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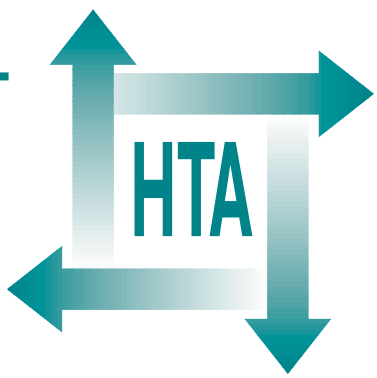
Review

The diagnosis, management, treatment and costs of prostate cancer in England and Wales

Jocelyn Chamberlain
Jane Melia
Sue Moss
Jackie Brown

Health Technology Assessment
NHS R&D HTA Programme



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The diagnosis, management, treatment and costs of prostate cancer in England and Wales

Jocelyn Chamberlain FRCP, FFPHM [1]
Jane Melia PhD, Hon MFPHM [1]
Sue Moss PhD, Hon MFPHM [1]
Jackie Brown PhD [2]

[1] Cancer Screening Evaluation Unit, Institute of Cancer Research, Section of Epidemiology, D Block, Cotswold Road, Sutton, Surrey SM2 5NG

[2] Health Economics Research Group, Brunel University, Uxbridge, Middlesex UB8 3PH

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NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Diagnostics and Imaging Panel (see inside back cover).

A considered decision was taken to commission two similar reports in the area of prostate cancer as an experiment during the initial funding phase of the HTA programme. The aim was to explore the consistency of systematic reviews when commissioned from research teams with different backgrounds and research expertise. This report provides a strong link with health economic issues, whereas the related report [Selley S, *et al.* Diagnosis, management and screening of early localised prostate cancer. *Health Technol Assess* 1997;**1**(2)] has, as one of its main focuses, early localised prostate cancer. The two reports provide an excellent overview of this field and will greatly enhance the knowledge base from which future decisions in this field will benefit.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health.

The editors have tried to ensure the accuracy of this report but cannot accept responsibility for any errors or omissions. They would like to thank the referees for their constructive comments on the draft document.

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The National Coordinating Centre for Health Technology Assessment,
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University of Southampton,
Southampton, SO16 7PX, UK.
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Contents

List of abbreviations

ACTH	andrenocorticotropic hormone
BPH	benign prostate hyperplasia
CI	confidence interval
CT	computed tomography
DES	diethylstilbestrol
DRE	digital rectal examination
EORTC	European Organisation for Research in Treatment of Cancer
FHSA	Family Health Services Authority
GP	general practitioner
HES	Hospital Episode Statistics
IMS	International Medical Statistics
LH	luteinising hormone
LH–RH	luteinising hormone–releasing hormone
MAB	maximum androgen blockade
MRC	Medical Research Council
MRI	magnetic resonance imaging
PAP	prostatic acid phosphatase
PIN	prostate intra-epithelial neoplasia
PIVOT	Prostate cancer Intervention Versus Observation Trial
PLCO	Prostate, Lung, Colon, Ovary trial
PSA	prostate specific antigen
RSR	relative survival rate
SMR	standardised mortality rate
TNM	pathological staging of tumours: T – primary; N – regional nodes; M – metastatic
TRUS	transrectal ultrasound
TURP	transurethral resection of the prostate

Summary of conclusions and recommendations

Chapter 2: The burden of prostate cancer on health

Conclusions

1. The number of men requiring care for prostate cancer is certain to increase over the next decade

   (a) because of increased testing for prostate cancer
   (b) because of ageing of the population
   (c) if there continues to be a true increase in incidence.

   If (a) and (b) remain stable, ageing of the population alone will cause the annual incidence to increase from 13,481 in 1990 to 18,004 in 2011 and if there is a 10% increase in the incidence rate, to about 19,800.

2. The number of men who die from prostate cancer is also likely to increase (although not so steeply) because of (b) and (c) above.

3. Apparent improvements in survival may merely reflect length-biased sampling resulting in increased diagnosis of slow-growing tumours.

Recommendations

1. Clinicians should explicitly record as much information as possible on stage, ideally pathological TNM staging, but otherwise clinical staging as far as they can.

2. Cancer registries should set up a standardised system for recording stage at diagnosis so that stage-specific incidence can be monitored. Priority should be given to recording pathological TNM staging, but if this is not available, clinical stage should be recorded.

Chapter 3: The burden of prostate cancer on the health services

Conclusions

1. Because of increasing incidence, the burden of prostate cancer on all sectors of health care is bound to increase. If incidence increases from 13,481 in 1990 to 18,004 in 2011 because of ageing of the population alone, finished consultant episodes may increase from about 24,209 to 32,331. The prevalence of diagnosed prostate cancer will increase from 48,531 to 64,814 and, thus, the total number of consultations with GPs will increase from 189,271 to 252,775.

2. The items of health care for which an approximate average cost is available (GP consultations, GP prescriptions, in-patient days) suggest that prostate cancer in England and Wales costs the health service at least £45 million per annum.

3. The burden and costs are underestimated because there are no national statistics with which to estimate (i) the extent and cost of radiotherapy, hospital prescribed hormone therapy and chemotherapy; (ii) the burden of out-patient consultations; (iii) the burden of home nursing and palliative care. The true total costs are likely to exceed £55 million per annum.

Chapter 4: Pathogenesis and natural history

Conclusions

1. Within prostate cancer there is a spectrum of tumours with different growth rates, with slow-growing variants predominating.

2. With present knowledge, histological grade is the best predictor of progression.

Recommendation

Since the majority of prostate cancers are slow growing, a priority area for basic research is the identification of more prognostic markers which will identify those tumours likely to progress and, hence, require active treatment, thus avoiding unnecessary treatment of those that are not life-threatening.

Chapter 5: Prostate specific antigen

Conclusions

1. The extent of PSA testing is believed to be increasing rapidly, particularly for investigating men with urinary outflow obstructive symptoms. This is likely to lead to increasing diagnosis of early stage prostate cancer for which the effectiveness of treatment is unknown.

2. Although a national scheme exists for monitoring laboratory quality of PSA testing, there is no equivalent scheme for monitoring the volume of tests, the indications and the results.

3. Based on an estimate of 1.4% of men aged 45–84 years having one PSA test for diagnosis per annum, this could cost the health service up to £1.2 million per annum. This, however, is only the tip of the iceberg as PSA testing generates intense diagnostic activity and unproven treatment of the asymptomatic men found to have cancer.

Recommendations

1. Commissioning agencies might consider restricting PSA testing by limiting funding to certain categories of doctor, for example, urologists, clinical oncologists.

2. If PSA testing becomes widespread, the establishment of a national computerised information system, using a standard request/report form, should be considered to permit regular routine analyses of the number of tests, the indications for undertaking them and the results. This would inform commissioning agencies of the activity in their own population, and enable comparison with others.

3. Education about the potential disadvantages and uncertainties surrounding PSA testing should take place, directed both at GPs and at the general public.

Chapter 6: Screening for prostate cancer

Conclusions

1. There is at present no evidence on the number of prostate cancer deaths (if any) which could be averted by screening asymptomatic men.

2. This, combined with the lack of evidence about the optimum treatment of early disease, makes it impossible to estimate the cost-effectiveness of screening at present.

3. Screening may lead to unnecessary physical and psychological morbidity from biopsy and treatment side-effects.

4. Existing trials of prostate cancer screening in the USA and some EU countries may not be adequate to provide information on the balance between benefit, harm and costs.

5. A trial conducted in the UK could avoid the problems of randomised control group contamination, and would provide complete and accurate follow-up information.

6. Although PSA testing appears to be the potentially most efficient screening test, further research is needed to establish the optimum levels for identifying those men who should be referred for further investigation.

Recommendations

1. Opportunistic screening should be discouraged and commissioning agencies should not purchase screening services for prostate cancer, other than in the context of a randomised controlled trial.

2. Because of the increasing use of uncontrolled PSA testing, priority should be given to a randomised controlled trial of PSA screening in the UK, commissioned by HSR funding agencies. Such a trial should include investigation of possible alternative criteria for referral, as well as quality of life measures, and resource costs. It should also address the uncertainties surrounding appropriate treatment of screen-detected disease.

Chapter 7: Diagnosis of symptomatic prostate cancer

Conclusions

1. In men with urinary outflow obstruction symptoms a differential diagnosis between BPH and cancer is initially attempted by the GP. Diagnostic tests are believed increasingly to include PSA.

2. Those men with severe BPH or suspected cancer are referred for confirmation of diagnosis to surgeons with variable urological experience.

3. Diagnostic tests in hospital may include PSA, TRUS and core-needle biopsy, the latter being performed under antibiotic cover.

4. The practice of histological examination of tissue from TURP performed for relief of BPH has developed without evaluation of its effects on increasing diagnosis of latent cancer.

Recommendations

1. While the treatment of localised disease remains unevaluated histopathology departments and urology/surgical departments should develop explicit joint policies on (a) core needle biopsy procedure, and (b) criteria for performing histology of transurethral prostatectomy, both of which contribute to detection of early prostate cancer.

2. The cost of different diagnostic procedures needs further investigation.

Chapter 8: Treatment of localised prostate cancer

Conclusions

1. The effectiveness of the three main methods of management (watchful waiting, radical prostatectomy and radical radiotherapy) is still not known. Research into prostate cancer treatment has until recently focused more on variations of one particular method rather than on a comparison between them.

2. Current trials comparing the three main methods will still take many years to reach conclusions.

Recommendations

1. In the meantime, watchful waiting, because of its lower incidence of side-effects, would seem to be the best option for men with a life expectancy of less than 10 years and for those with a T1a Gleason grade < 4 tumour.

2. Commissioning agencies should ensure that men referred for radical prostatectomy are treated by specialist urologists trained in this technique, which may imply an increase in extra-contractual referrals. Similar considerations apply to men referred for radical radiotherapy. If an increasing number of men are referred for radical prostatectomy, then a system for auditing complications should be established.

3. If the UK MRC trial PRO6 is to succeed, the problem of poor recruitment needs urgent attention. Possible solutions include recruitment of patients into its PRO6 trial by general surgeons and urologists prior to referral to a specialist unit, financial incentives to cover the clerical costs of participation, and training of surgeons and urologists in communicating the uncertainty to patients.

Chapter 9: Treatment of advanced prostate cancer

Conclusions

1. Much more effort has been put into development of treatments for small, short-term gains in disease-free survival and palliation in advanced cases than has gone towards evaluation of potentially curative treatments for localised disease.

2. Androgen deprivation by surgical or medical castration, using LH–RH analogues, is the standard treatment for advanced local and metastatic cancer. Evidence is emerging that starting androgen deprivation immediately when advanced disease is diagnosed, rather than deferring it until symptoms of bone metastases develop, delays progression of the cancer.

3. Present evidence suggests that the additional costs and side-effects of maximum androgen blockade, i.e. adding anti-androgens to castration, are not matched by any significant improvement in survival. Continuation of current research trials is needed to confirm its lack of effect.

4. In patients whose disease has escaped from hormonal control, palliative surgery, radiotherapy, and analgesic drug treatments will be needed.

5. External beam radiotherapy may be used for some non-metastatic locally advanced cases.

6. Cytotoxic drugs and growth factor inhibitors confer little survival advantage in prostate cancer, and have serious toxicity. Research on new drugs is continuing.

Recommendations

1. Continuation of current research trials into the cost-effectiveness of maximum androgen blockade is required. Meanwhile, there is no case for men to be treated by this method

unless participating in a randomised, controlled trial.

2. Further research is needed in the UK on the quality of life of prostate cancer patients and the cost-effectiveness of treatment.

3. Terminally ill prostate cancer patients in their last weeks of life should be managed by a specialist palliative care team, working in collaboration with the GP, urologist and clinical oncologist.

Chapter 10: Aetiology and primary prevention

Conclusions

1. Dietary factors seem to play a role in the aetiology of prostate cancer but, as yet, the relative importance of different components of the diet such as fat and fibre is unclear. The protective effect of soya products and retinoids is uncertain.

2. High levels of the enzyme 5-α reductase are associated with the high prevalence of prostate cancer in Black Americans. Chemoprevention by finasteride which blocks 5-α reductase is being evaluated in the USA.

3. Studies of the effect of vasectomy on the risk of prostate cancer are inconclusive.

Recommendations

1. Research is needed to identify the components of diet associated with prostate cancer and their interaction with other factors such as hormone levels and exercise, if appropriate hypotheses can be advanced.

2. The burden of prostate cancer in ethnic minorities in the UK should be studied.

Chapter 11: Inherited genetic susceptibility to prostate cancer

Conclusions

1. Less that 10% of all prostate cancer cases appear to be inherited.

2. Inherited prostate cancer presents at a younger age than sporadic cancer.

3. Men who seek advice because of a history of prostate cancer in a first degree relative may be referred to a Cancer Family Clinic or Clinical Genetics Centre for investigation and counselling.

Recommendations

1. There is no intervention of proven effectiveness to offer to men at familial risk of prostate cancer, and therefore no reason to seek them out, other than for their contribution to genetic research.

2. There is no case for screening for prostate cancer routinely on the basis of family history. However, where this does happen, the effects of cancer screening should be monitored and evaluated.

Chapter 1

Introduction

Despite its frequency, prostate cancer has been a relatively neglected subject of investigation, particularly with regard to the efficacy of potentially curative treatments. The age and common co-morbidity of prostate cancer patients, coupled with a slow rate of growth of many tumours, has resulted in the past in widespread adoption of conservative policies of surveillance and symptom palliation rather than active treatment. However, following therapeutic fashions in North America and mainland Europe there is now increasing enthusiasm in the UK for radical surgery and radiotherapy for early stage cancer. A major factor contributing to this has been the identification of prostate specific antigen (PSA), the level of which in the serum is a marker for prostate cancer. PSA can be used not only for monitoring the progress of disease in known cancer patients but also as a diagnostic test in men presenting with symptoms of urinary outflow obstruction (in most of whom the symptoms are caused by co-existing benign prostatic hyperplasia rather than by cancer itself), and as a screening test in asymptomatic men.

This review was commissioned by the Health Technology Assessment panel of the NHS Executive. Its purpose is:

- to inform NHS Commissioning Agencies about services of established or generally accepted value in the diagnosis and management of men with prostate cancer
- to identify where possible their resource costs and comment on their cost-effectiveness
- to identify areas where current ongoing research has not yet reached a conclusion
- to indicate areas where there is a need for further research.

This report attempts a comprehensive review of the demands which all phases of the management of prostate cancer may place on the NHS. As well as conducting literature searches, information has been obtained from meetings with specialists and various data sources (see Appendix). The report is divided into a number of sections that describe trends in incidence and mortality, the current burden of prostate cancer on health services, its natural history, screening, methods of diagnosis with a special section on PSA, methods of treatment of local and advanced disease, aetiology and primary prevention, and genetic susceptibility to prostate cancer. The cost consequences of diagnosis and management procedures are discussed. However, only the direct costs to the health care system were considered. Indirect costs to the patient, although important, were not reported as no studies relating to this issue were found. The conclusions and, where relevant, recommendations of each chapter are presented and are summarised at the beginning of the report.

Chapter 2

The burden of prostate cancer on health

Incidence

In the UK, prostate cancer is the fourth commonest cancer in men, after cancers of the skin, lung and large bowel. In England and Wales, 13,481 new cases were registered in 1990, an incidence rate of 54.2 per 10^5 in males of all ages (Office for National Statistics, personal communication, 1996). Only 12% of cases arise before age 65 but incidence rates rise steeply thereafter. Incidence has risen steadily during the past 15 years *(Figure 1)*. Part of this increase is likely to be real but improved ascertainment of cases by cancer registries, and improved diagnostic accuracy will also have contributed towards the increase. Another reason for the trend is the increasing practice of case-finding, by histological examination of prostate tissue removed at transurethral resection of the prostate (TURP) for relief of symptoms of benign prostate hyperplasia (BPH) and, more recently, by measuring PSA levels. These tests have led to diagnosis of many cancers, some of which might not have presented within the life-times of men concerned. In Scotland, Duncan and Garraway[1] reported an increase in the use of TURP for BPH during the 1970s and 1980s, and this is also likely to have occurred in England and Wales.

Even if incidence rates were to remain at their present level, ageing of the population means that the number of prostate cancers requiring care is bound to increase over the next 15 years. Using the Office of Population Censuses and Surveys population predictions[2] and incidence rates in 5-year age groups for 1990, it is estimated that even if incidence remained steady there would be 18,004 new cases in 2011. If the incidence rate continues to rise by perhaps 10%, the incidence of prostate cancer in 2011 will be approximately 19,800.

The standardised registration ratio for new cases of prostate cancer shows some variation between regions, ranging from 87 in the Northern and Oxford regions to 126 in Wales *(Table 1)*. Swerdlow and Silva[3] suggest that regional variation is more likely to be linked to the geographical patterns of prostatectomies, which includes TURP,[4] rather than to differences in level of ascertainment by cancer registries.

