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Title

Prevention and early detection of prostate cancer

Permalink

<https://escholarship.org/uc/item/99829759>

Journal

The Lancet Oncology, 15(11)

ISSN

1470-2045

Authors

Cuzick, Jack
Thorat, Mangesh A
Andriole, Gerald
[et al.](#)

Publication Date

2014-10-01

DOI

10.1016/s1470-2045(14)70211-6

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Prevention and early detection of prostate cancer

Jack Cuzick, Mangesh A Thorat, Gerald Andriole, Otis W Brawley, Powel H Brown, Zoran Culig, Rosalind A Eeles, Leslie G Ford, Freddie C Hamdy, Lars Holmberg, Dragan Ilic, Timothy J Key, Carlo La Vecchia, Hans Lilja, Michael Marberger, Frank L Meyskens, Lori M Minasian, Chris Parker, Howard L Parnes, Sven Perner, Harry Rittenhouse, Jack Schalken, Hans-Peter Schmid, Bernd J Schmitz-Dräger, Fritz H Schröder, Arnulf Stenzl, Bertrand Tombal, Timothy J Wilt, Alicja Wolk

Prostate cancer is a common malignancy in men and the worldwide burden of this disease is rising. Lifestyle modifications such as smoking cessation, exercise, and weight control offer opportunities to reduce the risk of developing prostate cancer. Early detection of prostate cancer by prostate-specific antigen (PSA) screening is controversial, but changes in the PSA threshold, frequency of screening, and the use of other biomarkers have the potential to minimise the overdiagnosis associated with PSA screening. Several new biomarkers for individuals with raised PSA concentrations or those diagnosed with prostate cancer are likely to identify individuals who can be spared aggressive treatment. Several pharmacological agents such as 5 α -reductase inhibitors and aspirin could prevent development of prostate cancer. In this Review, we discuss the present evidence and research questions regarding prevention, early detection of prostate cancer, and management of men either at high risk of prostate cancer or diagnosed with low-grade prostate cancer.

Introduction

Prostate cancer is a common malignancy in men, and its incidence continues to rise in many countries.¹ Screening for, and management of, early prostate cancer is one of the most challenging and controversial issues in medicine. In this Review, we discuss the evidence regarding risk assessment, early detection, and management of early prostate cancer, and identify the key issues for further research (figure). Improved identification of risk factors to guide risk-adapted screening and preventive interventions is important. This Review also focuses on potentially modifiable lifestyle factors, and preventive therapies that might reduce risk. Prostate-specific antigen (PSA) screening for prostate cancer is controversial, and results from the CAP/ ProtecT trial,² which is investigating PSA screening and three different methods for treating early screen-detected lesions, are eagerly anticipated. Work is in progress to assess new tests that might be offered either as part of primary screening, or for the triage of men with high PSA concentrations, and we discuss these tests in detail. Management strategies for low-grade cancers and for men with high PSA concentrations but negative biopsies are discussed. We assess new tests based on serum markers or tissue from needle biopsies and the role of multiparametric MRI, and outline the need for improved diagnostic methods. We conclude with a research agenda of areas most in need of further development and investigation.

Risk factors and biomarkers

Risk factors can be divided into non-modifiable factors (including known genetic mutations or polymorphisms, or specific genes not yet identified), and external factors (including lifestyle factors when modification might be possible). Blood-based markers, such as androgen levels or IGF-1, are not well established but are affected by both genetic and environmental factors.

Age, race, and geography

Age is the most important non-modifiable factor. In unscreened populations, prostate cancer has the steepest age–incidence curve of all cancers with a rapid increase in the seventh decade.^{3,4} Only 25% of prostate cancers are diagnosed before the age of 65 years in Europe.¹ Racial variation is pronounced: in the USA, compared with white men of European ancestry, black men of African ancestry have 58% greater incidence of prostate cancer and 144% greater mortality, whereas Hispanic men have 14% lower incidence and 17% lower mortality.⁵ Substantial geographical variation has also been reported. Within Europe, incidence and mortality in Sweden is about twice of that in Spain and 1.5 times of that in Italy.⁶ Incidence in immigrant populations from developing countries is lower than white populations in developed countries, suggesting that racial (genetic) factors are important.⁷ Asian Indians and Pakistanis living in the USA have a standardised incidence ratio of 0.54 (95% CI 0.49–0.59) compared with American white populations.⁷ However, the incidence in these immigrants is substantially higher than in their country of origin, which could be due, at least partially, to the absence of population screening in their country of origin or environmental factors.⁷ Similar differences have been reported in immigrant populations in Sweden, although the difference in incidence reduced with increased length of stay,⁸ suggesting that lifestyle is an important component of these differences.

