify some mechanism by which vasectomy might predispose to prostate cancer, including the presence of anti-sperm antibodies, reduced seminal androgen concentrations, and decreased prostatic secretory activity, but so far these hypotheses have not been proven experimentally. Other studies have failed to show any association between vasectomy and prostate cancer.[11,12]

3.8. **Racial factors** Worldwide, prostate cancer is the fourth most common male malignancy and its incidence and mortality rates vary markedly, being generally higher in Western populations than in developing countries. Asian countries, particularly Japan and China, have the lowest incidence and mortality rates while Scandinavian countries have an especially high rate of prostate cancer diagnosis and death. The incidence of prostate cancer is particularly high among the African American population of the United States. There are other significant differences between ethnic groups living in the same country; for example, the incidence among Japanese Americans is intermediate between White Americans and native Japanese. Migration studies have also shown an increased incidence of prostate cancer in first-generation immigrants from Japan and China into the United States. This may in due course point to factors that increase prostate cancer risk and suggest others that may reduce it. The part played by diet has come under particular scrutiny.

3.9. **Diet** Some research has led to the view that diet may affect prostate cancer risk. More specifically, it has been proposed that diet may play a role in converting so-called latent or histological cancers into clinically manifest cancers. While the global incidence of latent or histological prostate cancers is similar, (see 2.2) the incidence of clinically manifest cancers varies considerably between populations, as indicated in 3.2 above. These differences suggest that while diet may not initiate prostate cancer it may in some way promote its progression. A number of dietary factors have been epidemiologically linked to prostate cancer.

3.9.1. **Fat** For some years, fat consumption has been suspected as a risk factor and there is a correlation between the level of dietary fat in different countries and prostate cancer mortality rates. A number of explanations have been proposed; for example the observation that fat can raise androgen levels, or that fat may be a source of carcinogenic free radicals. Additionally, fatty acid metabolites such as arachidonic acid can stimulate the growth of prostate cancer cells in vitro. A recent critical appraisal of the literature concluded that while the evidence for an association between dietary fat intake and prostate cancer was consistent, further corroborative work was necessary.[13]

3.9.2. **Meat** There is some evidence of an association between eating meat and prostate cancer,

particularly for advanced disease, and cohort studies have reported positive associations between prostate cancer and red meat consumption, total animal fat consumption, and intake of fatty animal foods.[14,15] One possible explanation is that meat produces carcinogenic heterocyclic amines when cooked at high temperature, and polycyclic aromatic hydrocarbons are generated when meat is grilled over flames. However, many studies of this topic have produced equivocal results and the evidence remains inconclusive.[16]

3.9.3. **Calcium** A number of studies have found an association between high calcium consumption and an increased risk of prostate cancer. The mechanism by which calcium could increase prostate cancer risk is conjectural; it is suggested that high levels of calcium may down-regulate vitamin D production, thereby promoting cell proliferation.

3.9.4. **Selenium** It has been proposed that selenium, an essential trace element, may exert a protective effect for the development of prostate cancer, but so far no definite conclusions have been reached.[17,18]

3.9.5. **Other dietary elements** A large amount of information has accumulated regarding the use of other agents as possessing a protective effect, including vitamins E and D, other 5-alpha-reductase inhibitors, cyclooxygenase-2 inhibitors, lycopene (found in cooked tomatoes), and green tea. So far the results of research have been inconclusive.[19]

3.10. **Infection and inflammation** There has been a renewed interest in the possibility that chronic or recurrent prostate inflammation may contribute to the development of prostate cancer. This has arisen as a result of a number of lines of evidence. Firstly, two of the inherited susceptibility genes for prostate cancer encode proteins that function in infection. Secondly, a newly identified precursor lesion of prostate cancer, proliferative inflammatory atrophy (PIA), appears to arise as a result of prostate inflammation. Thirdly, prostate cancer cells acquire defects in genes, which encode enzymes that defend against damage inflicted by oxidants of the type produced by inflammatory cells. The possibility offers the prospect of considerable therapeutic advances but requires further research.[20,21,22]

3.11. **Miscellaneous factors** A number of **morphological factors** (e.g. height and weight) have been proposed as affecting the risk of prostate cancer, but as yet no clear links have been established. The results of studies to explore the relation between the body-mass index (BMI) and the risk of prostate cancer are controversial, and so far research has failed to establish a clear connection.[23,24] **Sexual activity** has been identified by some workers as a risk factor for prostate cancer, akin to the relationship between human papillomavirus and cervical cancer in women, but no consistent connection has been found and there is no evidence of a viral basis to prostate cancer akin to that of cervical cancer. Neither **cigarette smoking** nor **alcohol consumption** has been shown to have any relationship with the disease.