In Scotland,[5] the incidence rate of cases diagnosed from 1981 to 1990 was higher in the least deprived

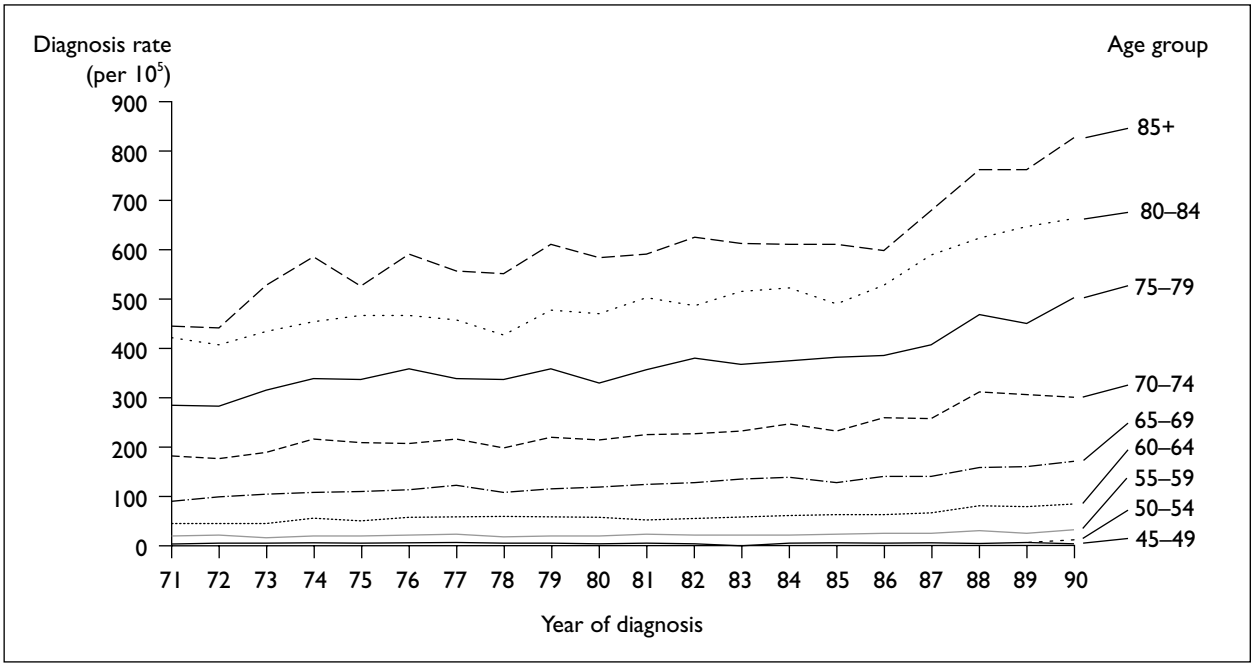

FIGURE 1 *Rate per 10^5 of newly diagnosed cases of prostate cancer in England and Wales presented by age and year, 1971 to 1990*

TABLE 1 *Regional Standardised Registration Ratios (SRRs) in 1989[144] and Standardised Mortality Ratios (SMRs) in 1992[145] for prostate cancer by region*

Regional Health Authority of residence	SRR	SMR
Northern	87	93
Yorkshire	102	97
Trent	90	99
East Anglia	111	97
North West Thames	95	99
North East Thames	93	100
South East Thames	96	111
South West Thames	98	99
Wessex	130	106
Oxford	87	107
South Western	102	110
West Midlands	99	101
Mersey	102	96
North Western	91	89
Wales	126	89

(55 per 10^5) than in the most deprived postal code sectors (44 per 10^5).

International incidence rates show a 63-fold difference between countries, being lowest in the Far East countries such as China – Shanghai (2.5 per 10^5) – and highest in US Blacks in Detroit (158 per 10^5)[6] *(Table 2)*. US Blacks have a particularly high risk of prostate cancer with almost a two-fold higher incidence rate than that for US Whites. The incidence rate increases in those Japanese who migrate to Hawaii and mainland USA, suggesting an environmental effect rather than a genetic difference. During 1975 to 1988 the incidence rate increased in most countries.[6]

Part of the international variation and time trends in incidence rates will have been caused by differences in detection of cancers through screening and use of TURP for BPH. In the USA, for example, it has been estimated that 88% of the incidence trend could be explained by the increase in TURP.[7] Following the widespread use of PSA as a screening test an initial increase in incidence rate followed by a decrease in older age groups has been reported by one US cancer registry.[8]

Mortality

In British men, prostate cancer is the third commonest cause of cancer death after cancers of the lung and large bowel. In 1993 in England and Wales there were 8689 prostate cancer deaths,[9] a mortality rate of 33.8 per 10^5. As with disease incidence, only a small proportion of deaths (7.2%) occur under the age of 65 years and mortality increases steeply with increasing age.

Mortality rates have also been increasing over several decades, the average percentage increase between 1971 and 1993 being around 40% for each age group *(Figure 2)*. Some of this increase may reflect increasingly accurate recording of cause of death in elderly men, and in 1984 changes in the coding of underlying cause of death[10] caused an apparent sharp rise in deaths among men aged 85 years or more *(Figure 2)*. However, even in men under age 74, mortality from prostate cancer has been increasing by an average of 13% every five years between 1975 and 1988.[6] This

TABLE 2 *International trends* in incidence of prostate cancer[6] using world-standardised truncated rates per 100,000 per year in 30–74 year-old men*

Country		1985 incidence rates per 10^5	1975–88 trend+
Europe (non-EU):			
Finland		48.7	15.9
Hungary – County Vas		32.6	27.5
Norway		63.6	5.7
Poland – Warsaw City		17.1	-10.3
Sweden		74.7	7.9
Europe (EU):			
Denmark		43.3	12.8
France – Bas-Rhine		46.8	19.9
Italy – Varese		36.8	26.9
Spain – Navarra		32.4	38.4
England & Wales – South Thames		32.4	12.3
Scotland		37.5	19.3
Asia:			
Australia – NSW		55.0	21.0
China – Shanghai		2.5	(4.3)
Japan – Osaka		8.0	38.0
New Zealand – non-Maori		46.7	6.5
Americas:			
Canada – Alberta		82.1	22.2
USA – Bay area	Black	151.6	(3.1)
	White	88.5	12.6
– Detroit	Black	158.2	13.5
	White	92.6	23.8

* *Trends are an estimated mean percentage change per 5-year period in 30–74 year-olds.*

\+ *Trends in brackets either not significant at 5% level or figures should be interpreted with caution.*

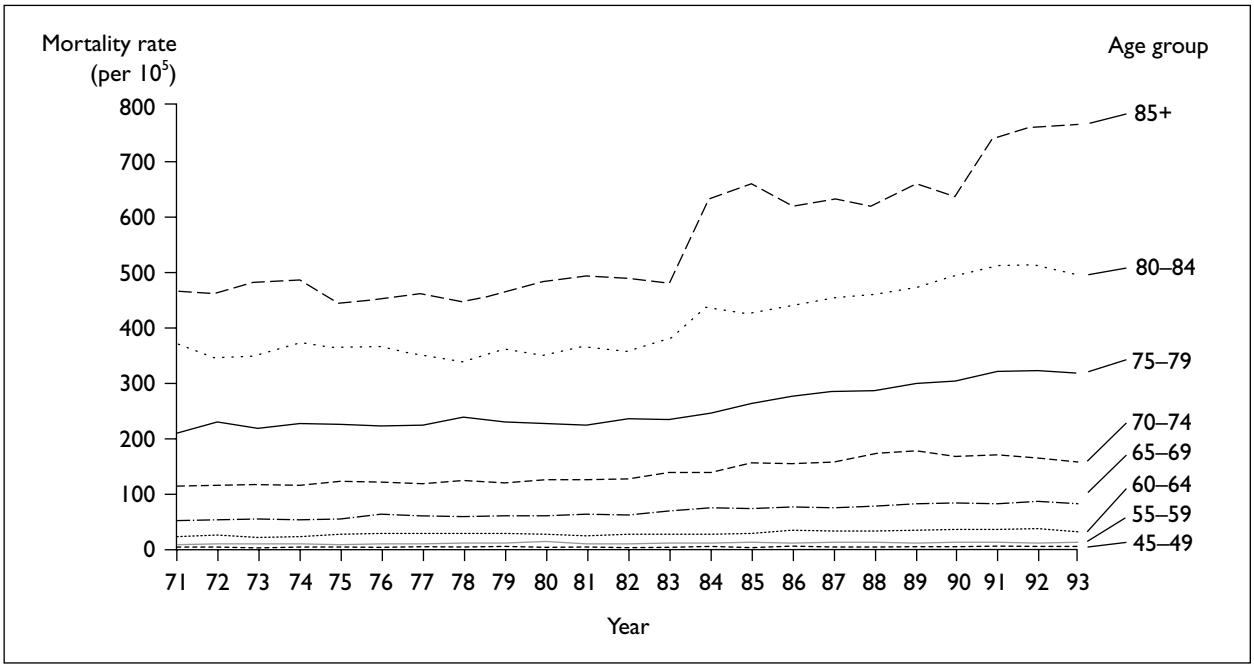

FIGURE 2 *Mortality rate per 10^5 of prostate cancer in England and Wales presented by age and year, 1971 to 1993*

indicates a substantial true rise in the frequency of death from prostate cancer, confirming that at least part of the incidence trend is due to an increase in the diagnosis of clinically significant prostate cancer.

In 1992 the standardised mortality ratio ranged from 89 in the North West and Mersey to 111 in South East Thames Regional Health Authorities *(Table 1)*. In 1979–80 and 1982–83, the standardised mortality ratios (SMRs) for prostate cancer in England and Wales showed no consistent trend by social class.[11]

International comparisons[6] showed that in 1988 there was a seven-fold difference between countries in the mortality rates for 30–74 year-olds, the lowest rates being found in the Far East, such as in Japan (3 per 10^5), and the highest rate in Norway (22 per 10^5) *(Table 3)*. During 1975–88, the rate has increased in most countries, with England and Wales and Scotland having the highest mean percentage increases. The mortality rate in Black Americans is high and rising, as is the incidence for this ethnic group.[12]

Survival rates and stage distribution

Mortality rates reflect not only the frequency of disease but also survival, which in turn is influenced by the stage at presentation and the efficacy of treatment. The 5-year relative survival rate (RSR) in

TABLE 3 *International trends* in mortality from prostate cancer[6] using world-standardised truncated rates per 100,000 per year in 30–74 year-old men*

Country	1985 mortality rates per 10^5	1975–88 % trend+
Europe (non-EU):		
Finland	17.1	8.3
Hungary	17.9	0.9
Norway	22.2	4.8
Poland	11.9	8.5
Sweden	21.6	(0.6)
Europe (EU):		
Denmark	20.5	12.7
France	16.7	4.5
Italy	12.6	(1.0)
Spain	12.8	-4.4
England & Wales	15.2	13.4
Scotland	13.0	13.5
Asia:		
Australia	16.2	5.0
Japan	3.3	10.1
New Zealand	18.3	10.5
North America:		
Canada	16.2	8.4
USA	17.5	2.3

**Trends are an estimated mean percentage change per 5-year period in 30–74 year-olds.*

+*Trends in brackets either not significant at 5% level or figures should be interpreted with caution.*

England and Wales for prostate cancer cases registered in 1971–73 was 36%,[13] and for 1981 registrations, 43%.[14] Information from Scotland also indicates an improvement in 5-year RSR from 38% for 1981 registrations to 48% for 1988 registrations (Scottish Registry, personal communication, 1995). This trend is likely to result from a shift towards an increasing proportion of early stage cases at diagnosis, as metastatic disease remains largely incurable.

Table 4 presents the results on age-specific survival data for three Cancer Registries from which these data were available; East Anglia, South Thames and Wessex. There seems to be no consistent trend in 5-year RSR by age. This is in contrast to the findings of Wilson and colleagues[15] in which the 5-year RSR for cases registered in Scotland from 1966 to 1976 appeared to be worse before the age of 55 years than for older age groups. However, it is possible that a smaller proportion of localised cancers were diagnosed in the younger men in the earlier period.

Stage at presentation is not routinely available from most cancer registries because of the poor recording of stage in clinical case-notes from which registration data are abstracted, and therefore trends in stage-specific incidence rates for England and Wales are unknown. The Thames Cancer Registry uses its own method of recording stage based on patients' notes. In 1992, 71% (1369) of registered prostate cancers in men aged 45 years and over in South Thames had some information on stage; of these, 62% were localised; 4% had local extension; < 1% had nodal involvement, and 34% had distant metastases. Five-year RSRs for cancers diagnosed in 1987 fell from 72% in localised cases to 19% in metastatic cases. Trends in incidence rates by stage from 1983 to 1992 show that in men aged 55–64 years there was an increase from 18 to 30 per 10^5 for localised cancers but little change in

TABLE 4 *5-year relative survival rate (RSR) (%) for prostate cancer (ICD9:185) in patients aged 45 years or more diagnosed in 1982 and 1987, presented by age and year of diagnosis, and cancer registry*

	Age (years)					
	45–54	**55–64**	**65–74**	**75–84**	**≥ 85**	**Total**
South Thames:						
1982 cases						
%	70.0	51.6	45.6	36.5	37.0	43.8
95% CI	(42.9–97.0%)	(41.5–61.8%)	(39.2–52.0%)	(28.2–44.8%)	(14.0–59.9%)	(39.4–48.2%)
Number surviving	11	93	231	129	17	481
1987 cases						
%	32.7	51.5	49.5	54.8	56.8	51.6
95% CI	(0.0–67.4%)	(40.6–62.4%)	(42.6–56.4%)	(47.7–61.8%)	(37.8–75.8%)	(41.3–55.9%)
Number surviving	7	81	202	194	26	510
Note: RSRs calculated using actuarial life-table techniques						
East Anglia:						
1982 cases						
%	76.7	38.4	40.9	40.3	31.2	37.4
Number surviving	2	14	66	36	2	120
1987 cases						
%	–[+]	29.2	42.4	39.5	29.9	34.0
Number surviving	0	18	69	68	4	159
Wessex:						
1982 cases						
%	78.1	48.9	62.5	54.6	24.7	54.2
Number surviving	6	33	108	81	7	235
1987 cases						
%	29.9	37.4	49.1	45.6	22.0	43.6
Number surviving	2	19	90	76	7	195
Note: Death certificate only cases excluded and zero survivors excluded RSRs calculated using regional life tables						
[+] *All four patients died and RSR not calculated*						

the incidence rate of metastatic disease *(Figure 3)*, again suggesting the increased use of tests for prostate cancer either *ad hoc* or in men presenting with urinary flow obstruction.

Prevalence of diagnosed disease

Prevalence can be estimated from incidence and case-fatality data and gives a measure of the total burden of diagnosed disease present at any given time. In 1990 the prevalence of prostate cancer in south-east England was estimated to be 3.6 times the incidence: 12,008 registered cases alive in the population, with 3339 being newly registered (Thames Cancer Registry, personal communication, 1995). Applying this ratio to the annual incidence of 13,481 newly registered cases for England and Wales in 1990, it is estimated that there were 48,531 cases in total, a prevalence of 195.1 per 10^5.

Conclusions and Recommendations

Conclusions

1. The number of men requiring care for prostate cancer is certain to increase over the next decade

   (a) because of increased testing for prostate cancer
   (b) because of ageing of the population
   (c) if there continues to be a true increase in incidence.

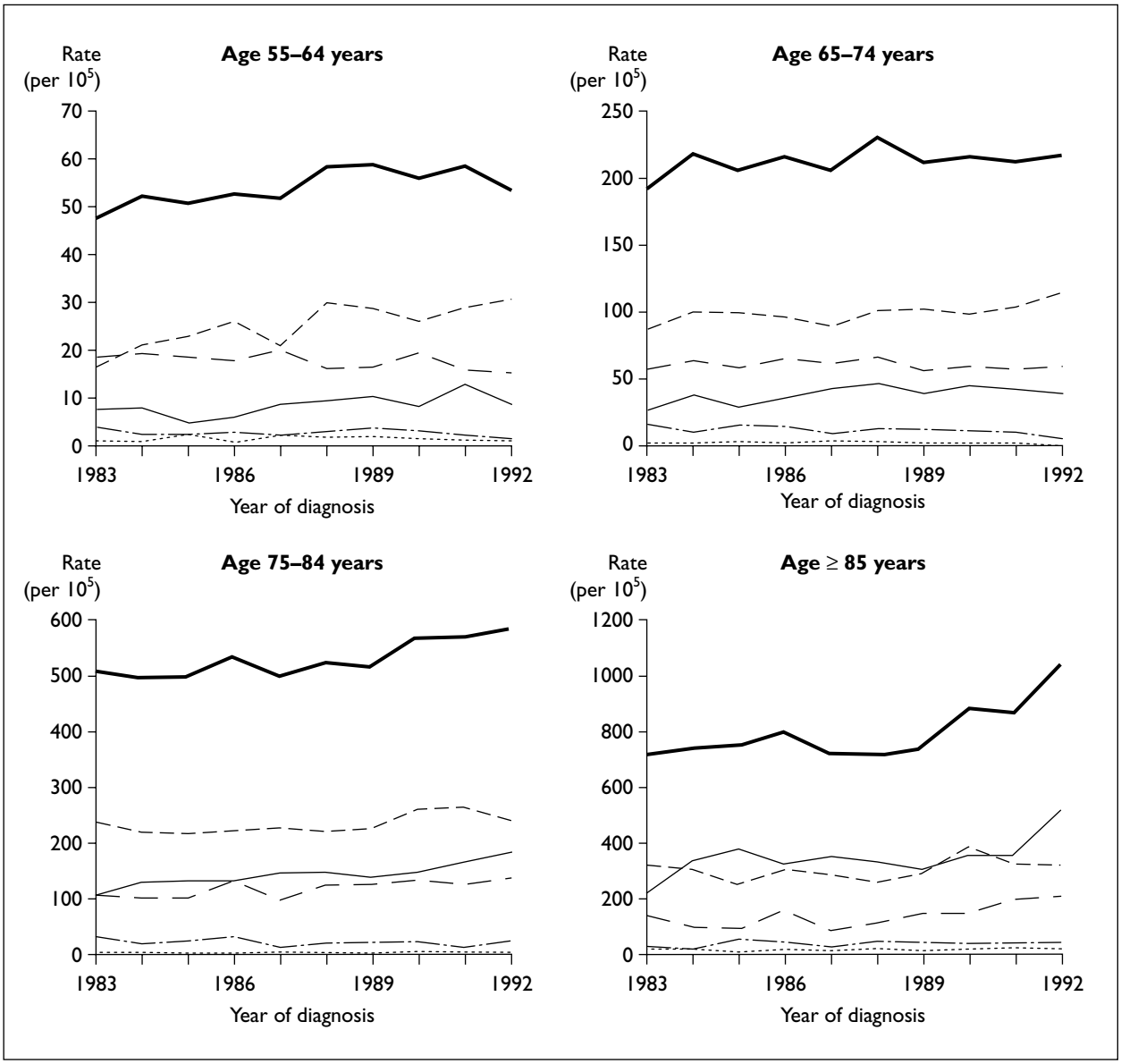

FIGURE 3 *Registration rates of prostate cancer (per 10^5) in South Thames by year and stage at presentation for 10-year age groups (––– all stages; - - - local; – – – metastases; —— all stages; – · – · – direct extension; ····· nodal involvement)*

If (a) and (b) remain stable, ageing of the population alone will cause the annual incidence to increase from 13,481 in 1990 to 18,004 in 2011 and, if there is a 10% increase in the incidence rate, to about 19,800.