Familial and genetic factors

The relative risk (RR) of developing prostate cancer is higher in men who have a first-degree relative with prostate cancer (RR 2.48, 95% CI 2.25–2.74) than men without a first-degree relative with prostate cancer. This risk is higher in men younger than 65 years who have a first-degree relative than in older men with a first-degree relative with prostate cancer (RR 2.87, 2.21–3.74 vs 1.92, 1.49–2.47; p interaction=0.002) and if the affected relative

Lancet Oncol 2014; 15: e484–92

Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK (Prof J Cuzick PhD, M A Thorat MBBSc); Division of Urologic Surgery, Barnes-Jewish Hospital, Washington University School of Medicine, St Louis, MO, USA (Prof G Andriole MD); Office of the Chief Medical Officer, American Cancer Society, Atlanta, GA, USA (Prof O W Brawley MD); Department of Hematology and Oncology, Emory University, Atlanta, GA, USA (Prof O W Brawley); Department of Clinical Cancer Prevention, Cancer Prevention and Population Sciences, The University of Texas MD Anderson Cancer Center, Houston, TX, USA (Prof P H Brown MD); Molecular Pathology, Department of Urology, Innsbruck Medical University, Innsbruck, Austria (Z Culig MD); Division of Cancer Genetics and Epidemiology, The Institute of Cancer Research, London, UK (Prof R A Eeles PhD); Academic Urology Unit, Royal Marsden NHS Foundation Trust, London, UK (C Parker MD, Prof R A Eeles); Division of Cancer Prevention, National Cancer Institute, Bethesda, MD, USA (L G Ford MD, L M Minasian MD); Urology (Prof F C Hamdy MD), Nuffield Department of Surgical Sciences (Prof H Lilja MD), and Cancer Epidemiology Unit, Nuffield Department of Population Health (Prof T J Key DPhil), University of Oxford, Oxford, UK; Medical School, King's College London, London, UK (Prof L Holmberg MD); Regional Cancer Center Uppsala Orebro and Department of Surgical Sciences, Uppsala University, Uppsala, Sweden (Prof L Holmberg); School of Public Health and Preventive Medicine, Department of Epidemiology and Preventive

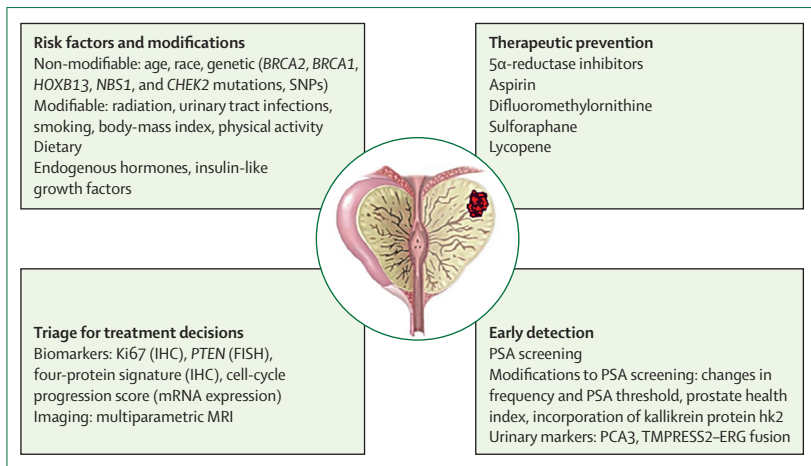


Figure: Prevention and early detection of prostate cancer

Modifiable and non-modifiable risk factors, pharmacological agents, and triage strategies for prevention and early detection of prostate cancer, many of which are yet to be established. IHC=immunohistochemistry. FISH=fluorescent in-situ hybridisation. SNP=single-nucleotide polymorphism.

Medicine, Monash University, Melbourne, VIC, Australia (D Ilic PhD); Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy (Prof C La Vecchia MD); Department of Surgery (Urology), Laboratory Medicine, and Medicine (GU-Oncology), Memorial Sloan-Kettering Cancer Center, New York, NY, USA (Prof H Lilja); Department of Laboratory Medicine, Lund University, University Hospital UMAS, Malmö, Sweden (Prof H Lilja); Department of Urology, Vienna University Medical School, Vienna, Austria (Prof M Marberger MD); Biological Chemistry, Public Health, and Epidemiology, School of Medicine, University of California, Irvine, CA, USA (Prof F L Meyskens MD); Prostate and Urologic Cancer Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD, USA (H L Parnes MD); Department of Prostate Cancer Research, Institute of Pathology, University Hospital of Bonn, Bonn, Germany (Prof S Perner MD); Director of Assay Development, IR2Dx Inc Moraga, CA, USA (H Rittenhouse PhD); Urology, Radboud University Medical Center, Nijmegen, Netherlands (Prof J Schalken PhD); Department of Urology, Kantonsspital St Gallen, St Gallen, Switzerland

was a brother rather than a father (RR 3.14, 2.37–4.15).⁹ Family history is important, but only 35% of the familial risk is explained by known genes.^{10,11} Although rare (about one per 300), a *BRCA2* mutation confers up to 8.6 times increased risk in men younger than 65 years, and these mutations have been associated with aggressive cancer.^{12,13} Other rare mutations that confer greater RR of prostate cancer have been reported in *BRCA1*, *HOXB13*, *NBS1*, and *CHEK2* genes.¹³ The *HOXB13* G84E mutation is the only other identified mutation with a substantial RR (3–4 times), occurring in 1.3–1.4% of the general population.¹⁴