4. Prognosis

4.1. When the prostate gland is examined at post-mortem in men age 50 years or older who had no clinical evidence of the disease, cancer is identified in approximately 30% of cases (see 2.2). However the lifetime risk of developing clinically detectable prostate cancer is about 1 in 12. This discrepancy raises the question whether some prostate cancers might best be managed by "watchful waiting" i.e. without immediate treatment.

4.2. The prognosis of men with prostate cancer correlates well with the histological grade and stage of the tumour. Yet a number of studies provide strong evidence that clinically localised prostate cancer, although slow growing, can affect patient morbidity and mortality. Some prostate cancers do progress slowly and present little risk to the overall health of the patient. In these cases watchful waiting may be a reasonable option, especially for those with a low grade tumour and/or a life expectancy less than 10 years. However, there is evidence that most clinically detected prostate cancers are not indolent; they adversely affect health and life expectancy, and should be treated with the intent to eradicate the primary tumour. The current guidelines for treatment of localised prostate cancer therefore recommend potentially curative therapy (e.g. surgical treatment, radiotherapy, brachytherapy) for patients whose remaining life expectancy is 10 years or more.

4.3. New surgical techniques are currently under development, such as laparoscopic radical retropubic prostatectomy. It is not known if this method provides any additional benefit over the traditional surgical approach. Research also continues in the refinement of other experimental treatments, such as cryotherapy, and the development of new forms of treatment, such as high-intensity focused ultrasound and radio frequency interstitial tumour ablation.[25]

4.4. In recent years, the identification of certain molecular alterations or gene products has been shown to be of value in the assessment of prognosis. However prospective trials are required to evaluate these markers more thoroughly before their implementation is recommended in current management.

5. Summary

5.1. Prostate cancer is the most commonly diagnosed life-threatening cancer in men in the United Kingdom. The clinical course is unpredictable and as yet no single investigation will reliably indicate the probable progression of the disease. Evaluation rests on clinical examination, PSA testing and biopsy.

5.2. The incidence varies widely between racial groups, being least common in people of Asian origin and most prevalent among African Americans.

5.3. The cause is unknown, but the two factors most clearly associated with the disease are increasing age and familial susceptibility. Others, such as androgen levels, vasectomy, racial variations, diet, infection, and miscellaneous factors, await further research.

5.4. The prognosis varies according to a number of factors including the stage and histological features of the tumour on diagnosis, and the age of the patient. No form of treatment is free of the risk of untoward side-effects but in general, potentially curative treatment is usually advised. However the consensus view is that regardless of local treatment, the disease pursues its own biological course.

6. Related Synopses

Cancer of the Testes

Cancer of the Breast

7. Glossary

adenocarcinoma	A form of cancer that forms from cells originating in the lining of the walls of certain organs.
androgen	General term for any male sex hormone.
antibodies	A large variety of protein molecules produced as a primary immune defence.
benign prostatic hyperplasia	A non-malignant enlargement of the prostate gland encountered in older men.
biopsy	A procedure that involves obtaining a tissue specimen for microscopic analysis to establish a precise diagnosis.
body-mass index	A measure which correlates with the amount of fat in the body. BMI = body weight in kilograms/square of height in metres.
brachytherapy	A type of radiation therapy is which radioactive materials are placed in direct contact with the tissue being treated.
cryosurgery	A surgical technique which destroys unwanted tissue by freezing it.
haematuria	Blood in the urine.
infarction	Death of tissue due to interruption of blood supply.
luteinising hormone-releasing hormone	A hormone which stimulates the release of luteinising hormone, which in the male stimulates testicular cells to produce the androgens and a small amount of oestradiol and oestrogen (q.v.).
medical castration	The use of drugs to suppress the function of the testicles.
metabolites	Substances which are a by-product of the chemical processes of the body.

metastatic	Referring to a deposit of a malignant tumour in a distant site in the body. Hence *metastasis*, *metastasise*.
nomogram	A form of line chart showing scales for the variables involved in a particular formula.
oestrogens	A class of sex hormones associated with the development and maintenance of secondary female sex characteristics.
orchidectomy	Surgical removal of the testicles.
oxidants	Oxidizing agents in chemical reactions, some of which act as tumour promoters.
proctitis	Inflammation of the rectum.
prostate	A small conical gland at the base of the male bladder, which surrounds the first part of the urethra.
testosterone	Male sex hormone (androgen) secreted by the interstitial cells of the testis.
trans-rectal ultrasonography	A technique which enables the visualisation of the prostate by means of ultrasonic waves.

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