2. The number of men who die from prostate cancer is also likely to increase (although not so steeply) as a result of (b) and (c) above.

3. Apparent improvements in survival may merely reflect length-biased sampling resulting in increased diagnosis of slow-growing tumours.

Recommendations

1. Clinicians should explicitly record as much information as possible on stage, ideally pathological TNM staging, but otherwise clinical staging as far as they can.

2. Cancer registries should set up a standardised system for recording stage at diagnosis so that stage-specific incidence can be monitored. Priority should be given to recording pathological TNM staging, but if this is not available, clinical stage should be recorded.

Chapter 3

The burden of prostate cancer on the health services

Effect of prostate cancer on primary care workload

Data from *Morbidity Statistics in General Practice 1991–1992*[16] show that among consultations with general practitioners (GPs) for cancer in men, prostate cancer is the most frequent cause. This survey provides information on a 1% sample of the population on the NHS lists of 60 practices in England and Wales which have volunteered to take part. Person-years at risk were calculated using the number of days each patient was registered with a study practice during the year. For every 10,000 man-years at risk (all ages), there are 43 consultations (that is, visits by patients to their GP) for prostate cancer, of which four are new cases. Consultation rates increase with increasing age from 34 per 10^5 in men aged 45–64 years to 671 per 10^5 in men aged 85 years and over.

The rate of men consulting at least once a year with BPH is nearly three times that for prostate cancer and shows a similar increase with age *(Table 5)*. However, the total number of consultations per annum is higher for prostate cancer than for BPH in men aged ≥ 75 years. The National Prostatectomy Audit recently carried out by the Royal College of Surgeons found that, in men primarily being investigated for BPH, 18% were subsequently confirmed histologically as having prostate cancer.[17]

Data from *Morbidity Statistics in General Practice 1991–1992*[16] suggests 3.9 consultations per year per person consulting with regard to prostate cancer. Multiplying this figure by the prevalence of prostate cancer in England and Wales for 1990 suggests a total of 189,271 consultations per year for prostate cancer. The average cost of a consultation in 1991–92 was £11.13 (1994 prices).[18] The total cost of GP consultations for prostate cancer can thus be estimated to be £2,106,585 per year.

Costs of prescribing are mainly borne by the primary care sector, since the hospital sector is only responsible for patients' prescription costs during hospital stay and for one week thereafter. Data were obtained from International Medical Statistics (IMS) on GPs in MediPlus, a computerised general practice information system which is used by a national sample of 500 GPs and covers dispensing, training and fundholding practices, although probably under-representing single practices. The data give a

TABLE 5 *Findings from* Morbidity Statistics in General Practice 1991–1992 *presented as rates per 10,000 person years at risk* by age*

	Age (years)					Total (all ages)
	25–44	45–64	65–74	75–84	≥ 85	
Rate of patients consulting at least once in year						
Prostate cancer	–	7	45	137	155	11
BPH	1	41	136	182	149	28
Rate of new and first ever episodes						
Prostate cancer	–	4	19	46	36	4
BPH	1	29	96	121	71	19
Rate of total consultations						
Prostate cancer	–	34	176	465	671	43
BPH	1	65	229	302	184	44

* *Person years at risk = the sum of number of days each patient in a particular category was registered with a study practice during the year divided by the number of days in the year (366).*

total cost of £409,683 for prescriptions (including drugs and other medical aids, such as catheters) issued in general practice in 1994 to 647 men aged 45 years and over with a diagnosis of prostate cancer, giving an average cost per patient of £633. The breakdown of prescriptions is discussed in Chapter 9. A total of 198 patients received no prescription. Applying these data to the estimated 48,531 prevalent cases of prostate cancer in England and Wales in 1990 gives an estimated total of 37,159 patients receiving GP-prescribed treatment for prostate cancer at a cost of £23,521,798 per year.

Although these estimated costs are approximate, and the incidence of prostate cancer may have increased since 1989, it appears that the cost of prescriptions issued by GPs for prostate cancer is, however, relatively small (less than 1%) when compared to the total cost of NHS prescriptions for 1994 estimated to be £3730 million for England and Wales.[18]

The burden of prostate cancer on home nursing services and palliative care cannot be specifically quantified, but must be considerable in view of the palliative care required among the nearly 9000 men who die from the disease each year.

Effect of prostate cancer on hospital workload

In 1993/94, Hospital Episode Statistics data for England and Wales on finished consultant episodes showed that a main diagnosis of prostate cancer accounted for 24,209 in-patient episodes.[19] A finished consultant episode is an episode where the patient has completed a period of care under a consultant and is either transferred to another consultant or is discharged. It is not possible from these data to distinguish between new patients and those re-admitted for further investigation or treatment. For prostate cancer as the **primary** diagnosis in men aged 45 years and over (for which specific analyses were requested), there were estimated to be 18,372 ordinary admissions and 1072 day cases. The total number of bed days for treatment was estimated as 171,917, giving an average length of stay of 9.4 days, increasing from 7.0 days in patients aged 45–64 years to 10.3 in patients aged 75–84 years *(Table 6)*. If the average cost per patient day for the speciality of urology is taken to be £114 (inflated to 1994 prices),[20] the total cost attributable to in-patient stay can be estimated to be around £19,598,538.

Forty-nine per cent (8914 out of 18,372) of ordinary admissions of patients with prostate cancer as a primary diagnosis underwent a surgical procedure (specifically for endoscopic operations of bladder outlet and prostate, and other operations of bladder outlet), of which the most frequent category was endoscopic procedures (7797, 87%), the majority being transurethral resections. It is not possible to say what proportion of these were performed for relief of symptoms in men already known to have prostate cancer, and what proportion were for BPH at which an 'incidental' prostate cancer was discovered. There were also 757 (8%) excision biopsies and 98 (1%) radical prostatectomies. Among day cases, 61% had surgical procedures; of these, 589 (90%) were

TABLE 6 *Distribution (%) of finished consultant episodes in NHS hospitals in England in 1993/94 with prostate cancer as the primary diagnosis (ICD9:185) presented by length of stay and age*

Age (years)		Day cases	Ordinary admissions: length of stay (days) 0–1	2–3	4–7	8–14	15–21	≥ 22	Total	Mean duration for ordinary admissions
45–64	%		14.8	18.8	39.2	15.0	7.4	4.8	100	
	Number	196	321	407	848	325	161	103	2165	7.0
65–74	%		11.3	12.9	43.1	21.6	5.8	5.3	100	
	Number	463	766	877	2926	1461	395	358	6783	7.8
75–84	%		9.8	10.7	35.5	25.4	8.8	9.8	100	
	Number	350	724	786	2610	1873	646	724	7363	10.3
≥ 85	%		10.4	10.8	24.5	24.2	14.3	15.8	100	
	Number	63	214	222	506	498	296	325	2061	13.3
Total	%		11.0	12.5	37.5	22.6	8.2	8.2	100	
	Number	1072	2025	2292	6890	4157	1498	1510	18372	

biopsies and 12 (2%) endoscopic procedures. Biopsies and endoscopic procedures did not vary greatly across the age group 45–84 years, but no radical prostatectomies were recorded in men over 74 years of age.

There has been an increase in hospital workload for prostate cancer during the past 15 years. From 1979 to 1985 the discharge rate for all discharges for and deaths from prostate cancer increased from 2.9 to 4.0 per 10^4 population.[21] Between 1989/90 and 1993/94, ordinary admissions for completed consultations for prostate cancer as the primary diagnosis increased by 6% from 22,810 to 24,209.[19,22] Discharge rates for prostatectomies[21] and consultations for endoscopic procedures, although not specifically for prostate cancer, also increased during this period.[19,22] A similar increase, specifically for TURP in patients with BPH, has been reported in Scotland.[1]

There are no national statistics with which to study the number of prostate cancer patients or hospital episodes for treatment by radiotherapy, hormone therapy, chemotherapy or palliative care. Data on outpatient consultations for prostate cancer are not available but these will be considerable, as most cases remain under consultant surveillance for the remainder of their lives.

Conclusions

1. Because of increasing incidence, the burden of prostate cancer on all sectors of health care is bound to increase. If incidence increases from 13,481 in 1990 to 18,004 in 2011 because of ageing of the population alone, finished consultant episodes may increase from about 24,209 to 32,331. The prevalence of diagnosed prostate cancer will increase from 48,531 to 64,814 and, thus, the total number of consultations with GPs will increase from 189,271 to 252,775.

2. The items of health care for which an approximate average cost is available (GP consultations, GP prescriptions, in-patient days) suggest that prostate cancer in England and Wales costs the health service at least £45 million per annum.

3. The burden and costs are underestimated because there are no national statistics with which to estimate (i) the extent and cost of radiotherapy, hospital prescribed hormone therapy and chemotherapy; (ii) the burden of out-patient consultations; (iii) the burden of home nursing and palliative care. The true total costs are likely to exceed £55 million per annum.

Chapter 4

Pathogenesis and natural history

Anatomy

The prostate gland is a small organ situated at the base of the male bladder surrounding the proximal urethra. Its function appears to be to produce secretions which, at the time of ejaculation, liquefy seminal fluid produced by the seminal vesicles. Three anatomical zones are recognised, the peripheral zone comprising about 65% of the normal gland, the central zone comprising 25%, and the transitional zone, consisting of two bilateral symmetrical lobules on either side of the prostatic urethra, comprising 10%. Benign prostate hyperplasia usually originates within the transitional zone and expands to compress the adjacent peripheral zone. Carcinoma, by contrast, usually originates in the peripheral zone.

Hormonal influence

Although the precise mechanisms of carcinogenesis are unknown (apart from the small proportion of cases with inherited genetic mutation) it is clear that androgenic hormones play a major role. The presence of testosterone, and its active metabolite dihydrotestosterone, is essential for development of normal prostate epithelium and androgen deprivation is an effective, albeit temporary, treatment for prostate cancer.

Premalignant phase

As with many other epithelial cancers, the development of prostate cancer appears to be a multistep progression from normal epithelium, through grades of dysplasia of increasing severity to intra-epithelial neoplasia, to invasive cancer. Prostate intra-epithelial neoplasia (PIN) is thought to precede invasive cancer because of its morphological and phenotypic similarity to cancer cells and the fact that it is frequently found adjacent to invasive cancers, but direct evidence of progression is lacking because of the difficulty of knowing whether or not serial biopsies have sampled the same area. Although it seems reasonable to assume that some cancers pass through a recognisable PIN phase, the proportion which do so and the distribution of sojourn time in the PIN phase are unknown. Another histological entity, atypical adenomatous hyperplasia, is similar to low grade carcinoma but the evidence that it precedes malignancy is less certain.

BPH, although frequently found in association with carcinoma, is not thought to be a precursor. The association is a reflection of the high prevalence of BPH[23] and the fact that histological examination of tissue from TURP, performed to relieve the symptoms of BPH frequently reveals the presence of unsuspected cancer.

Progression rates of invasive cancer

It has long been recognised that there is a wide variation in rates of progression of invasive prostatic cancer, many lesions remaining latent and unrecognised. In 1954, Franks[24] noted the discrepancy between the high incidence of prostate cancer in post-mortem specimens and its relative infrequency as a cause of death. In a study of 220 autopsies of men who had died of other conditions, he found unsuspected prostate cancer to be present in 38%. Other studies have reported prevalence rates between 14% and 48%, the rates increasing with increasing age.[25,26]

An international comparison of autopsy prevalence of prostate cancer between countries with high, medium and low registration rates of prostate cancer found a correlation between the prevalence of high grade latent tumours and incidence of clinical disease, but no clear equivalent correlation between low grade latent disease and incidence.[26] Extrapolating from this study, Whittemore and colleagues[25] suggest that the volume of low grade prostate cancers determines the subsequent incidence of high grade clinical cancer, and that this explains the observed disparities in incidence of clinical cancer in populations with a similar prevalence of latent cancer.

Although it seems that the majority of prostate cancers are very slow growing and not life-threatening, a minority of cases progress rapidly,

invading surrounding tissues and metastasising, usually to bone. The identification of which lesions, which are still confined to the prostate, will progress and therefore require active treatment, and which will remain slow-growing, is still unclear and is the key area of current research into the natural history of prostate cancer.

Prognostic factors

Major prognostic factors so far identified are stage and histological grade.

Stage

The main criteria used in pathological staging are tumour volume, extension beyond the prostatic capsule and lymph node involvement. Of the various clinical staging systems, the Whitmore-Jewett system (ranging from A to D) is most commonly used in the USA while a modification of TNM is more common in Europe. *Table 7* describes the criteria for different stages. Tumour volume is the only clinical indicator of prognostic importance for T1 and T2 tumours; but where pathological stage as well as clinical stage is available, it is generally found that clinical methods, even ultrasound imaging, tend to underestimate tumour volume.[27] For this reason, preoperative estimates of volume are not very useful. Estimates of what is 'significant' tumour volume in terms of risk of progression range from 1.4 cm down to 0.5 cm.[28]

Histological grade

A wide variety of schemes for histological grading exist but the most commonly used is the Gleason score. This recognises five different patterns of glandular tissue in prostate cancer, pattern 1 being most differentiated (good prognosis) and pattern 5 least differentiated. Any given tumour may have several different patterns and the scores for the two most dominant patterns found are added together to give the Gleason score. (If only one pattern is present its score is doubled). The Gleason scores are usually put into three groups for prognostic purposes, 2–4 (low grade), 5–7 (medium grade), and 8–10 (high grade). Because the score is applied to the tissue pattern, rather than the cellular pattern, it cannot be derived from cytology specimens. There is some evidence that, over time, some tumours will progress to higher grade. Studies of patients managed by a watchful waiting policy have shown that Gleason grade is a good predictor of progression. In a recent meta-analysis,[29] it was found that 13% of high grade tumours went on to develop metastases each year, compared with 5% of medium grade and 2% of low grade.

TABLE 7 *Staging prostate cancer by Whitmore-Jewett and TNM classification*

Description	Whitmore-Jewett	TNM
Disease localised to prostate		
Incidental histological finding (TURP)	A	T1
Low grade, < 5% specimen	A1	T1a
High grade, > 5% specimen	A2	T1b
Either identified by needle biopsy or involves both lobes		T1c
Risk recognised clinically	B	T2
Tumour confined to one lobe	B1	
≤ 1.5 cm : in one lobe with normal prostate on four sides	B1N	T2a
: surrounded on three sides by normal tissue	B1	T2a
> 1.5 cm or tumour in both lobes	B2	T2b
Periprostatic disease		
Extension beyond prostate:		
Lateral extension	C1	T3,T4 *
Seminal vesicle extension	C2	T3,T4
Both	C3	T3,T4
Distant disease	D0	T1–4, N1–3+, M0–1
Elevated acid phosphatase level only	D1	T1–4, N0–3, M1
Pelvic lymph nodes	D2	T1–4, N1–3, M0
Bones, lung, extrapelvic nodal involvement		T1–4, N0–3, M1

+*N0, no lymph node involvement; N1, single lymph node, homolateral; N2, multiple or contralateral lymph nodes; N3, bulky pelvic lymph nodes*

**T3, penetrates capsule with or without seminal vesicle invasion; T4, fixed to periprostatic side wall or adjacent organs*

Other prognostic markers

A number of other indicators are being studied. These include PSA level (see Chapter 5), ploidy, oncogenes and tumour suppression genes, invasion markers and cell adhesion factors. However, none so far has led to any greater specificity in predicting progression than histological grade.

Conclusions and Recommendation

Conclusions

1. Within prostate cancer there is a spectrum of tumours with different growth rates, with slow-growing variants predominating.
2. With present knowledge, histological grade is the best predictor of progression.

Recommendation

Since the majority of prostate cancers are slow growing, a priority area for basic research is the identification of more prognostic markers which will identify those tumours likely to progress and, hence, require active treatment, thus avoiding unnecessary treatment of those that are not life-threatening.