Genome-wide association studies have uncovered more than 70 low-penetrance susceptibility loci (odds ratio [OR] per allele of 1.1–1.3) with high allele frequencies.¹³ These loci are individually of little direct value, except for their potential to identify a mechanism of carcinogenesis, but if they act multiplicatively when used collectively in panels, they might improve risk stratification; in such a case, they could identify 1% of the population with a RR of 4.7.¹³

Possible familial risk factors for which the genetic basis is not known include some types of male pattern baldness¹⁵ and digit length,¹⁶ but their value in risk stratification is unknown. Adult height has been associated with increased risk, with an OR of 1.06 for every 10 cm increase.¹⁷

External exposure

Both ionising radiation¹⁸ and ultraviolet radiation from sun exposure¹⁹ have been linked to prostate cancer, but confirmation of this link and more detailed risk estimates are needed. Increased risk in individuals exposed to cadmium has been reported, but high exposure is rare, and as such the risk is small with a negligible effect on public health.²⁰

Urinary tract infections

Risk for prostate cancer might be increased in men with a history of urinary tract infections.²¹ There is evidence for a role for *Trichomonas vaginalis*, but evidence for other agents such as human papillomavirus and cytomegalovirus is weak.²² Infections might affect the risk for prostate cancer by causing chronic intraprostatic inflammation, and pathological studies show that inflammation could be involved in the development of prostate cancer.²³ The role of urinary tract infections and chronic inflammation in the development of prostate cancer is uncertain and more research is needed.

Smoking

Smoking is associated with a moderate increase in the risk for prostate cancer.²⁴ This association is much stronger, and the increase more pronounced, for aggressive or fatal cancers, particularly in current or heavy smokers who could have double or more risk as non-smokers.²⁵ Current smokers are at a higher risk of prostate cancer-specific mortality and recurrence than non-smokers and past-smokers. The stronger association with aggressive cancers suggests that smoking might play a part in the promotion of metastatic spread.²⁵

Diet, weight, and physical activity

Increased body-mass index is associated with an increase in advanced prostate cancer but a decrease in localised disease,²⁶ which could explain the conflicting findings in early reports. Analysis of the Prostate Cancer Prevention Trial (PCPT) showed similar findings.²⁷ Although no clear links with specific dietary factors have been established, red meat, dairy protein, dietary fat, and coffee²⁶ have been mentioned as factors. Sedentary lifestyle has been linked to high PSA concentrations in one large survey,²⁸ and a meta-analysis of 19 cohort and 24 case-control studies reported a small inverse relationship between physical activity and prostate cancer risk.²⁹

Endogenous hormones

Prospective epidemiological studies have investigated the role of endogenous hormones in prostate cancer. A pooled analysis of individual patient data from 18 studies found no significant associations with sex hormones,³⁰ but more data are needed to examine the relation with high grade cancer.^{30,31} For insulin-like growth factors (IGF), a pooled analysis of individual patient data from 12 studies showed a significant positive association between circulating IGF-I and prostate cancer risk;³² more data are needed for IGF-II and IGF-binding proteins.

Early detection of prostate cancer

PSA screening

The value of PSA screening is contentious. Five screening trials have been completed, but three are not of adequate quality to be informative;³³ the other two are of higher methodological quality. These two large trials, the Prostate,

Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)³⁴ and the European Randomized Study on Screening for Prostate Cancer (ERSPC),³⁵ have reported different results³⁶ possibly because of differences in design.

The PLCO trial was done in the USA, where PSA testing is common, and examined opportunistic versus organised annual screening.³⁶ Equal proportions of men in the opportunistic screening group (34·3% screened once and 9·8% two or more times) and annual screening groups (34·6% once and 9·4% two or more times) had undergone PSA testing within 3 years before recruitment to the trial.³⁴ Although the rate of PSA testing in the opportunistic screening group (40%) was lower than that in the annual screening group (85%) in the first year, it increased to 52% in the sixth year. Men randomly assigned to the annual screening group had a higher incidence of prostate cancer (RR 1·12, 95% CI 1·07–1·17) but no reduction in prostate cancer mortality (1·09, 0·87–1·36). The absence of benefit might not be entirely due to contamination (screening in the control group) in the control group because the results did not vary by PSA-screening status at baseline, but those men who were screened before recruitment had 25% lower risk of prostate cancer death than those who were not screened.

By contrast, the European ERSPC trial³⁵ examined the role of PSA screening in a largely unscreened population (7–30% of control men screened during the trial, depending on the trial centre) from seven countries with different screening and treatment strategies. Overall, the investigators noted a significant 21% reduction (rate ratio 0·79, 95% CI 0·68–0·91, $p=0\cdot001$) in death from prostate cancer in a predefined subgroup of men aged 55–69 years after 11 years of follow-up. Comparisons of treatments used in the two randomised groups have been done to explain the differences.^{37,38} More patients in the screening group (PSA screening every 2–4 years, interval between screens depending on the participating country) received radical prostatectomy and more in the control group (no intervention) were given hormone therapy, but this difference was largely explained by the worse tumour characteristics of the control group, as a result of their later diagnosis.³⁷ Treatment differences could not entirely explain the mortality benefit.³⁷ Differences in screening interval and follow-up protocols exist between the two trials, but the major difference could be explained by the high screening rates in the controls of the PLCO trial. Three trials with lower methodological quality did not report a reduction in prostate cancer mortality.³³

A majority of the authors of this Review (62%) agree that PSA screening does reduce death from prostate cancer; others (GA, OWB, PHB, LGF, FCH, DI, LMM, HLP, BT, TJW, and AW) thought that the present evidence is not sufficiently conclusive. We all agreed that the magnitude of the effect was uncertain and that substantial overdiagnosis and overtreatment exists, which needs to be reduced before recommendations for PSA screening in the general

population can be made. The CAP/ProtecT trial of 450 000 men (ISRCTN92187251 and ISRCTN20141217) will report its initial findings in 2016, and should clarify the value of PSA screening. The authors of this Review agree that death from prostate cancer should be the primary endpoint for screening studies. Although cause of death in older men can be difficult to ascertain, overall mortality has insufficient power because the number of deaths from unrelated causes is very large and substantially dilutes any effect. Every effort should be made to accurately identify the specific cause of death. Development of metastatic disease is a useful secondary endpoint, and it can provide earlier evidence of a screening effect if thoroughly assessed in both trial groups.

New triage and screening markers

A major focus of new research should be the development of new methods and markers to more clearly separate indolent (low-risk) cancers from aggressive, potentially lethal cancers, which will enable conservative management of more patients. Ideally, this would be achieved by non-invasive and inexpensive assays for biomarkers in serum (eg, Kallikrein proteins) or in urine (eg, PCA3 or TMPRSS-ERG fusions). Multiparametric MRI or assays that can be done on needle biopsies (such as the cell-cycle progression score) could be useful in safely avoiding radical treatments like prostatectomy or radiotherapy and the morbidity associated with these treatments.

Modifications of existing PSA-screening strategies such as changes in screening frequency and PSA thresholds could reduce harms from screening. Increasing the interval between PSA tests, from annual tests (as in the PLCO trial) to tests every 2–4 years (as in the ERSPC trial) might reduce harms from overdiagnosis without a detrimental effect on prostate cancer mortality. Similarly, data from population-based studies and randomised controlled trials, such as the Prostate Cancer Intervention Versus Observation Trial (PIVOT), support an increase in the threshold for abnormal PSA from 3–4 ng/mL to 6–10 ng/mL.³⁹

Serum and urine markers

Several improvements to the most widely used PSA assay have been developed. Of these, the prostate health index, which is an assay based on the concentration of a molecular isoform of free PSA,⁴⁰ is much further along the biomarker discovery–credentialing–validation pathway, and has a greater specificity than total PSA or percentage-free PSA. Addition of the Kallikrein protein hK2 to PSA-based markers has also improved the specificity of PSA-based assays,⁴¹ but both need further validation in a screening context, with a particular focus on their integration into screening algorithms and how they compare against present risk calculations.

Urinary markers need prostatic massage by digital rectal examination to obtain enough cells to be sensitive,

(Prof H P Schmid MD); Urologie, Schön Klinik Nürnberg/Fürth & Urologie 24, Fürth, Germany (Prof B J Schmitz-Dräger MD); Erasmus University and Erasmus Medical Centre, Rotterdam, Netherlands (Prof F H Schröder MD); Department of Urology, University Hospital Tübingen, Tübingen, Germany (Prof A Stenzl MD); Department of Urology, Université Catholique de Louvain, Brussels, Belgium (Prof B Tombal MD); Center for Chronic Disease Outcomes Research, Minneapolis Veterans Affairs Health Care System, and Section of General Medicine, University of Minnesota School of Medicine, Minneapolis, MN, USA (Prof T J Wilt MD); and Division of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Prof A Wolk DrMedSci)