Chapter 5

Prostate specific antigen

The measurement of PSA

PSA is a glycoprotein secreted only by prostate epithelium. It is present in very high concentrations in the prostate ducts and in seminal fluid, and a small amount is also absorbed into the blood. Over the past 15 years immuno-assays have been developed to measure levels of PSA in serum. The amount of PSA absorbed into the blood, and hence the serum level, increases when the baseline membrane is damaged. Thus, high levels are found in men with prostate cancer, increasing with increasing stage of disease; high levels are also sometimes found in men with acute prostatitis, and moderately raised levels in men with BPH.

Before the advent of PSA testing, the only serum marker available for monitoring the progress of prostate cancer was the level of serum acid phosphatase. This is a good indicator of skeletal metastatic disease but lacks sensitivity for detecting organ-confined prostate cancer, and hence is of limited diagnostic value. It has now been superseded by PSA both for initial staging and for monitoring progress.

Over the past few years, the apparent widespread increase in PSA testing has had an influence on the management of all stages of prostate cancer. The early warning it can give of disease progression in men in whom prostate cancer has already been diagnosed and treated, may result in earlier intervention using hormonal treatments or radiotherapy. Its use in men presenting with BPH is a form of 'case finding', similar to histological examination of TURP chips except that it is not confined to those undergoing surgery. If, as current research suggests, TURP is to some extent replaced by drug treatment of BPH using 5-α reductase inhibitors or α-blockers,[30] there will be increasing pressure for PSA measurement in all men with urinary outflow obstruction symptoms.

The laboratory tests for PSA measurement are radio- or enzyme immunoassays using either monoclonal or polyclonal antibodies. About 40 different commercial test-kits are available, of which Hybritech Tandem® (monoclonal) and Abbott IMX® (polyclonal) are the most widely used. PSA testing kits are available to laboratories with the requisite equipment from the different manufacturers. Each individual assay includes quality control standards and measures two samples (from which results are averaged) from each patient being tested. The serum from up to 40 men can be tested in each Hybritech assay. A certain level of technical laboratory skill is required in setting up the assay and ensuring accurate record-keeping. The laboratory cost per man has been quoted to us in 1995 prices as between £4.00 and £8.00 (Ward, personal communication, 1995), but it has been given elsewhere as up to £10.00.[31]

About 95% of UK laboratories participate in a National External Quality Assurance Scheme for PSA run by Dr A Milford Ward at the Northern General Hospital in Sheffield. This scheme has led to improved consistency between laboratories using the same kit but there remain large variations in levels reported on quality assurance samples from laboratories using different kits.

At present, in-service-use kits measure the total amount of PSA in serum, and most research into PSA levels in health and disease has been done using total PSA values. However, the total amount of PSA in serum can be split into two components, the majority being bound to two proteins, antichymotrypsin and alphamacroglobulin, leaving only a minority of free PSA. Assays are now being developed which can measure the free component only, and these may prove useful in that the proportion of free PSA appears to vary from 30–40% of total PSA in normal men and in those with BPH to 15–25% in men with Stage II cancers.[32]

Until now most researchers have chosen a cut-off level of 4 ng/ml regardless of age as an indicator of possible prostate cancer. However, the normal range of total serum PSA varies with age increasing from 0–2.5 ng/ml in men under 50 to 0–6.5 ng/ml in men over 70,[33] suggesting that the cut-off level should be lower in younger men. The sensitivity and specificity of PSA cut-off levels in screening asymptomatic men for cancer are discussed in detail in Chapter 6.

Specificity is lower in symptomatic than in normal men because of the fact that 20% or more of men with BPH may also have serum PSA levels of 4 ng/ml or more.[34] Another variable possibly lowering specificity is the escape of PSA into serum following invasive diagnostic procedures such as needle biopsy or urethral instrumentation,[35] and for this reason PSA measurements should be made **before** these investigations, although digital rectal examination alone does not have this effect.

All of the specialists we have consulted while conducting this review have reiterated the belief that the number of men subjected to PSA testing both by urologists and GPs is increasing rapidly. PSA testing of men already diagnosed, for the purpose of monitoring disease progression, is believed to be increasing, providing an indicator to decide the timing of therapeutic interventions. The more worrying trend is a possible increase in PSA testing as a diagnostic aid in men with urinary outflow obstruction symptoms, and as a screening test in asymptomatic men. These tests will inevitably increase the number of men diagnosed with T1 disease for whom the efficacy of treatment is unknown, and the possibility of 'over-diagnosis' of non-life-threatening disease is very real. For this reason, some commissioning agencies are currently refusing to fund PSA testing by GPs (Burns, personal communication, 1995).

Data from MediPlus found that, in 1994, 2109 out of 150,353 men (1.4%) aged 45 years plus, with no prior history of prostate cancer, had a PSA test noted on their record. It is not known how many of these tests were done at the request of the GP, and how many were reported to the GP from hospital consultants. The cost to the health service of 1.4% of men aged 45–84 years having one PSA test for diagnosis per annum in England and Wales is up to £1.2 million per annum.

The cost of PSA tests is, however, only the tip of the iceberg. PSA testing generates intense diagnostic activity in terms of speciality referral, ultrasound and biopsy which are needed to exclude cancer. Moreover, PSA testing leads to unproven treatment (surgery or radiotherapy) of asymptomatic men when cancer is diagnosed. For example, in one study of PSA screening in the USA, where the incidence rate for prostate cancer is much higher than for the UK, 8.3% of men had raised PSA levels (i.e. at least 4 ng/ml), resulting in 7% of asymptomatic men having biopsies and 2.2% being diagnosed with cancer.[36]

Conclusions and Recommendations

Conclusions

1. The extent of PSA testing is believed to be increasing rapidly, particularly for investigating men with urinary outflow obstructive symptoms. This is likely to lead to increasing diagnosis of early stage prostate cancer for which the effectiveness of treatment is unknown.

2. Although a national scheme exists for monitoring laboratory quality of PSA testing, there is no equivalent scheme for monitoring the volume of tests, the indications and the results.

3. Based on an estimate of 1.4% of men aged 45–84 years having one PSA test for diagnosis per annum, this could cost the health service up to £1.2 million per annum. This, however, is only the tip of the iceberg as PSA testing generates intense diagnostic activity and unproven treatment of the asymptomatic men found to have cancer.

Recommendations

1. Commissioning agencies might consider restricting PSA testing by limiting funding to certain categories of doctor, for example, urologists, clinical oncologists.

2. If PSA testing becomes widespread, the establishment of a national computerised information system, using a standard request/report form, should be considered to permit regular routine analyses of the number of tests, the indications for undertaking them and the results. This would inform commissioning agencies of the activity in their own population, and enable comparison with others.

3. Education about the potential disadvantages and uncertainties surrounding PSA testing should take place, directed both at GPs and at the general public.

Chapter 6

Screening for prostate cancer

The growing impact of prostate cancer on mortality and morbidity, and the lack of curative treatment for metastatic disease, has led to increasing interest in the possibilities for early detection.

Whilst several screening tests for prostate cancer are available, studies to date only allow estimation of interim measures of validity of screening such as detection rates, sensitivity and specificity, and positive predictive value. Large-scale studies, including follow-up of subsequent incidence and mortality, are only just being developed. The most useful information on validity of screening tests comes from studies which have applied one or more tests to an asymptomatic population, which have recently been reviewed.[37] However, care is required in interpretation of the results because of differences between studies in the method of identification of the population, the criteria used for recommending further investigation, the level of acceptance of these further procedures and whether the results of repeat screening are included. Variations in any of these factors will have an effect on the measures of validity. In addition, sensitivity is difficult to measure accurately unless a population screened negative is followed-up to determine subsequent cancer incidence; most estimates of sensitivity of screening for prostate cancer are of the **relative** sensitivity of one test compared with another.

The three recognised methods of screening for prostate cancer are digital rectal examination (DRE), transrectal ultrasound (TRUS) and measurement of PSA.

Digital rectal examination

DRE has been used in case-finding during medical examinations for many years, but has recently also been investigated as a screening test. One of its major drawbacks as a screening test is poor sensitivity, partly because of its inability to detect tumours in the anterior and medial lobes of the prostate. DRE also appears to be of limited value in detecting early stage cancer. In one study, 66% of apparently early tumours detected by DRE were upstaged following surgery.[38] The sensitivity of DRE relative to TRUS has been estimated in a number of studies where both screening tests have been used, with subjects found positive on either test referred for further investigation. The estimates of sensitivity vary from 32% to 58%,[39,40] although a study by Palken using a high index of suspicion found a higher value of 74%.[41]

Studies which have examined screening by DRE in asymptomatic populations have reported values of specificity between 69% and 98%.[39–43] The detection rate of cancer in most such studies ranges from 0.35% to 1.4%,[44] although a rate of 5.4% has been reported by one study.[41]

Transrectal ultrasound

As a screening method, the ability of TRUS to detect impalpable lesions has led to it being combined with DRE in a number of studies; TRUS will mainly detect hypoechoic areas. Many, but not all, authors have reported a higher sensitivity of TRUS than of DRE, and differences in reported sensitivity and specificity may reflect differences in patient selection.[45] It is a relatively time-consuming, expensive and uncomfortable procedure, which means that it is most commonly used as a secondary method of investigation in men with an initially raised PSA or positive DRE.

In studies of asymptomatic populations, the estimated specificity of TRUS ranges from 81% to 97%.[40,43] The detection rate of cancers by TRUS ranges from 1.8% to 2.6%, and its sensitivity from 77% to 92%.

Measurement of serum PSA

Measurement of serum PSA is the most recent and simplest method proposed for prostate cancer screening. It requires a blood sample to be taken, which is then sent to a laboratory for immunoassay. A cut-off level of 4 ng/ml is commonly used to define positive tests requiring further investigation, this being the recommended reference level for the Tandem-R® assay produced by Hybritech. However, reported PSA levels, and the recommended reference level, will vary according to the assay used.

PSA testing has been evaluated both by nested case-control studies and in samples of asymptomatic men. (Although most studies use a cut-off of 4 ng/ml, there is some variation as to whether the cut-off is > 4 or ≥ 4.)

The specificity of PSA in such studies ranges from 87% to 97%.[42,46,47] The yield of cancers in studies of asymptomatic men will vary with the age range included. Labrie and colleagues[47] found cancer in 4% (41/1002) of men aged 45–80 with positive PSA tests. Other studies have shown detection rates of 2.2–2.6% in men aged 50 years and over.[35,46]

In studies where more than one test is performed, the sensitivity of one test can be estimated, relative to the others, as the proportion of all cancers detected which are identified by that test. In most studies where PSA has been measured and DRE and/or TRUS performed, not all PSA-positive men have been investigated. However, sensitivity can also be measured from nested case-control studies, using the number of cancers occurring within a certain time after a 'negative' PSA test to estimate the proportion which would be missed by screening. Gann and colleagues[48] found the sensitivity to be 73% for tumours occurring within 4 years, and 46% for those within 10 years. Parkes and colleagues[49] found that raised PSA levels could identify 81% of prostate cancers that would be diagnosed within 3 years, 40% of those within 5 years and 22% of those within 10 years. In this study,[49] the variation in PSA with age and possible variations in measurement between centres were adjusted for by expressing each PSA value as a multiple of the median for a given centre and age.

The fact that PSA levels increase with age in normal subjects has led to suggestions of the use of age-specific reference levels,[33] with proposed cut-off levels of 2.5 at 40–49, 3.5 at 50–59, 4.5 at 60–69 and 6.5 at 70–79 years. The aim is to increase sensitivity in younger men and specificity in older men. This suggestion has been supported by other authors, for example, by Lankford and colleagues,[50] although using these levels they noted a significant decrease in sensitivity in older symptomatic men. A similar observation was made by Mettlin and colleagues,[51] who recommended retaining the use of a single value, and it has recently been argued that, because of the increasing prevalence of prostate cancer with age, use of age-specific reference points would reduce the overall benefit in a screening cohort, a decreased sensitivity in older men outweighing an increased sensitivity at younger ages.[52]

Following observations that the rate of increase of PSA level with age is greater in men with prostate cancer than in healthy men or those with BPH, it has been proposed that the measurement of rate of change of PSA level may be a more specific test,[53] with a cut-off of an increase of 0.75 ng/ml per year. The use of age-specific ranges of PSA velocity has also recently been suggested.[54]

Assays are now being developed which will measure levels of free PSA, and it has been suggested that the free:total PSA ratio may be a more reliable measurement than total PSA.[32]

The measurement of PSA appears more sensitive than testing by DRE, and further refinements may improve its specificity. Combined with its simplicity and acceptability this makes it a more suitable test for mass screening intervention.

Effect of screening on mortality

There is no direct evidence available of the effectiveness of any of the screening tests in reducing mortality from prostate cancer. The majority of studies to date have not included an unscreened control group or any detailed follow-up of screened subjects.

A study in Japan of screening by DRE and measurement of serum prostatic acid phosphatase (PAP) compared stage-specific survival in screen-detected cases and in hospital-diagnosed controls,[55] but did not include information on interval cases or those in non-participants in the screening programme. Improved survival was observed in the screen-detected cases at all stages, but the difference was only significant for stage D, and the extent to which these differences merely reflect lead-time bias is impossible to determine. A 'prostate cancer awareness program' in the USA, which has resulted in 2 million men being screened over 6 years, claims to have contributed to the increasing percentage of localised prostate cancer being detected. However, no evidence is available that indicates that rates of advanced disease have decreased.

In 1991, a case-control study[56] compared a history of DRE screening in 139 cases of metastatic prostate cancer and matched, disease-free controls. They found screening to have had little effect, with a relative risk of 0.9 in men with one or more screening examinations after adjustment for racial differences (95% CI, 0.5–1.7). However, the results of such case-control studies require cautious interpretation.

In the UK, two studies have looked at the feasibility and acceptability of inviting men for prostate cancer screening. Kirby and colleagues[57] achieved an uptake of 66% in men aged 55–70 years invited for screening by DRE and PSA in a GP-based study. Chadwick and colleagues[58] using the same tests studied different methods of recruitment in men aged 55–69 years, and obtained 74–78% uptake in those offered a specific appointment, with 67% in those whose notes were 'tagged' at the GP practice in order to prompt screening at their next visit.

Whilst early detection is an attractive option, there are strong arguments for caution in the implementation of mass screening. One problem is the extent of latent disease which if undetected by screening would not progress to significant clinical disease within the lifetime of the patient. Estimates of the screen-detected prevalence to incidence ratio of the order of 10–15 to 1 suggest that such over-diagnosis is a very real problem. Men diagnosed with prostate cancer that would not have resulted in death or serious morbidity gain no benefit from screening, but suffer from the side-effects of treatment, particularly if radical treatment is carried out.

The anxiety resulting from a diagnosis of cancer is another harmful effect of screening. Men who are initially found positive by a screening test but are negative on further investigation will also suffer from increased, if temporary, anxiety, and will undergo unnecessary investigation and biopsy in many cases. Estimates of specificity suggest that between 5% and 20% may be wrongly found positive, although some of these will have other conditions which may benefit from treatment.

These potential disadvantages of screening, together with the financial costs involved and uncertainty over amount of benefit, particularly in view of the age of men affected, has led to much debate over the justification for screening, with some even questioning the ethics of conducting a randomised trial.[59] Nevertheless, it is evident that without proper evaluation, screening by PSA, in particular, will become increasingly widespread, with the danger that this will eventually make proper evaluation impossible.

Ongoing research into the effectiveness of screening

The first randomised trial to be initiated for prostate cancer screening is the Prostate, Lung, Colon, Ovary (PLCO) trial funded by the US National Cancer Institute.[60] The main trial aims to recruit 74,000 men, aged 60–74 years, who are being randomised to two equal arms. Men randomised to the study arm will be offered four annual screening tests by DRE and PSA, as well as chest X-ray, flexible sigmoidoscopy (three-yearly) and examination of the mouth, neck and skin. The trial is designed to have a high power (> 90%) of showing a 20% reduction in prostate cancer mortality in the study arm over a 10-year period (alpha = 0.05, one-sided test).

During the first 2 years of the study it has been piloted in ten centres in the USA, and so far approximately 10,600 men have been randomised. Informed consent is obtained from all subjects prior to randomisation. However, the methods of recruitment, mainly local advertising and through volunteer groups, have resulted in the self-selection of a highly educated and motivated population, of whom 50% were already undergoing routine PSA testing. There is, therefore, a major problem of contamination of the control group in the pilot study. Recruitment methods have now been changed to attempt to bring in a more representative population, including more Blacks and Hispanics.[60]

A multi-centre trial has also started in several European countries.[61] This is coordinated by a central committee and all participating centres have agreed that data should be made available for meta-analysis, as well as being analysed locally. The number of men it is intended to recruit to the trial in the centres so far participating (Belgium, the Netherlands, Italy, Portugal, Finland and Sweden) is 254,900.[62] The difference in the planned sample sizes of the US and European trials reflects the different age-range included. The central aim of the European trial is common to all centres, namely to compare prostate cancer mortality in men randomised to be offered screening or to a control group. However, inevitably there are differences in protocol between centres. Some of these concern methods of recruitment (volunteers or general population), the number of screening modalities offered and the cut-off points between positive and negative, the interval between routine re-screens, and the duration of follow-up. Others are determined by legal constraints at national level on important issues such as whether informed consent must be obtained from men in the control arm (inevitably leading to contamination), and laws preventing linkage of names of men in the trial to subsequent cancer incidence and mortality. For these reasons there must be doubt about the extent

to which the European trial can provide unbiased, population-based evidence with a sufficiently large sample size, even though some centres (e.g. Finland) fulfil all the requirements. There is a strong case for setting up a trial in the UK in which men are randomised from FHSA lists to be offered screening or to a control group with no intervention, and their subsequent cancer incidence and mortality monitored through linkage of the trial register to the Office of National Statistics. This approach has been successfully used in the Nottingham trial of screening for colorectal cancer.[63]

A trial of screening by PSA alone may be more acceptable to the general public; the inclusion of DRE will increase costs and may decrease specificity without significantly increasing sensitivity.