Correspondence to: Prof Jack Cuzick, Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London EC1M 6BQ, UK j.cuzick@qmul.ac.uk

which restricts their use to the triage of men at increased risk. The assays are complicated and require a specialist laboratory. Two assays have received the most attention. The *PCA3* assay measures the non-coding prostate cancer gene 3 mRNA,⁴² which is markedly overexpressed in prostate cancer cells, and produced only in prostate tissue. *PCA3* is more specific than PSA, which is secreted by all prostate cells and is heavily affected by prostate volume. Initial findings show that the *PCA3* assay does identify cancer, but does not discriminate between low-risk and aggressive disease.⁴³ A urinary marker that detects the fusion of *TMPRSS2* with *ERG* is under development, and might better distinguish aggressive from low-risk early lesions.⁴⁴ Measurement in urine of gene fusions between *ERG* and other important genes, or multiplexing of *PCA3* and *TMPRSS2-ERG* with genes such as *SPINK1* and *GOLPH2*, is also of interest. Methylation markers might be useful for the diagnosis and prognosis of prostate cancer, but work is still at an early stage. Further research is needed to validate their use in needle biopsies and serum or urine samples.

The prostate health index, the four-marker Kallikrein panel, and *PCA3* are more accurate than conventional PSA in the detection of cancer, mainly as a result of improved specificity.^{41,45} PSA concentrations in men aged 40–60 years are predictive of which patients will develop prostate cancer several years later, and they might help to identify cancers that will become metastatic or lead to death.^{46,47} Further investigations are needed to improve screening and triage strategies.

Multiparametric MRI

Multiparametric MRI is a combination of high-resolution T2-weighted images and at least two functional MRI techniques—such as diffusion-weighted imaging, dynamic contrast enhancement, or MR spectroscopy—to improve specificity.^{48,49} Compared with conventional MRI, multiparametric MRI provides better anatomical delineation, improved specificity in characterisation of lesions, and a more reliable assessment of organ confinement of the tumour to guide therapy. Whether multiparametric MRI can identify which Gleason 6 cancers can be safely managed by active surveillance is a key question. Multiparametric MRI highlights areas of aggressive disease, and improves staging by identification of extracapsular extension or disease in anterior or apical locations, which might not be reliably established with digital rectal examination or standard systematic biopsies.⁴⁸ Apart from improved planning of curative treatments, multiparametric MRI could improve the selection of patients for active surveillance. Additionally, its potential to monitor patients managed by active surveillance should be investigated.⁴⁹ MRI-guided biopsies and MRI-transrectal ultrasound fusion-guided biopsies have higher detection rates for clinically relevant tumours than standard systematic biopsies.⁴⁹ Trials such as the Prostate MRI Imaging Study (PROMIS; ISRCTN 16082556) are likely to

clarify when to use multiparametric MRI in the diagnostic pathway, and whether its use is cost effective. Incorporation of multiparametric MRI in models predicting cancer risk in patients with previous negative biopsy requires further study.^{48,49}

Markers in needle biopsies

Although done at a later stage, progression markers identified in needle biopsies might help to avoid unnecessary radical treatment. Ki67 expression, as measured by immunohistochemistry, is the most used marker, and can distinguish between aggressive and indolent prostate cancer.⁵⁰ Immunohistochemistry and fluorescent in-situ hybridisation (FISH) assays for *PTEN*,^{51,52} and FISH assay for *TMPRSS2-ERG* fusions have shown promise,⁵³ but with conflicting results.⁵⁴ Similarly, overexpression of *MYC*⁵⁵ by FISH and TP53⁵⁶ by immunohistochemistry have some prognostic potential. A four-protein signature—*PTEN*, *SMAD4*, cyclin D1, and *SPP1*—identified with immunohistochemistry predicts biochemical recurrence.⁵⁷

A cell-cycle progression score (Prolaris, Myriad Genetics), which has stronger prognostic value than current prognostic biomarkers such as Gleason grade, PSA level, and extent of disease, was predictive of outcome in several studies of transurethral resection of the prostate, needle biopsy, and radical prostatectomy specimens.⁵⁸ Because this material contains more tumour cells and their components than a serum or urine sample, the potential for improved assessment exists. However, inadequate sampling is a problem with needle biopsies, especially when few cores are taken, and the performance of various assays in 12-core or template biopsies is an important research area. Other mRNA marker panels have been used with some success, often containing *PTEN*, *p53*, or *TMPRSS2-ERG*.⁵⁹

Management of men with raised PSA concentrations

An important issue is how best to manage men with raised PSA concentrations who have had negative biopsies. Study findings^{60,61} show a high incidence of prostate cancer during follow-up after negative biopsy. The Göteborg sub-cohort of the ERSPC trial showed a 26% incidence within 4 years,⁶¹ whereas 10% of such men in the PLCO trial developed prostate cancer within 3 years of negative biopsy.⁶⁰ The placebo group of the Prostate Cancer Prevention Trial (PCPT) had high positive rates (15% overall) for cancer in biopsies of men with normal PSA concentrations at the end of a 7-year study period.⁶² Use of additional markers such as Kallikrein panels for triage of such men needs further investigation.⁴¹

Management of low-grade prostate cancer

An equally important issue is the management of men with low-grade (eg, Gleason score 6) cancer. Gleason 6 is poorly defined, and its natural history and the appropriate

active surveillance protocols need to be refined and clinically validated.