The economic issues associated with screening for prostate cancer

Given that resources are finite, it is now widely accepted that health care programmes should be not only effective, but also cost-effective. This requires a systematic comparison of the costs incurred with the effectiveness of the programme. In the case of population screening for prostate cancer, costs are incurred by the screening process, that is, recruitment; the screens and any further tests and biopsies would be offset by the cost savings associated with diagnosis had the disease presented naturally with no screening. Similarly, the costs of treating early stage disease need to be offset against the costs of deferred treatment with no screening.

The cost-effectiveness of screening for prostate cancer is likely to depend on several factors. These include the screening test used, the age group screened as well as the frequency of screening. Literature on the cost-effectiveness of screening for prostate cancer is, however, currently limited by the lack of available data on the effectiveness of screening tests and treatment options, which in turn is mainly due to the absence of large-scale, randomised, controlled trials. In a UK pilot study of screening for prostate cancer, in men aged between 55 and 70 years, using PSA and DRE in a general practice setting, the financial cost of detecting one prostate cancer was estimated to be £1654.10.[58] Only the costs of the screening process were accounted for. The cost savings associated with diagnosis had the disease presented naturally were not included, nor were the treatment costs.

Several studies[64–66] have suggested that the cost of detecting one prostate cancer through screening is favourable when compared with other cancer detection screening programmes, such as those for breast or cervical cancer. The important question of whether screening for prostate cancer actually prolongs life remains uncertain, however. Love and colleagues,[67] for example, conducted a cost-effectiveness analysis of screening for prostate cancer by DRE using a computer simulation of a large cohort study. They found small increases in life expectancy in direct proportion to the frequency and increasing costs of screening. In another study, Krahn and colleagues[68] used decision analysis to model the clinical and economic effects of screening for prostate cancer. They found that, in men between the ages of 50 and 70 years, screening with PSA or TRUS increased unadjusted life expectancy but reduced life expectancy adjusted for quality of life. DRE alone produced no decrease in mortality at any age.

More evidence on effectiveness of screening is required before these issues can be resolved.

Conclusions and Recommendations

Conclusions

1. There is at present no evidence on the number of prostate cancer deaths (if any) which could be averted by screening asymptomatic men.

2. This, combined with the lack of evidence about the optimum treatment of early disease, makes it impossible to estimate the cost-effectiveness of screening at present.

3. Screening may lead to unnecessary physical and psychological morbidity from biopsy and treatment side-effects.

4. Existing trials of prostate cancer screening in the USA and some EU countries may not be adequate to provide information on the balance between benefit, harm and costs.

5. A trial conducted in the UK could avoid the problems of randomised control group contamination, and would provide complete and accurate follow-up information.

6. Although PSA testing appears to be the potentially most efficient screening test, further research is needed to establish the optimum levels for identifying those men who should be referred for further investigation.

Recommendations

1. Opportunistic screening should be discouraged and commissioning agencies should not purchase screening services for prostate cancer, other than in the context of a randomised controlled trial.

2. Because of the increasing use of uncontrolled PSA testing, priority should be given to a randomised controlled trial of PSA screening in the UK, commissioned by HSR funding agencies. Such a trial should include investigation of possible alternative criteria for referral, as well as quality of life measures, and resource costs. It should also address the uncertainties surrounding appropriate treatment of screen-detected disease.

Chapter 7

Diagnosis of symptomatic prostate cancer

The presenting symptoms of men with prostate cancer fall into two main groups, symptoms of urinary outflow obstruction (60–70%) and symptoms of advanced disease (30–40%) based on an extract from the stage distribution (Thames Cancer Registry, personal communication, 1995). The information presented here comes largely from discussion with specialists. An outline showing possible pathways to diagnosis is shown in *Figure 4*.

Investigating symptoms of urinary outflow obstruction in primary care

Poor urinary stream, difficulty in starting to urinate, and sensation of incomplete emptying are caused by occlusion of the urethra by abnormal prostatic tissue. Irritative symptoms such as frequency, nocturia, urgency and urge incontinence indicate instability of the detrusor muscle of the bladder, resulting from chronic pressure. The GP confronted by a middle-aged or elderly man complaining of some or all of these symptoms first has to attempt a differential diagnosis between prostate cancer and BPH (which is more than four times more common) (see *Table 5)* and second, if BPH is the likely diagnosis, has to decide whether the symptoms are sufficiently severe to warrant referral to a surgeon for further investigation.

Although no data are available on diagnostic procedures in general practice, typically the GP will perform a DRE which may help to distinguish between the discrete nodule of a carcinoma, hard and craggy in advanced cases, and the generalised smooth enlargement of the whole gland, typical of BPH. Clinical examination of the abdomen may also be performed, looking specifically for enlarged inguinal lymph nodes which raise the suspicion of carcinoma. As discussed in Chapter 6, DRE may be less accurate in detecting small cancers in asymptomatic men, and the skill of GPs in carrying it out may vary.[58] Doubt has been cast on GPs skill at using DRE to find small carcinomas in asymptomatic men, but we have found no studies of delay in diagnosis of symptomatic prostate cancer and therefore are unable to assess the extent of any failure by GPs to recognise the possibility of malignancy. As already mentioned, GPs are believed to be increasingly taking blood samples for PSA testing.

Referral patterns for secondary care

The GP will then refer men suspected of having carcinoma, and those with suspected BPH warranting investigation and treatment, to an appropriate surgical team. Under existing patterns of service organisation, the surgical team will probably be the same regardless of the provisional diagnosis, although suspected cancer patients may be given a more urgent appointment. In a recent Royal College of Surgeons audit of management of BPH,[17] 31% of BPH patients were managed by specialist urologists, 50% by general urologists, 16% by general surgeons who spend half their time on urology, and 7% by surgeons with little urological practice. It is likely that this pattern equally applies to patients with early prostate cancer, but as and when the recommendations of the Policy Framework for Commissioning Cancer Services[69] are implemented, suspected cancer patients may be referred direct to a Urological Cancer Unit. BPH patients, however, who will include some unsuspected cancers, will continue to be referred to surgeons of varying specialisations.

Hospital investigation

The surgeon, like the GP, will, after taking a history, perform a DRE with the principal aim of differentiating between cancer and benign disease. Those men thought to have BPH will undergo flow urodynamic studies and kidney function tests to decide if surgery is needed. Those men thought to have prostate cancer will undergo TRUS and biopsy. Many, but not all, urologists and other surgeons investigating these patients will also take a blood sample for the measurement of serum PSA level. Some recommend only doing the test on men below a certain age, such as 65 or 70 years, arguing that any cancers found by PSA alone in men over this age are unlikely to cause morbidity within a man's lifetime. But it is probable that this test is increasingly being ordered, in addition to other routine serum investigations, such as kidney function tests.

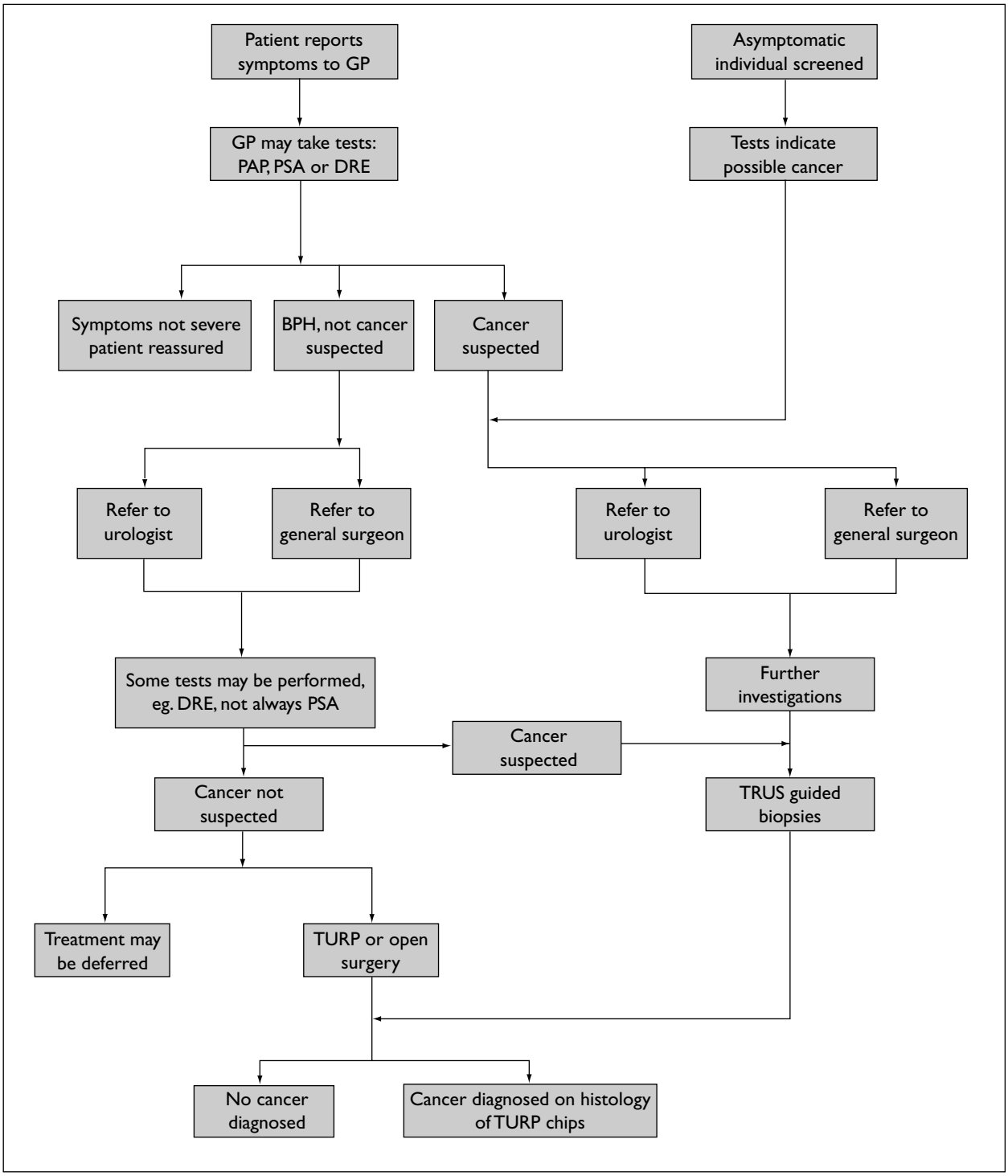

FIGURE 4 *Flowchart showing pathway to diagnosis of non-metastatic prostate cancer*

Transrectal ultrasound

The prostate gland can be imaged using an ultrasound transducer inserted in the rectum. Hypoechoic areas indicative of cancers can be visualised, but as a diagnostic test, ultrasound lacks both sensitivity and specificity. Its main value is now recognised to be in visualising the prostate while taking tissue core biopsies.

Biopsy

Methods include fine needle aspiration cytology, core-needle biopsy, transurethral resection or simple open (retropubic) prostatectomy. Fine-needle cytology, although widely used in Scandinavia, is unable to give information on histological grade and gives variable accuracy. Core-needle biopsy is now the method of choice.

A spring-loaded biopsy device used in conjunction with ultrasound visualisation enables multiple tissue cores from different quadrants or sextants of the gland, and from any suspicious areas, to be obtained. This can be performed as an outpatient procedure, without anaesthesia. However, the risk of infection is not negligible and antibiotic cover is required. About 1–2% of men undergoing core needle biopsy develop infective complications and mortality is not inconceivable (Kirby and Malone, personal communication, 1995).

The smaller tissue sample resulting from a decrease in core needle diameter may result in high observer variability in Gleason grading.[70] In the past a 14-gauge biopsy needle has been used but current practice is to use an 18-gauge biopsy needle guided by TRUS.[71]

The histopathologist examines multiple sections of each tissue core, reporting on the presence of PIN, the proportion invaded by adeno-carcinoma, the Gleason score, the extension of the tumour if this is assessable, vascular and perineural invasion. The diagnosis of invasive cancer is greatly helped by the use of a high molecular weight cytokeratin stain (CK903) which specifically highlights the basal cell layer and shows whether the basement membrane is still intact or has been breached. However, this stain, which costs £2.22 per slide, is not widely used, except by those histopathology laboratories with a research interest in prostate cancer.

Case-finding by histological examination of TURP specimens

The commonest surgical procedure for the relief of the symptoms of BPH is transurethral prostatectomy. In 1993/94 there were 53,327 hospital admissions for this procedure in England.[19] The procedure involves insertion of a device into the urethra which progressively removes small chips of prostatic tissue thus increasing the lumen of the obstructed urethra. For many years it has been standard practice to send the chips of tissue to the histology laboratory for the express purpose of diagnosing unsuspected carcinoma, although in principal this case-finding is no different from case-finding by PSA testing of men with obstructive symptoms, and is analogous to screening. Although it raises the same questions about how to manage the early cancers found, its value seems to have been accepted by urologists, even by those who are sceptical about the value of PSA testing. The proportion of patients undergoing TURP in whom incidental cancer was found in the Royal College of Surgeons audit of BPH management[17] was 18%, similar to the 14% reported by Rohr.[72]

The probability of detecting carcinoma increases with the percentage of TURP chips examined. In three studies comparing a variety of restricted and total sampling methods of TURP chips, prostate cancer was diagnosed in 7–8% and 14–19% of TURPs, respectively.[73–75] In Canada, part of the increase in incidence of prostate cancer has been attributed to an increasing number of slides being analysed per gram of tissue.[76]

With a potentially large volume of tissue to examine, histology laboratories may adopt rationing policies for sampling. Harnden and Parkinson[77] suggest that the entire specimen from men aged under 60 years is processed and one section examined from each block. For older men, urologists who favour radical treatment should select an age below which they wish all tissue to be processed on the assumption that those with T1b tumours will be eligible for radical treatment. For men above that age some form of sampling, based on weight of the available tissue, is usually adopted. It is important that the urologists are aware that a sampling system is in operation so that some corporate responsibility is taken.

Histopathology workload

It is clear that the policies of multiple transrectal biopsies and histological examination of TURP chips impose a heavy workload on histology departments. To this can be added the examination of pelvic lymph nodes prior to radical surgery, the examination of radical prostatectomy specimens, and examination of tissue from repeated TURP for recurrent obstruction in known cancer patients; in the latter case only a small sample of tissue is processed, to compare the grade with the initial specimen.

Investigating symptoms of advanced disease

Patients with local extracapsular extension of prostate cancer present with symptoms referable to the organs concerned. These may include haematuria, dysuria and incontinence, perineal pain, loin pain, rectal bleeding or obstruction, impotence and haemospermia. GP investigations

may include DRE, at which the diagnosis will usually be obvious, renal function tests, and tests for haematuria and bladder cytology. The severity of symptoms will lead to referral for secondary care, although, if the diagnosis of prostate cancer is not suspected, referral may be to a nephrologist or general surgeon rather than to a urologist. Investigations in secondary care include PSA level, renal function tests, straight X-rays of the pelvis, other imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI), and possibly biopsy.

Patients with metastatic disease most commonly present with sudden-onset progressive low-back pain due to secondaries in the pelvic bones and lumbar spine, although bony metastases may occur anywhere in the skeleton and pathological fractures are common.[78] Spinal cord compression due to collapsed vertebrae is another presenting symptom that requires prompt relief to avoid permanent neurological damage. Lymph node metastases may cause lymphoedema of the lower leg or ureteric obstruction, and systemic symptoms of carcinomatosis include lethargy (due to anaemia resulting from bone marrow involvement), weight loss and cachexia. Bone X-rays, and haematology will establish the cause of the symptoms. Biopsy and/or PSA may be used to confirm the site of the primary.

Referral for specialist care may be to a urologist, a clinical oncology unit, or possibly direct to a palliative care unit such as a hospice.

Conclusions and Recommendations

Conclusions

1. In men with urinary outflow obstruction symptoms a differential diagnosis between BPH and cancer is initially attempted by the GP. Diagnostic tests are believed increasingly to include PSA.

2. Those men with severe BPH or suspected cancer are referred for confirmation of diagnosis to surgeons with variable urological experience.

3. Diagnostic tests in hospital may include PSA, TRUS and core-needle biopsy, the latter being performed under antibiotic cover.

4. The practice of histological examination of tissue from TURP performed for relief of BPH has developed without evaluation of its effects on increasing diagnosis of latent cancer.

Recommendations

1. While the treatment of localised disease remains unevaluated histopathology departments and urology/surgical departments should develop explicit joint policies on (a) core needle biopsy procedure, and (b) criteria for performing histology of transurethral prostatectomy, both of which contribute to detection of early prostate cancer.

2. The cost of different diagnostic procedures needs further investigation.

Chapter 8

Treatment of localised prostate cancer

The choice of treatments for prostate cancer is influenced mainly by the stage of disease at diagnosis, but also by histological grade, by the age and co-morbidity of the patient, patient and consultant choice, and by costs. For men with cancer apparently confined within the prostatic capsule (T1–2), and no clinical evidence of nodal involvement or metastases, the alternative options for treatment are (i) a policy of watchful waiting, delaying radical or systemic treatment until the cancer shows signs of progression; (ii) radical surgery; and (iii) radical radiotherapy, the latter two of which aim to eradicate the disease.