Role of observation

In selected low-risk subgroups of the PIVOT trial,³⁹ passive observation led to the same prostate cancer mortality as radical prostatectomy, and observation alone is an important management option. In SPCG-4, the radical prostatectomy group had reductions in prostate cancer death, all-cause mortality, and development of distant metastases, but only the effect on distant metastases was statistically significant in men aged 65 years or older.⁶³ Apart from morbidity and mortality related to radical treatment, observation alone also avoids biopsy-related morbidity associated with active surveillance. The challenge is to identify as large a subgroup as possible that can be safely managed this way. New markers to identify aggressive cancers need to be developed and validated, especially in men with Gleason 6 cancer and PSA less than 10 ng/mL.

Preventive therapy

Role of 5 α -reductase inhibitors

The use of 5 α -reductase inhibitors either for prevention or management of early disease has produced complex outcomes. The PCPT⁶⁴ investigated finasteride in men with low PSA (≤ 3 mg/mL) and no evidence of disease. Biopsies were recommended at the end of the study or if digital rectal examination was abnormal and PSA exceeded 4.0 ng/mL in the control group or 2.0 ng/mL (1.75 ng/mL after first 4 years) to allow for the reduction of PSA level with this drug. After 7 years of follow-up, a 24.8% reduction (95% CI 18.6–30.6) in overall prostate cancer incidence was reported compared with the control (placebo) group, but this effect was restricted to cancers with a Gleason score of 6 or less, and an increase of 27% in high-grade tumours was noted (RR 1.27; 95% CI 1.07–1.50). Similar results were reported in the REDUCE trial,⁶⁵ which assessed dutasteride, another 5 α -reductase inhibitor, in a high-risk population of men with a PSA concentration between 2.5 ng/mL and 10 ng/mL and a negative initial prostate biopsy. After 4 years of follow-up, a 23% reduction in overall prostate cancer incidence was reported compared with controls who received placebo, but there was no effect on cancer with Gleason score 7 or above, and there was an increase in Gleason 10 tumours. Although both drugs have a beneficial effect on benign prostatic disease, the absence of effect on high-grade cancer is a major concern. An increase in the sampling accuracy of the prostate with the then common six-needle biopsy, because of smaller total prostate size, has been offered as an explanation for this finding.⁶⁶ Investigators of a large population-based case-control study also reported a significantly lower risk of cancer with Gleason scores 2–7 in men given 5 α -reductase inhibitors compared with age and county matched men in the general population who did not receive these drugs; however, by

contrast with the randomised controlled trials, no evidence of an increased risk of cancer with Gleason scores 8–10 was detected.⁶⁷ Prevention of low-risk prostate cancer is beneficial because it avoids harm related to diagnosis and treatment, and it might even be cost effective;⁶⁸ however, neither finasteride nor dutasteride have been approved by the Food and Drug Administration for cancer prevention. Long-term results from the PCPT have confirmed their earlier findings, and 15-year overall survival rates were similar in both groups even though more high-grade prostate cancers were diagnosed in the finasteride group than the placebo group.⁶⁹ However, the trial had insufficient power to detect a difference in overall survival. It is important to note that, for individuals on 5 α -reductase inhibitors, clinicians should adjust the PSA biopsy thresholds by 50%⁷⁰ because these agents lower PSA values. Retrospective analysis of data from the REDUCE trial has shown that PSA maintains its predictive value for men on dutasteride when lower biopsy thresholds are used than for men not taking this drug.⁷¹

Dutasteride was used as an adjuvant treatment in the REDEEM trial of 302 men (289 evaluable) with Gleason 5–6 cancer managed by active surveillance.⁷² After 3 years of follow-up, a 38% reduction (hazard ratio [HR] 0.62, 95% CI 0.43–0.89) in progression was reported with dutasteride but no metastatic disease or prostate cancer-related deaths were reported in either group. A large trial with longer follow-up is needed to assess 5 α -reductase inhibitors for the prevention of aggressive prostate cancer.

Other preventive agents

Trials of dietary agents thought to have a beneficial effect on prostate cancer have been negative.⁷³ Randomised studies of β -carotene for those at high risk of lung cancer showed an increase in lung and stomach cancers.⁷⁴ Investigators of another study with prostate cancer as the primary endpoint, the SELECT trial,⁷⁵ reported that in 35533 men with PSA of 4 ng/mL or less and a negative digital rectal examination, neither selenium nor vitamin E supplementation had a beneficial effect on the incidence of prostate cancer; incidence of prostate cancer increased with vitamin E dietary supplementation.