Watchful waiting

This form of management, which is applied to the great majority of localised cases in the UK, entails regular check-ups using symptom history, DRE, PSA testing and, where indicated, TRUS to monitor local progression of the cancer as well as bone X-rays and other imaging or biochemical tests to monitor development of metastases. A typical schedule of follow-up outpatient visits would be examination at 3 months, 6 months and 12 months following diagnosis, and annually thereafter. We have found no evidence that routine scheduled surveillance achieves any better results than waiting for the patient to present when he develops symptoms (i.e. that **watchful waiting** is any better than just waiting). There may, however, be an implicit feeling of responsibility on the part of the specialist, and/or dependence on the part of the patient, that having made the diagnosis of a potentially life-threatening disease, regular contact between specialist and patient represents optimum care. Where symptoms increase, or tests (especially PSA) indicate progression of the cancer, the interventions applied may be surgery for the relief of urinary outflow symptoms (e.g. TURP), or radiotherapy or hormonal treatment. Exceptionally, some specialists, may apply radical prostatectomy or radical radiotherapy in the case of a rapidly rising PSA level in a tumour which is apparently still confined within the prostatic capsule.

Several observational studies have reported on disease-free survival and metastasis-free survival in localised prostate cancer patients managed by watchful waiting. For example, in one English health district 152 patients with histologically confirmed cancer and negative bone scan, and with a mean age of 74.8 years, were managed by watchful waiting and followed for 7 years. Five patients died of prostate cancer and 48 from other causes. Excluding non-prostate cancer deaths, survival rates at 5 and 7 years were 80% and 75%, respectively.[79] Chodak and colleagues[80] conducted a meta-analysis of six similar studies providing individual data on 828 patients followed for an average of 70 months. At the time of the analysis, 72 men had died from prostate cancer and 243 from other causes. Disease-specific survival in 720 men whose tumours were histologically grade 1 or 2 (Gleason score less than 8) was 87% at 10 years compared with 66% among the 63 men with grade 3 tumours (Gleason score 8–10). Similarly, metastasis-free survival at 10 years was related to histological grade; 19% of grade 1 patients had developed metastases, compared with 42% of grade 2 patients and 74% of grade 3 patients.

The side-effects of watchful waiting may include the anxiety which living with a potentially fatal disease may entail, and possibly physical morbidity resulting from urinary obstructive symptoms and their treatment. One US study found that watchful waiting patients reported significantly more emotional problems, after adjusting for age and co-morbidity, than patients receiving more active treatment.[81] However, another study[82] of men with all stages of prostate cancer, found fewer physical and sexual problems in those conservatively managed than in patients receiving surgical or radiation treatments.

Radical radiotherapy

Hospital-based series from the USA, the Netherlands and the UK suggest that the number of men referred for radical radiotherapy is steadily increasing.[83] However, it is not known how much of this increase is a reflection of the increased number of localised cases being diagnosed, and how much results from a greater proportion being selected for radiotherapy as choice of treatment. The choice of patients for radical radiotherapy depends to a large extent on the surgeon or urologist who makes the tertiary referral. It is likely to be offered to patients with localised disease who are less fit or with

shorter life-expectancy than those referred for radical prostatectomy. Of 842 localised cases registered in South Thames in 1992, 134 (16%) were treated by radiotherapy *(Figure 5,* Thames Cancer Registry, personal communication, 1995).

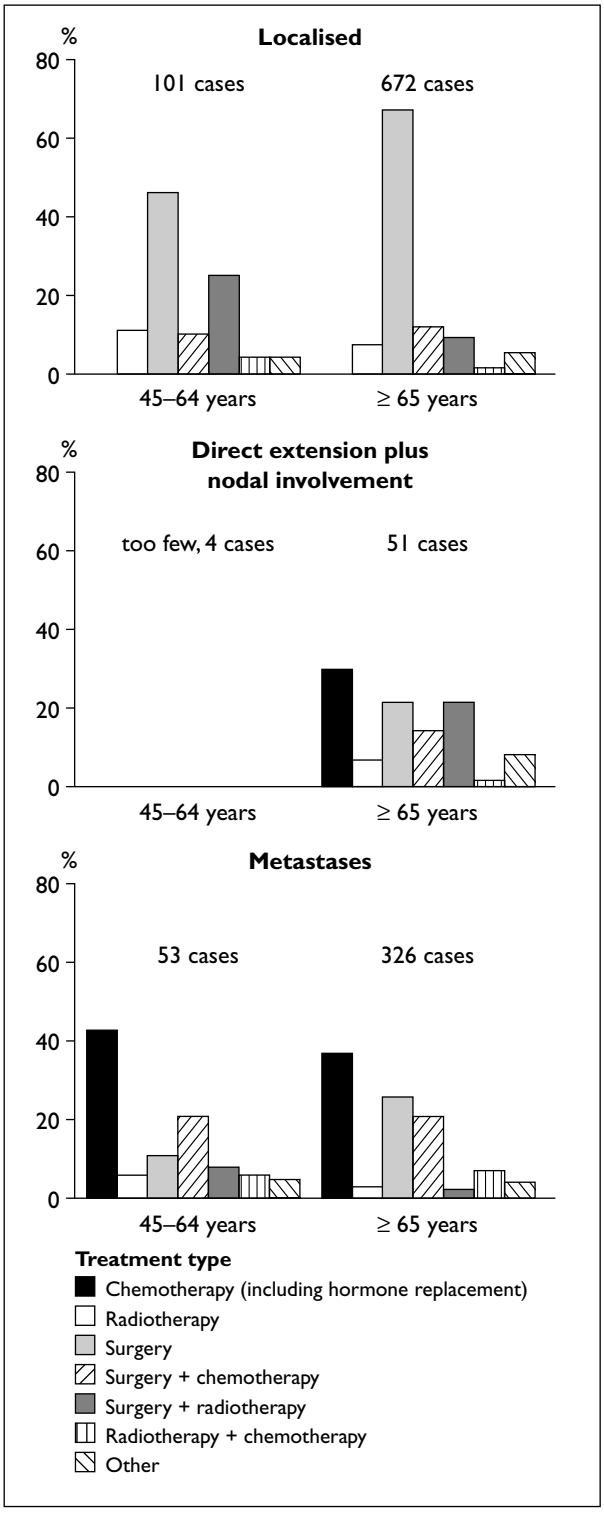

FIGURE 5. *Distribution (%) of treatment by age and stage of prostate cancer at the time of registration in 1992 in South Thames. Stage not known for 554 out of 1923 cases. Treatment not known for 162 out of 1369 cases with data on stage.*

External beam radiotherapy, focused on the prostate gland plus or minus the seminal vesicles but making no deliberate attempt to include pelvic lymph nodes, is usual practice. This requires CT localisation, and planning using three or four fixed beams or rotational techniques. Using a linear accelerator of at least 6 MeV, typically 16–32 fractions of 50–60 Gy would be given over 3–6 weeks.[31] Having completed the course of treatment, patients are normally followed up in the same way as those managed by watchful waiting. PSA levels fall gradually after radiotherapy, sometimes taking up to a year to reach their nadir, and there is often uncertainty about whether all of the tumour has been eradicated.

A number of series reviewed by Adolfsson[84] have reported on disease-specific survival following radical radiotherapy, which ranged from 74% to 96% at 5 years and from 62% to 86% at 10 years. One study[85] reported 8-year metastasis-free survival of 90% for grade 1 tumours, 65% for grade 2 and 25% for grade 3.

The complications of radical radiotherapy are damage to adjacent organs, particularly the rectum and bladder. In one series from Edinburgh which included some T3 cancers,[86] 36% of patients had bowel complications and 36% bladder complications. Various US series have reported complete incontinence in 1.2%, any incontinence in 6.1%, urethral stricture in 4.5%, bowel injury in 2.3% and impotence in 41%.[87–89] Rectal bleeding was found to increase from 16% to 34% with a dose increase from 67.2 Gy to 75.6 CGE (Cobalt Gray Equivalent).

Radical (total) prostatectomy

Although widely practised in North America and mainland Europe, this is still a very uncommon procedure in the UK. HES for 1993/94[19] show that only 98 patients in England and Wales had a radical prostatectomy for prostate cancer, and we have been told that there are probably less than 20 urologists in the whole country who have the necessary skill and experience. Only seven out of 842 (0.8%) localised cases registered in South Thames in 1992 were treated by prostatectomy *(Figure 5).* Because it is a major operation with serious side-effects, those British urologists who undertake it normally only offer it to men with a life-expectancy of 10 or more years (half the patients recorded in 1993/94 HES were aged under 65 years), who have been informed of its possible side-effects and of the alternative forms of management.

The operation may be performed either abdominally or perineally and aims to remove the whole prostate gland, while sparing the adjacent neurovascular bundles that are essential if erectile potency is not to be lost. It is assumed that cure is impossible if the pelvic lymph nodes are already involved; therefore, pelvic lymph node dissection and histology is normally performed (either by laparoscopy, or, at surgery, using frozen section biopsy) before proceeding with the prostatectomy. However, even if nodes are negative, many clinically T2 cancers are found at surgery to have invaded the capsule (T3). In one US study,[90] 42.5% of patients were found on surgical–pathological evaluation to have T3,T4 disease. In another study[91] of 955 men with clinically localised disease, 63% of cancers were found to have spread beyond the capsule on pathological staging.

Following surgery, the patient would normally be followed up by a schedule of repeat visits similar to that employed in a watchful waiting regime. The PSA level should fall to less than 2 ng/ml after surgery, and long-term results of surgery are often expressed in terms of biochemical remission, that is, no increase in PSA.

There are several observational follow-up studies of radical prostatectomy, mainly from the USA. For example, a US National Institutes of Health consensus conference in 1988 noted 15-year disease-free survival rates of 86–93%.[92,93] A more recent international pooled analysis[94] of 2975 radical prostatectomies performed on men with clinically localised prostate cancer reported that 5-year metastasis-free survival ranged from 88% to 100% for grade 1 tumours, from 88% to 92% for grade 2 tumours and from 56% to 91% for grade 3 tumours.

The complications of radical prostatectomy include operative mortality, incontinence and impotence. Surveys of unselected series from the USA have found that complications are more common in non-specialised centres than specialist centres.[95] This suggests that radical prostatectomy procedures should be restricted to specialist centres in order to minimise complication rates. Wasson and colleagues[95] concluded that the overall mortality rate was 1.1%, the rate of complete incontinence was 6.8% and intermittent incontinence 20%. A recent national survey by the American College of Surgeons[90] found that only 27% of patients recovered potency, and a separate survey of Medicare patients[96] found that 89% were impotent. There has been no large, detailed report of the complications associated with this surgery in the UK. Studies of quality of life of patients after radical prostatectomy have given mixed results partly because of different mixes of patients, the lack of standardised measures of quality of life suitable for studying patients with prostate cancer, and variable periods of follow-up. A small psychological study of 86 patients made 12–48 months after radical prostatectomy found that although two-thirds had erectile problems and 30% occasional urinary problems, these had only a minimal impact on overall quality of life, and the great majority were willing to accept more morbidity in a trade-off for (assumed) survival benefit.[97] For example, Braslis and colleagues[98] concluded that radical surgery had minimal impact upon patient quality of life, and yet there was significant deterioration in sexual function, continence and hardship scores post-operatively.

Comparison of treatment modalities

Surprisingly for such a common disease, the effectiveness of these different methods of treatment has not until recently been subjected to randomised controlled trials. Attempts have been made to compare the likely benefits and side-effects of different policies, based on a number of follow-up studies of different series of patients. In one US study of men with localised prostate cancer,[99] observation patients reported significantly more role limitations due to emotional problems after adjusting for age and co-morbidity than those receiving active treatment, but general health-related quality-of-life scores, in contrast, did not differ significantly between the groups. Another study of men with all stages of prostate cancer[82] showed that spouses experienced greater psychological distress than the patients, and that men with no treatment seemed to have fewer physical and sexual problems than those receiving surgery or radiation treatment. However, it is not clear how long patients had been living with their diagnosis of prostate cancer. From a structured review of the literature, Fleming and colleagues[100] used estimated probabilities of transition from one health state to another to construct a Markov model. The model was used to analyse expected outcomes by tumour grade for men of 60–75 years of age with T1–2, N0, M0 prostate cancer. Their results indicated that watchful waiting would be the preferred option treatment because radical prostatectomy or radical radiotherapy decreased quality adjusted life expectancy in patients older than 70 years. It was only among patients with moderately or poorly differentiated tumours

(Gleason score ≥ 5), who were aged 60–65 years that radical prostatectomy or radical radiotherapy gave more benefit than watchful waiting. Radiotherapy gave better outcomes than radical prostatectomy because of its lower complication rate. However, comparisons of effectiveness based on uncontrolled observational studies must be regarded with great caution, especially since the accuracy of both stage and grade is likely to be less accurate in men managed by watchful waiting or radiotherapy than in those undergoing surgery. The question can only be resolved by long-term, randomised, controlled trials, some of which have now started.

There will be a sizeable difference in costs between the three main choices of treatment. The UK Medical Research Council (MRC) has estimated the cost of prostatectomy to be £4110 per patient and the average cost of radical radiotherapy to be £2216 per patient.[31] The full cost of watchful waiting is not known, but all three would have pretreatment costs of about £410 per patient with subsequent follow-up.

Randomised controlled trials of management of localised prostate cancer

Four trials addressing the question of radical versus conservative management are in progress, two in Scandinavia, one in the USA and one in the UK.

Scandinavian trial of watchful waiting versus radical prostatectomy

The main aim of this trial is to compare mortality rates at 5 and 10 years in men randomised to radical prostatectomy rather than watchful waiting;[101] disease-free survival and metastasis-free survival will be intermediate endpoints, and measurements of quality of life and economic costs will be included, as well as sub-studies of histopathology and biopsy methods. A sample size of 230 patients in each arm was chosen to give an 80% chance of detecting a 10% survival advantage from radical prostatectomy at 5 years significant at the 5% level.[101] Recruitment started in 1989 and the target sample size has now been exceeded but, to allow for drop-outs, it is being increased to 520, which is expected to be reached in mid-1996. Fourteen centres, in southern Sweden, Finland and Iceland are participating. Criteria for entry to the trial are age < 75 years, clinically stage T1b–T2, NX, M0, well- or moderately well-differentiated histological grade (from a fine-needle core biopsy, according to WHO) and PSA ≤ 50 ng/ml. Within each centre eligible patients are randomised by the urologist, who is allowed a choice of whether to inform the patient before or after randomisation, and most patients have agreed to remain in the group to which they were randomised. Four out of 250 men allocated to watchful waiting subsequently requested radical prostatectomy. Some analyses will start in 1997, 1 year after recruitment is completed. While this trial is well advanced and should reach a definite conclusion on management of well- and moderately well-differentiated tumours, it will not provide information on whether the cure rate of poorly differentiated cancers, which are most likely to progress, can be improved by radical surgery.

US PIVOT trial

The main aim of the Prostate cancer Intervention Versus Observation Trial (PIVOT) is to compare all-cause mortality rates between watchful waiting and radical prostatectomy.[102] Two thousand participants will be enrolled from at least 80 Veterans Administration and National Cancer Institute Medical Centers. Men aged < 75 years with T1/T2, NX, M0 disease who are eligible for surgery will enter the trial (NX being node involvement not known).

The sample size of 2000 will allow a 90% power to detect a 15% relative decrease in all-cause mortality and a 35% relative decrease in prostate-cancer-specific mortality in either arm. The sample size was based on an assumed prostate-cancer-specific survival of 80% at 15 years and allows for a proportion of men allocated to watchful waiting to have radical treatment during follow-up. Recruitment is expected to take 3 or more years from November 1994, and there will be an average follow-up of 12.5 years. It differs from the Scandinavian trial in its greater statistical power and in the fact that all histological grades will be included.

The UK MRC (PRO6) trial

The aim of this trial is to compare survival in patients treated by watchful waiting, by radical prostatectomy, or by radical radiotherapy.[31] Quality of life and economic costs will also be compared.

A sample size of 400 patients in each arm gives a 90% power for detecting a 10% difference in survival at 10 years in any arm, significant at the 5% level. However, to allow for the fact that some patients will only agree to randomisation between two, not three arms, the trial aims to recruit 1800 men.

Criteria for entry are stage T1b or T1c, N0, M0, negative bone scan and newly-diagnosed biopsy

confirming adenocarcinoma of the prostate. There is no age limit. There should also be no previous malignancy of any site except the skin. Lack of nodal involvement is assessed in all patients by a CT scan or MRI. All histological grades will be included.

The trial was launched in 1994 but only 21 patients had been randomised by the end of November 1995. There are likely to be several reasons for poor recruitment. Informed consent is obtained prior to randomisation and this is proving a serious problem for recruitment. Some specialist urologists and radiotherapists participating in the trial see mainly tertiary referrals, that is, men who have been referred by general urologists or surgeons for the particular treatment in which the specialist is expert. It is then difficult for the specialist to explain that the best treatment is not known, particularly as the specialist tends to have a preference for his own expertise. It would be preferable for randomisation to be done by general urologists and surgeons prior to referral for radical prostatectomy or radiotherapy. This might ease the difficulty of explaining the uncertainty to patients but would not diminish the fact that some men would put greater value on having the cancer removed and would express a definite preference for radical treatment, rather than agree to randomisation while others would prefer to avoid side-effects and would opt for watchful waiting.