A short-term study of the polyamine synthesis inhibitor difluoromethylornithine⁷⁶ noted significantly lower polyamine content in the prostate within 1 month, that suppression of prostate putrescine concentrations was maintained, and that the rate of prostate growth was decreased at 12-month follow-up compared with placebo. Further long-term follow-up studies are needed.

Evidence for other preventive or therapeutic interventions is scarce and comes from epidemiological studies and randomised trials in which prostate cancer was a secondary endpoint. Aspirin has the most promising profile, and findings from case-control and cohort studies⁷⁷ suggest a small but consistent reduction in disease incidence of about 10%. A meta-analysis of randomised

controlled trials⁷⁸ reported a larger but non-significant reduction in mortality in patients taking aspirin regularly (19%, $p=0.12$), compared with controls who did not take regular aspirin, suggesting that aspirin is of benefit for aggressive tumours. This finding has been corroborated in the Health Professionals Follow-up Study, which noted a 16% reduction (HR 0.84, 95% CI 0.69–1.02) in lethal prostate cancers (cancer death or metastasis) in patients who took aspirin regularly as opposed to those who did not.⁷⁹ These studies were undertaken in individuals at average risk for prostate cancer, with or without cardiovascular risk factors, and further studies of high-risk individuals and those with tumours of Gleason score 7 or above are needed. Aspirin could exert an effect through an antiplatelet mechanism to slow metastatic spread and improve survival, but effects through other pathways have been proposed.⁷⁹ A range of adjuvant trials in different tumour types including prostate cancer are either underway (ClinicalTrials.gov identifiers NCT00565708 and NCT01058902) or being planned. A meta-analysis of observational studies shows that statins have a beneficial effect in reducing the incidence of prostate cancer, particularly advanced disease.⁸⁰ However, reduction in the incidence of prostate cancer has not been seen with long-term statin use and when data from randomised controlled trials are considered.⁸¹ Residual confounding due to health awareness in statin users and screening frequency probably underlies the observational studies' findings; any beneficial effect is unclear in the absence of long-term follow-up data, and so further research and longer follow-up of randomised controlled trials are needed.

Studies of other dietary supplements have not been very promising. Vitamin D showed promise in initial epidemiological studies, but recent work has been negative.⁸² However, several studies are underway and they need to be completed before a full conclusion can be reached.⁸³

Lycopene, an open-chain carotenoid found in cooked tomatoes showed initial promise, but a systematic review of all randomised controlled trials has not shown any overall effect,⁸⁴ although data are still sparse. Meta-analysis of observational data indicates no overall effect with low-to-moderate intake, but a potential effect with high lycopene intake (RR 0.89, 95% CI 0.81–0.98),⁸⁵ although the evidence is very scarce. The naturally

occurring isothiocyanate sulforaphane that is found in broccoli and other cruciferous vegetables is being investigated (ClinicalTrials.gov identifiers NCT01265953 and NCT00946309).

Research and policy agenda

Research should focus on developing better biomarkers for identification of aggressive disease. Urinary markers such as PCA3 and TMPRSS2-ERG are the most developed, but still require further validation. Multi-parametric MRI has potential to identify the highest grades of lesion and guide biopsies to be taken from the most aggressive regions, especially in men with high PSA concentrations, but further studies are needed. Once a biopsy sample has been taken, expression profile panels such as the cell-cycle progression score could be used to determine tumour aggressiveness, but they need to be assessed in a range of contexts based on the treatment options under consideration and combinations with other more standard markers of tumour aggressiveness. A substantial proportion of cases with high PSA or cases identified as high risk by conventional means do not progress or cause death. Biomarkers that show indolent disease are needed to identify men who can be spared treatment and its adverse effects. When better biomarkers become available, future studies of modifiable risk factors should focus on those associated with aggressive prostate cancer.

Careful consideration of the population who would benefit from screening is needed. Men older than 70 years or younger men with serious comorbidities are not good candidates. Lengthening of the screening interval to every 2–4 years might reduce harms without substantially reducing benefits. Primary screening markers that improve specificity are needed, and assays such as PHI and the four-marker Kallikrein panel need to be assessed in the appropriate clinical setting.

Additionally, further research is needed into the appropriate treatment and management of individuals without cancer but who are at high risk (often due to high PSA but negative biopsy), those with low-grade tumours (Gleason 6 and PSA <10 ng/mL), or those with a genetic predisposition to prostate cancer. Although aspirin is one of the more promising agents, more studies of dietary supplements including vitamin D, difluoromethylornithine, lycopene, and sulforaphane are warranted. Despite the many issues that remain unresolved, further study of the 5 α -reductase inhibitors will be difficult because of the small increase in high-grade cancers in two randomised controlled trials and prohibitively large sample size needed to see a mortality reduction.

Conclusions

Evidence for several of the modifiable prostate cancer risk factors is uncertain. However, lifestyle modifications such as smoking cessation and exercise can decrease the

For clinical trials see <https://clinicaltrials.gov/>

Search strategy and selection criteria

References for this Review were identified through searches of PubMed. Publication date or language restrictions were not applied. Search terms "prostate cancer", "risk factors", "screening", "early detection", and "prevention" were used. Articles identified through searches of the authors' own files were used. The reference list is based on originality and relevance to the broad scope of this Review. Additional references are listed in the appendix.

See Online for appendix

risk of developing prostate cancer. Although associated with an increased number of high-grade prostate cancers, 5 α -reductase inhibitors reduce overall prostate cancer burden. In the absence of any detrimental effect on survival, these agents can be cost effective for the prevention of prostate cancer. Several other pharmacological agents are being investigated in clinical trials. PSA screening is a controversial topic, but overdiagnosis associated with screening can be minimised by modification of the PSA threshold, change in the screening frequency, and the use of other biomarkers (eg, Kallikrein panel and free PSA). Prospective investigations of these screening modifications and biomarkers should be a priority. Newer biomarkers such as urinary PCA3 and TMPRSS2-ERG need further assessment in a screening setting. Similarly, new methods to distinguish between aggressive prostate cancers and indolent cancers diagnosed during screening are needed. Ki67, cell-cycle progression, or imaging methods such as multiparametric MRI need further investigation so that they can be included in management algorithms to minimise overtreatment.

Contributors

JC, MAT, PHB, and FLM had the original idea for this Review. JC and MAT wrote the first draft, and all authors contributed to writing and critical review of successive drafts. All authors approved the final manuscript. JC is guarantor and had final responsibility for the decision to submit for publication.

Declaration of interests

JC reports grants from Cancer Research UK, Prostate Cancer UK, and the Association for International Cancer Research, during this study; grants and personal fees from Myriad Genetics; personal fees and non-financial support from Bayer; and membership of the advisory board of Myriad Genetics and Bayer, outside the submitted work. MAT reports grants from Cancer Research UK, Prostate Cancer UK, and the Association for International Cancer Research, during this study. GA reports grants from NCI, during this study; personal fees from Augmenix, Bayer, Genomic Health, GlaxoSmithKline, and Myriad Genetics; research grants from Johnson & Johnson, Medivation, and Wilex, outside the submitted work. PHB serves as a Scientific Advisory Board Member for Susan G Komen Foundation, outside the submitted work. RAE reports Medical Education support from Janssen, personal fees, and expenses from Succinct Communications, outside the submitted work. LH reports support from Swedish County Authorities, during this study, in his capacity as the head of a publicly funded regional cancer centre that has the remit to oversee early detection and prevention for cancer in one of six health-care regions in Sweden. HL reports grants from National Cancer Institute (R01CA160816; P50-CA92629) to Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY, USA; grants from David H Koch through the Prostate Cancer Foundation to the Sidney Kimmel Center for Prostate and Urological cancers at MSKCC, New York, NY, USA; grants from Swedish Cancer Society (number 11-0624) to Lund University, Malmö, Sweden; grants from Fundacion Federico SA to Lund University, Malmö, Sweden; and grants from the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Program, University of Oxford, Oxford, UK, during this study; in addition, HL holds a patent for free PSA, intact PSA, and hK2 assays with royalties paid to Arctic Partners, and a patent application for a statistical method to detect prostate cancer filed by Arctic Partners and licensed to OPKO. MM reports grants and personal fees from GlaxoSmithKline and MSD, during this study; grants and personal fees from GlaxoSmithKline and MSD, outside the submitted work. FLM reports travel support from Cancer Prevention Pharmaceuticals, outside the submitted work; FLM is a co-Founder of Cancer Prevention Pharmaceuticals. CP reports grants and personal fees

from Bayer; and personal fees from Astellas, BNIT, Janssen, Sanofi-Aventis, and Takeda, outside the submitted work. BT reports personal fees from Amgen; grants and personal fees from Astellas and Ferring; personal fees from Medivation, Bayer, and Dendreon; and non-financial support from IPSEN, outside the submitted work. The other authors declare no competing interests.

Acknowledgments

We thank Vesna Florijancic, Liz Pinney, and Ellie Stewart for administrative assistance. This Review was sponsored and funded by the International Society of Cancer Prevention (ISCaP), the European Association of Urology (EAU), the National Cancer Institute, USA (NCI) (grant number 1R13CA171707-01), Prostate Cancer UK, Cancer Research UK (CRUK) (grant number C569/A16477), and the Association for International Cancer Research (AICR). Sponsors and funding sources had no role in the discussion or writing of this manuscript. The findings and conclusions in this report are those of the authors and do not represent the official position of the authors' respective institutions.

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