Scandinavian trial of watchful waiting versus radical radiotherapy

This trial aims to compare outcomes of watchful waiting and external beam radiotherapy, and is being conducted in northern Sweden and in Denmark. In northern Sweden 155 patients have so far entered, and in Denmark 55 patients. Recruitment has now stopped in Denmark because of poor accrual, partly due to the fact that histological proof of lack of nodal involvement, which required lymphadenectomy, was a criterion for entry. In addition, some urologists believe that interstitial radiotherapy which is practised in southern Sweden is more successful and has less morbidity than external beam radiotherapy (L Holmberg and B Norlen, personal communication, 1995).

New variations in treatment of localised disease

Future developments in radiotherapy that are still under evaluation include brachytherapy, using seeds containing iridium-192 and palladium-103, or iridium wires; conformal techniques to enable a higher dose to be more accurately focused on the tumours; particle beam therapy using neutrons or protons; and adjuvant or neo-adjuvant androgen deprivation drugs in association with external beam radiotherapy. Randomised controlled trials comparing survival in men treated by these new methods with men treated by external beam radiation alone are now starting.[83]

Adjuvant[103] or neo-adjuvant[104] androgen-deprivation drug therapy may also be used in association with radical prostatectomy. More research is needed to study the timing, dosage and period for which these therapies should be applied, and randomised controlled trials are needed to identify the high risk groups who would benefit most from adjuvant therapy.[105] The European Organisation for Research in Treatment of Cancer (EORTC) is organising two trials in men with T1–T3 disease. One is randomising men managed by watchful waiting, in whom PSA levels are rising, to immediate androgen-deprivation therapy or to delayed androgen deprivation therapy after the development of symptoms. Four hundred men out of a planned sample size of 700 have been recruited. The second trial is similar, except that the subjects are men who have had radical prostatectomy or radical radiotherapy, and whose PSA is subsequently rising. The pharmaceutical company, Zeneca, is also sponsoring a trial with men with T1–T4 tumours but no metastases. This is comparing survival in men randomised to the anti-androgen drug, Casodex®, or to a placebo.

Conclusions and Recommendations

Conclusions

1. The effectiveness of the three main methods of management (watchful waiting, radical prostatectomy and radical radiotherapy) is still not known. Research into prostate cancer treatment has until recently focused more on variations of one particular method rather than on a comparison between them.

2. Current trials comparing the three main methods will still take many years to reach conclusions.

Recommendations

1. In the meantime, watchful waiting, because of its lower incidence of side-effects, would seem to be the best option for men with a life expectancy of less than 10 years and for those with a T1a Gleason grade < 4 tumour.

2. Commissioning agencies should ensure that men referred for radical prostatectomy are treated by specialist urologists trained in this technique, which may imply an increase in extra-contractual referrals. Similar considerations apply to men referred for radical radiotherapy. If an increasing number of men are referred for radical prostatectomy, then a system for auditing complications should be established.
3. If the UK MRC trial, PRO6, is to succeed, the problem of poor recruitment needs urgent attention. Possible solutions include recruitment of patients into its PRO6 trial by general surgeons and urologists prior to referral to a specialist unit, financial incentives to cover the clerical costs of participation, and training of surgeons and urologists in communicating the uncertainty to patients.

Chapter 9

Treatment of advanced prostate cancer

Included in this category are prostate cancers that have locally invaded through the prostate capsule, and/or have involved lymph nodes, and/or have metastases in bone or other organs.

Whether first diagnosed at an advanced stage, or progressed after diagnosis and treatment, it is generally accepted that curative surgery or radiotherapy is no longer possible. Life expectancy in men with locally advanced disease averages 5 years, and in those with metastases it averages 3 years. The aims of treatment are to slow the progression of the cancer and to palliate symptoms. The main types of management are androgen-deprivation therapy, radiotherapy and palliative analgesic treatments.

Androgen-deprivation hormone treatment

Prostate cancer is dependent for its growth to a large extent on the androgenic hormones testosterone and dihydrotestosterone, which are produced by the testes and the adrenal glands. Up to 80% of prostate cancers will cease growing or shrink in volume when deprived of these androgens. Unfortunately this effect is not permanent and eventually the cancer will become hormone-resistant, almost certainly due to clonal selection of androgen-independent cells. Nevertheless, a prolonged period of remission can often be obtained, and androgen deprivation is normally the first line of treatment for both locally advanced disease and metastatic disease. Methods of androgen deprivation are summarised in *Table 8*.

TABLE 8 *Methods of androgen deprivation*

Category	Examples of drugs	Effectiveness	Side-effects	Cost
Surgical orchidectomy (castration)		Delays progression of disease and controls symptoms for 2–3 years	Erectile impotence Loss of libido	£714–£1056*
Medical castration by LH–RH analogues	Goserelin Leuprorelin	As effective as surgical orchidectomy	As for surgical orchidectomy but reversible when drug is withdrawn	£122–£125 per month
Maximum androgen blockade				
(a) LH–RH analogue + steroidal anti-androgen	Goserelin + Megestrol Leuprorelin + Cyproterone	No more effective than surgical or medical castration	As for castration + cardiovascular events	£151–£222 per month
(b) LH–RH analogue + non-steroidal anti-androgens	Goserelin + Flutamide Leuprorelin + Casodex®	No more effective than surgical or medical castration	As for medical castration + diarrhoea, liver impairment, alcohol intolerance	£232–£253 per month
Non-steroidal anti-androgen monotherapy	Casodex®	Not yet known (ongoing RCT)	Mild gastrointestinal side-effects Gynaecomastia	£128 per month
Oestrogens	Diethylstilbestrol	As effective as surgical or medical castration	Cardiovascular events Gynaecomastia	£4 per month
Medical adrenalectomy	Ketoconazole Aminoglutethamide	Limited improvement in relapsed cases	Requires cortisone replacement	£16–£20 per month

* *Range varies from day case to 4-day hospital stay and uses an operation cost of £600 (based on a BUPA upper estimate)*

Surgical bilateral orchidectomy is an effective and cheap way of permanently interrupting the supply of testicular hormones; the procedure can normally be done as a day-case. Its side-effects are loss of libido and erectile impotence. The same effect can be obtained by luteinising hormone–releasing hormone (LH–RH) analogue drugs *(Table 8)* which block the production of LH by the pituitary gland; since LH controls production of testosterone by the testes, blockage of LH leads to testosterone deprivation. The LH–RH drugs are administered by depot subcutaneous injections and last up to 3 months. They have been shown in randomised trials [106,107] to be as effective as surgical orchidectomy with the same side-effects, but they are considerably more expensive. Surgical orchidectomy costs £1056 assuming 4 days hospital stay (BUPA operation costs and £114 per patient day for the speciality of urology) compared with £125 per month for some LH–RH treatment, which may have to be continued until death, or until the tumour becomes independent of androgens. However, because the side-effects can be reversed by withdrawing the drug, drug treatment ('medical castration') is preferred to orchidectomy ('surgical castration') by many men.

Neither orchidectomy nor LH–RH analogues can block the testosterone produced by the adrenal gland, which is controlled by andrenocorticotropic hormone (ACTH). While only 5% of circulating testosterone comes from the adrenal gland, 15% or more of intraprostatic dihydrotestosterone is of adrenal origin.[108] The action of adrenal androgens can be stopped by addition of an anti-androgen to surgical or medical castration to give 'Maximum Androgen Blockade' (MAB) *(Table 8)*.

Several trials using anti-androgens have been done or are in progress,[109–115] some but not all, showing a beneficial effect. A recent large meta-analysis of 22 trials comparing MAB with medical or surgical castration alone, reported on 3283 deaths in 5710 patients (Prostate Cancer Collaborative Group).[116] At a median follow-up of 40 months, analysis showed a non-significant improvement in 5-year survival of 3.5% (95% CI 0–7%) in the MAB group. The slight survival advantage appeared after the second year of follow-up, and longer-term follow-up is planned with a repeat meta-analysis in 1997. One other large trial of MAB with 1200 patients should soon be completed in the USA (South West Oncology Group). For the present, however, available evidence does not warrant the use of MAB in addition to medical or surgical castration for men with asymptomatic advanced prostate cancer.

Anti-androgen monotherapy (i.e. without medical or surgical castration) is thought to be less effective than MAB, but, as already seen, a randomised, controlled trial of Casodex®, which has fewer side-effects than other anti-androgens, is now in progress in all non-metastatic stages of prostate cancer. Another EORTC trial is comparing the effects of steroidal and non-steroidal anti-androgen monotherapy in metastatic disease.

Oestrogen, in the form of diethylstilbestrol (DES), is as effective as castration in controlling advanced prostate cancer and used to be the standard treatment. However, it has fallen out of fashion because it has serious cardiovascular side-effects as well as causing feminisation including gynaecomastia.[117] It has been suggested that concurrent administration of low-dose aspirin could be used to control cardiovascular side-effects and would provide a much cheaper therapy than LH–RH analogues. However, the effectiveness of aspirin as a preventive measure has only been shown in well men[118] and further study of possible pharmacological interaction between oestrogen and aspirin may be advisable prior to setting up a trial to compare the cost-effectiveness of DES plus aspirin versus medical castration in treatment of prostate cancer.

In addition to trials comparing different forms of androgen deprivation, other studies are looking at its effectiveness combined with surgery and with radiotherapy, and at the timing of treatment. An MRC trial (PRO3 – not yet published) of starting androgen deprivation immediately after metastases are diagnosed by routine monitoring, compared with deferring treatment until symptoms appear, has found a significant reduction in prostate cancer deaths and in major complications but no difference in overall survival (Boreham, personal communication, 1995). Another EORTC trial of metastatic disease is comparing intermittent androgen deprivation with continuous treatment to test the hypothesis that stopping treatment allows atrophic cancer cells to differentiate under the stimulus of androgen until, as they progress through cell division cycles, they become pre-apoptotic again when treatment can be restarted. It is hoped that this will delay the time when the tumour becomes independent of hormones. PSA levels are used as the criteria for stopping and restarting treatments.

Radiotherapy for advanced local disease

External beam radiotherapy may be used for non-metastatic tumours of T3 and T4 stages in the same

way as radical radiotherapy is used for organ-confined prostate cancer. Clinical local control of the disease may be achieved.[119] However, in some studies, residual cancer cells have been found at biopsy, and PSA levels have not been suppressed reliably.[120]

Palliative treatments for hormone resistant disease

Eventually, unless the patient dies from another condition, virtually all advanced prostate cancers will escape from control by androgen deprivation, and will require other treatments.

Palliative surgical treatments

Local progression of disease commonly causes bladder outflow obstruction, and/or haematuria both of which may be treated by TURP, although there is a higher incidence of incontinence following transurethural resection of malignant tissue than BPH.[78] Other options are long-term catheterization or a urethral stent. Progression of disease may also lead to obstruction of one or both ureters, and to rectal obstruction, which exceptionally may eventually require colostomy.

Palliative radiotherapy

The skeleton is the most common site of metastasis from prostate cancer and, in addition to causing intractable pain, may lead to marrow failure; occasionally, vertebral metastases may result in spinal cord compression. Bone pain arising from skeletal metastases responds to radiotherapy with a single dose of 8 Gy, in 70–80% of cases. Where there are multiple sites of bony metastases, local radiation is less effective and hemibody irradiation may be required. However, hemibody radiotherapy is associated with several gastrointestinal or haematological side-effects. A single intravenous injection of strontium-89, a radioactive isotope that concentrates in the skeleton, has been shown to relieve bone pain for 5 weeks after each treatment.[121] It costs about £1000.

One study compared local and hemibody irradiation with or without strontium-89.[122] Both forms of radiotherapy improved with the use of strontium-89, and hemibody irradiation with or without strontium-89 was associated with a higher proportion of patients experiencing effective pain relief that was sustained for 3 months compared with local radiotherapy.

Palliative drug therapy

When a tumour escapes from control by androgen deprivation it may initially respond to oestrogens, either given as DES or as estramustine phosphate, which combines an oestrogen with nitrogen mustard. The latter drug may produce an objective response in up to 30% of patients[123] but has severe side-effects including granulocytopaenia, anaemia and nausea. A current EORTC trial in patients whose disease has escaped from hormonal control is comparing estramustine alone versus estramustine with vinblastine.

Numerous other cytotoxic drugs have been tried singly and in various combinations but none have been found superior to palliation with radiation, corticosteroids and analgesics, and have much greater toxicity.[78] The growth factor inhibitor, suramin, has been shown to shrink both bony and soft-tissue metastases in 30–50% but has severe neurotoxic and haematological complications as well as leading to adrenal insufficiency, requiring concurrent administration of corticosteroids. It has been questioned whether the subjective response obtained with this therapy is not due to the corticosteroids rather than to suramin.

Another drug shown to be effective in controlling bone pain is clodronate which only has mild gastrointestinal side-effects.[124] Two current MRC trials are looking at the value of clodronate. One (PRO4)[125] is randomising patients with locally advanced disease but no metastases to clodronate or placebo to test its effect as a prophylactic for delaying bone metastases. The second (PRO5),[126] in patients who already have bone metastases on X-ray or bone scan, is looking at whether clodronate given with androgen deprivation extends the time before symptomatic progression of bone metastases.

Eventually, as the volume of disease increases, the patient will become terminally ill, and control of pain and other symptoms at this stage ideally should involve a palliative care team, in association with a urologist and GP. It is not known how many of the 8000 patients who die from prostate cancer each year in England and Wales are managed in whole or part by medical and nursing specialists in care of the dying.

Proportion of prostate cancer patients receiving treatment for advanced disease

The number of patients receiving all these treatments each year is not known, but data from the IMS MediPlus system shows the proportion of general practice prescriptions in different categories for 647 prostate cancer patients (all

stages) in 1994. *Table 9* shows that 40% of patients received medical castration drugs (LH–RH analogues), and almost the same number, received anti-androgens. The overlap between the two categories is not known and it is also not known how many patients did not receive LH–RH analogues because they had had a surgical orchidectomy. Nevertheless, it is apparent that 40% of patients were being managed by maximum androgen blockade, a treatment which has been suggested to have no significant benefit over castration alone. Since these 647 patients include all stages of prostate cancer, the proportion of advanced stage patients receiving these treatments must be considerably higher. Moreover *(Table 10),* the anti-androgen, cyproterone, which is less effective in suppressing testosterone and has cardiovascular side-effects, was used three times more than flutamide. Narcotic analgesics were required by 12% of patients for pain relief.

There is a lack of available data on the cost-effectiveness of different treatment regimes. By the end of 1995, the Scottish Urology Oncology Group/Scottish Cancer Therapy Network will provide detailed information on treatment by stage from their National Prostate Cancer Audit. This will provide baseline data with which to make further estimates of cost of treatment.

Conclusions and Recommendations

Conclusions

1. Much more effort has been put into development of treatments for small, short-term gains in disease-free survival and palliation in advanced cases than has gone towards evaluation of potentially curative treatments for localised disease.

2. Androgen deprivation by surgical or medical castration, using LH–RH analogues, is the standard treatment for advanced local and metastatic cancer. Evidence is emerging that starting androgen deprivation immediately when advanced disease is diagnosed, rather than deferring it until symptoms of bone metastases develop, delays progression of the cancer.

3. Present evidence suggests that the additional costs and side-effects of maximum androgen blockade, i.e. adding anti-androgens to castration, are not matched by any significant improvement in survival. Continuation of current research trials is needed to confirm its lack of effect.

4. In patients whose disease has escaped from hormonal control, palliative surgery, radiotherapy, and analgesic drug treatments will be needed.

5. External beam radiotherapy may be used for some non-metastatic locally advanced cases.

6. Cytotoxic drugs and growth factor inhibitors confer little survival advantage in prostate cancer, and have serious toxicity. Research on new drugs is continuing.

Recommendations

1. Continuation of current research trials into the cost-effectiveness of maximum androgen

TABLE 9 *Breakdown of top ten prescriptions* issued in 1994 in general practice to 647 men aged 45 years and over for a problem of prostate cancer (MediPlus data held by IMS)*

Class		Number of prescriptions	% of all prescriptions (n = 8203)	% of patients receiving prescriptions (n = 647)
L02A	LH–RH analogues	2087	25.4	41.6
L02B	Anti-androgens	1371	16.7	39.9
N02B	Non-narcotic analgesics	463	5.6	19.0
N01B	Anaesthetics local	603	7.4	16.2
N02A	Narcotic analgesics	453	5.5	12.4
A06A	Laxatives	292	3.6	10.8
M01A	Anti-rheumatic non-steroid	249	3.0	10.5
Y05C	Drainage bags	270	3.3	9.1
J01E	Trimethoprim combs	76	0.9	7.4
Y05B	Catheters	84	1.0	6.8

* *Ranked according to percentage of patients. Source: IMS MediPlus*

TABLE 10 *Breakdown of LH–RH analogues and anti-androgens issued in 1994 in general practice to 647 men aged 45 years and over for a problem of prostate cancer (MediPlus data held by IMS)*

Class	Number of prescriptions	% of all prescriptions (n = 8203)	% of patients receiving prescriptions (n = 647)
LH–RH analogues			
1. *Goserelin*			
Zoladex (®Zeneca)	1419	17.3	30.9
Goserelin	423	5.2	8.7
2. *Leuprorelin*			
Prostap SR (®Lederle)	153	1.9	2.9
Leuprorelin	31	0.4	0.6
3. *Fosfestrol*			
Honvan (®Asta Medica)	31	0.4	0.6
Fosfestrol	9	0.1	0.5
4. *Megestrol*			
Megace (®Bristol-Myers)	21	17.3	5.2
Anti-androgens			
1. *Cyproterone*			
Cyproterone acetate	750	9.1	24.1
Cyprostat (®Schering HC)	222	2.7	6.2
Androcur (®Schering HC)	39	0.5	1.1
2. *Flutamide*			
Flutamide	317	3.9	9.4
Drogenil (®Schering Plough)	42	0.5	0.9
3. *Aminoglutethimide*			
Aminoglutethimide	1	0.0	0.2

Source: IMS MediPlus

blockade is required. Meanwhile, there is no case for men to be treated by this method unless participating in a randomised, controlled trial.

2. Further research is needed in the UK on the quality of life of prostate cancer patients and the cost-effectiveness of treatment.

3. Terminally-ill prostate cancer patients in their last weeks of life should be managed by a specialist palliative care team, working in collaboration with the GP, urologist and clinical oncologist.

Chapter 10

Aetiology and primary prevention

Major risk factors

As yet, there have been no conclusive aetiological studies leading to prevention strategies. The principal environmental and social factors that have been investigated are occupation, diet, sexual habits and sexually transmitted infections.[127] Among occupations, workers with cadmium and other heavy metals are at increased risk, and some, but not all, studies have indicated that farmers may have an increased risk. Recently an increased risk has been identified in men occupationally exposed to a number of radionuclides.[128]

Dietary studies have shown that fat intake is associated with prostate cancer, both in international correlations and in a majority of case control studies. However, the relationship is complex and the results of epidemiological studies inconsistent. Animal fat and alpha-linolenic acid from vegetable sources may be the most important components[48] but the mechanism by which they contribute to prostate cancer is not known. Beta-carotene consumption seems to be protective, as for other epithelial tumours, but with less effect in men aged over 75 years. The high soya intake in China and Japan could be associated with their low rates of prostate cancer. Soya beans are a dietary source of isoflavone genistein, which is a specific inhibitor of protein tyrosine kinases and inhibits DNS topo-isomerases as well as other enzymes involved in signal transduction.[129] Genistein has been shown to suppress proliferation of prostate cancer cells *in vitro*.[130,131] Studies of sexual factors have shown that age at first intercourse, frequency of intercourse, number of sexual partners and history of sexually transmitted disease may all be associated with some elevation of risk, but these findings are not consistent across all studies. Similarly, some but not all studies have found a positive association between vasectomy and subsequent prostate cancer risk.

Hormones have been extensively researched in numerous studies comparing men with prostate cancer with age-matched controls but the results are inconsistent and inconclusive.[127] Hormonal factors also have an important role in the aetiology of prostate cancer. A large number of hormones could have an aetiological role, including testosterone, dihydrotestosterone, prolactin, follicle-stimulating hormone, oestradiol, oestrone, luteinizing hormone and sex hormone binding globulin. Some of the difficulties in studying hormonal factors are that, in general, serum levels of total hormone have been measured rather than free (unbound) hormone; the hormone levels may not have been measured in the same way (e.g. at the same time of day) in cases and controls; the levels in cases may have been influenced by the disease itself, and some of the smaller studies lacked statistical power. Testosterone in its reduced form, dihydrotestosterone, is related to cell division and the conversion to the reduced form is metabolically controlled by the enzyme 5-α reductase.

One hormonal prevention trial is already starting, using finasteride which blocks the activity of 5-α reductase and thus reduces or blocks the conversion of testosterone to dihydrotestosterone.[132] Eighteen thousand men are to be randomised to receive 5 mg finasteride or a placebo daily for 7 years. Only men with a normal result from DRE and a serum PSA level less than 3 ng/ml will be entered. The placebo group will be screened annually by DRE and PSA, and biopsies will be taken if the results indicate a possibility of cancer. An equal number of men in the intervention arm will also undergo biopsy. All men will be biopsied at the end of the 7-year follow-up.

Hormonal factors could be the main reason for some of the differences in incidence between ethnic groups. Young adult African-American men have at least 10% higher circulating testosterone levels than young adult white men so they may have increased cell division and risk of alteration in alleles holding proto-oncogenes or tumour suppressor genes. Moreover it has been hypothesised that the risk in African-American men may be increased *in utero* as African-American women have higher first-trimester testosterone levels than white women which could affect the hypothalamic-pituitary-testicular system.[133] Chinese and Japanese men may have lower 5-α reductase activity than White- and African-Americans and thus have reduced cell division and risk of alterations to genetic material.

The interaction between dietary and hormonal factors is being keenly investigated because of its potential for primary intervention. A reduction in dietary fat in adulthood reduces circulating

testosterone levels. This may link in with other dietary factors such as fibre which can reduce reabsorbtion of steroid hormones excreted through the biliary tract.[48]

A history of BPH has also been investigated as a potential risk factor. However, the association between the two conditions, as already seen, is in large part due to diagnostic bias, in that surgery for BPH leads to diagnosis of otherwise silent prostate cancer. BPH occurs in the central zone of the prostate while carcinoma arises in the peripheral zone so progression of benign hypertrophy to neoplasia is unlikely. However, the two conditions may have similar but as yet unidentified hormonal stimuli.

Conclusions and Recommendations

Conclusions

1. Dietary factors seem to play a role in the aetiology of prostate cancer but, as yet, the relative importance of different components of the diet such as fat and fibre is unclear. The protective effect of soya products and retinoids is uncertain.

2. High levels of the enzyme 5-α reductase are associated with the high prevalence of prostate cancer in Black Americans. Chemoprevention by finasteride which blocks 5-α reductase is being evaluated in the USA.

3. Studies of the effect of vasectomy on the risk of prostate cancer are inconclusive.

Recommendations

1. Research is needed to identify the components of diet associated with prostate cancer and their interaction with other factors such as hormone levels and exercise, if appropriate hypotheses can be advanced.

2. The burden of prostate cancer in ethnic minorities in the UK should be studied.

Chapter 11

Inherited genetic susceptibility to prostate cancer

Inherited genetic susceptibility

It is recognised that the risk of prostate cancer is increased if there is a family history of the disease. One study[134] found a relative risk of 2.0 (95% CI 1.2–2.3) if one first degree relative was affected, rising to 8.8 (95% CI 2.8–28.1) if both first and second degree relatives were affected. The age of onset of familial cancers is lower than that of sporadic cases. Although cases with an inherited susceptibility comprise only a small proportion of all prostate cancers, the proportion varies with age. Carter and colleagues[135] have estimated that 43% of cases diagnosed under the age of 55 years (of whom there were 163 (1.3%) in England and Wales in 1989[136]) have an inherited risk, falling to 9% of cases diagnosed over the age of 80.

Identification of the affected gene or genes, and of the relative mutations, is the subject of much current genetic research and it can be expected that the inherited abnormality will soon be identified. Cytogenetic studies show loss of the long arm of chromosomes 10[137] and 7,[138] and loss of chromosomes 1, 2, 3 and Y.[139] Studies of allele loss show regions of highest loss on chromosome 8 in prostate cancer tissue which suggests that a tumour suppressor gene may be involved, and also 10q and 16q.[140,141] Whether the same genetic mutation contributes to sporadic cases as well as to familial cases is still unknown. One study[142] interprets the fact that progression rates are similar in sporadic and hereditary cancers to indicate that the same mutation is involved in both.

Apart from their valuable contribution to genetic research, there is, with present knowledge, no reason to search for men in prostate cancer families because there is no proven effective intervention to offer them. However, men with a history of prostate cancer in a first degree relative who seek medical advice on their risk may usefully be referred to a Family Cancer Clinic or Clinical Genetics Centre where the family pedigree can be constructed and appropriate genetic counselling given. In the UK, the Cancer Research Campaign Collaborative Study[143] aims to identify the gene or genes which predispose families to prostate cancer. Recruitment is underway and so far 114 families have been identified (December 1995).

There is no standard method of management of people with a high risk of prostate cancer; the value of cancer screening is not known.

Conclusions and Recommendations

Conclusions

1. Less that 10% of all prostate cancer cases appear to be inherited.

2. Inherited prostate cancer presents at a younger age than sporadic cancer.

3. Men who seek advice because of a history of prostate cancer in a first degree relative may be referred to a Cancer Family Clinic or Clinical Genetics Centre for investigation and counselling.

Recommendations

1. There is no intervention of proven effectiveness to offer to men at familial risk of prostate cancer, and therefore no reason to seek them out, other than for their contribution to genetic research.

2. There is no case for screening for prostate cancer routinely on the basis of family history. However, where this does happen, the effects of cancer screening should be monitored and evaluated.

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Appendix

Specialists consulted

Professor A Barrett, FRCP,FRCR, Beatson Oncology Centre, Western Infirmary, Glasgow

Dr H Burns, FRCS, Director of Public Health, Greater Glasgow Health Board

Dr D Dearnaley, FRCP, FRCR, Radiotherapy Department, Royal Marsden Hospital, London

Mr M Emberton, FRCS, Urology Department, St. George's Hospital, London

Dr C Fisher, FRCPath, Histopathology Department, Royal Marsden Hospital, London

Dr J Gohagan, PhD, Chief, Early Detection Branch, National Cancer Institute, Bethesda, MD, USA

Professor K Griffiths, PhD, BSc, Tenovus Centre for Cancer Research, University of Wales College of Medicine, Cardiff

Mr R R Hall, MS, FRCS, Urology Department, Freeman Hospital, Newcastle upon Tyne

Professor L Holmberg, Department of Surgery, University Hospital, Uppsala, Sweden

Mr R S Kirby, MA, FRCS, Urology Department, St. George's Hospital, London

Professor D C Mant, MA, Msc, MFPHM, Department of Primary Health Care, University of Southampton

Professor B J Norlen, Department of Urology, University Hospital, Uppsala, Sweden

Dr M C Parkinson, BSc, FRCPath, Department of Histopathology, University College Hospital Medical School, London

Dr P C Prorok, PhD, Chief, Screening Section, National Cancer Institute, Bethesda, MD, USA

Mr R J Shearer, MB, FRCS, Department of Urology, Royal Marsden Hospital, London

Mr A M Ward, MA, FRCPath, Department of Immunology, Northern General Hospital, Sheffield

Dr A Walker, PhD, Department of Public Health, Greater Glasgow Health Board

Dr J Waxman, Bsc, MB BS, FRCP, Department of Oncology, Hammersmith Hospital, London

Dr T J Wilt, MD,MPH,Chariman, PIVOT: CSP #407, Department of Veterans' Affairs, Minneapolis, USA

Data sources for special analysis

Hospital Episode Statistics, Department of Health

MediPlus GP database, International Medical Statistics

National Prostatectomy Audit: Audit Office, Royal College of Surgeons

Cancer Intelligence Unit, Wessex Institute of Public Health Medicine

Thames Cancer Registry

East Anglia Cancer Registry

Acute Sector Panel

Chair: Professor John Farndon, University of Bristol †

Professor Senga Bond, University of Newcastle-upon-Tyne †

Professor Ian Cameron, SE Thames RHA

Ms Lynne Clemence, Mid-Kent Health Care Trust †

Professor Cam Donaldson, University of Aberdeen †

Professor Richard Ellis, St James's University Hospital, Leeds †

Dr David Field, Leicester Royal Infirmary NHS Trust †

Mr Ian Hammond, Hillingdon HA †

Professor Adrian Harris, Churchill Hospital, Oxford

Dr Chris McCall, General Practitioner, Dorset †

Professor Alan McGregor, St Thomas's Hospital, London

Mrs Wilma MacPherson, St Thomas's & Guy's Hospitals, London

Professor Jon Nicoll, University of Sheffield †

Professor John Norman, Southampton University

Professor Gordon Stirrat, St Michael's Hospital, Bristol

Professor Michael Sheppard, Queen Elizabeth Hospital, Birmingham †

Dr William Tarnow-Mordi, University of Dundee

Professor Kenneth Taylor, Hammersmith Hospital, London †

Diagnostics and Imaging Panel

Chair: Professor Mike Smith, University of Leeds †

Professor Michael Maisey, Guy's & St Thomas's Hospitals, London*

Professor Andrew Adam, UMDS, London †

Dr Pat Cooke, RDRD, Trent RHA

Ms Julia Davison, St Bartholomew's Hospital, London †

Professor MA Ferguson-Smith, University of Cambridge †

Dr Mansel Hacney, University of Manchester

Professor Sean Hilton, St George's Hospital Medical School, London

Mr John Hutton, MEDTAP Europe Inc., London †

Professor Donald Jeffries, St Bartholomew's Hospital, London †

Dr Andrew Moore, Editor, Bandolier †

Professor Chris Price, London Hospital Medical School †

Dr Ian Reynolds, Nottingham HA

Professor Colin Roberts, University of Wales College of Medicine †

Miss Annette Sergeant, Chase Farm Hospital, Enfield

Professor John Stuart, University of Birmingham

Dr Ala Szczepura, University of Warwick †

Mr Stephen Thornton, Cambridge & Huntingdon Health Commission

Dr Gillian Vivian, Royal Cornwall Hospitals Trust †

Dr Jo Walsworth-Bell, South Staffordshire Health Authority †

Dr Greg Warner, General Practitioner, Hampshire †

Methodology Panel

Chair: Professor Anthony Culyer, University of York †

Mr Doug Altman, Institute of Health Sciences, Oxford †

Professor Michael Baum, Royal Marsden Hospital

Professor Nick Black, London School of Hygiene & Tropical Medicine †

Professor Martin Buxton, Brunel University †

Dr Rory Collins, University of Oxford

Professor George Davey-Smith, University of Bristol

Professor Ray Fitzpatrick, University of Oxford †

Professor Stephen Frankel, University of Bristol

Dr Stephen Harrison, University of Leeds

Mr Philip Hewitson, Leeds FHSA

Professor Richard Lilford, Regional Director, R&D, West Midlands †

Mr Nick Mays, Kings Fund Institute, London †

Professor Ian Russell, University of York †

Professor David Sackett, Centre for Evidence Based Medicine, Oxford †

Dr Maurice Slevin, St Bartholomew's Hospital, London

Dr David Spiegelhalter, Institute of Public Health, Cambridge †

Professor Charles Warlow, Western General Hospital, Edinburgh †

Pharmaceutical Panel

Chair: Professor Tom Walley, University of Liverpool †

Professor Michael Rawlins, University of Newcastle-upon-Tyne*

Dr Colin Bradley, University of Birmingham

Professor Alasdair Breckenridge, RDRD, Northwest RHA

Ms Christine Clarke, Hope Hospital, Salford †

Mrs Julie Dent, Ealing, Hammersmith and Hounslow HA, London †

Mr Barrie Dowdeswell, Royal Victoria Infirmary, Newcastle-upon-Tyne

Dr Desmond Fitzgerald, Mere, Bucklow Hill, Cheshire †

Dr Alistair Gray, Wolfson College, Oxford †

Professor Keith Gull, University of Manchester

Dr Keith Jones, Medicines Control Agency

Professor Trevor Jones, ABPI, London †

Dr Andrew Mortimore, Southampton & SW Hants Health Authority †

Dr John Posnett, University of York

Dr Frances Rotblat, Medicines Control Agency †

Dr Ross Taylor, University of Aberdeen †

Dr Tim van Zwanenberg, Northern RHA

Dr Kent Woods, RDRD, Trent RO, Sheffield †

Population Screening Panel

Chair: Professor Sir John Grimley Evans, Radcliffe Infirmary, Oxford †

Dr Sheila Adam, Department of Health*

Dr Anne Dixon Brown, NHS Executive, Anglia & Oxford†

Professor Dian Donnai, St Mary's Hospital, Manchester †

Professor George Freeman, Charing Cross & Westminster Medical School, London

Dr Mike Gill, Brent & Harrow Health Authority †

Dr JA Muir Gray, RDRD, Anglia & Oxford RO †

Dr Ann Ludbrook, University of Aberdeen †

Professor Alexander Markham, St James's University Hospital, Leeds †

Professor Theresa Marteau, UMDS, London †

Professor Catherine Peckham, Institute of Child Health, London †

Dr Connie Smith, Parkside NHS Trust, London †

Dr Sarah Stewart-Brown, University of Oxford †

Professor Nick Wald, University of London †

Professor Ciaran Woodman, Centre for Cancer Epidemiology, Manchester †

Primary and Community Care Panel

Chair: Professor Angela Coulter, Kings Fund Centre for Health Services Development, London †

Professor Martin Roland, University of Manchester*

Dr Simon Allison, University of Nottingham

Mr Kevin Barton, Bromley Health Authority †

Professor John Bond, University of Newcastle-upon-Tyne †

Professor Shah Ebrahim, Royal Free Hospital, London

Professor Andrew Haines, RDRD, North Thames RHA

Dr Nicholas Hicks, Oxfordshire Health Authority †

Professor Richard Hobbs, University of Birmingham †

Professor Allen Hutchinson, University of Hull †

Mr Edward Jones, Rochdale FHSA

Professor Roger Jones, UMDS, London †

Mr Lionel Joyce, Chief Executive, Newcastle City Health NHS Trust †

Professor Martin Knapp, London School of Economics & Political Science †

Professor Karen Luker, University of Liverpool

Dr Fiona Moss, North Thames British Postgraduate Medical Federation†

Professor Dianne Newham, Kings College, London

Professor Gillian Parker, University of Leicester †

Dr Robert Peveler, University of Southampton †

Dr Mary Renfrew, University of Oxford

Dr John Tripp, Royal Devon & Exeter Healthcare NHS Trust †

* Previous Chair
† Current members

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Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 1703 595 639 Email: hta@soton.ac.uk
http://www.soton.ac.uk/~hta

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